METHODOLOGICAL ISSUES IN MENSTRUAL RESEARCH: MENORRHAGIA RECONSIDERED

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Methodological issues in menstrual research: menorrhagia reconsidered

Background:

Menorrhagia (excessive periods) is a very common reason for consultation with general practitioner, and the most common reason for referral to gynaecology clinic. The clinical definition is blood loss exceeding 80mls per period but measurement is seldom undertaken in routine clinical practice. Research has shown that many women presenting with menorrhagia have volume of blood loss in the normal range and that women's concerns are mainly the impact of periods on their lives, less about the volume of blood loss. The clinical definition of menorrhagia requires reconsideration, to better reflect the contemporary menorrhagia complaint.

Aim:

To examine the multi-faceted menorrhagia complaint in terms of: subjective account of menstrual periods and symptoms, psychosocial measures, socio-demographic factors, and objective measurement of the menstrual loss.

Study design:

The research comprises three overlapping parts: (1) a cross-sectional survey with (2) an embedded detailed prospective menstrual collection study, and (3) a follow-up (cohort) study of the earliest recruits to the survey group, the latter undertaken by case-note review. Local Ethical Research Committee approval was obtained for the study.

Study population:

All women aged 25 to 49 years newly referred for menstrual problems to collaborating consultants at gynaecology clinics at Edinburgh and Glasgow Royal Infirmaries, and Glasgow Western Infirmary. Problems eligible for inclusion in the survey were excessive periods, period pain, premenstrual changes, 'period problems' (non-specific) and irregular periods. Only those with putatively heavy periods (referral for that reason, or subjective judgement) were invited to have their blood loss measured.

Methods:

Survey data were collected using the brief Clinic Questionnaire (ascertaining minimal essential data from as many as possible of the eligible clinic population); a more detailed Menstrual Evaluation Questionnaire; and the Menstrual Background Questionnaire (addressing contraceptive and obstetric history, and general health). The SF-36 quality-of-life questionnaire was also used. A Menstrual Chart was developed for the menstrual collection, and both total menstrual fluid loss and blood loss volume were measured. The case note review follow-up was undertaken for all women recruited before March 1998, for the 8 months after recruitment to the study, extracting data on tests and investigations performed, diagnoses and treatments, and outcome at 8 months.

Results:

The 952 women recruited were representative, in terms of age, socio-economic status and referral condition, of all 1506 eligible referrals. The 226 who had their menstrual loss measured were socio-demographically representative of all 865 women eligible for this stage. Case notes were found and reviewed for 665 (89%) of the 748 recruited early enough to be followed-up. The study sample is described in terms of socio-demographic factors, referral reasons, subjective report of periods, quality-of-life, well-being and clinic outcome, and for the relevant subset, menstrual loss volumes. Prior hypotheses with regard to associations between these factors are evaluated and reported. Methodological issues in menorrhagia assessment and measurement are considered.

Conclusions:

The current focus on volume of blood loss in menorrhagia complaint is unhelpful, since it ignores the associated symptoms and social disability that play a key role in leading a woman to seek help for her periods. The 80 ML criterion is of dubious clinical utility as it is neither sensitive nor specific for adverse impact of periods, compromised iron status, or pathology.

Preface

This study was originally envisaged as a clinical research study rather than a PhD project. The initial idea for the study was mine, but design was refined in discussion with the clinical co-investigators for the study, Professors Hilary Critchley, University of Edinburgh, and Professor Mary Ann Lumsden, University of Glasgow, and with clinical collaborator Dr Mary Campbell Brown, also of University of Glasgow. Funding for the study was provided by the Chief Scientist Office for Scotland (K/MRS/50/C2472, Principal investigator PW). The grant covered salaries for two half-time research nurses, one each in Edinburgh (Elaine Kacser) and Glasgow (Dorothy Lyons), and for a half-time data manager in Edinburgh (Anne Douglas). The research was overseen by means of regular study meetings of myself, the three clinical collaborators, the two research nurses and the data manager.

I devised all the in-house questionnaires and drew up study information sheets, recruiting guidance notes and similar, and obtained ethical approval in Edinburgh. Professor Lumsden obtained ethical approval for the Glasgow centre. The nurses recruited patients, administered questionnaires, chased up non-returns, undertook laboratory measurement of menstrual blood loss, and reviewed case notes for follow-up. The data manager co-ordinated the study, assisted with questionnaire development, coded free-text items after strategy discussion with me, oversaw data entry, and checked and accumulated the study data set.

Since registering for PhD there have been regular meetings with my supervisors mainly addressing the reporting, publication and dissemination strategy for the study. The three papers so far published have been my ideas but have been commented on and approved by all three co-investigators, by Anne Douglas and by Professor Murray. The papers already published, off-prints of which are included in the Appendix, are:

> Warner P, Critchley HOD, Lumsden MA, Douglas A, Campbell-Brown M, Murray G. *Referral for menstrual problems: cross-sectional survey of symptoms, reasons for referral, and management.* B M J. 2001; 323: 24-28.
>
> Warner P, Critchley HOD, Lumsden MA, Campbell-Brown M, Douglas A, Murray G. *Menorrhagia I: Measured blood loss, clinical features, and outcome in women with heavy periods: a survey with follow-up data.* Am J Obstet Gynecol. 2004; 190: 1216-1223.
>
> Warner P, Critchley HOD, Lumsden MA, Campbell-Brown M, Douglas A, Murray G. *Menorrhagia II: Is the 80mL blood loss criterion useful in management of complaint of menorrhagia?* Am J Obstet Gynecol. 2004; 190: 1224-1229.

The study could not have been achieved without the input of the co-investigators and the efforts of the research staff involved. Furthermore, I have received invaluable advice about my thesis from my PhD supervisors Professors Murray and Critchley. Nevertheless I feel confident in declaring that this thesis is my own composition. The work has not been submitted for any other degree or qualification.

Signed:

Acknowledgements

I have been helped in numerous ways by many people in the preparation of this PhD thesis. An essential component was the research study, and that would not have been possible without my clinical collaborators and the research team. I thank them for their many and varied contributions.

The evolution of my thinking around menorrhagia has benefited over some years from intermittent but very helpful discussions with Professor Ian Fraser, University of Sydney, Australia, and collaboration with him regarding some of his research. In recent years I have been fortunate to enjoy the stimulus of involvement with Dr Miriam Santer and Dr Sally Wyke (both at that time University of Edinburgh) in a mixed methods primary care menorrhagia project. This rewarding collaboration has opened my eyes to deeper sociological insights, and further developed my ideas.

However, I wish most especially to thank my supervisors, Professor Gordon Murray and Professor Hilary Critchley for their willingness to take on the role, and for their excellent advice and encouragement. I am enormously grateful for their supervision.

Finally, I have been supported and encouraged by my family, Chris, Alison, Libby and Richard. I am very grateful that they, on my behalf, were as enthused by the venture as I have been.

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LIST OF ABBREVIATIONS

a	Intercept for linear regression
b	Slope coefficient for linear regression
BMI	Body mass index
CI	confidence interval
CQ	In-house Clinic Questionnaire
CSO	Chief Scientist Office
df	Degrees freedom
dL	decilitre
DUB	dysfunctional uterine bleeding
e	Base for natural logarithms (2.71828..)
EPQ-R	Eysenck Personality Questionnaire- Revised
F	F statistic computed in analysis of variance and regression
g	gram
GP	General Practitioner
Hb	haemoglobin
IQR	Inter-quartile range (lower quartile, upper quartile)
IUCD	Intra-uterine contraceptive device
L	litre
ln	Natural logarithm
M	Volume of menstrual blood loss
MBQ	In-house Menstrual Background Questionnaire
MC	In-house Menstrual chart
MEQ	In-house Menstrual Evaluation Questionnaire
mL	millilitre
MORI	Market & Opinion Research Institute
NaOH	Sodium hydroxide
NSAID	Non-steroidal anti-inflammatory drug
OD	Optical density
odds	Ratio of 'cases' to non-cases
OPCS	Office of Population Censuses & Surveys

OR	Odds ratio, which is a ratio of two odds, odds in the 'exposed' group over the odds for the unexposed group
$OR_{McNemar}$	Summary OR corresponding to McNemar test for comparing paired proportions
p	Probability or significance
PC	Principal component
PCd	'Dealing with periods' principal component
PCf	'Feelings about periods' principal component
PCOS	Polycystic ovary syndrome
PI	prediction interval
PMS	Used both as premenstrual syndrome, and premenstrual symptoms
Q-o-L	Quality of life
R^2	% of variance in the y accounted for by regression on x or x's
s	Secondary dilution factor
SF-36	Quality of life measure
TMF	Total menstrual fluid volume
UK	United Kingdom
US/ USA	United States (of America)
WWD	In-house Weekly Well-being Diary

Chapter 1

INTRODUCTION

1.1 INTRODUCTION TO THE RESEARCH PROJECT

1.1.1 Overview of menstrual problems

Since earliest times there have been anecdotal reports of the discomfort and inconvenience that some women experience during menstruation (Drife 2000a), but never before have women been exposed to such a large number of menstruations per life-course. Whereas in primitive societies women would have experienced about 40 to 50 menstrual periods, provided they escaped obstetric fatality, it was estimated in the 1970s that contemporary women experienced in excess of 400 cycles (and periods) during a typical reproductive life-course (Short 1976). The repeated hormonal swings (and the cascade of cellular events in response to these), and repeated menstruation (some of it possibly retrograde) that are the consequence, are believed to be implicated in a number of reproductive pathologies - endometriosis, cysts, reproductive and breast cancers (Dennis 1992). An important contemporary question has been posed: is life-time menstruation on such a scale 'healthy' or 'normal'? (Blanchard 2003; Coutinho & Segal 1999; Dennis 1992; Kaunitz & 2000; Short 1976; Thomas & Ellertson 2000; Wilbush 1988) The repeating menstruations are often accompanied by severe menstrual symptoms. So a more specific question, whose answer may be of greater relevance to women, and their reproductive health advisers, is whether this 'over-use' of the physiological process of menstruation, per se, leads to covert physiological dysfunction and is hence the cause of menstrual problems.

There have been a number of large scale population studies addressing aspects of menstruation (Andersch et al. 1986; Andersch & Hahn 1981; Andersch & Milsom 1982; Brown et al. 1988; Corrado 1990; Gath et al. 1987; Hallberg et al. 1966; Kauraniemi 1969; Kjerulff et al. 1996; McCance et al. 1937; Rybo et al. 1985; Shapley et al. 2004; Snowden & Christian 1983; Treloar et al. 1967; Warner & Bancroft 1990; Widholm & Kantero 1971). From the surveys undertaken there is considerable evidence of menstrual co-morbidity - heavy bleeding with pain, premenstrual syndrome with pain and/or heavy periods, irregularity with heavy bleeding (Bancroft et al. 1993; Brooks-Gunn 1985; Corrado 1990; Granleese 1990;

Hurskainen et al. 2001; Marshall 1998; Warner 1998; Warner & Bancroft 1988; Warner & Bancroft 1990; Warner 1995).

Survey-type research endeavour has mainly assessed not menstrual problems but menstrual *descriptors* (Andersch et al. 1986; Andersch & Hahn 1981; Andersch & Milsom 1982; Brown et al. 1988; Gath et al. 1987; McCance et al. 1937; Shapley et al. 2004; Warner & Bancroft 1990), or been directed at the elucidation of reference ranges for the menstrual parameters (Hallberg et al. 1966; Kauraniemi 1969; McCance et al. 1937; Rybo et al. 1985; Snowden & Christian 1983; Treloar et al. 1967; Widholm & Kantero 1971). Other studies have concentrated on women *consulting for menstrual reasons* (Bancroft et al. 1993; Shapley et al. 2000; Shapley et al. 2003; Warner 1995; Wood et al. 1979), resulting in various organic explanations being proposed for excessively heavy periods (Lumsden 1985) or severe dysmenorrhoea (Rees 1988; Turnbull 1985). One survey addressed the extent of *problem* with premenstrual syndrome (Warner & Bancroft 1990), one assessed menstrual *disorder* (Kjerulff et al. 1996), and the market research poll asked women to identify from a list, which included heavy periods and period pain, 'any *health problems* you have ever had' (Corrado 1990). There is therefore a dearth of surveys of the prevalence of subjective report of menstrual *problem*, and of associated factors.

1.1.2 Introduction to research project

Among women in their late reproductive years, menorrhagia (excessive periods) is a very common reason for consultation with general practitioner (Prentice 1999a; Royal College of General practitioners et al. 1990; Vessey et al. 1992), and the most common reason for referral to gynaecology clinic (Bradlow et al. 1992; Coulter 1995; Coulter et al. 1989; Prentice 1999a). The clinical definition of menorrhagia is blood loss exceeding 80mls per period. Laboratory measurement of blood loss that has been undertaken has shown that many women presenting with menorrhagia have volume of blood loss well within the normal range (Bonnar & Sheppard 1996; Chimbira et al. 1980; Coulter 1995; Fraser et al. 1984; Higham et al. 1990; Hurskainen et al. 1998; Janssen et al. 1995; Prentice 1999a). Qualitative research

suggests that women's concerns are often not about the *volume* of blood loss, but the impact of periods on their daily lives (Byles et al. 1997; Marshall 1998; O'Flynn & Britten 2000).

It has been observed that in the past there has been frequent attribution of women's menstrual symptoms to psyche, in the absence even of minimum evidence (Laws 1992; Lennane & Lennane 1973; Scambler & Scambler 1993). The complex interplay of physiological, psychological, cultural and individual history factors means that past menorrhagia research projects have tended to obtain either objective measurements of menstrual blood loss, but scant psychological or individual data, for example (Cole et al. 1971; Fraser et al. 1984; Haynes et al. 1977; Higham et al. 1990; Janssen et al. 1995), or they have assessed subjective report of symptoms, or occasionally problem, and perhaps also psychological factors, but have not obtained objective measurement of blood loss (Bancroft et al. 1993; Brown et al. 1988; Gath et al. 1987; Kjerulff et al. 1996; Shapley et al. 2000; Shapley et al. 2003; Shapley et al. 2004; Warner & Bancroft 1990). Attributions to psyche that have been proposed have therefore been made in the absence of corresponding research evidence (Gath et al. 1987; Greenberg 1983; Hallberg et al. 1966; Levitt & Lubin 1967; Rogers 1950; Shapley et al. 2000; Shapley et al. 2002; Shapley et al. 2003). Ideally, prospective data would be necessary to support an assertion of psychosomatic origin for complaint, since reverse causation means that months of troubling menstruation could be the cause of psychological distress. This could happen even with moderately severe symptoms, if persisting over a long time-frame, particularly if periods are unpredictable and hence difficult to accommodate. That some such mechanism is a possible scenario is supported by findings of marked improvement in psychological well-being after hysterectomy (Gath et al. 1982).

It would appear therefore that:

(i) quantitative menstrual research has tended to address menstrual descriptors or parameters, whereas the conceptualisation of menstrual *problem* has been on the whole neglected; and

(ii) the 80mL blood loss criterion for menorrhagia is not relevant to contemporary menorrhagia complaint; and

(iii) there has in the past been attribution of complaint of menorrhagia to psychosomatic factors in the absence of a supporting evidence base.

The key aim of this research project is therefore to reconsider the clinical definition of menorrhagia. In order to do this, a multi-faceted examination of the contemporary menorrhagia complaint is required, encompassing subjective account of menstrual periods and other menstrual symptoms, assessment of health, psychosocial and socio-demographic factors, and prospective measurement of the menstrual loss. The initial study would be predominantly descriptive and hypothesis generating.

In the remainder of this chapter there will be an overview of physiological and epidemiological understandings of menstruation, together with a reflection on the transition from menstruation to menstrual complaint, while in Chapter 2 methodological issues in menstrual research are reviewed. A systematic search was used in the first instance, but to limit length this was followed by selection, by means of scanning all abstracts, of papers that addressed issues of definition or methodology. The literature review is followed by specification of the research design in Chapter 3. In **3.8.4** a number of general prior hypotheses have been specified, for the purposes of sample size calculation, these having been identified from the literature and previous research.

Chapters 4 to 9 report results, each chapter incorporating some immediate and chapter-specific discussion. Chapter summaries are provided at the end of each chapter, for ease of cross-referencing. Chapter 4 reports on recruitment, and background description of the study sample, including basis for referral and quality-of-life, while Chapter 5 describes menstrual problem and history, as well as clinic outcome. Chapters 6 and 7 report on quantification of menstrual loss, and exploration of methodological issues that emerged regarding quantification. Chapter 8 examines comparability of participants between centres, and across levels of participation, in terms of background data reported in Chapters 4 to 6.

Finally, Chapter 9 reports the key multivariate analyses modelling menorrhagia, and examining basis for referral for heavy bleeding and the utility of the 80mL blood loss criterion for menorrhagia. The chapter begins with a statement of the three themes to be addressed: referral for heavy bleeding, measured volume of menstrual loss, and subjective menorrhagia complaint. The reporting of the analyses is structured in terms of nine research questions which are listed at the start of the chapter (**9.1**). The detailing of these research questions is held over until this point in the thesis as it is felt that the precise meanings of the questions, and the subtleties of the distinctions between them, would be better appreciated once the basic description of the study data, and of the assessment methods used, has been completed.

The thesis concludes with a final chapter (10) undertaking overview and integrative discussion, followed by conclusions, including some ideas for further research.

1.2 PHYSIOLOGICAL UNDERSTANDINGS OF MENSTRUAL PROBLEMS

1.2.1 Heavy periods

Many mechanisms and part-explanations for heavy menstrual bleeding (or menorrhagia) have been established (Mayou et al. 1995), but despite many years of research the likelihood of being able to identify the entire mechanism for a specific case of heavy periods is low (Smith 2000). Some of the causes described are systemic disease, neoplasms (benign or malign), contraception (non-hormonal IUCD), hormonal disturbance, and blood diseases (for example, clotting disorders) (Fogel CI 1995). Hormonal disturbance can arise in a number of ways, ageing, stress, liver or kidney disease, and in the case of obese women, via anovulation caused by increased peripheral conversion of androstendione to oestrogen (Fogel CI 1995). Bleeding in anovular cycles tends to be irregular, painless and heavy (Rees 1997). These anovular cycles used to be thought a lot more common than they are (Smith 1998). It has been found that the proportion is only about 10% (Cameron et al. 1990). For a single episode of heavy bleeding early pregnancy loss may be the explanation (Fogel CI 1995). Fibroids are a common cause of menorrhagia, but not always a cause of heavy bleeding (Fogel CI 1995; Mayou et al. 1995). High rates of subsequent hysterectomy in sterilised women has raised the question of whether sterilisation could somehow be causally implicated in menorrhagia, for example through reduction in excretion of oestrogen through occlusion of the Fallopian tubes (Coulter 1998). Coulter notes the profound methodological problems of answering this question through observational data (Coulter 1998). Only one study involved before and after blood loss measurement, with no effects being found (Kasonde & Bonnar 1976). However, the study involved only 25 women, and follow-up was only 6 to 12 months.

Fine detail of sub-mechanisms have been described – steroid receptor expression throughout the menstrual cycle (Critchley 2000); local uterine haemostatic factors (Sheppard 2000); specific factors in endometrial growth (Rees et al. 2000); and angiogenesis (Smith 2000), but Smith comments 'surprisingly little is known about

the factors which cause heavy or irregular bleeding' (Smith 2000). All these authors note that further research is required (Critchley 2000; Rees et al. 2000; Sheppard 2000; Smith 2000).

Rees envisaged a categorisation for menorrhagia as local, systemic, iatrogenic or essential (Rees 1987). Essential menorrhagia is that where no aetiology is known, and at that time this comprised half of all cases. It is likely that for a number of other cases, where a cause is identified, this is some coincidental finding, such as fibroid, and not actually causally implicated. The finer mechanism that seems to be found most compelling is altered prostaglandin synthesis, because prostaglandins can have action on myometrial contractility and on haemostasis (Smith et al. 1981). The evidence is strengthened by the fact that menstrual blood and uterine tissues contain very high levels of prostaglandins, women with menorrhagia or dysmenorrhoea have even higher levels, and inhibitors of prostaglandin synthesis are used successfully as treatments for these disorders (Rees 1997). Increased endometrial fibrinolysis is another agreed cause of some menorrhagia, supported by the efficacy of antifibrinolytic agents as treatment (Rees 1997). Recent findings have been varicosities and uterine artery blood flow (Hurskainen et al. 1999).

1.2.2 Period pain

Period pain or dysmenorrhoea ('difficult monthly flow') has traditionally been classified into two classes, primary and secondary. According to the original classification the criterion for primary dysmenorrhoea is that the pain occurs in the absence of pathology (Akerlund 1998; Brosens et al. 2000). Onset of primary dysmenorrhoea is typically about six months after menarche, with symptoms most prevalent during the first two days of the period, and seldom associated with menorrhagia (Rees 1997). It is salutary to realise that up until a few decades ago, before the advent of intrauterine pressure readings which have confirmed the acute pain being experienced in many cases (Lumsden 1985), young women claiming to suffer severe dysmenorrhoea were frequently dismissed as neurotic(Laws 1992; Lennane & Lennane 1973; Scambler & Scambler 1985). This is an example of the

circumstance described earlier, inadequate technology to elucidate mechanism resulting in a rebound but erroneous misattribution to psyche.

The classification 'primary dysmenorrhoea' is no longer accurate as mechanisms have been identified to account for the dysmenorrhoea, predominantly abnormal uterine activity associated with excessive prostaglandin production (Fogel CI 1995; Rees 1997). On the other hand, although there have been findings of excessive levels of leukotrienes, vasopressin and prostaglandins, it remains unknown what in turn causes the raised levels (Rees 1997).

The criterion for secondary dysmenorrhoea is that the pain is secondary to some pathology, such as endometriosis, pelvic inflammatory disease, adenomyosis, fibroids and polyps (Rees 1997). Alternatively, it may also be iatrogenic, resulting from use of the non-hormonal IUCD (Rees 1997). Secondary dysmenorrhoea may have onset of symptoms prior to menses, and pain can last the whole period (Rees 1997). As already noted for heavy periods, these pathological findings could in some cases be coincidental, as fibroids, polyps and possibly even early endometriosis do not inevitably cause period pain. The mechanisms by which pain is produced are not clear (Rees 1997). The role of prostaglandins has already been noted. Secondary dysmenorrhoea often occurs in conjunction with heavy periods, with 79% of women over 25years of age referred for dysmenorrhoea also reporting heavy periods (Warner 1995) The onset of secondary dysmenorrhoea is typically after some years of pain-free menses (Fogel CI 1995; Rees 1997). However, there must be some unfortunate women who suffer primary dysmenorrhoea, and by the time that is resolved, which is often not until after the first pregnancy, they have developed some condition which results in secondary dysmenorrhoea. This scenario has been acknowledged in the case of young patients with endometriosis (Stones & Thomas 1998).

1.2.3 Irregular bleeding

In gynaecology text books there is a distinction between intermenstrual bleeding and irregular cycles (Landgren & von Schoultz 1998). Irregular cycles are taken to be a result of the approach of menopause, due to ageing of the ovary, and/or anovulation

(Fogel CI & Woods NF 1995; Landgren & von Schoultz 1998). In the approach to the menopause a woman can expect alterations in 'regularity, frequency, pattern, volume and flow', all the consequence of failing ovarian response (Fraser 2000). A number of the authors commented that women find changes to their bleeding patterns very worrying (Landgren & von Schoultz 1998; Rees 1997). At this age there are some risks that the changes in bleeding are a symptom of serious disease, so this menstrual disturbance presents a challenge for the gynaecologist as well as the woman herself (Fraser 2000)

1.2.4 Cyclic symptoms

Cyclic changes in emotional and physical state across the menstrual cycle are very common, and for some women they are so marked as to be distressing (Gardner & Sanders 1997). Complaint of troublesome cyclic symptoms (premenstrual syndrome, PMS) can be classified into four levels (Joshi et al. 1998):

- physiological premenstrual symptoms – but not disruptive/severe/consistent enough to be classified as PMS;
- primary PMS – disruptive symptoms that occur in four out of the six previous cycles and where the symptoms have eased completely by the end of the period;
- secondary PMS – similar to primary PMS except that there is only partial resolution of symptoms, probably because in addition to PMS the patient has an underlying psychological disorder; and
- psychiatric disorder wrongly attributed to PMS.

Categorisation and assessment of PMS has been the subject of much research effort, and of endless and often very heated debate, leaving this health/research domain fractured (Rapkin 2000). Many groups would argue that the third classification in the list above is *not* PMS. The 'take-over' of PMS by the nosological diagnostic system for psychiatry, The American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*, under the label premenstrual dysphoric disorder (PMDD), means that 'primary PMS' which is expressed mainly somatically would be left in diagnostic limbo, and much of 'secondary PMS' would be declassified as not 'PMS' (Joshi et al. 1998).

Cyclic symptoms do not occur before menarche, during pregnancy, or post-menopausally, so there is wide-spread acceptance they are related in some way to ovarian function (Rapkin 2000). However, almost all women have ovarian cycles and by no means all women have disabling PMS. What the additional factor or factors are that result in severe PMS is not at all clear. Hence the assertion that 'the syndrome has no known aetiology' (Joshi et al. 1998). Cyclic symptoms may be experienced more severely if there is underlying psychological ill-health (Gardner & Sanders 1997). There is a view that for some women the cyclic symptoms may be secondary to very heavy or painful periods (Gardner & Sanders 1997).

1.3 EPIDEMIOLOGY OF MENSTRUAL PROBLEMS

Women's self-reports of their menstrual experience are a worthy topic for study since the individual's perception of change, problem, or abnormality is the first step on the path to the gynaecology clinic. What has been established about the epidemiology of menstrual problems, and in particular menorrhagia, complaint of heavy bleeding?

1.3.1 Issues in menstrual epidemiology

1.3.1.i Attitudes to menstrual morbidity

Concern has been expressed that our society inhibits women from complaining when they experience menstrual distress (Drife, 1992; Scambler 1993), and that the complaints of those who do seek help have not been taken as seriously as they should have been (Laws 1992; Lennane & Lennane 1973). Historically menstrual complaints have been regarded with considerable misgiving, with doubts as to the validity of the majority of complaints (Gath et al. 1987). Where the patient was unresponsive to treatment, or if no explanation could be found for the complaint, it may have been dismissed as psychogenic: either as a ploy to avoid domestic or employment commitments, or as resulting from an "unwholesome attitude to menstruation" (Levitt & Lubin 1967) or a "neurotic" temperament. There are tensions between menstruation as natural/normal and medicalisation of menstruation, between medical 'disease' and lay illness, between what is biologically normal (bleeding, menstrual discomfort) and what is socially unacceptable (being seen to bleed, needing to rest during work hours), between femininity and sexuality (Shaw et al. 1998). Many women hold strong and often disparate views about what is and what is not appropriate menstrual behaviour (playing for sympathy versus soldiering on and suffering in silence).

The powerful cultural attitudes around menstruation, health and illness are bound to affect responses to surveys, depending on the way questions are framed and worded, and the perceived purpose of the survey.

1.3.1.ii Ascertainment

Key to good epidemiology is clear definition of the health condition being studied, and an operationalisation of the definition that allows reliable and unbiased ascertainment.

DEFINING THE CONDITION OF INTEREST

The four main menstrual problems do not have definitions amenable to survey. Menorrhagia has a clear and objective definition expressed in terms of volume of blood loss (Wyatt & O'Brien 2000). However, this is impracticable for community survey, as would be clinical history-taking. Therefore the usual approach is to ask how 'heavy' the menstrual loss is. There is no agreed definition for period pain (Wyatt & O'Brien 2000). There is lack of consensus about the definition of premenstrual syndrome and even more so about assessment (Wyatt & O'Brien 2000). Prospective assessment is considered essential, but this would not be feasible for large surveys. One-off methods of assessment such as Moos (Moos 1968) are now largely discredited. Irregularity of periods is a composite of a number of perturbations of the 'ideal' menstrual cycle, and so very difficult to assess precisely by questionnaire.

SUBJECTIVE REPORTS OF SYMPTOMS AND PROBLEMS

Symptoms versus problems There is a profound distinction between 'symptom', a manifestation of the body or the emotions, and 'problem', which denotes an evaluation of some health circumstance, and a decision that it is unacceptable/ intolerable/dangerous. In general surveys ask about symptoms, and it would be perfectly valid to report an epidemiology of symptoms. However, all too often the true condition of interest is a medical *problem*, perhaps for the purposes of ascertaining potential demand for health services. In that case there would be a dissonance between the focus of the research and the information being collected.

To take an example for menorrhagia, the condition of interest is complaint of excessive bleeding, a problem. What is typically ascertained is the heaviness of the menstrual loss, a symptom. Many a woman in her late reproductive years would

describe her menstrual loss as heavy, without any connotation of that loss being problematic. To add to the confusion, the response options offered for heaviness in questionnaire surveys are typically 'light/moderate/heavy' (Hallberg et al. 1966; Snowden & Christian 1983). For the sake of a less crude measuring scale, particularly when used in clinical research where there may be danger of a ceiling effect for the rating scale, some researchers add 'very heavy', giving 4 options (Bancroft et al. 1993). However, such a change can materially affect the distribution of responses, to all three lower categories, making very difficult any comparison between surveys using the different approaches.

It should be noted also that a symptom response given in a community survey, should be considered an '*elicited* symptom' (Santer 2004), because it will almost certainly have very different meaning to the same description proffered (or, symptom reported) by a woman in the context of consulting her GP about her periods, or attending gynaecology clinic.

Subjective reports There is most often no alternative to subjective report of symptoms/ problems, but the weaknesses must be borne in mind. The main one is the potential for confounding with individual response style. Symptom reporting in general has been shown to be related to the personality dimension of negative affectivity (sometimes called neuroticism, but the label negative affectivity is preferred to avoid confusion with neurotic illness) (Watson & Pennebaker 1989). Individuals with this dimension or personality more pronounced tend to score more highly on any self-report health or symptom scale and are more likely to perceive problems (for the same degree of underlying physical or emotional disturbance) (Fender et al. 1999). Another weakness of subjective reports is the extent to which they can be affected by cultural attitudes, health beliefs, previous health experiences, setting, wording of questionnaire and similar factors.

1.3.2 Overview of epidemiology

1.3.2.i Heavy periods

There is some doubt as to whether the appropriate epidemiology to be considered is of objectively heavy bleeding (as measured) or of subjectively heavy periods (as reported). There is a dearth of the former type of survey, and with regard to the latter, insight is limited by the crude response scale that has generally been used, often simply 'light/moderate/heavy'. In Hallberg's population survey of nearly 500 women the subjective assessment of periods was not reported for the various age or parity groups, only that 31% of women overall rated their periods as "heavy" (Hallberg et al. 1966). In a survey undertaken by a market research company, 31% of women affirmed having ever had heavy periods which for them constituted 'a health problem', as did 40 to 45% of those aged over 35 years (Corrado 1990). Other 'health problems' in the list were backache, headaches/migraine, depression and anxiety. Among the subgroup who had ever had a problem with heavy periods, considering only women with current symptoms (that is, heavy period in the last 4 months) brought the prevalence overall down to 20%. Analyses were not presented adjusted for current hormonal contraception, but that concern notwithstanding, while the survey comprised 70% parous women, among the subgroup with heavy periods in the last 4 months, 82% were parous. In a recent community survey of 1425 women menorrhagia was defined as a response of 'heavy' periods, and the prevalence was 52% overall (sample aged 18 to 54 years), 60% in those aged 35 to 44 years (Shapley et al. 2004). This survey also asked about increased periods (23% and 29% for the same age groups as for menorrhagia) and prolonged periods (9% and 9%).

Considering measured blood loss, parity has been found to be associated with a small increase in average loss, and in the older age groups there is a slightly increased proportion of women with excessive blood loss i.e. exceeding 80mls (Cole et al. 1971; Rybo et al. 1985). Duration of period is related to overall blood loss and if it is longer than seven days the bleeding is likely to be excessive (Rybo et al. 1985). Other factors that have been found to be associated with heavy periods are parity,

smoking, body mass index and chronic iron deficiency (this last as both cause and effect) (Coulter 1998).

1.3.2.ii Period pain

Dysmenorrhoea is commonly described as a young woman's complaint and yet in a study of adolescent girls and their mothers the prevalence of "painful periods" among 1570 girls aged 16 to 20 years was 45% "occasionally" and 17% "continuously", whereas for the mothers of all adolescents in the survey (n=6543) the corresponding proportions were 70% and 8% (Widholm & Kantero 1971). In the Kauraniemi survey (Kauraniemi 1969), using a more stringent criterion, the prevalence of "regular" dysmenorrhoea was 9% overall, 12% in the youngest age band, 7% in the oldest. These are the only two research surveys to include a substantial number of women over 30 years of age. In the market research survey already mentioned, 38% of women affirmed having ever had painful periods as a health problem, with the rate of affirmation being highest in those aged 30 to 34 years (43%) and, paradoxically, given the question pertained to 'ever', lowest for those aged 40 to 45 years (35%) (Corrado 1990). However, there were about 160 to 200 women per age-band, so numbers were not large for comparisons between age groups (standard error for difference between age group prevalences is approximately 5 percentage points, 95% confidence interval plus/minus 10 percentage points). In discussions of the epidemiology of "period pain" there is considerable confusion and blurring between primary dysmenorrhoea and later-onset dysmenorrhoea.

Parity and age are both believed to alleviate primary dysmenorrhoea for a proportion of sufferers, the latter via the effect of increasingly regular ovulation, the former via the effect on the uterus of child-bearing. However it has been noted that period pain is experienced by 30 to 40% of women in their thirties (Akerlund 1998). In the market research poll, notwithstanding the same reservations as above regarding confounding by hormonal contraception, 65% of women with painful periods in the last 4 months were parous, compared to 70% overall (Corrado 1990). There is a grey area between 'experience of period pain' and disabling symptoms, with the relative proportions being quoted as 50% of women:10% (Fogel CI 1995).

1.3.2.iii Irregularity of bleeding

Irregularity of cycles has been reported to reduce steadily from 43% among girls in the first year after menarche to 20% for girls more than five years post-menarche (Widholm & Kantero 1971), while their mothers were less likely to report irregular cycles (9%). In another series of data, also collected before the oral contraceptive pill was in widespread use, irregular cycles were common in the early years of menstruation but then became less and less common, with maximal regularity at about 36 years of age (Treloar et al. 1967). A second phase of irregularity commenced approximately six years later, culminating in the menopause. A community survey of 1425 women found changed pattern of cycle to be reported by 32% of the entire sample (18 to 54years) and by 53% of those aged 45 to 54 years (Shapley et al. 2004). Similarly, intermenstrual bleeding was reported by 14% and 13%.

1.3.2.iv Cyclic symptoms

The epidemiology of PMS is even more fraught than that for heavy periods and period pain, with 20 to 95% of women being said to experience perimenstrual *symptoms*, 20 to 40% report some degree of *problem* with PMS, and 3 to 5% being severely affected (Fogel CI 1995). PMS is experienced across the menstruating age range, but it is agreed that the age group most troubled by PMS is women in their thirties and forties (Fogel CI 1995). However, it has been noted that PMS can be exacerbated pre-menopausally, and then just blur into symptoms of the menopause (Gardner & Sanders 1997). There may therefore be an ascertainment/discrimination problem in the oldest age groups of still-menstruating women.

1.3.3 Other factors related to problems with periods

1.3.3.i Contraception

Cross-sectional surveys would not be the design strategy of choice to elucidate any concurrent effect of contraceptive method on menstruation, because of the self-selected nature of the various groups of established contraceptive-users. Decisions regarding method of contraception are likely to be influenced by a number of factors,

one of which may be menstrual distress itself e.g. heavy periods are a contra-indication for non-hormonal intra-uterine devices (IUCD), and the reputation of oral contraceptives is such that they may be taken solely for their menstrual effect (Fogel CI 1995; Fraser 1986), thus selecting into the oral contraceptive group women at high risk of reporting relatively heavy or painful periods. That said, surveys typically show women using oral contraception to have less severe menstrual symptoms (Brown et al. 1988; Warner & Bancroft 1990). In studies measuring blood loss it has been shown that oral contraceptives reduce the duration of period and amount of blood loss (Cole et al. 1971; Fraser 1986), and they are also believed to relieve dysmenorrhoea (Fogel CI 1995). However in a survey of university entrants the prevalence of period pain among pill-users was high (41%, compared to 45% among non-pill users) (Sheldrake & Cormack 1976). This could be explained if the therapeutic effect of oral contraceptives is on severity rather than prevalence of pain, or if the pill-using group included more women prone to period pain, possibly "selected in", in line with the scenario outlined above.

The after-effects of contraceptive method on menstruation are even harder to ascertain than concurrent effects. The study of after-effects of oral contraceptive use has largely been confined to issues of fertility while the possibility of menstrual *sequelae* has on the whole been dismissed as a perceptual or adjustment problem. The earlier surveys of the effect of female sterilisation on subsequent menstrual reports involved women who had been sterilised on the grounds of multigravidity or for medical or social indications, women whose health had possibly already been compromised. Increased reporting of pain, and in the latter two surveys, of heavy periods, has been found (Neil et al. 1975; Punnonen & Erkkola 1984; Ringrose 1974). Even when the severer criterion of hospital referrals for menstrual problems was used a higher rate was found among women who had been sterilised, and between methods a higher rate for diathermy (Vessey et al. 1983). The recent development of a hormone-releasing IUCD, the levo-norgestrel LNG IUCD, and its increasingly wide-spread use, has the potential to provide very effective reversible contraception and to have a beneficial effect on heaviness of periods.

1.3.3.ii Socioeconomic status

In the Corrado market research poll, rates of reporting ever having had heavy or painful periods were very similar across the binary socio-economic class classification used (Corrado 1990). However other research has shown that women of lower social class are more likely to report menstrual problems and are more likely to consult their GPs (Coulter 1998). The distinction between symptom and 'problem' has been noted, but assuming this higher rate of problems reflects more severe symptoms, caution is required because there is likely to be some confounding by the differing child-bearing patterns by class. Women of lower socio-economic status complete their families sooner, and have higher age-specific rates of sterilisation, so for them there is a longer span of years of repeated menstruation prior to menopause.

1.3.3.iii Psychosomatic factors

There is all too much past evidence of attribution of women's reproductive health symptoms to psyche (Gath et al. 1987; Greenberg 1983; Hallberg et al. 1966; Harris 1989; Laws 1992; Lennane & Lennane 1973; Levitt & Lubin 1967; Rogers 1950; Shapley et al. 2000; Shapley et al. 2002; Shapley et al. 2003; Stolberg 2000). This was most likely to happen if no cause can be found for the complaint. It is salutary to remember that many of the techniques required to identify a number of the potential organic "causes" have come into routine clinical use only in recent years e.g. laparoscopy and prostaglandin assays. So in the past there must have been many incorrect diagnoses of "no organic cause" and, consequently, many misattributions to psyche (Warner 1998). Or rather, misattributions *entirely* to psyche. Current thinking is that in most cases complaint or problem is an interaction between physiological processes, psychological/personality factors and feedback from others (Mayou et al. 1995). It has been hypothesized that trends in psychosomatic 'disorders' are a reflection of cultural changes in medicine and clinical service ethos (Porter 2004), and that reporting of common physical symptoms is a reflection of a pattern of illness behaviour than may have origins in childhood, and which will be influenced by concurrent stress and any physiological symptoms (Mechanic 1980).

However, it has also been pointed out that findings of stress among clinic patients should not be taken as indicative of causality with respect to symptoms experience, since it is more likely to be related to the decision to consult (Mechanic 1961). Most complaints will be subject to some degree of psychosomatic influence, even where a 'cause' is found (Mayou et al. 1995; Mechanic 1961). However, it was found that women consulting their GP for heavy bleeding had no higher likelihood of anxiety or depression compared to a random sample from the same practice (Shapley et al. 2000).

A high prevalence of psychological problems and/or minor psychiatric problems among women with menstrual distress has been reported (Gath et al. 1987; Greenberg 1983; Hurskainen et al. 2001). However such a picture is common across a range of health symptoms, as evidenced by a survey across a range of hospital clinics, involving men as well as women (Mayou et al. 1995), and among medical patients (Stoeckle et al. 1964). Counter to this, it has been pointed out that much of the association between psychological morbidity and menstrual symptoms may be due to reverse causation, with the menstrual symptoms and their impact on the woman's life, repeating on a monthly cycle, eventually leading to secondary psychological problems (Brooks-Gunn 1985; Coulter 1998; Warner 1998). This possibility has been supported by findings of marked improvement in psychiatric morbidity after hysterectomy for menstrual symptoms (Gath et al. 1982). In contrast, in a recent longitudinal study (1513 women completed all three questionnaires) it was found that psychological distress at baseline was associated with the subsequent reporting of heavy periods in the following 6 months, and conversely that women with heavy periods at baseline were no more likely than others to develop psychological distress in the follow-up (Shapley et al. 2003). However, it needs to be borne in mind that this survey reports an association with symptom reporting, not with presentation of menstrual complaint, that negative affectivity is a possible mediating factor (Watson & Pennebaker 1989), and that there is a general tendency for periods to become heavier with age (Hallberg et al. 1966), so time may be a confounding factor.

1.4 FROM MENSTRUATION TO MENSTRUAL COMPLAINT

The most common menstrual symptoms are excessive periods (menorrhagia), period pain, cycle-related changes in mood and/or physical health (PMS), or irregular periods and/or inter-menstrual vaginal bleeding. Each of these can also be characterised as a menstrual problem. For a particular woman it is likely to be mainly the severity of the symptoms, along the continuum of possibilities, that transforms what would otherwise be commonplace – another period – into a problem. However, between women, taking into account also the lives they lead, the point of transition may occur at markedly differing severities of symptoms (Scambler & Scambler 1993).

1.4.1 Factors influencing perception as problem

'Severity' may be an obvious factor transforming a symptom into a problem, but this effect will be moderated or amplified by other factors, both individual (for example sensitivity to pain; low embarrassment threshold regarding menstrual accidents; phlegmatic personality) and context (background health; employment role and its amenability to time out when pain is at its peak, or to wearing multiple sanitary protection when the period is full flow; home circumstances; family commitments) (Scambler & Scambler 1993). Attitudes to menstruation and overall menstrual morbidity will also play their part (Brooks-Gunn 1985; Geller et al. 1999).

There is no published quantitative research on the interface between menstrual symptom severity and perception as problem, perhaps because the distinction between the two is usually overlooked. A clear example of the failure to distinguish symptom and problem is subjective report of menstrual loss, in that the symptom label 'heavy periods', or even having experienced this as a health problem, is used as a short-hand for clinically presenting menstrual problem. The market research poll's 31% *lifetime prevalence* for the *elicited symptom* 'heavy periods as a health problem' is in many publications cited as the *point prevalence* and/or as referring to *clinical complaint* (problem) (Hurskainen et al. 1998; Prentice 2000; Smith 1998).

Considering menstrual problems from the woman's perspective, it has been noted that important factors in deciding if they are problematic are expectation (having an ideal view of periods is not helpful), and impact on family life health and work (Twaddle 2000). It was also noted that menstruation imposes an unavoidable cost, for provision of sanitary protection (Drife 2000b; Twaddle 2000). The cost of periods will escalate for a woman with excessive flow, as may laundry costs, and for those suffering period pain effective pain-killers will also consume financial resources.

In this section the focus has been on 'severity in context', but that is just another way of saying 'impact of symptoms' for the individual.

1.4.2 Factors influencing consulting and referral

Subsumed within factors influencing consulting and referral are the factors, whatever they may be, influencing classification of the symptoms as problematic. However, consultation/referral may occur in the absence of symptoms that are of themselves problematic. For example, where there is concern that a symptom that is otherwise tolerable is an early sign of serious disease. This may explain the fact that 57% of referrals to gynaecology clinic for menorrhagia did not rate their menstrual loss as even 'very heavy' (Bancroft et al. 1993).

The four period problems are very similar to each other in a number of ways:

- the symptoms are *signs* of potential clinical importance (although not so much so for PMS);
- how much of a *problem* the symptoms are has relevance for management strategy; and
- associated *worry* often plays a part in help-seeking.

The symptoms as 'signs' are important with respect to general practitioner referral to gynaecology clinic, and also with respect to gynaecologist decisions regarding investigation. To a lesser extent there may be lay understandings of what symptoms constitute such signs. That aside, pain and abnormal bleeding are for humans inborn or inculcated signifiers of health 'danger' so for those patients with high susceptibility to anxiety any unexplained change in these might be construed as a potential 'sign'. Therefore even where symptoms are not of themselves intolerable,

consultation with GP or referral to the gynaecology clinic may be necessary solely for exclusion of serious disease. For these patients then, once pathology is excluded, nothing more needs to be done.

In contrast, for patients where the symptoms, unexplained or not, are intolerable, and seriously diminish quality of life, exclusion of serious pathology is not enough. Such a woman will be hoping for some therapeutic intervention. These scenarios are illustrated in the middle column of **Table 1.1**.

Menstrual problems also have in common the potential to provoke anxiety in the sufferer. Even where there is no clinical concern, the GP may refer in the absence of severe symptoms, if the patient is very anxious and investigation and reassurance are judged to be potentially helpful. (Paradoxically, referral by the general practitioner to a hospital clinic can confirm an anxious individual's fears.) Therefore, in the population of *referred* patients anxiety is more likely to be apparent in the subgroup with less severe symptoms, since they are more likely to be 'selected in' on the basis of their anxiety. This hypothetical situation is shown in the final column of **Table 1.1**. Two dimensions of anxiety are used, as commonly used in psychology: *trait* (general susceptibility to anxiety), and *state* (overlay anxiety in response some provocation, in this case the current, possibly exacerbated, symptoms).

Table 1.1 Hypothetical scenario for menstrual problems in terms of impact of symptoms, likely need for therapeutic intervention, and associated anxiety in patient

Impact of Menstrual Problem Symptoms	If no serious disease, is patient looking for treatment of symptoms?	Associated anxiety likely in patients consulting/referred?	
		Trait	State
Moderate...			
..& stable	*Probably not*	✓✓✓	✓
..& recently increased	*Possibly not*	✓✓	✓✓
Severe...			
..& stable	*Very likely*		✓
..& recently increased	*Probably*		✓✓

Societal constraints around discussion of menstrual matters (Laws 1992; Scambler & Scambler 1985) may make the clinical consultation difficult. The woman may not find it easy to convey her menstrual experience, nor to articulate the impact of the symptoms on her life. Certainly she will usually have had little opportunity to compare experiences with other women, even those in her close social circle. Therefore an individual woman is likely to have some difficulty in judging her periods in relation to the population of women similar to herself.

It has been found that those seeking help for menstrual problems are more likely to have low self-esteem or to be depressed, and that those with symptoms but not seeking help tend to have a low opinion of medical science or the medical profession (Morse et al. 1988). In a study of referrals for menstrual disorders the best independent predictors of referral were: family doctor's belief that surgery would be necessary; patient preference for surgery; GP belief that patient wished surgery; number of previous surgical operations; older age of patient; male GP (Coulter et al. 1994a). It has been found that the strongest predictor of consulting for increased periods was interference with life caused by the periods, stronger than the heaviness itself (Shapley et al. 2002).

1.4.3 Management of menstrual complaint

Menorrhagia is of clinical concern because changed bleeding pattern in a pre-menopausal woman can be an indicator of organic pathology, of a benign or malignant nature (Fraser 2000; Rees 1997). There is clear and urgent need to detect and treat malignant disease, but even if the pathology is benign suitable intervention may be required. If the pathology causes excessive menstrual loss then there may be adverse effects on iron status and vigour (Fraser 1994; Milman et al. 1993). Even if this does not pertain, efforts to contain excessive flow, and the consequences when these efforts fail, can have an adverse impact on quality of life.

Like excessive menstrual loss, period pain (dysmenorrhoea) may indicate the incidence of pathology, especially if the pain has developed in adult life (Rees 1997; Stones & Thomas 1998). Some degree of period pain is very common, but if the pain is prolonged and/or acute, then daily-life may be intolerably affected. Therefore

treatment may be required for some underlying serious or progressive pathology or, even if no pathology is found, simply because of the disabling nature of the pain symptoms.

The aetiology of PMS (cycle-related changes in emotional and physical health) has been much debated, but it is very unlikely there has ever been a case attributed directly to serious pathology. However, recurrent pain or recurrent adverse impact on quality of life, due to uncontainable flow, either of which may have a serious cause (as noted above), may lead to reactive cycle-related emotional disturbance. Therefore the possibility remains that what is presented as PMS, and therefore presumed to be benign in origin, may be a sign of serious disease. When serious disease is not implicated, the symptoms can be very disabling and disrupting, and may also be prolonged, starting a week to ten days before the period, with no real relief until perhaps three to five days into the period. Furthermore, recurrent cyclic disturbance may have potential longer-term serious consequences for relationships and family life.

On occasion irregular menstruation (or inter-menstrual bleeding or spotting) may be a consequence of serious pathology and so is of potential significance to the clinician, especially if it has recent onset in the older woman (Fraser 2000; Landgren & von Schoultz 1998; Rees 1997; Stones & Thomas 1998). Neither irregularity of periods nor inter-menstrual bleeding/spotting are usually acutely disabling symptoms, although they may cause some inconvenience with respect to containment of vaginal bleeding. However, these symptoms, especially if they represent change from a woman's usual pattern, may be worrying for the woman concerned.

1.5 CHAPTER SUMMARY

Many factors play a part in the transition from symptom to menstrual problem, and in the decision to seek help. Attitudes to menstruation and menstrual morbidity are bound to be important. Cultural reticence about discussion of menstrual matters probably makes it more difficult for the woman to convey her problem to her doctor.

What epidemiology there is tends to address the partitioned menstrual *symptoms*, most usually heavy periods, period pain and PMS. In all cases the subjective nature of reporting of symptoms, and varying severity thresholds used, makes the collection and interpretation of population evidence very difficult. Subjective judgements are very likely to be based on perception of impact of symptoms, and so will be largely inextricable from social and reproductive life-course context.

The main surveys cited above are all quite old. In recent years women's "life-time" experience of natural menstruation has been radically changed by the availability of effective methods of contraception, both reversible and irreversible, for longer time-spans during their reproductive years. New profiles of child-bearing became possible from the 1960s onwards. Furthermore, menstrual experience is directly affected by the use of hormonal oral contraception, which for the time it is used disrupts the endocrine cycle, suppresses ovulation in many cases, and, as is often not realised by the individual user, substitutes "withdrawal bleeds" for natural menstruation. The new LNG-IUS, which when used will usually be retained for years at a time, has minimal systemic effect but does have a 'local' beneficial effect on periods if they are heavy. We are now at the threshold of a new era for profiles of menstruation through the reproductive life-course. There is need for a better understanding of women's subjective experience of menstruation, and as these new profiles become more and more common, a monitoring of societal changes in expectations.

There are many gaps in our knowledge of the prevalence of menstrual symptoms, of the interrelationship between them, and of their relationship to socio-demographic factors, in particular reproductive life-course. There is a dearth of knowledge about the epidemiology of menstrual problems, and menstrual health care needs.

Chapter 2

METHODOLOGICAL ISSUES IN MENORRHAGIA RESEARCH

2.1 INTRODUCTION

There will be situations in which there is a need to estimate blood volume, specifically. However, for the general menorrhagia complaint it could be argued that the impact on the daily life of a reasonably well-nourished woman suffering heavy periods derives directly from the total volume of the menstrual fluid loss, because of the containment challenge it poses. In this conceptualisation the volume of the blood component adds little. Further consideration raises the possibility that the total volume of menstrual loss is only a part explanation of menorrhagia complaint, but that the pattern of flow, and the extent to which this leads to menstrual accidents, is strongly implicated. Despite the fact that relatively few studies measure blood loss, and among those that do very few assess personality or psychosocial factors, many theories have been expounded as to the aetiology of subjective complaints of excessive periods, and the psychosocial reasons why so many women with complaint of menorrhagia are found on measurement to have normal menstrual blood loss (Fraser et al. 1984; Hodges 1989). Research into menstrual problems, and menorrhagia in particular, has been hampered by a number of methodological issues. Some important factors have been noted in the previous chapter: attitudes to menstruation and to menstrual morbidity, the subjective nature of menstrual problems; vague definitions. In this chapter the focus will be on menorrhagia research methodology.

2.1.1 Clinical definition of menorrhagia

2.1.1.i Objective definition

The objective definition for menorrhagia followed on from a Swedish study which measured blood loss in a population sample of 476 women (Hallberg et al. 1966). It found a significantly greater prevalence of impaired iron status among women with losses exceeding 60 mL. Using estimates of daily dietary intake for Swedish women *then,* 1966, and of likely daily and menstrual excretion of iron, it was calculated that menstrual blood loss of 63 mL or more endangered iron status. After excluding women with abnormal iron status or who considered themselves unhealthy or to have

abnormal menstruation, it was found that the 95th percentile of blood loss for the 183 'healthy' women remaining was 76 mL. The authors concluded that the upper limit of 'normal' menstrual blood loss lay *between* 60 and 80 mLs, but the most extreme endpoint of this range, 80 mL, was subsequently adopted as the threshold for menorrhagia (Hallberg et al. 1966). On a single measured period this simply identifies the 3%-4% of the 'healthy' population with greatest loss. It is well recognised that the problem with a statistical definition of this sort is that symptoms (losses) less than this may be statistically fairly common, but for some women may not be tolerable, whereas other women with abnormally heavy losses may find them manageable (Rose & Barker 1978).

2.1.1.ii Definition based on clinical history

The consensus among clinicians is that menorrhagia means 'excessively heavy uterine bleeding', this judgement being based on the clinician's initial interpretation of the woman's description of her perception of her menstrual loss (Fraser & Inceboz 2000). Excessively heavy in what sense? Is this the 80mL definition rather vaguely gauged, or is it a shift away from that conceptualisation, to allowing some contextual judgement? Perhaps it is a move towards judging 'excessively heavy' for someone who has this background health, or needs to hold down that sort of job, or lives in such home circumstances. It seems this must be what a lot of clinicians do when confronted with a patient distressed by her periods, but it would be helpful to have the 'definition' articulated and discussed. This has been found in qualitative research with primary care professionals, that they find the medical definitions of menstrual disorder unhelpful, and would more information about standards of normality (O'Flynn & Britten 2003). In another study addressing objective assessment of blood loss very few primary care professionals stated they would ever attempt objective assessment for a patient, while one third rejected the notion of being so focussed on the volume of loss (Chapple et al. 2000).

2.1.2 Lay 'menorrhagia complaint'

Qualitative research of women presenting to their GP with menorrhagia found that all used the term heavy to describe their periods, but the meaning that seemed to be

conveyed by this term varied between duration of period, impact and the look of the blood, and at times denoted a relative judgement, that the period had increased. For almost all women a change in the pattern of their bleeding had been important in deciding to consult. Blood loss volume and measurement were dismissed as irrelevant compared to how they felt during the period and all the efforts needed to contain the period (O'Flynn & Britten 2000).

In another study with referrals to a gynaecology clinic the researcher characterised the ways the interviewees perceived their loss to be problematic as amount of loss but also duration of period, frequency, unpredictability, clots and change from 'normal'. Other contributory factors reported were accompanying physical symptoms, anxiety about symptoms and the consequences of their heavy periods (Marshall 1998). Some interviewees expressed doubts as to whether the gynaecologist would be interested in anything other than blood loss, whereas it seemed to the researcher that most women had a range of symptoms that concerned them. Other studies have given a similar picture of a broad profile of symptoms and consequences of them (Byles et al. 1997). A holistic orientation to menstrual health care has been urged, addressing reasons underlying women's decisions to consult and the significance of the presenting problems in their lives (Scambler & Scambler 1993).

Therefore it appears that the lay menorrhagia complaint is deceptive. At first sight the complaint is amount of loss, but closer reflection reveals that it is actually the impact of volume that is more important: the restriction to activities, accidents, impact on roles, clots, strain of containing the period. Yet closer reflection reveals that the issues are not confined to volume and its impact, but involve other menstrual symptoms as well, such pain, tiredness, breast tenderness. Scratch menorrhagia and what you find beneath the surface is menstrual distress.

2.2 ASSESSMENT OF MENORRHAGIA COMPLAINT

2.2.1 Quantifying volume

Menstrual loss volume has been measured in various ways over the past six decades – for example before 1960 by using vaginal cups to contain flow for later measurement, or estimation by weight of used products, by acid haematin or by iron content. Baldwin in 1961 reported on the use of an injection of radio-active iron about 10 days before menses was expected, and then measurement of radioactivity in soaked used sanitary products (Baldwin et al. 1961). Cups and weighing would have been measuring the total fluid volume, whereas haemoglobin-based methods would have been measuring volumes of whole blood. The alkaline haematin method developed by Hallberg (Hallberg & Nilsson 1964) has been the most widely-used method (Bonnar & Sheppard 1996; Chimbira et al. 1980; Cole et al. 1971; Fraser et al. 2001; Fraser et al. 1985; Haynes et al. 1977; Higham et al. 1990; Hurskainen et al. 1998; Reid et al. 2000; The Menorrhagia Research Group 2004; van Eijkeren et al. 1986).

The main barrier to measurement of blood loss is the cultural etiquette against discussing, still less handling, women's used menstrual protection. Furthermore, measurement involves a relatively complex laboratory procedure. To address these problems other approaches to quantification of menstrual loss have been proposed, with the two main contenders involving estimation of blood loss volume from data that is more easily obtained. One alternative is estimation of blood loss from the simpler objective assessment, of total menstrual fluid loss volume (Fraser et al. 2001; Fraser et al. 1985), and the other involves estimation of blood loss from recording of subjective judgements of the degree of soaking/soiling of every menstrual protection product used (Higham et al. 1990; Janssen et al. 1995; Wyatt et al. 2001).

2.2.1.i Objective measurement of blood volume

The Hallberg method requires retention of used sanitary products and soaking of these in 5% sodium hydroxide (Hallberg & Nilsson 1964). This process extracts haemoglobin, which is converted to haematin. Soaking time needs to be 24 to 48

hours but this can be reduced if the products are mashed, so in some laboratories a stomacher is used for this purpose. An aliquot of the filtered soaking solution is then compared in terms of optical density (by means of a spectrophotometer) to a sample of venous blood taken from the woman around the time of menses, and also diluted with sodium hydroxide.

Many women with severe menorrhagia will experience flooding and leakage of blood onto underwear or bedding, or will pass clots, which are often lost into the toilet. Clearly these components of the menstrual blood loss are not collected, and therefore the final measured volume will be less than the actual blood lost. There have recently been efforts to adjust measured blood loss for the fraction lost in this way (Hurskainen et al. 1998; The Menorrhagia Research Group 2004; Wyatt et al. 2001). However, as the size of the adjustment is based on women's reports of numbers of used products uncollected (Hurskainen et al. 1998) and on their subjective judgement of the size of clots lost (Hurskainen et al. 1998; Wyatt et al. 2001), size of spillages (Hurskainen et al. 1998), or of deepness of blood colour of toilet bowl water (Wyatt et al. 2001), this introduces toilet design, recall and subjective elements into measurement of menstrual blood loss. Furthermore, no scientific rationale has been advanced for the blood volume adjustments made for specific sizes of clots or spillages (Hurskainen et al. 1998; The Menorrhagia Research Group 2004; Wyatt et al. 2001). In the case of an uncollected sanitary product the adjustment involved increasing the measured blood volume by the average blood volume per sanitary product for the rest of the period (Hurskainen et al. 1998). However, this may be a substantial under or over adjustment, depending on whether the product was 'regular' or 'super' absorption, and on whether the uncollected pad or tampon was used early or late in the period. Fraser has shown that in women with menorrhagia it is not uncommon to observe changes in measured daily blood loss volume in excess of 40mL, from one day to the next, so greater disparities may be expected between days that are further apart (Fraser et al. 1984). If the quantity of sanitary protection used varied proportionately to total volume of blood loss then the proposed adjustment would be reasonable, but most women change regularly even on light days, managing containment of excess flow in the

first instance by varying the *capacity* of the products they use, from 'regular' to 'super' or 'super plus' and back to 'regular'.

The purpose of measuring blood loss is to verify objectively the menorrhagia complaint. Therefore even if blood volume measurement quality is maximised, by taking care with regard to the factors above, the accuracy with which the of menorrhagia has been quantified depends on the extent to which the menstrual loss for the specific period collected is representative of the woman's menorrhagia complaint. For some women there is marked variation in loss between periods.

Other factors potentially influencing the accuracy of measurement of blood loss in a specific menstrual period are:

- type of sanitary protection
- completeness of containment of flow on sanitary protection
- collection of all used products
- taking blood sample just prior to menses
- squeezing of soaked products to equalise concentration of haematin in supernatant and products
- avoiding substantial evaporation of soaking solution
- laboratory technique
- optimising comparative performance of spectrophotometer.

2.2.1.ii Objective measurement of total fluid volume

As has been shown by Fraser and Levin (Fraser et al. 2001; Fraser et al. 1985; Levin & Wagner 1986) the menstrual loss consists of a mixture of blood and non-blood fluid, with blood comprising about half by volume (Fraser et al. 2001). The non-blood fluid is believed to be endometrial transudate, and comprises about 50% of the total menstrual loss, across a wide range of menstrual loss volumes (Fraser et al. 2001).

Since it is likely that complaint of excessive periods reflects concerns about or difficulties with containment of total flow, measuring total fluid volume of menstrual loss has a sound conceptual rationale. This measurement also has potential clinical utility as it is easier to achieve.

The volume of menstrual blood loss has been shown to be on average 48% to 50% of the total menstrual fluid loss, for women with moderately heavy to very heavy blood loss, that is, respectively >60mL to 99mL and >100mL measured blood loss (Fraser et al. 2001; Fraser et al. 1985). Work on total fluid loss was originally undertaken to ascertain whether the much more easily-measured total fluid loss could provide a clinically satisfactory estimate (prediction) of the feature that was germane to the clinical definition of menorrhagia, the volume of menstrual blood loss. Using logged volumes this proved to be the case, with good prediction possible, despite individual variation in proportion of blood in the total menstrual loss (Fraser et al. 2001). Even better estimation would be possible in assessment of period-to-period changes in blood loss, as might be required in n-of-1 trials of treatment. This is possible because in such a scenario the patient acts as her own control, so pervasive individual contributions to errors in prediction, across the group studied, are eliminated (Fraser et al. 2001).

The methodology used in Fraser's study was research-driven and labour-intensive, and would not be feasible for routine clinic use. However it is possible that some simpler version of it could be adopted.

Factors potentially influencing the accuracy of measurement of total fluid in a specific menstrual period are:

- accurate weighing of products before use
- completeness of containment of flow on sanitary protection
- collection of all used products
- evaporation of water content from pads/bags
- accidental wetting of products with urine or while bathing/showering
- any other extraneous material included with the product, such as toilet paper
- accurate weighing of collection.

The methodology required for measurement of total fluid volume is so simple that it is surprising that it has not been used much more widely.

2.2.1.iii Estimating blood volume by menstrual charting

Although measurement of total fluid by weighing is considerably easier than measurement of blood volume by laboratory methods, both are inconvenient for women, and there is often marked reluctance to collect used sanitary protection for handling by a laboratory technician. A new development for quantifying menstrual loss has been the menstrual chart, first reported in 1990 (Higham et al. 1990). The menstrual chart typically requires the woman to record sanitary protection usage and to match each pad or tampon used to a pictogram, indicating the amount of visible blood. There were three pictograms for each type of product. (*Pictogram* = pictorial or diagrammatic presentation of values/statistics.) An accumulation of this record yields a point score related to volume of menstrual blood loss. The points do not accumulate to a predicted blood volume, but to a 'PBAC' score for which a cut-off of 100 was equivalent to a cut-off of 80mL of blood loss. The sensitivity and specificity (for detecting blood volume >80mL) on the development data set were good (86% and 89% respectively) (Higham et al. 1990).

Since the start of the present research project other charts have been produced, one retaining the three pictograms (Janssen et al. 1995). This had slightly less good performance than the original chart. The other new chart added two extra pictograms for pads, and one for tampons (The Menorrhagia Research Group 2004; Wyatt & O'Brien 2000). In this chart patients also have to specify the absorbency of each product used. The method is not clearly described, and there is no indication as to how the blood volume is calculated from the product usage data. The statistics on performance are not interpretable.

The point scores used in all charts are ascertained by test wetting of products to the degrees of 'soaking' represented by the pictograms, and then converting millilitres to points (Higham et al. 1990; Janssen et al. 1995; The Menorrhagia Research Group 2004; Wyatt & O'Brien 2000). The relationship between total products/points and measured blood volume tends to drift at higher volumes. Perhaps this does not matter if the point is only to detect losses over or under 80mL. However this limits the

charts use to confirmation of complaint, and rules it out for studies of treatment effect.

It should be noted that the charting method retains a strong subjective component, and this may have a greater effect in routine rather than research use, where the products are not also being collected for blood loss measurement, as a check. Performance in a founding study is not usually maintained on a further test data set. For the Higham chart there was poor performance in a subsequent validation study (Reid et al. 2000).

2.2.2 *Assessing subjective menorrhagia complaint*

A number of questionnaires have been developed for assessment of menorrhagia, but none appears to have been adopted as a useful clinical or research tool.

2.2.2.i Health Status Assessment

A health status assessment was developed in 1995, but despite excellent credentials in terms of its development and validation it has not been adopted for routine use (Ruta et al. 1995). The development sample comprised 351 women with menorrhagia, 105 from primary care. The questionnaire has 15 items, asking about periods and accidents, associated symptoms, product use and impact on usual activities. The questionnaire had good internal consistency and test-retest reliability, and was validated by comparison to SF-36 scores.

A menorrhagia outcomes questionnaire has also been developed (Lamping et al. 1998). It is designed for assessing outcome after surgical treatment for menorrhagia, and so is not intended to assess the menorrhagia complaint per se. However, it is of interest to consider the items included in the questionnaire, as they must have been deemed pertinent to menorrhagia recovery. It comprises 18 items apart from the demographics, and only two of them ask about bleeding symptoms (one for before, and one for after). The woman is asked to compare herself to before in terms of energy, irritability, depression, carrying out every-day activities, and sex life. The menorrhagia complaint seems to have been envisaged as more than volume of blood loss.

Some interesting work was undertaken exploring patient preferences for menorrhagia treatments in terms of utilities (Shaw et al. 1998). This was in two stages, the first establishing by interviews with many patients the weights they attached to various domains of health. In order, the most important domains were family life, physical health, interruption to work, practical difficulties, psychological effects, and effects on social life. These weightings were then used to develop a health status scale. There is one item for each domain, and the patient selects one of four possible answers. The answers are assigned weights which are accumulated to achieve a final the score representing the patient's health on a scale of 1-100. The interesting thing about this scale is that only one item deals with bleeding. The others would be as relevant for period pain or premenstrual symptoms. So it appears this menorrhagia assessment could be giving a lot of weight to associated menstrual symptoms, and to background psychological health. Indeed, a very poor 'menorrhagia health status' score could be achieved with modest menstrual loss, provided there was pain and/or cyclic symptoms.

2.2.2.ii Quality-of-life

General quality-of-life measures could be used for assessment in menorrhagia, instead of disease specific measures. In recent years quality-of-life assessments have assumed a central place in health services and outcome research. It is generally agreed that these are a good approach to health assessment (Clark et al. 2002; Jones et al. 2002). The most widely used of the quality of life scales is the SF-36 – Short Form 36-item generic health-related quality-of-life questionnaire (Garratt et al. 1993; Ware & Sherbourne 1992). A further advantage of SF-36 is that there are normative data available for the UK (Jenkinson et al. 1993).

The SF-36 was devised to assess important generic health concepts as may be used in a wide range of outcome studies and health surveys (Ware & Sherbourne 1992). It comprises 36 items, 35 of which are accumulated into 8 scale scores (Medical Outcomes Trust 1994). SF-36 covers all aspects of health: general health and vitality, physical and social functioning, physical and emotional role functioning, bodily pain and mental health. It has been used successfully in menorrhagia outcome research

(Coulter et al. 1994b). The remaining free-standing item is, on its own, a measure of reported health transition (HT), asking for evaluation of current health compared to a year ago. Five levels of response are possible: much better, better, about the same, worse, much worse.

The validity and reliability of SF-36 are considered to be excellent (McHorney et al. 1993; McHorney et al. 1994). However, an internal reliability and face validity study undertaken with menorrhagia patients revealed some problems (Jenkinson et al. 1996). These were attributed to conditions such as menstrual problems that are not life-threatening, that the sufferer knows will not last for ever, and with intermittent symptoms (Jenkinson et al. 1996). This supports the conclusion of a recent review of quality of life instruments in studies of menorrhagia, that there is a need to develop a disease specific quality-of-life instrument for menorrhagia, because the generic ones do not have sufficient *clinical* face validity (Clark et al. 2002).

2.2.2.iii Overview

In order to develop a menorrhagia specific quality-of-life instrument with 'clinical face validity' there is an urgent need to clarify exactly what the 'face' of menorrhagia complaint is. It is clear from the diversity of three health status measurements presented above, and from their item content, that there is confusion about just what it is that should be assessed. This probably derives from a dissonance between the narrow clinical definition of menorrhagia, and the complaint as expressed by women in terms of utilities (Shaw et al. 1998), and as enshrined in the outcomes questionnaire (Lamping et al. 1998).

2.3 RECONSIDERING MENORRHAGIA

Menorrhagia has been defined in terms of volume of blood loss, and is of clinical concern both because of adverse effects of excessive loss on iron status and vigour, but also because containment of excessive flow can have an adverse impact on quality of life. This bi-partite nature has led to a lot of confusion in research and clinical practice. There is one simple question (in two parts): if a woman's health is severely affected by her periods, in particular the flow, how should her problem be assessed to inform discussion between her and her doctor as to appropriate strategies of management? Would it make any difference to these discussions to know that her blood loss was 66mL, 86mL or 106mL?

Chapter 3

STUDY DESIGN AND METHODS

3.1 INTRODUCTION

A brief review of physiological and epidemiological understandings of menstrual problems has been presented in Chapter 1, and a critique of existing approaches to assessment of menorrhagia has been set out in Chapter 2. Concerns regarding the currently prevailing tendency for partitioned thinking about menstrual problems, viewing dysmenorrhoea, menorrhagia and premenstrual syndrome as distinct conditions, led to the key objective of this research - to develop a broad clinical assessment for menstrual problems. In the first instance what was required was a multi-faceted examination of the contemporary menorrhagia complaint.

3.2 DESIGN, AIMS AND OBJECTIVES

3.2.1 Aims and objectives

The study aims were:

I. To develop a clinical assessment for the contemporary menorrhagia complaint that encompasses the spectrum of relevant symptoms and clinical parameters, and also impact on quality of life and health.

II. To define and quantify menorrhagia, by relating objective measurement of blood and total fluid loss to health impact and quality of life.

III. To relate outpatient outcome (i.e. management up to 8 months later) to menorrhagia assessment profile.

This determined the objectives of the study which were to:

I. Undertake a cross-sectional survey of women referred to gynaecology clinics with the menstrual complaints heavy periods, irregular periods, premenstrual syndrome or period pain, addressing the nature of the complaint and background details.

II. Identify the subgroup with 'complaint of excessive menstrual bleeding' and request more detailed questionnaire assessment of their complaint, health, quality of life, personality, psychological well-being and medical history. In

addition, request each such woman that she undertakes menstrual charting and menstrual collection of her next period to allow objective measurement of menstrual loss volumes.

III. Undertake a case-note review follow-up at 8 months after recruitment to ascertain clinic outcome.

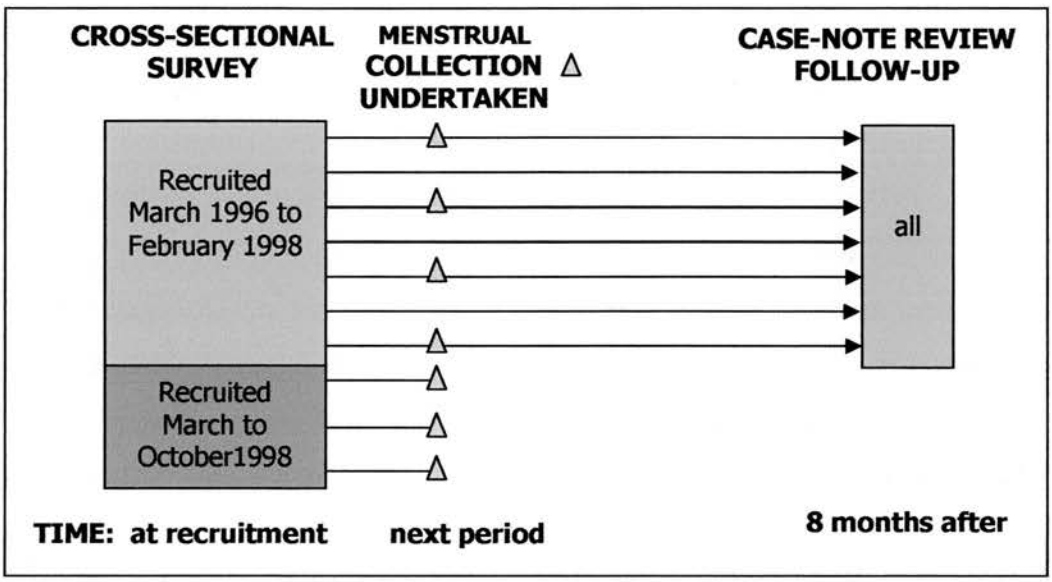
3.2.2 Design Overview

The key element of the research design was the detailed menstrual loss study, involving prospective data collection for one period and measurement of menstrual loss. This was embedded within a cross-sectional survey of all referrals for menstrual complaint. All women with any of a range of menstrual problems were invited to participate in the cross-sectional study.

In addition there was a case note review 8 months after recruitment, to ascertain management and outcome. However, because funding constrained the duration of the study, this 8-month follow-up review was possible only for those women recruited to the cross-sectional study eight months or more before the end of data collection, i.e. all women recruited before the end of February 1998. The time-course of the study is illustrated in **Figure 3.1**.

This means that the design is 'mixed', with a follow-up or cohort study of a subset of the entire cross-sectional survey, and also a more detailed menstrual collection study embedded within the wider cross-sectional survey, but overlapping both the cohort and survey-only subgroups. In what follows the design and methods for each of these sub-studies will be described:
the cross-sectional survey (**3.3**);
the menstrual collection study (**3.4**); and
the cohort (follow-up) study (**3.5**).

Figure 3.1 Schematic diagram of time-course of study



This is followed by details of funding and research support (**3.6**), consideration of ethical issues (**3.7**) and an overview of the statistical methods used (**3.8**). The chapter concludes with a summary of study design and rationale (**3.9**).

3.3 CROSS-SECTIONAL SURVEY

3.3.1 Design

What was envisaged was a cross-sectional questionnaire survey of patients newly-referred to gynaecology clinics with menstrual problems. The self-completed questionnaires used are detailed below (**3.3.2**). They were a mixture of established or published questionnaires that have been used extensively in menstrual research, and of questionnaires devised specifically for the study, albeit in part developments of questionnaires used in earlier research. Areas addressed by the questionnaires were current menstrual and general health, personality, psychiatric well-being, socio-demographics, contraceptive and obstetric history, illness behaviour and quality-of-life.

3.3.2 Study questionnaires

3.3.2.i Development of new questionnaires

MEQ -MENSTRUAL EVALUATION QUESTIONNAIRE.

This was devised as a prototype menorrhagia assessment, evaluating menstrual complaint in breadth and detail. It built on earlier research work, and incorporated findings from the literature (as described in (Bancroft et al. 1993; Warner 1995)) and ideas developed from reflections on these findings (Warner 1992; Warner 1994). The novel aspect of the MEQ is that it seeks to evaluate menstrual complaint broadly, both in terms of a 'clinical menstrual history' (including accidents and use of sanitary protection and pain-killers), and also in terms of impact on daily life and work, practicalities and cost, and feelings about periods. (A copy of the MEQ questionnaire is provided as **Appendix 3.1**)

It was intended that ultimately MEQ would be shortened, by deletion of items established by analysis as redundant, but before this is attempted it would be better if there could be a consensus agreement as to a menorrhagia definition that is relevant to women's concerns underpinning the contemporary 'menorrhagia' complaint. Consideration of this latter issue is the subject of this thesis.

CQ - CLINIC QUESTIONNAIRE.

This very brief questionnaire 'audited' the referral population by asking minimal details about the complaint, as well as some background and demographic data. It was devised to ensure that at least some (key) data were obtained on a range of issues, as a precaution, as it was anticipated there would be women who would be reluctant to complete extensive questionnaires. There was therefore some duplication of basic menstrual and demographic detail with the longer and more detailed questionnaires described below. (A copy of the CQ questionnaire is provided as **Appendix 3.2**.)

CQ is novel in that it asks not merely for, say, subjective judgements of heaviness of loss (elicited symptom), but for evaluations of a range of 'aspects' of menstruation, including aspects of volume of loss, with respect to their occurrence or not, and if they do occur, the *extent of problem*. The distinction CQ makes between *symptom* and *problem* circumvents the confusion that can arise, for example, when a woman reports her periods as 'heavy'. (See also **1.3.1.ii**) Such a judgement may *not* constitute a complaint of *excessive* volume, or problem. 'Heavy' can be simply a straightforward value-free account of how the woman classifies her period, most probably in relation to her own previous experience, but possibly also from type and quantity of sanitary protection required to contain the period, or possibly on the basis of discussions comparing experience with other women. This distinction as to extent of problem, for all aspects, is of potential benefit for research and for clinical communication with the patient.

Furthermore, the difficulties with assessment of premenstrual syndrome, (Wyatt & O'Brien 2000), and the attitudes there are to that illness label, led to a decision to side-step the medical definition of PMS (or rather the lack of such a definition that can feasibly be assessed by questionnaire). Instead respondents were asked about problems with 'mood changes around the period', and with 'other bodily changes before the period'. This was felt to have the further advantage that there may be women who were experiencing such symptoms as problematic, and would affirm this, but who would not define them as PMS.

Similarly for menstrual pain. For CQ, specification of intensity of pain, duration of pain of various intensities and use and effectiveness or not of painkillers was replaced by a simple prompt 'Do you have period-type pain with your periods', giving the respondent the responsibility of determining the extent of problem for her. There were similar items for pain before the period, and for cycle-long pain.

The questionnaire was piloted with a number of gynaecology patients, who were very positive about the approach taken, and the opportunity provided to describe the broad range of aspects of their periods (menstrual symptoms experienced) and the extent of impact (problem) on their lives (Warner & Critchley 1995).

MBQ - MENSTRUAL BACKGROUND QUESTIONNAIRE.

MBQ assesses menstrual history and background, addressing contraceptive, menstrual, and obstetric history, alcohol consumption and smoking, and previous psychological problems. It was based partly on the Menstrual Health Questionnaire that had been used extensively in earlier research (Warner et al. 1991). A number of questions were added, in particular items on general health symptoms, and common medical conditions, taken from another questionnaire used extensively in women's health research (Morse et al. 1988). The novel aspect of MBQ was an attempt to obtain life-course data regarding age at onset of menstrual problems, first consultation for menstrual problems with general practitioner, first attendance at hospital gynaecology clinic, and also of changes in severity of symptoms over time. In addition, some questions on illness behaviour with regard to periods, adapted from a previous study on menorrhagia, were included as MBQ multi-part question 23 (Hodges 1989). These items are not analysed for this thesis so will not be described further. (A copy of the MBQ questionnaire is provided as **Appendix 3.3**.)

3.3.2.ii Selection of established questionnaires

In menstrual research the most widely used psychological/psychiatric questionnaires have been the General Health Questionnaire (GHQ), which screens for psychiatric morbidity (Goldberg 1972), and the short form of the revised Eysenck Personality

Questionnaire (EPQ-R), which assesses personality dimensions (Eysenck & Eysenck 1964). It was therefore important that they were included in the present study.

SF-36, the most widely-used generic health-related quality-of life measure, was also included in the study (Garratt et al. 1993; Ware & Sherbourne 1992). SF-36 was included in order to be able to compare with other published research, in particular some work in menorrhagia (Coulter et al. 1994b), and there were normative data available for the UK (Jenkinson et al. 1993).

For this thesis only the data for SF-36 will be reported, therefore only this questionnaire will be discussed below. Analyses of the remaining questionnaire data will be reported in papers in due course.

SF-36 – QUALITY-OF-LIFE QUESTIONNAIRE

The SF-36 was devised to assess important generic health concepts and has been discussed in **2.2.2.ii** (Ware & Sherbourne 1992). (A copy of the SF-36 used is provided as **Appendix 3.4**). **Table 3.1** lists the conceptualisation for each of its 8 scales, the number of items in the scale, the range of possible scores (levels), and a resume of the content of the items comprising the scale (Medical Outcomes Trust 1994). The single additional (non-scale) item is a measure of health transition (HT). It asks for evaluation of current health compared to a year ago. Five levels of response are possible: much better, better, about the same, worse, much worse.

Usage in this study The SF-36 used was the 'developmental' version, prior to making item 9j into a new separate question 10, with five possible responses instead of six. The questionnaires were scored as per the manual with question 9j re-coded so that the scale scores can be interpreted as equivalent to scores on the current standard SF-36 (Medical Outcomes Trust 1994). To achieve this, the six possible responses for item 9j, in order from 'all of the time' to 'none of the time', were re-coded to be 1, 1.8, 2.6, 3.4, 4.2 and 5.

As a first step a raw score was obtained for each multi-item scale. These scale raw scores were then transformed into percent scale scores, by means of the formula:

$$\text{Transformed score} = \frac{[\text{Actual raw score} - \text{lowest possible raw score for that scale}]}{\text{Range of scores possible for that scale}} \times 100$$

It should be noted that because the denominators for the scaled scores (the possible range of scores as presented in **Table 3.1**) range from 3 to 25, the scaled scores will have discrete values. If the range of possible scores is 3, as for RE scale, then the possible scaled scores are 0, 33.3, 66.7, and 100. On the other hand if the range of possible scores is 25, as for MH, then the possible scaled scores are 0, 4, 8, 12, and so on up in multiples of four to a maximum scaled score of 100.

The single-item Health Transition (HT) 'scale' was not transformed but is, as advised in the SF-36 manual, reported as a simple frequency distribution, and analysed as an ordinal variable (Medical Outcomes Trust 1994).

Table 3.1 SF-36 multi-item scales and content

Scale concept	Number of items	Range of scores possible	Content of scale
GH: General Health	5	20	Self-reported health, health prospect and susceptibility to illness
VT: Vitality	4	20	Degree of feeling of vigour versus fatigue
PF: Physical functioning	10	20	Ability to walk, exercise, bend, lift and climb stairs
SF: Social functioning	2	8	Extent to which health interferes with normal social activities
RP: Role functioning - physical	4	4	Difficulty in performing activities or work due to physical health
RE: Role functioning - emotional	3	3	Extent to which emotional problems limit activities or work
BP: Bodily Pain	2	10	Intensity of pain and impact on work and activities
MH: Mental Health	5	25	Mental wellbeing and degree of depression, anxiety and emotional problems

3.3.3 Iron status

One of the reasons for concern about excessive menstrual blood loss is the risk of depleted iron stores (Fraser & Inceboz 2000; Fraser 1994; Milman et al. 1993). It

would therefore have been desirable to have iron status test results for every participant. However, there were a number of concerns about such a design. Firstly, it was not felt to be ethical to request a blood sample for this purpose from every participant. Secondly, if such a test was imposed by us, and the results showed low iron stores, this would be likely to affect subsequent management of the patient, and hence bias our findings at the follow-up. Finally, it was thought that the fact of a blood test may discourage some women from participation in the study. It was therefore decided to take a pragmatic approach, and record iron status test results for each woman for whom a test was requested by her managing clinician, which would be when such a test was judged to be clinically indicated. Therefore the group receiving blood iron tests would inevitably be a biased subgroup, those judged to need the test by their clinicians and hence more likely to have low iron status. However, they would be representative of women who would be tested, and so their management, and the management of women not tested, would be representative of usual clinical practice in the clinics surveyed.

The most widely used test of iron status is haemoglobin which indicates iron circulating in the blood (Rees 1997). Physiologically this is protected, in that depletion or loss of iron from the body will be followed by an attempt to remedy the shortfall in iron in the blood as quickly as possible, so that very soon a 'normal' haemoglobin level may be obtained. On the other hand, serum ferritin concentration reflects iron reserves, and it is depletion in these that is the first indicator of a chronic depletion or loss of iron. Therefore serum ferritin concentration is likely to be a more sensitive indicator of threat to iron status.

At the Glasgow clinics measurement of serum ferritin levels was a standard test in use, together with haemoglobin. In Edinburgh the test was initially available, and could be requested whenever haemoglobin was indicated. However, some months after the study started measurement of ferritin levels became non-routine at Edinburgh. Therefore extra funds had to be sought so that the test could be purchased in Edinburgh, as an additional test for every woman for whom a haemoglobin test was indicated. The numbers of women having the two tests at the Edinburgh and Glasgow centres is presented in Chapter 4.

A further difficulty experienced with the ferritin tests was the different methods of laboratory measurement in use at the three clinics, and over the time course of the study. Edinburgh used one system throughout the study, *Abbot Axsym* system (normal range for premenopausal women 7-280). Glasgow Royal Infirmary used *IMX Technology* (normal range for premenopausal women 6-81). At Western Infirmary Glasgow *Ciba Corning Magic Irma* was used until June 1996, and from then on *Ciba Corning AC5180* (both systems had normal range for premenopausal women as 12-300.) The systems differed in the ranges for results, but none of the companies marketing the systems was able to provide a conversion formula from one system to the other. However each did state a cut-off value, which delineated 'low ferritin' values from the rest. For simplicity of combining the data from the four systems this binary value was used for multivariate analyses.

3.3.4 Ascertaining socio-economic status

A number of approaches were taken. At the individual level the woman's job, or most recent job, was elicited in the CQ questionnaire. Since we were able to ask only the most cursory information this enabled very crude classification in terms of Social Class by means of the Registrar General's Manual (OPCS 1992). A further caveat is that the jobs undertaken by women in their child-rearing years may not be indicative of their true social class, especially if bringing up children single-handedly. We also ascertained years of formal education, a variable known to be closely linked to socio-economic status.

All these methods of ascertaining individual socio-economic status depend on obtaining specific details on employment or education. Since we could not obtain from non-participants the data necessary for determining individual social class we would have been unable to compare their socio-economic status with that of the participant group. For this comparison we used instead an area level indicator of socio-economic status, the deprivation score, derived from the postcode (Carstairs & Morris 1990). The Carstairs postcode-based deprivation score categorises the population into 7 ordinal categories in terms of relative affluence or deprivation. Affluence/ deprivation is determined from the 1991 Census data and reflects the

prevalence by postcode of various indicators of affluence, including car ownership. Carstairs score 1 is assigned to those who live in postcodes that are among the 'most affluent' areas in Scotland, whereas those living in postcodes corresponding to score 7 live in the 'most deprived' areas, with intermediate affluence/deprivation ranged across the scores 2 to 6. For participants the deprivation score (Carstairs & Morris 1990) also provided an indicator of socio-economic status that could be used as an alternative to social class and education described above.

3.3.5 Ascertaining referral reason

Reason for referral was ascertained from general practitioner letters by dedicated study research nurses. As just over half the letters cited more than one reason it was decided that the first two reasons should be recorded, to minimise the need for subjective judgements, and to allow for the diffuse nature of menstrual complaint. The letters tended to be very brief, so there was little loss of information. Coding of referral reasons is described in **3.8.5.i**.

3.3.6 Target population

Referral 'menstrual problems' eligible for recruitment to the study were defined as any described in the referral letter as:

- Excessive periods – including menorrhagia (heavy menses), heavy periods, periods going on too long, periods too much, periods increased, flooding, clots
- Period pain – dysmenorrhoea
- Premenstrual syndrome – premenstrual tension, perimenstrual problems
- Period problems (non-specific)
- Irregular periods.

Initially the target population was all such women aged 25 to 45 years referred for 'new' menstrual problems to collaborating consultants at gynaecology clinics at Edinburgh and Glasgow Royal Infirmaries, and Glasgow Western. A problem was defined as 'new' if the woman had *not* attended the gynaecology clinic in the past year for the same problem. The rationale for the age range was to exclude at the younger end the adolescent menstrual problems that are common until gynaecological maturation is achieved (Fraser 2000; Widholm & Kantero 1971), and

at the upper end to try to avoid complaints that are allegedly menstrual but where menopausal problems are strongly implicated in the decision to consult or refer (Fraser 2000). After a few months recruiting it was realised that a substantial number of women between 45 and 50 years of age, with main complaint of excessive periods, were having to be excluded from the study because of the upper age limit, so about 6 months into the study a decision was made to extend the upper age limit to 49 years.

For this study there was a need to be able to read and complete questionnaires, so women unable to speak/read English, had to be excluded. In the clinics targeted this was a very small proportion of women. Questionnaire completion makes demands on reading ability but the research nurses were present and able to help with any difficulties. Women with poor reading ability could therefore be included in the cross-sectional survey because 'minimal participation' was possible, involving completion only of the very brief CQ (Clinic Questionnaire).

3.3.7 Recruitment procedure

The recruitment procedure adopted was to scan the referral letters for appointments before a clinic, and note any patients who seemed eligible for the study.

The research nurses worked part-time, and had to undertake laboratory work (measurement of menstrual blood loss) in addition to spending time in clinics recruiting patients. Therefore they were not able to cover all gynaecology clinics. They sought to maximise recruitment by, after a few months, focussing on the clinics which from early experience of study recruitment had been found to have the greatest numbers of menstrual problem referrals (and the greatest number of collaborating consultants).

When the clinic took place, the research nurse would try to talk to each potential participant, to explain the study to her and invite her to participate. Sometimes this proved impossible because patients spent hardly any time in the waiting room before being called in to see the gynaecologist, or because appointments of two potential recruits were too close together and while one was having the study explained the other potential recruit was missed.

3.3.7.i Referral log

A log was kept of all potential recruits identified from the referral letters, including age, referral reason(s) ascertained from letter (up to two -see **3.3.5**), and post-code. If a woman was subsequently recruited she would be given a study number and this would be entered on the log. The rationale for the log was to enable those successfully recruited to be compared to the remainder in terms of age, deprivation code and referral condition(s).

3.3.7.ii Balancing recruitment against questionnaire completion

The number of questionnaires to be completed posed an organisational challenge for the nurses, and there was concern also that the questionnaire load may have a detrimental effect on recruitment to the study. It might restrict participation to those who were more compliant or altruistic, and very probably also to those with better reading ability. To maximise recruitment it was decided to conduct the survey at three levels:

- Minimal – completing the brief Clinic Questionnaire (CQ) only;
- Basic – completing also the Menstrual Evaluation Questionnaire (MEQ);
- Research 1- completing, in addition to Basic, the questionnaire providing background data, the Menstrual Background Questionnaire (MBQ), and also the General Health Questionnaire (GHQ), the Eysenck Personality Questionnaire (EPQ-Revised) and the quality-of-life questionnaire SF-36.

The aim was to have as many participants supply as much detail as possible about themselves, but it was accepted that not all women would complete all questionnaires. To ensure maximal recruitment the design allowed for some women completing only to the 'Minimal' or 'Basic' levels. The research nurses tried to ensure that the brief CQ (Minimal) was completed at the clinic, but if the woman was short of time any uncompleted questionnaires were given to her to take away, with a reply paid envelope for posting back to us. If these were not returned then the nurse would make one phone-call requesting return of the questionnaires (even if uncompleted), or if no phone contact number was available, write one letter.

Since the 'Research 1' questionnaires were mainly for the purposes of elaborating understanding of relationships between measured menstrual loss and other questionnaire variables (MEQ and CQ), it was felt to be unethical to impose them on women who were not eligible for menstrual blood loss collection (see **3.4.4.i**). Therefore detailed instructions addressing recruitment eligibility for the various levels, including menstrual blood loss collection, were devised for the study nurses, together with a diagrammatic representation. These are provided as **Appendices 3.7**and **3.8** respectively.

3.4 MENSTRUAL COLLECTION STUDY

3.4.1 Design

To explore fully the nature of the menorrhagia complaint, and practicable but meaningful ways to assess it, it was determined that in addition to the traditional menstrual blood loss assessment both total fluid volume measurement and also a development of menstrual charting should be employed. These will be described in more detail in the methods section of Chapter 6, so a very brief outline only will be provided here.

3.4.2 Estimation of menstrual loss by prospective menstrual charting

A menstrual chart was developed specifically for this study based on the published chart of Higham (Higham et al. 1990). This presents pictograms representing used sanitary pads or tampons for a range of degrees of soaking, and the respondent must match the product she has just changed to one of the pictograms. A copy of the Menstrual Chart (MC) is provided as **Appendix 3.5**. The rationale for adaptations to the Higham chart, and the approach taken, are described in detail in the Methods section of Chapter 6. This stage also involved completion of a Weekly Well-being Diary up to six weeks, until the end of the menstrual collection. These data also are not reported in this thesis.

3.4.3 Objective 'measurement' of menstrual loss

3.4.3.i Determining menstrual blood volume

Blood loss measurement was undertaken by the alkaline haematin method described by Hallberg (Hallberg & Nilsson 1964) which involves collection of all used sanitary products for one period, and the taking of a blood sample around the time of the period, for comparative purposes. In this study only one period was to be collected, as it was felt this was all it was reasonable to ask of women participating out of altruism, and not as part of their care. To explore to some extent within-woman variability in menstrual loss, women were asked in their Menstrual Chart (see

3.4.2 above) how the period collected compared with periods over the previous 6 months (the time period on which questionnaire responses were to have been based).

A detailed description of the method used is given in the Methods section of Chapter 6 and there is further extensive elaboration of methodological issues in Chapter 7.

3.4.3.ii Total menstrual fluid volume measurement

As an alternative method of objective measurement, Fraser (Fraser et al. 1985) has explored use of total menstrual fluid measurement. This measurement is far simpler to undertake than blood volume measurement since it involves simply pre- and post-weighing of all sanitary products used. Clearly evaporation must be avoided before weighing of the used products. The difference in total weight converts directly to millilitres of total menstrual loss. Total fluid volume can be used to estimate menstrual blood volume, which is typically about 45 to 50% of the total menstrual fluid volume (Fraser et al. 2001). However, since the total menstrual fluid volume is what the woman has to contain with menstrual protection, it may be a menstrual parameter of utility in its own right.

A detailed description of the method used is given in the Methods section of Chapter 6 and there is some further elaboration of methodological issues in Chapter 7.

3.4.3.iii Checks on measurement

The research nurses undertook initial training and checks by their trainers. They then started measuring blood volumes of menstrual collections. Total fluid volume was also ascertained by weighing (see below). The early data were examined descriptively separately for the two centres. While the tendency to higher blood volumes that was found in Glasgow could have been a reflection of a true difference, the disparity observed in the *proportion* of blood to total fluid would be unexpected even if Glasgow women tended to have heavier blood losses. It was therefore decided part way through the study to undertake some validation laboratory studies to test the basis for the observed differences between the two centres. These are described in Chapter 7.

3.4.4 Identification and recruitment of women prepared to undertake menstrual blood loss collection

3.4.4.i Inclusion criteria

There were two inclusion criteria for undertaking menstrual collection. The first was that all the study questionnaires had been completed (**3.3.2i**). The second was that at least one of three menstrual complaint conditions needed to be satisfied:

- the woman was referred by her general practitioner for 'excessive bleeding' – including terms such as menorrhagia, heavy periods, periods going on too long, periods too much, periods increased, flooding, clots; or
- on the Clinic Questionnaire (CQ) she subjectively rated her menstrual loss as 'heavy' or 'very heavy'; or
- on CQ she gave her (free text) reason for clinic attendance as excessive bleeding – including terms as above.

The rationale for this was to be as inclusive as possible regarding the participants who were eligible to be invited to collect. There have been reports of misunderstandings, between women and the doctors they consult, about the specific nature of the menstrual problem leading to consultation (Bancroft et al. 1993; Coulter et al. 1989). Furthermore, we found that in some referral letters doctors cited not the (presumed) menstrual complaint, but the suspected *cause* - fibroids, say. ('Presumed' here is in the sense that the presentation is much more likely to have been a menstrual symptom - for example, heavy periods- than an organic pathology such as fibroids.) A referral reason such as fibroids could not be taken as equivalent to the occurrence of excessive bleeding as fibroids do not necessarily cause heavier bleeding. For women referred for this reason the original consultation may have been for other reasons, such as problems due to pressure by a large fibroid. We reasoned that in cases where the doctor had referred the patient with 'fibroid', and excessive bleeding *was* the complaint, it would be likely that the woman would either state her reason for attendance as excessive bleeding, or would rate her menstrual loss as heavy or very heavy. She would therefore be deemed eligible for the study by one of these other routes.

Conversely, there have also been numerous reports, albeit often anecdotal, that some women believing their periods to be 'normal' in fact have excessive blood loss. (Of course, the periods may indeed be 'normal' for the woman concerned, if similar to what she has always experienced.) It is possible that in some of these cases questioning by an experienced general practitioner, prompted perhaps by presenting symptoms of tiredness, would elicit the fact of excessive bleeding. This may lead to referral for this excessive bleeding, even though the woman may not even rate her menstrual loss as 'heavy' or 'very heavy'.

Finally, in discussions of menorrhagia, and in some research questionnaires, there is often failure to distinguish degrees of subjective heaviness. In the RCOG guidelines (Royal College of Obstetrics & Gynaecologists 1998) and in other guidance as to management of menorrhagia or excessive bleeding (American College of Obstetricians and Gynecologists 2000; Prentice 1999b) there is no requirement for objective assessment of menstrual loss, nor is there a detailing of the specific features of the menstrual history suggestive of excessive bleeding. 'Heavy periods' is used as a synonym for menorrhagia, and management is outlined without any further elucidation as to what is meant by the term. It is however possible that many women in their late reproductive years, who do *not* believe they have a problem of excessive bleeding, would nevertheless label their periods as 'heavy', reflecting the fact that they have become 'heavier' in recent years. The question is whether subjective rating as 'heavy' necessarily denotes a problem with the volume of menstrual loss.

The wish was to invite to collect all women where either they or their doctors indicated that bleeding was deemed to be excessive, or where the subjective rating of menstrual loss was at least 'heavy'.

3.4.4.ii Exclusion criteria

If a woman satisfied the two inclusion criteria then before she was asked to collect, two exclusion criteria were applied:

(a) There was a decision to confine collection requests to women with usual menstrual cycle length of 54 days or less, to avoid long time-lags until the collection could be accomplished. Unwarranted approaches to potential collectors could be

avoided as it was possible for usual cycle length to be checked first by the research nurse, since the relevant information was requested and hence would have been supplied in the Menstrual Evaluation Questionnaire already completed by each woman.

(b) For safety reasons it was decided to exclude from the collection study women who were intravenous drug-users or who were recorded in their notes as HIV positive. The diagram and instructions provided for the nurses to guide recruitment to the survey and for the menstrual collection study are shown in **Appendices 3.7** to **3.8.**

3.4.4.iii Recruitment of collectors

In the event that a woman satisfied the inclusion criteria, and did not have reason to be excluded (see above), then the research nurse would ask her if she would be prepared to undertake a menstrual collection for the purpose of research into women's menstrual problems.

3.4.5 Procedure for collection

A key aim for us was to make the collection procedure as easy and acceptable as possible for the women agreeing to help our research, and to ensure that measurements made were as accurate as possible.

3.4.5.i Provision of sanitary protection

Women were provided with free menstrual products, Regular and Super Tampax tampons as required, and Bodyform Ultra sanitary pads in Super and Super plus sizes, as required. This was mainly to standardise products used so as to avoid as far as possible the need to pre-weigh each product individually, as will be described (**6.2.1**). It was also hoped that free sanitary protection would encourage some women to participate.

3.4.5.ii Bags for storing each used product

Given the prevailing menstrual etiquette, it was judged very likely that used and blood-stained tampons or pads in clear polythene bags, needing to be conveyed home

to the 'collection' point, would be difficult for many women. This may lead either to defaulting, or use of toilet paper to wrap used products, thus affecting data completeness, weight measurements and/or calculations. We therefore sought to obtain opaque bags suitable for the research. Opaque polythene bags were not available in laboratory suppliers catalogue, but it was realised that infant 'nappy sacks', for transporting used disposable nappies, and available from supermarkets and high street chemists, were ideal for our purpose. The nappy sacks used (Safeway own brand) were an opaque pale apricot colour, an ideal size, pleasantly perfumed, and shaped to enable a water-tight seal by tying.

3.4.5.iii Container for accumulating collection of bagged used products

The most simple and practical way to collect and then transport the bagged used products would be in a copious plastic bag. However this was felt to be unseemly, given that the collection would either be brought back to the clinic by the woman, or collected by the nurse from the woman's home. We therefore obtained sturdy green plastic mail courier bags, with the capacity of a largish briefcase. They had a strong zip closing, and the added advantage that the bag could if wished be fastened closed, proof only against tampering, with small plastic fasteners that could be provided to the women. For added safety the bag was lined with a large and robust yellow plastic hospital waste sack. The courier bags could be sterilised after use and re-cycled for the next collector.

3.4.5.iv The procedure

Women consenting to 'Full' participation, i.e. to collect use menstrual products for one period, were carefully instructed on the menstrual collection, and advised on how to avoid accidents, or loss of blood in the toilet or shower. The instruction sheet is provided as **Appendix 3.9**. It should be noted that some of the requirements result from our wish also to ascertain total fluid volume (described above). The instruction sheet also gave the names and telephone numbers of the research nurses, in case any further help was needed.

Each collector was also provided with a Menstrual Chart (MC – see above **3.4.2**), a green courier bag lined with a strong yellow hospital plastic bag, and with sufficient

nappy sacks for sealing each product after use. The approximate date of next period was noted. About 10 days after the due date for the next period the nurse would telephone the collector to ask if the period was finished, and if so arrangements were made for hand-over of the collection once completed. Either the research nurse would uplift the collection from the woman's home, or the woman may prefer to bring it to the clinic. In the latter case travel costs would be reimbursed. At the time of hand-over a venous blood sample would be taken. In some cases the woman had decided for personal reasons not to collect the first period, but did do so for a subsequent period. However, in some cases no collection was ever made, despite the agreement to do so.

3.5 CASE NOTE REVIEW FOLLOW-UP

3.5.1 Design

Patients referred to gynaecology clinics have varied symptom profiles, often with combinations of menstrual problems (Bancroft et al. 1993). For the majority of those with complaint of heavy periods it is unlikely measurement of loss would confirm menorrhagia (Cameron et al. 1990), but regardless of this there may be associated pathology such as fibroids. It was therefore decided that the detailed cross-sectional survey and embedded menstrual collection should be complemented with a follow-up study of diagnosis, management and outcome. This would enable examination of the relevance to clinic outcome of subjective reports of periods, actual volume of menstrual loss, and other patient characteristics.

The overall time-span of the study was constrained by funding, and recruitment was expected to extend for almost all of this, so the longer the duration of follow-up the smaller the proportion of participants who could be followed up before the end of the study. Discussions with clinical collaborators led to a decision to set the follow-up at 8 months, as it was judged that the majority of gynaecology clinic patients referred for menstrual problems would within this time have been discharged or had decisions as to management. The shortest reasonable time-span was sought so as to maximise the proportion of recruits who could be followed up within the fixed time-frame of study funding.

3.5.2 Membership of cohort

To allow time for data entry and reporting, it was decided that case note review could continue only until the end of October 1998, three months before the end of the study. Counting back 8 months from this date identified the end of February 1998 as the latest possible recruitment for which follow-up could be accommodated.

3.5.3 Methods

Case notes were drawn 8 months or more after recruitment and reviewed by research nurses, for the 8 month period following recruitment. Data to be extracted were set

out on a Follow-up Form – **Appendix 3.6**. The main information sought was on tests and investigations performed, diagnoses and treatments, and outcome at 8 months – discharged, referral elsewhere, or still under care. Background medical information was also sought, including obstetric history, medication being taken at the time of referral, and any chronic medical conditions. The data-manager coded the data entered on the follow-up form, according to coding schemes discussed and agreed with the investigators.

3.6 FUNDING AND RESEARCH SUPPORT

Funding for the study was provided by the Chief Scientist Office for Scotland (CSO) (K/MRS/50/C2472, Principal investigator PW). Clinical collaborators for the grant application, and subsequently for the study, were Professor Hilary Critchley, Obstetrics and Gynaecology, University of Edinburgh, and Professor Mary Ann Lumsden, Department of Obstetrics and Gynaecology, University of Glasgow. Another key collaborator was Dr Mary Campbell Brown, who at that time supervised a menstrual problems clinic at Glasgow Royal Infirmary. She provided helpful advice at the design stage, and was very much involved in the clinical conduct of the study, and also in the laboratory assessment of menstrual loss.

Initially the grant awarded covered salaries for two years for two half-time research nurses, one each in Edinburgh (Elaine Kacser) and Glasgow (Dorothy Lyons), and for a half-time data manager in Edinburgh (Anne Douglas). It also provided funds to pay for data entry. The nurses were to recruit patients, administer questionnaires, chase up non-returns, undertake laboratory measurement of menstrual blood loss, and review notes for follow-up. The data manager designed a study management database, assisted with design and layout of in-house questionnaires, and organised their printing. Once the study was up and running she liaised with nurses regarding recruitment and follow up, maintained the study management database, checked and coded questionnaires, oversaw data entry, checked entered data, and accumulated the study data set. She also undertook descriptive summary analyses.

The research was overseen by means of regular study meetings of PW, the three clinical collaborators, the two research nurses and the data manager. Recruitment was monitored, and any potential problems discussed. After about 6 months it was realised that number of eligible potential recruits had been overestimated. The problem with ferritin tests in Edinburgh had also arisen. In the first year report to the CSO an application was made to extend the funding for the study for a further year, and included in this was extra resource to fund ferritin tests in Edinburgh. The application was successful, so ultimately the study ran for three years.

3.7 ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval for the study was obtained from the Lothian Research Ethics Committee (Reproductive Medicine and Paediatrics Sub-Committee, application made by PW), and shortly after funding was obtained, ethical approval was obtained from the West Research Ethics Committee, to cover the Glasgow clinics (application made by Professor Mary Ann Lumsden).

In addition to the verbal explanation of the study, women received written information sheets about the survey and menstrual collection stages of the study, and they signed consent forms for the stages to which they agreed participation. **Appendices 3.10 - 3.12** show the three information sheets, for (i) cross sectional survey; (ii) prospective charting of next period; and (iii) menstrual collection. Consent forms for Edinburgh are given in **Appendices 3.13 - 3.15**. Information sheets for Glasgow were the same and consent forms very similar.

3.8 STATISTICAL METHODS

3.8.1 Overview of statistical methods used

A range of statistical methods have been employed, encompassing descriptive statistics, hypothesis testing and statistical modelling. All analyses have been undertaken using the Statistical Package for the Social Sciences (SPSS) software, version 11. Specialised statistical methods used will be detailed in the relevant chapters. Association in r×c tables was tested by chi-square (χ^2). For ordinal data association has been summarised and tested by means of the non-parametric Spearman's rank correlation *rho* (see below **3.8.3**), or for 2×c tables by means of chi-square test for trend. For 2×2 tables chi square or Fisher Exact test was used. Continuous data have been compared by means of t-test, or analysis of variance. Where skewness of the data requires it the data have been subjected to log transformation. Linear regression has also been undertaken, where there is a need to be able to predict one variable from another (see methods **6.2.3.i**). For binary outcome data, logistic regression modelling has been undertaken, with the regression coefficients presented as odds ratios (see **9.2.4**). Principal components analysis has been undertaken in order to reduce the number of variables and elicit the underlying components of variation in the data (see **5.2.3**). Confidence intervals (95%) are presented wherever informative. However, in some tables, where a number of percentages are presented for proportions of almost the same large n (about 900 say), a footnote indicates the approximate width of the confidence intervals for values in the table (or a subset of them). This is felt to provide a more readable table, with minimal loss of relevant information about the summary statistics.

3.8.2 Graphical methods

Graphical methods have been used extensively, and have been produced using either SPSS or Microsoft Office Excel software. One graph that needs to be defined is the box-plot, or box-and-whisker plot. This was originally devised as a simple succinct depiction of the entire distribution of the data (Tukey 1977). The whiskers denote the range, minimum to maximum, and the central box shows the location of the middle

50% of the data, delineated by the quartiles, as well as the location of the median, which is indicated by a solid bar across the central box. The graph has subsequently been elaborated to indicate also potential outliers and extreme values, and it is this version that has been used in the chapters that follow, as it is the version that is provided by the SPSS computer package. In the form used in this thesis the whiskers do not necessarily denote the range, but may do so, if the data are compact. At each end of the box the whiskers extend from the box to the closer of two points, either the maximum (or minimum), or a point that is a distance 1.5 times the box length away from the end of the box. Any data values that are further than this distance from the end of the box are defined as 'outliers' and represented as open circles, and any that are more than 3 times the box length away are defined as 'extreme values' and represented by stars. Despite the terms 'outlier' and 'extreme value', in certain types of data, for example highly skewed menstrual loss measurements, distributional outliers and extreme values are commonplace, and generally denote perfectly valid values.

3.8.3 Summarising association

Spearman rank order (non-parametric) correlation has been widely used to summarise the strength of association between pairs of variables. If continuous data have a skewed distribution, or if data are ordinal, then if correlation is to be calculated it must be non-parametric. However, the method can validly be applied to continuous data that are not skewed. Therefore if associations between a mix of variables are to be calculated it is felt to be preferable for the sake of consistency to use Spearman for all correlations, even if data for some pairs were suitable for calculation of (parametric) linear correlation. In such circumstances there is very little loss of power due to use of the non-parametric method (9% loss) (Daniel 1978).

Spearman differs from other nonparametric correlation methods in that, if both variables of the pair would have been suitable for application of the parametric linear correlation (Pearson), then the non-parametric Spearman correlation applied to those data would also yield a very similar numerical value to the linear correlation. For example, Spearman rho of 0.48 in place of a linear correlation of 0.5, and 0.69 in

place of linear correlations of 0.71 (Kirkwood & Sterne 2003). (For null and perfect correlations values of zero and ±1 would be obtained, as for linear correlation.)

The strength of Spearman lies in the fact that it can be applied to any ordinal or continuous data. As used here, in most situations with a large n (600 to 952), what appear on the face of it to be quite modest correlations (in the region of 0.1) may nevertheless be statistically significantly different from zero. It should be noted that the purpose of applying this analysis method in this thesis is to summarise the ordinal associations pertaining, for comparison between them as to relative strength, not to imply that a particular size of correlation has a particular import. In general only correlations above a specified absolute size will be reported, with confidence intervals where space permits.

3.8.4 Power calculation from grant application

The multi-faceted research design meant that different sample size judgements were required for the disparate parts, and the novel nature of the research being planned meant there had to be an element of guesswork in some of the decisions as to sample size. In the first instance a target figure was chosen for the menstrual collection study based on knowledge of the sizes of studies that had been published in the past, the informativeness of their findings, and prior experience of this type of research. The target for this 'Full' participation was then factored up to adjust for the number of explanatory variables being assessed in this study, arriving at a figure of 300.

Initial (recruitment) sample size would have to be large enough to ensure adequate numbers with 'Full' participation, despite the various degrees of non-compliance anticipated. Experience of this type of research suggested 40% compliance with collection, within the context of treatment studies (Cameron et al. 1990), but in the context of this observational study it was expected that recruitment would be more difficult. Judgements were then made as to the attrition there would be moving through the various levels of participation, so as to be able to work back to a required figure for initial recruitment to 'Minimal' level. That is, if the number completing menstrual collections was to be ±300, the required n for the first level, 'Minimal', was judged to be ±1100, with ±900 and ±800 respectively projected as completing

the next two levels, 'Basic' and 'Research 1'. Over the recruitment period, originally envisaged as 18 months of a two-year study, this would necessitate ±14 new referrals per week, 4 of whom proceed to menstrual collection. From clinical judgements of throughput of such patients it was believed that this rate could be achieved by involving the two centres, Glasgow and Edinburgh.

For the purposes of calculating power, the aims presented in 3.2 were where possible formulated as a number of research hypotheses. However, it should be noted that these proposed hypothesis tests were not the sole purpose of the study which was essentially descriptive and hypothesis generating. The hypotheses formulated were as follows:

Hypothesis 1. Menstrual charting (of sanitary products used, degree of soaking, and accidents, impact on daily life) provides a clinically-adequate assessment of menstrual loss in the majority of cases.

Hypothesis 2. Total fluid loss reflects subjective evaluation of menstrual loss better than blood volume.

Hypothesis 3. Patients rating periods 'very heavy' but with menstrual blood loss less than 80 mLs will have one or more of:

> heavy fluid loss; very variable periods; flooding and/or many accidents; excessive concern about health; blood loss exceeding 60mls.; or one or more of the factors in (4) below.

Hypothesis 4. Patients referred for menorrhagia who do not rate their periods as very heavy will have one or more of:

> severe pain; prolonged bleeding; low well-being/ energy (that they attribute to their periods); a recent change in their periods; perimenstrual fluctuations in physical/ emotional health; generally poor physical or emotional health; circumstances making moderately heavy periods problematic.

Assuming the recruitment profile outlined above, culminating in 300 with 'Full' participation, the achieved sample sizes with adequate data, for the main hypotheses outlined above, would then be: Hypothesis (1) 300 for relating charting to measured

loss; Hypothesis (2) 300 with loss measured by both total fluid and blood volumes; Hypothesis (3) ±200 with loss subjectively rated as 'very heavy', and measured; Hypothesis (4) ± 700 referred for menorrhagia. In addition a survey of clinic presentation would be possible for all 1100 patients.

Hypotheses 1 and 2 both involved modelling, and explicit power calculations were not made. Hypotheses 3 and 4 were not unitary hypotheses, but rather each implied a set of comparisons in terms of the variables listed. For these the subgroups being compared were expected to be approximately 100 v 100 for hypothesis set 3, and 330 v 370 for hypothesis set 4. An example power calculation was made, as follows. If a feature occurs with a prevalence of 20% in one subgroup, these sample sizes give 90% power (at 1% significance one-sided) of detecting an increased prevalence in the comparison subgroup, provided the increase is by at least 14 percentage points (to 34% or more) for hypothesis 4, or by at least 24 percentage points (to 44% or more) for hypothesis 3.

3.8.5 Coding, and construction of new variables

3.8.5.i Coding referral reason

The two main reasons extracted from the referral letter and recorded in the referral log were considered to be equally important, with no cognisance being taken of order recorded. They were subsequently coded, and in addition four new binary variables were created indicating, respectively, referral (or not) for:

- **excessive bleeding** – encompassing referral reasons such as menorrhagia, excessive periods, 'metromenorrhagia', periods going on too long, frequent periods, flooding, continuous bleeding, clots, dysfunctional uterine bleeding
- **period pain** - encompassing all the variants of pain around periods but excluding dyspareunia and pelvic pain.
- **cycle-related changes** – mood changes around periods or physical symptoms around periods (other than period pain).
- '**other**' reason -for example fibroids, endometriosis, irregular periods, non-specific 'menstrual complaint' or 'period problems'.

These reflect the main menstrual problem groupings, and each woman could have a positive value (indicating referred for this reason) for up to two of the four reason-groupings. In a number of cases two reasons were extracted from the GP referral letter but both were categorised into the same referral-reason-grouping. For example referral reasons of flooding and clots would lead to a positive value only for the 'excessive bleeding' referral reason grouping, whereas GP referral reasons of heavy periods and fibroids would convert to positive values for both the 'excessive bleeding' and 'other' referral reason groupings.

For a patient subsequently recruited, the referral codes (and the four binary referral variables derived from the codes) were entered into the database as part of her data record.

3.8.5.ii Patient's stated reason for clinic attendance

The *patient's* understanding of the reason for her clinic attendance, the first (free text) item on the Clinic Questionnaire (CQ), was converted into four indicators as for referral reason.

3.8.5.iii Classification of participants with 'putatively heavy periods'

We created a classification of '**putatively heavy periods**' which included any women who:

- were referred by their general practitioner for 'excessive bleeding' (see **3.8.5.i** above); or
- subjectively rated their menstrual loss as 'heavy' or 'very heavy' (on the Clinic Questionnaire CQ); or
- stated their reason for clinic attendance as excessive bleeding (also on CQ – see **3.8.5.ii** above).

This definition is the same as the menstrual inclusion criteria for the menstrual collection part of the study (given in **3.4.4.i**). Therefore only women with 'putatively heavy periods' were invited to take part in this stage of the study.

3.8.5.iv Age grouping

For presentation of data and use as a stratification variable, age was categorised into five 5-year age bands from 25 to 49 years. For some analyses, this categorisation was further collapsed to increase subgroup sizes, to three age bands or to just two. The rationale for choice of adjacent categories to be combined was to make subgroup sizes as even as possible. The number of age bands, and the age ranges for the bands are shown in **Table 3.2**.

Table 3.2 Categorisation of ages into bands for the various age category variables used.

Age Variable	Age Band				
	25 to 29 yrs	30 to 34 yrs	35 to 39 yrs	40 to 44 yrs	45 to 49 yrs
Age Group (5)	1st	2nd	3rd	4th	5th
Age Group (3)	1st		2nd	3rd	
Age Group (binary)	1st			2nd	

3.8.5.v Deprivation code

For the purpose of analysis 'adjacent' deprivation subgroups were combined as necessary to obtain fewer larger strata (1&2, 3&4, 5, and 6&7), using the same rationale as for age above. For the various forms of the variable used the number of deprivation bands, and the code ranges for the bands are shown in **Table 3.3**.

Table 3.3 Categorisation of deprivation codes into bands for the two deprivation category variables used.

Deprivation variable	Deprivation Codes			
	1 & 2	3 & 4	5	6 & 7
Deprivation group (4)	1st	2nd	3rd	4th
Deprivation group (3)	1st	2nd	3rd	
Deprivation group (binary)	1st		2nd	

3.8.5.vi Body mass index

Body mass index is a ratio of weight to height (squared) and provides an indication of obesity. For women a BMI over 24 is regarded as overweight, and over 30 as obese. The formula used to calculate body mass index (BMI) was:

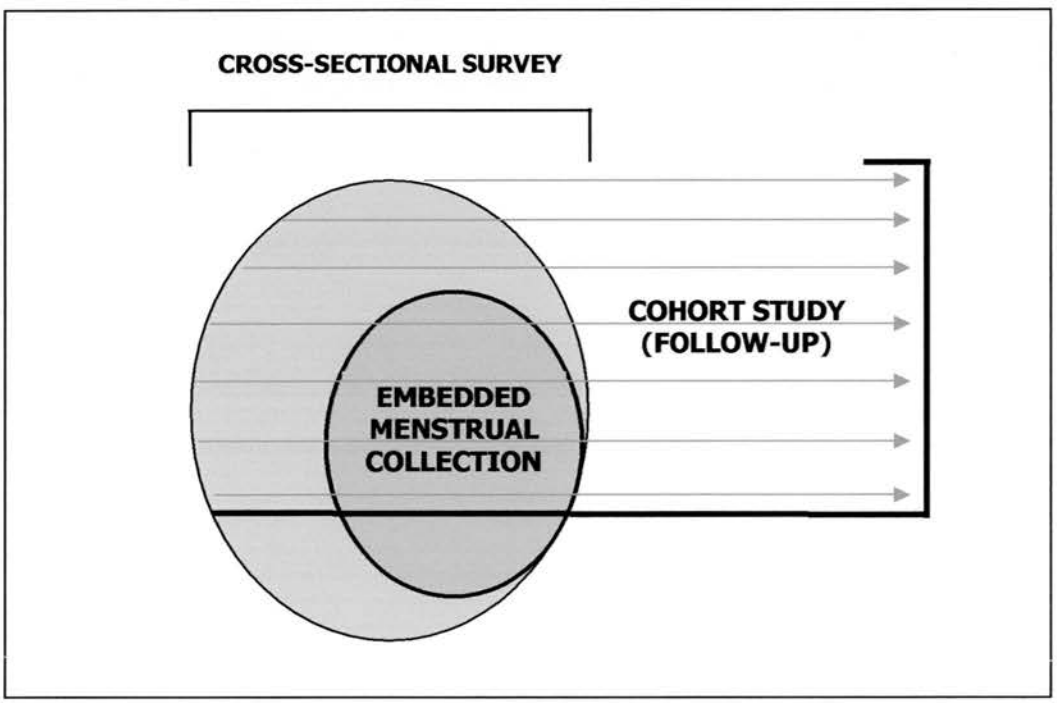
$BMI = weight(kg) / [height(m)]^2$

3.9 SUMMARY OF STUDY DESIGN AND RATIONALE

3.9.1 Summary of design

As has been noted, the study design was mixed, comprising a cross-sectional survey with an embedded detailed menstrual blood loss collection study, and also a follow-up (cohort) study of the (70%) earliest recruits to the survey group, so that the cohort includes both collectors and non-collectors. This is illustrated in **Figure 3.2** below.

Figure 3.2 Schematic diagram of study design



Taking into account the one-year extension to funding the research took three years, with recruitment continuing for 30 months. Numbers of women in the various subgroups, and completing the various levels of the questionnaire survey, are given in Chapter 4.

3.9.2 Rationale for aspects of design

3.9.2.i Cross-sectional survey

Referral log. This enabled recording of age, deprivation and referral reason of all eligible patients in the clinics targeted.

Participants are those referred for any menstrual problems, not just menorrhagia. This was to address discordance between referral reason and subjective report of periods.

*Identifying survey participants with '**putatively** heavy periods'.* Given the vagueness of 'menorrhagia complaint' it was necessary to identify those women where there was suggestive evidence of troublesome heavy periods on any one or more grounds.

Participants are confined to patients newly-referred to gynaecology clinics. If all patients attending the clinic had been surveyed it would have biased the study sample towards women with intractable period problems.

Use of multiple questionnaires. Reasons for this were: the many and varied causal attributions that have been advanced in the literature for women's menstrual complaints (see Chapter 1); the wish to assess the impact of menstrual problems on daily life; and the aim to develop a broad-based assessment of the contemporary menorrhagia complaint by cross-referencing the MEQ to other measures. There was also a need to be able to compare findings with research already published.

Allowing levels of participation. The aim was to maximise recruitment to the clinic survey by having an option of minimal participation (CQ only), but to obtain more detailed data wherever possible. A subsidiary aim was to be able to judge the representativeness of the sample participating fully.

Observational approach to iron status tests. This was to ensure usual clinical practice was unaffected, minimising bias in management and outcome data. It also avoided ethical and recruitment difficulties with imposing tests on all patients.

3.9.2.ii Menstrual collection study

Embedding the menstrual blood loss collection within a survey. Reasons were:

- This would involve a broad range of women with putatively heavy periods, who could then be asked to undertake menstrual blood loss collection.
- It would avoid dependence on the GP referral letter to identify women with heavy periods.
- We wanted to be able to compare the characteristics of those who agreed to collect with those who were eligible but declined.
- We would be able to make projections as to volume of loss from the detailed sub-study to the larger body of women participating in the survey.

Measuring total fluid We wished to explore the utility of total fluid measurement for the following reasons:

- It constitutes the containment challenge experienced by the woman.
- Total fluid volume measurement is far easier to undertake.

Menstrual chart The aim was to ascertain if the performance of charts could be improved, both in terms of quantification of menstrual loss, and also whether it provided a clinically useful broad assessment of the menstrual experience.

3.9.2.iii Follow-up study

Follow up of participants. The aim was to enhance insights provided by the cross-sectional survey, and by measurement of menstrual loss, with an examination of clinic outcome.

Follow up period set to 8 months. This was judged to be the best balance between maximising the number of participants who could be followed up within the time constraints of the study, and a time period within which the majority of referrals to gynaecology clinics would have been discharged or referred on elsewhere.

Chapter 4

STUDY SAMPLE:

RECRUITMENT, PARTICIPATION LEVELS, AND GENERAL DESCRIPTION

4.1 INTRODUCTION

The aim was to undertake a study of menorrhagia that collected data on a wide-range of variables, including both subjective assessment of heaviness of periods and objective measurement of menstrual blood loss. However, as has been explained in Chapter 3, for reasons of space data on personality, psychological well-being, alcohol consumption and smoking are not reported in this thesis.

Study results will be presented in Chapters 4 to 9. Given the separate but inter-linking facets of the study there will be discussion of results, sometimes fairly extensive, within each chapter. In addition, in a number of the results chapters extra more detailed/specialised explanation of methods specific to the chapter is provided. In an effort improve the flow of the thesis, and to constrain length, some of the specialised analyses, additional tables, and similar have been removed from the main text but are provided in the Appendices, in case there is a wish to refer to the material. (The Appendix numbering matches the associated chapter in each case).

Some of the study results have already been published, and copies of the papers are provided in the Appendix (Warner et al. 2001; Warner et al. 2004a; Warner et al. 2004b).

Material to be found in the following results chapters is:

- Description of current menstrual problem and clinic outcome - Chapter 5;
- Menstrual collection and charting results - Chapter 6;
- Measurement issues for quantification of menstrual loss - Chapter 7;
- Comparing Glasgow and Edinburgh participants, and addressing representativeness of participants, compared to the local general populations, and across the various levels of participation, in particular menstrual collection - Chapter 8; and
- Detailed examination of factors associated with subjective assessment of problem and measured menstrual loss - Chapter 9.

Finally, Chapter 10 will present an integrating discussion, and conclusions.

The present chapter begins by reporting recruitment success rate and participation, with a comparison of the study sample against those *not* recruited. Numbers of participants receiving iron status tests and undergoing case-note review are also reported. The background characteristics of the study sample are then summarised and there is some examination of the reliability of responses for questions replicated in more than one questionnaire.

4.2 METHODS FOR THIS CHAPTER

4.2.1 Referral log

As described in **3.3.7.i**, the Referral Log was used to record, for each woman attending any of the targeted clinics, her age and up to two referral reasons, extracted from the GP referral letter. Postcode was also recorded. Inclusion criteria were described in **3.3.6**.

4.2.2 Cross-sectional study questionnaires

Study questionnaires have been described in **3.3.2** (and copies for all but EPI and GHQ are provided in **Appendix 3**). The various questionnaires ascertained specific domains of data, except for the brief CQ, which was completed by all participants, and which sought to capture key data on a broad range of data domains. **Table 4.1** shows the data coverage of the six cross-sectional questionnaires used.

Table 4.1 Coverage of data derived from the study questionnaires

	Questionnaire *					
Data Domain	**CQ**	**MEQ**	**MBQ**	**SF-36**	**EPI**	**GHQ**
Menstrual complaint	✓✓	✓✓✓✓				
Demographics	✓✓✓					
Impact of complaint	✓✓	✓✓✓✓				
Menstrual history	✓	✓✓	✓✓✓✓			
Obstetric history	✓		✓✓			
Health (history)	✓		✓✓✓✓			
Contraception	✓		✓✓✓			
Health behaviour			✓✓✓✓			
Quality of life		✓✓		✓✓✓✓		
Alcohol/smoking	✓		✓✓			
Personality					✓✓✓	
Psychiatric wellbeing			✓			✓✓✓

* ***CQ*** *~ Clinic Questionnaire;* ***MEQ*** *~ Menstrual Evaluation Questionnaire;* ***MBQ*** *~ Menstrual Background Questionnaire;* ***EPI*** *~ Eysenck Personality Inventory;* ***SF36*** *~ Quality-of-Life questionnaire;* ***GHQ*** *~ General Health Questionnaire*

Extent of coverage: *✓=minimal, ✓✓ = moderate, ✓✓✓=fairly detailed, ✓✓✓✓=extensive*

Data reported in thesis: *✓…✓✓✓✓. =yes, ✓….✓✓✓✓. = no*

As has been indicated, data on smoking, alcohol consumption, personality and psychological well-being are not reported in this thesis. Preliminary analyses found considerable inter-correlations between SF-36, GHQ and EPI scores, and similar associations between some of their scores and other study variables, suggesting that as potential explanatory or elaborative variables the three measures offer overlapping conceptual coverage. SF-36 was chosen for reporting in this thesis because of its established reputation as a health outcome variable, and because the prototype Menorrhagia Evaluation Question (MEQ) has the aim, essentially, to assess menorrhagia complaint in terms of disease specific health impact and quality-of-life.

4.2.3 Participation level

As has been explained in **3.3.7ii**, it was envisaged that different women would participate to varying degrees. Level of participation was judged to be the cumulative extent of completion of study measures. **Table 4.2** shows the measures needing to be completed for the five participation levels in this study.

Table 4.2 Participation Levels for Study

Participation Level	Cross-sectional Measures completed *	Prospective Measures completed
Minimal	CQ	
Basic	CQ + MEQ	
Research 1	CQ + MEQ + (MBQ, EPI, SF-36, GHQ)	
Research 2	CQ + MEQ + (MBQ, EPI, SF-36, GHQ)	Menstrual Chart
Full	CQ + MEQ + (MBQ, EPI, SF-36, GHQ)	Menstrual Chart + Collection

** See footnote to **Table 4.1** above*

This shows that completion of the brief CQ only was labelled as 'Minimal' participation, whereas if all cross-sectional questionnaires were completed, participation was to level 'Research 1'. To be eligible for menstrual collection women must have been classified as having putatively heavy periods (*see **3.8.5.iii***), and must have completed questionnaires to level 'Research 1'. However in a few cases, where only one of the five extra 'Basic/Research 1' questionnaires was not

returned, then given the extent of the measures that had been completed the patient was deemed to be *nominally* 'Research 1'.

4.2.4 Iron status

As described in **3.3.3**, if an iron status test was requested by the managing clinician then test results were recorded for the study, but the tests were not imposed on all participants. The number of tests undertaken is reported here, and results in Chapter 5 (**5.3.2.ii**).

4.2.5 Menstrual chart and collection

Numbers completing the Menstrual Chart, and undertaking menstrual collection, are reported here, but the data from these are held over to Chapter 6.

4.2.6 Case-note review for 8-month follow-up

As has been explained in **3.5.2**, case note review was undertaken only for those women recruited before March 1998. The numbers of women reviewed will be reported here, descriptive findings in Chapter 5 and comparative analyses in Chapter 9.

4.2.7 Epidemiological/statistical issues for this chapter

4.2.7.i Statistical methods for this chapter

The main aim of this chapter is to describe the study population. Therefore, statistical testing will to a large extent will be eschewed in favour of graphical or tabular display of distributions to allow visual comparison, or summary statistics with confidence intervals. There will be some exploration of the associations of patient characteristics with the key socio-demographic variables. Statistical methods have been described in **3.8**.

4.2.7.ii Representativeness

The patients recruited are compared to those not recruited, in terms of age, deprivation code and referral reason.

4.2.7.iii Reliability

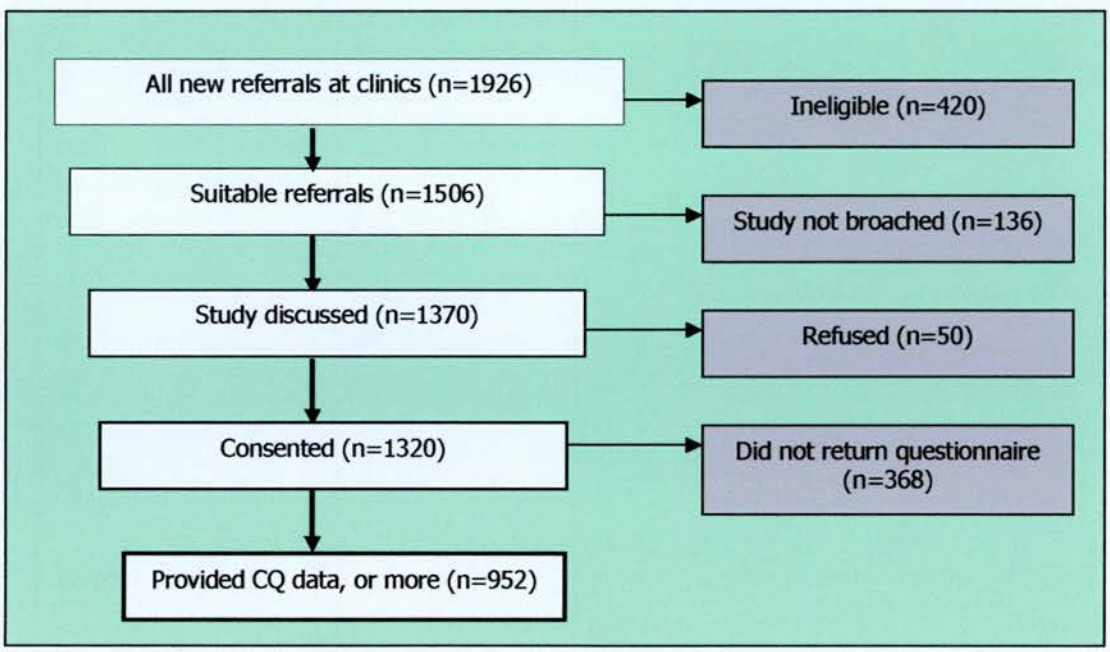
Where the same or similar information was obtained from the patient using more than one questionnaire item, the consistency of responses has been examined. Where the same information was obtained from more than one source (patient or referring doctor), concordance of some of these responses has been examined.

4.3 RESULTS

4.3.1 Recruitment and representativeness

Recruitment is summarised in **Figure 4.1.** To maximise recruitment within resource constraints, those clinics with greatest likelihood of suitable patients were targeted. Potential recruits (n=1926) were identified by scanning of new referral letters, and efforts were made to speak to all of them. Further investigation revealed that some potential recruits could not be included because of study exclusion criteria (n=420, 22%). The categories of 'unsuitability' were wrong age (38% of 420), other exclusion criteria (not new referral, language: 35%), non-participating consultant (22%), and other e.g. involved in another study (5%).

Figure 4.1 Recruitment



For a further proportion of potential recruits (n=136, 7%) there was in the event no opportunity for discussing the study with the eligible patient, the predominant reason being shortage of time in the clinic (93%). Of suitable patients approached, only 4% (n=50) refused, whereas 1320 consented. Of these, 368 (28%) took the questionnaires home but failed to complete and return them, despite a reminder

phone-call or letter. The 952 who ultimately participated to some degree in the study comprised 63% of the 1506 eligible patients.

Table 4.3 presents for the study group, and the 554 eligible referrals who did not participate, the data that were ascertainable for the entire target population - age, deprivation code and referral reasons. Participants were very similar to non-participants, in terms of age and deprivation code. The main reasons for referral were also very similar in the two groups.

Table 4.3 Description of study participants (and non-participants)

PATIENT CHARACTERISTIC	Study sample	Non-participants (eligible but not asked/ refused/ defaulted)
Age Group (n=952,554)	% distribution	% distribution
25-29y	10	10
30-34y	17	16
35-39y	23	23
40-44y	27	28
45-49y	23	23
Carstairs Deprivation Code (n=934, 544)	% distribution	% distribution
Least deprived: 1 & 2	19	16
3 & 4	35	33
5	20	25
Most deprived: 6 & 7	26	26
Referral by GP for: (n=952, 554)	independent % s*	independent % s*
Excessive bleeding	76	79
Pain	23	21
Cyclic changes	7	5
Other	35	36

* *up to two referral reasons per participant, so independent %s are reported, and add to more than 100%*

4.3.2 *Participation and data collected*

4.3.2.i Participation level

Level of participation was defined as the cumulative extent of completion of study measures (see **4.2.3** and **Table 4.2**). **Figure 4.2** shows for each participation level the numbers of women completing up to that level but no further (signified by n's), and also the *cumulative* numbers completing the various levels (N's).

Figure 4.2 Levels of participation and numbers completing to these levels

MEASURE		LEVEL OF PARTICIPATION *				
		Minimal	Basic	Research 1	Research 2	Full
	Current/Retrospective Measures					
CQ	Clinic Questionnaire					
MEQ	Menstrual Evaluation Q					
MBQ	Menstrual Background Q					
SF-36	SF-36 Quality of Life Q					
GHQ	General Health Q					
EPI	Eysenck Personality Q					
	Prospective Measure					
MC	Menstrual Chart					
	Menstrual Collection					
MBL	Measured Blood Loss					
TFV	Total Fluid Volume					
(n= no. completing this far only)		(n=99)	(n=139)	(n=402)	(n=85)	**Menstrual Loss Study** (n=226)
N= number 'completing' this level		N=952	N=853	N=714	N=312	N=226
		Survey of Menstrual Complaint Referrals (n=952)				

* ■ *or* ■ *= measures to be completed for this level of participation*

The N for a particular level therefore includes those stopping at that level (the corresponding n) *and* all those going on to higher levels of participation. It can be seen that 952 women participated to at least some extent in the cross-sectional survey of menstrual complaint referrals, and that 226 women (24% of 952) participated fully, completing all questionnaires and undertaking menstrual collection. Therefore, although total number participating fell somewhat below target (see target sample size in **3.8.4**), since only 952 participated whereas approximately 1100 had been estimated as required, the *proportion* participating fully was close to the predicted rate (24% v 25%).

Not all women were eligible for menstrual collection, as the inclusion criteria for this were to have putatively heavy periods (see **3.8.5.iii**) and to have completed the questionnaires up to Research Level 1 (see **3.4.4.i**). Altogether 865 (91%) women had putatively heavy periods, and of these 691 had also completed the necessary questionnaires. Therefore the women participating fully comprised 26% of those having putatively heavy periods, 33% of the subset also eligible for collection, in having completed questionnaires up to Research level 1.

4.3.2.ii Iron status tests

Overall 458 (48%) women were given haemoglobin tests and 288 (30%) ferritin tests. The percentage of study participants receiving haemoglobin tests and ferritin tests at the two centres, and overall, is shown in **Table 4.4**.

Table 4.4 Number of iron status tests undertaken, overall and by centre, and percentage of all participants tested

	Edinburgh	(n=530)	Glasgow	(n=422)	Overall	(n=952)
Test	n of tests	%	n	%	n	%
Haemoglobin	197	37%	261	62%	458	48%
Ferritin	67	13%	221	52%	288	30%

There was generally more testing of iron status at the Glasgow clinics than in Edinburgh. As explained in **3.3.3**, further disparities in testing rate between the two centres arose because there was also a period of some months when ferritin tests

were not possible at all in Edinburgh, as the test had been declared 'non-routine'. The test results are reported in **5.3.2.ii**, and the characteristics of participants receiving these tests are described in Chapter 8.

4.3.2.iii Follow-up case note review

Of all 952 women recruited to the study, 748 were recruited before the end of February 1998 (see **3.5.2**). Notes for 665 (89% of 748) women were retrieved and reviewed.

4.3.2.iv Data provided

All 952 participants completed the minimal CQ. The numbers of women providing data in addition to this, by completing further questionnaires, having iron status tests, or having their case notes reviewed, is summarised in **Table 4.5**.

Table 4.5 Data provided by participants, in addition to CQ questionnaire, by participation levels

		Data available for analysis, in addition to CQ * i.e. No. of questionnaires/forms provided by participants						
Measure (all did CQ)		Iron status (Hb)	Iron status (ferritin)	MEQ	MBQ	SF36	MC	Case note review
(No. of variables per 'measure')		(1)	(1)	(142)	(126)	(36)	(≤ 241)	(120)
Level	**n**							
Minimal	99	14	4	-	-	-	-	80
Basic	139	41	14	139	-	-	-	125
Res. 1	402	172	76	398	396	402	-	221
Res. 2	86	49	26	85	85	85	84	55
Full	226	182	168	224	226	224	211	184
Total	952	458	288	846	707	711	295	665

KEY: ***CQ*** *~ Clinic Questionnaire;* ***MEQ*** *~ Menstrual Evaluation Questionnaire;* ***MBQ*** *~ Menstrual Background Questionnaire;* ***SF36*** *~ Quality-of-Life questionnaire;* ***MC*** *~ Menstrual Chart*

* *Since data for the personality and psychological well-being measures (EPI and GHQ respectively) are not to be reported in this thesis, as explained above, the measures have been excluded from* ***Table 4.5*** *and will not be mentioned further.*

This shows that if the analysis involves CQ data only, the n will be 952, or slightly less where there is missing response for the specific item. However, if, say, the analysis includes data from SF-36, then the effective 'n' can be no higher than 711. This will be made clear when analyses are reported. For each measure or data extraction the typical number of variables per individual is also given, in the bottom row of the header section. While this shows that there were very many variables, in some questionnaires there is typically substantial data reduction, because the questionnaire is analysed as accumulated scale scores (SF-36) or because principal component analysis of items was undertaken (some of the MEQ data).

4.3.3 Description of study sample

4.3.3.i Demographic and socio-economic data

The age distribution for the study sample was presented in **Table 4.3** and the remaining demographic data are presented in **Table 4.6**. The modal age group for patients was 40 to 44 years old, modal family size was two children and modal employment status was 'working'. Modal values for the two domestic status variables were 'married or cohabiting' and still having two children living at home.

Table 4.7 presents socio-economic data for the study sample. The patients were living predominantly in areas with deprivation codes 3 to 6, and the majority left school at 16 years of age. Of those who worked, and provided job descriptions that could be classified, the majority were social classes II and III non-manual.

The interrelationships amongst the socio-demographic variables were summarised. Number of babies was correlated with age (rho=0.24, n=950, 95% CI 0.18 to 0.30) and negatively correlated with extent of working (rho=0.24, n=941, 95% CI 0.18 to 0.30), but no association was detected with deprivation. Living with husband or partner (as opposed to being single) was linearly associated with age, going from 59% in youngest age band to 81% in highest and even more strongly with parity, going from 52% in nulliparous women to 84% in para 3+. There was a *negative* linear association with deprivation, with 85% of the least deprived women living with a partner but the proportion dropping to 68% in the most deprived subgroup.

Table 4.6 Demographic characteristics

Variable	n	%
Age (n=952)		
25 – 29 years	90	10
30 – 34 years	164	17
35 – 39 years	224	23
40 – 44 years	257	27
45 – 49 years	217	23
Relationship (n=950)		
Married/cohabiting	703	74
Single - Separated/divorced	127	13
Single - Widowed	10	1
Single – never married	98	10
Single – subgroup unspecified	12	1
Working (n=942)		
No job	241	25
Part-time work	280	30
Full-time work	421	45
Parity (n=951)		
No births	211	22
1 baby	150	16
2 babies	351	37
3 babies	188	20
4 to 6 babies	51	5
Number of own children living at home (n=949)		
Not applicable – no births	211	22
None	68	7
1 child	220	23
2 children	313	33
3 children	112	12
4 or 5 children	25	3
Number of other children living at home (n=949)		
None	934	98
1 child	10	1
2-3 children	5	1

Table 4.7 Socio-economic characteristics

Variable	n	%
Deprivation score (n=952)		
Least deprived - 1	99	11
2	80	9
3	131	14
4	196	21
5	183	20
6	133	14
Most deprived - 7	112	12
Highest level of education reached (n=947)		
Left school at 16 years	554	59
Studied A-levels or Highers	124	13
Full-time student at College/ University	269	28
Social class (n=860)		
I	35	4
II	294	34
III (non-manual)	294	34
III (manual)	53	6
IV	122	14
V	62	7

4.3.3.ii Current health

COMPARATIVE HEALTH

Report of general health compared to most other women the same age was 'worse' 20%, 'about the same' 64%, and 'better' 16% (CQ item, n=944). Ratings of 'worse' health were more common in younger patients, in more deprived patients, those of higher parity and those not working. This will be explored further in the comparison of Edinburgh and Glasgow recruits (Chapter 8).

BODY MASS INDEX

Table 4.8 gives the participants' height and weight, as reported in the MBQ, and the body mass index (BMI) calculated from these two variables (see **3.8.5.vi**). It can be seen that half the participants had BMI exceeding 24, and so were 'overweight', while just under a quarter had BMI exceeding 29, and were therefore 'obese'.

Table 4.8 Height, weight and body mass index (BMI) of participants

Variable	n answering question	Median	Lower quartile	Upper quartile	Minimum	Maximum
Height (cm)	690	162	157	167	142	186
Weight (kg)	673	65.3	58	76	38	146
BMI (kg/m^2)	672	24.6	22	29	15	47

BMI increased with parity (rho=0.133, n=666, 95%CI 0.06 to 0.21), age (rho=0.104, n=666, 95%CI 0.03 to 0.18) and deprivation code (rho=0.094, n=660, 95%CI 0.02 to 0.17) and with self-assessed comparatively worse health (rho= 0.119, n=659, 95%CI 0.04 to 0.19).

LONG TERM ILLNESSES

Of the 702 women answering the question on the MBQ addressing long-term health problems, 41% did not affirm any of the conditions, whereas 36% affirmed just one, 14% two, 6% three, and 3% three to six conditions. **Table 4.9** gives the proportions reporting the long-term health problems specified, together with the difference in prevalence for these conditions between those rating their general health worse than others, and the remainder (i.e. those with self-reported general health the same or better than others). The most prevalent conditions were migraine, allergies, arthritis and asthma. The large category of 'other' health problems comprised predominantly gastro-intestinal conditions (4% of 580), central nervous system conditions (3%), musculoskeletal conditions (3%), uro-gynaecological conditions (2%), haematological/nutritional conditions (2%), endocrinological conditions (1%) and cardio-vascular conditions (1%). The six women reporting past cancer specified the site of their cancer as breast (3 cases), head/neck (2 cases) and skin (1 case).

Inspection of the table shows that there was, for high blood pressure, arthritis and 'other conditions', an absolute difference in prevalence between those rating their health 'worse than others' and the remainder rating their health same or better, that was substantial (over 16 percentage points). There was a smaller but statistically

significant difference (over 3 percentage points) for ulcer, migraine, asthma and heart disease.

For those women who were followed up (n=665), up to three chronic conditions were also ascertained from the case notes. The prevalences of the condition groups most frequently recorded were: central nervous system 11%, respiratory 7%, cardiovascular 6%, gastrointestinal 6%, endocrine 4%, gynaecological 3%, nutrition/blood 3%, musculoskeletal 3%, skin 2% and endometriosis 2%. Therefore the prevalences of chronic conditions recorded in the case notes are generally lower than self-report.

Table 4.9 Long-term health problems and association with comparative health

		Long term health problems?		
Self-reported Health problem	**n** answering question	**Yes %**	**Difference in % prevalence (95% CI) 'Worse' health – 'Same'/Better'**	
Migraine	692	21	8	(2, 16)
Allergies/eczema	692	18	3	(-4, 10)
Arthritis	694	12	18	(12, 24)
Asthma	696	12	8	(2, 13)
High blood pressure	696	8	17	(12, 22)
Ulcer (stomach or bowel)	696	6	9	(4, 13)
Thyroid	624	4	2	(-2, 6)
Diabetes	695	1	1	(-1, 3)
Cancer	686	1	1	(-6, 3)
Heart disease	690	1	4	(2, 5)
Other	580	18	32	(24, 40)

CURRENT MEDICATION

Overall 53% of women (367/690) reported on MBQ that they were taking regular 'drugs, pills or medicines' and 359 women specified the drug being taken and the condition for which it was being taken. In order of prevalence these were 18% central nervous system drugs, 15% endocrine, 11% nutritional/ haematological, 8% cardiovascular, 8% respiratory, 8% rheumatic drugs but for menorrhagia, 5% gastrointestinal, 5% musculoskeletal and 4% cardiovascular drugs but for menorrhagia. Where drugs were specified as being taken for menstrual reasons (n=108), these were subjected to a finer classification. In order of prevalence menstrual treatments being taken were 38% prostaglandin synthetase inhibitors, 25% progestogens, 23% antifibrinolytic agents, 10% oral contraceptive and 1% each clomiphene, danazol and HRT. **Appendix 4.1** considers data reliability for health problems and medications, by comparison with self-report and case-note data. There was fairly low concordance between the two data sources, with case-notes less likely to have cardio-vascular medications recorded.

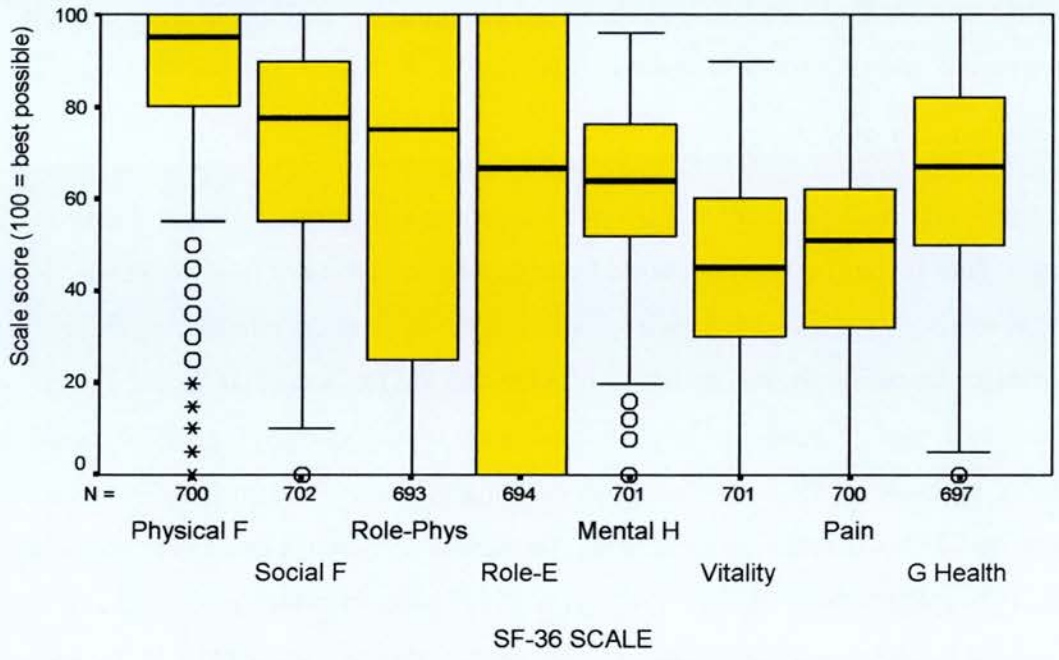
COMMON MINOR SYMPTOMS

MBQ (question 1) also presented a list of 24 common minor symptoms, and asked the participant if she had been bothered by any of them in the last two weeks. A yes/no response was offered for each symptom and the numbers completing these items ranged from 703 for headaches to 693 for craving for particular foods. The prevalence of 'yes' responses ranged from 88% for lack of energy, then 69% feeling sad, 67% headaches, 65% backache, 65% swelling of parts of the body, 55% trouble sleeping and 54% difficulty concentrating, through to 19% migraine, 14% persistent cough, 14% cold sweats and, least prevalent, 6% bladder infection problems. For each patient the total number of these symptoms reported as experienced in the last fortnight was counted up. The number of patients who answered either yes or no for every symptom was 630, and for these respondents the total number of symptoms reported ranged from 0 to 22 (median 9 and inter-quartile range 6 to 12).

4.3.3.iii Quality-of-life

Out of 703 participants completing the Health Transition item, 10% reported their health in general better than a year ago, 54% about the same, 32% somewhat worse, and 4% much worse. The distributions of eight scaled scores for the SF-36 are shown in **Figure 4.3**. The scaling is such that the possible range of scores is 0 to 100, and a higher score means better health status or functioning. It can be seen that participants have least favourable scores for Bodily Pain and Vitality, and over a quarter of participants have worst possible score (zero) for Role-Emotional. However, it is also the case that over a quarter have *best* possible score for Role-Emotional, that is, no limitation of role for emotional factors. In addition over a quarter have maximum (positive) score for Physical Functioning and Role-Physical.

Figure 4.3 Box-plots of distribution of SF-36 scaled scores for study participants.



The number of long term conditions affirmed (as reported in **Table 4.9**, section **4.3.3.ii**) was also correlated with SF-36 scale scores, negatively, such that long-term illnesses were reflected in poorer status/functioning scale scores (all $p<0.012$). The strongest correlations were with General Health, Physical Functioning, Role-Physical, Bodily Pain and Social Functioning (rho= –0.325, –0.310, –0.237 and –0.231 respectively, all $p<0.001$, n= 674 to 682).

SF-36 scale scores were markedly less favourable for the 122 participants with 'worse' self-reported comparative health (as described in **4.3.3.ii**), than for the 551 with 'same' or 'better' health (Mann-Whitney, $p<0.001$), and this effect was strongest for, in order, General Health, Physical Functioning, Vitality and Role-Physical.

4.3.3.iv Contraceptive and obstetric history

All participants completed the brief Clinic Questionnaire (CQ), which ascertained number of births (reported in **4.3.3.i**), years since last pregnancy ended, current contraception (broadly categorised), years since operation if female sterilisation, and, if ever used, years since stopping oral contraceptive pill. The MBQ ascertained current contraception in more detail, and explored menstrual, contraceptive and obstetric history further.

CURRENT METHOD OF CONTRACEPTION

The current method of contraception is presented in **Table 4.10**, both as ascertained by CQ and also as ascertained by MBQ (the relevant items being completed by 947 and 700 participants respectively). The wording on the CQ item was of necessity very succinct, allowing only 5 choices, as shown in the last column of Table **4.10**. The most common method in use was sterilisation (46%), then 'other' (20%), while a relatively high proportion was using no contraception (26%). The distribution of responses to this 5-option CQ item was very similar for the subset of 700 who also went on to complete MBQ (second to last column). For this subset the more detailed responses regarding current contraception that were obtained via MBQ can be used to further elucidate contraceptive use (first column of percentages in table). For example, those answering 'none' can be subdivided into 3% trying for pregnancy, 8% with no sexual relationship, and 15% with no explanation, and so perhaps risking unplanned pregnancy. Similarly, sterilisation breaks down to 20% male and 28% female, and 'other' is revealed as predominantly condom (18%).

Table 4.10 Current Method of Contraception

CONTRACEPTION	Ascertained from MBQ *Completing this item* n=700 %	Ascertained from MBQ *Completing this item* n=700 Subtotal %	Ascertained from CQ *Subset completing MBQ too* n=700 %	Ascertained from CQ *All CQ* n=947 %
None		26	25	26
No sexual relationship	8			
Wanting pregnancy	3			
No explanation	15			
IUD/ Coil	2	2	2	2
Sterilisation		48	48	46
Vasectomy of male	20			
Female sterilisation	28			
Hormonal	5	5	5	6
Other		20	20	20
Condom/sheath	18			
Rhythm, cap, other	2			

The succinct wording of the CQ contraception item ran the risk of misunderstandings. **Appendix 4.2** reports checks that could be made by cross-referencing to MBQ responses, where these were available. Where such data were available CQ responses were if necessary altered to concur with the more detailed responses of MBQ. If the errors found applied commensurately to the 252 women who completed only CQ, for whom MBQ checks were therefore not possible, it would mean that the proportions responding 'Sterilisation' and 'Other' on the CQ variable may be an underestimate (by approximately 8 and 2 individuals respectively), and the proportion responding 'None' may be overestimated (by about 10 individuals). This would make a difference of up to1 percentage point to the figures presented in the last column of **Table 4.10**.

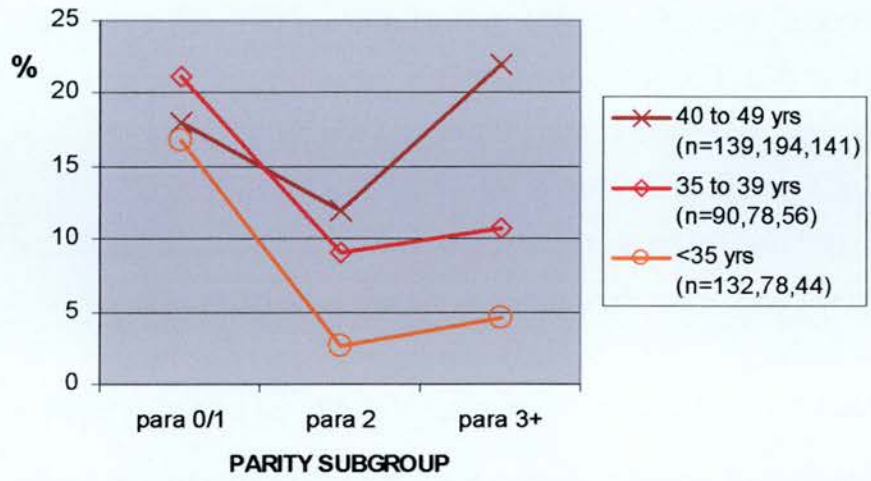
PAST ORAL CONTRACEPTIVE USE

Although relatively few women referred for menstrual problems were currently using hormonal contraception (n=58, 6% of 947), the vast majority had used it at some time (n=815, 86% of 952). This was calculated by accumulating as 'ever-pill-users' all respondents to items addressing current or past oral contraceptive use on CQ or MBQ. **Appendix 4.2** reports checks that could be made by cross-referencing to MBQ responses. Applying the proportions in **Appendix 4.2**, it would be estimated that of the 55 who did not answer the relevant item on CQ, and did not go on to complete MBQ, a further 21 (39%) are likely also to have been past pill users. If so, the overall estimate of 'ever-pill-users' is an underestimate, and it should be 88%.

Among those who had ever used oral contraception, 69% of women (out of n=610 who responded to this item) started the pill for contraception only, 29% for menstrual or 'other' reasons only, and 2% for a combination of contraception and menstrual/other reasons. The 'menstrual/other only' reasons were 11% period pain, 6% irregularity only; 4% heaviness; 2% premenstrual syndrome or 'other', and 6% some combination of these. Recalled effect of oral contraception on periods will be reported in **4.3.3.vi**.

The patterns of past oral contraceptive use were examined in relation to the main demographic variables. Never having used the oral contraceptive pill was unrelated to deprivation and weakly related to self-rated comparative health, with those with worse health being more likely never to have used the pill (19% compared to 14% overall, χ^2=6.3, 2df, n=944, p<0.042). **Figure 4.4** shows the proportions of women who had never used the pill by parity (x-axis) and age (separate lines). In general never having used the pill was less likely the younger the age group. In each age band the para 2 women were least likely to have never used the pill (that is, most likely *to have used* the pill). However, within age bands the subgroups most likely never to have used the pill differed by age band, being the least parous women (para 0/1) within the two younger age bands, but the most parous (para 3+) in the oldest age group.

Figure 4.4 Proportions who have *never* used the oral contraceptive pill, by age group and parity



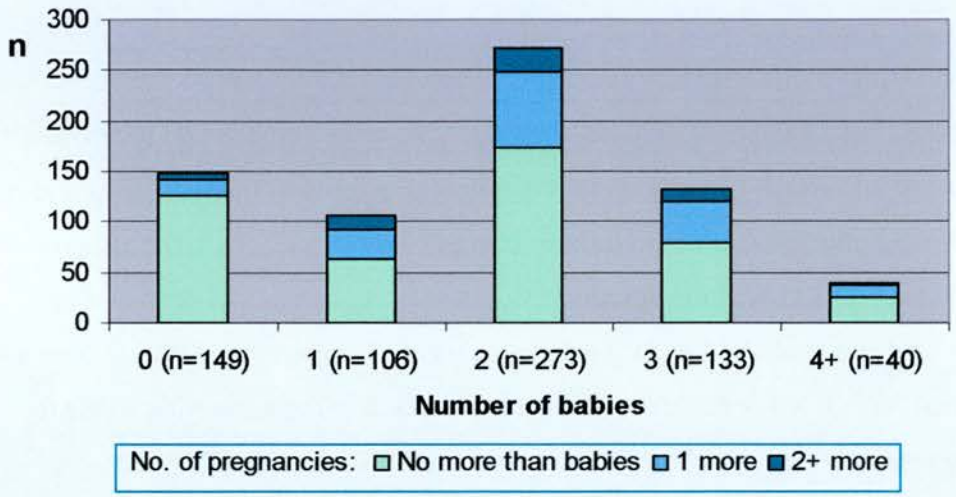
Overall 239 women gave affirmative responses to the MBQ item asking 'Have you been troubled by side-effects while on the pill?'. This comprises 38% of the 625 ever-users of oral contraception who completed MBQ. This is a substantial proportion, considering that it was not just experience of symptoms but *troubling* side-effects that was being ascertained. Furthermore, in an effort to avoid suggestion, there was no explanation as to what the term 'side-effects' meant. This may have prevented some who should have done so from answering. Those reporting troubling side-effects cited bloating/weight problems (29% of 239), headache/migraine (26%), mood changes (12%), nausea (9%), inter-menstrual bleeding (6%) and other assorted effects (18%).

Obstetric history

Whereas the parity information used so far has been derived from the CQ completed by all participants, it was ascertained by asking how many *babies* the respondent had had. On MBQ there was an explicit question as to the number of *pregnancies*. For each of the 701 women who completed both items the number of babies (CQ) was subtracted from the number of pregnancies recorded (MBQ). **Figure 4.5** shows this difference by parity. For 233 women (33%) there had been one to five more pregnancies than babies, and for 7 (1%) there had been one fewer, presumably

because of a twin birth. Of the149 recording no babies born, 22 (15%) had nevertheless experienced one or more pregnancies.

Figure 4.5 Distributions of numbers of babies born, showing within each parity column the relative number of pregnancies experienced (n=701 who completed both items).



If she had had any pregnancy at all the woman was also asked to record the outcome of the pregnancies, by providing counts for number of pregnancies resulting in each of miscarriage, abortion, still birth and live birth. Of the 573 who recorded having experienced one or more pregnancies, and who were therefore eligible to complete this item, 569 did so (99%). Overall only 16 (2.8% of 569) women who had been pregnant had experienced still births (nobody had experienced more than one), so still births were combined with miscarriages for presentation and analysis. Altogether 30.2% (172/569) of the women had experienced miscarriage or still birth, the majority of these had experienced only one (79% of 172), 13% two and 8% three to five. With regard to abortion, 17.2% (98/569) of the women had had abortions, the majority only one (88% of 98), 10% two, 2% three to four. It should be noted that it is possible that for this item there could have been mistakes in completion in the case of multiple pregnancies. This is considered further in **Appendix 4.3**. For presentation and analysis of the data for abortion and miscarriage/stillbirth, the variables have been re-coded into binary form, signifying for each respondent the occurrence or not of at least one pregnancy with such an outcome. By cross-referencing it was

established that 23 women had had multiple pregnancies (4% of 569). Consideration of the reliability of obstetric and contraceptive data was also undertaken by comparison of questionnaire self-report and case note data, as described in **Appendix 4.4**.

TIMINGS OF CONTRACEPTIVE AND REPRODUCTIVE MILESTONES

Table 4.11 presents the data summaries of ages for various reproductive events, and time-spans. Both the actual number responding to each item (n) and the *potential* number are presented. In some cases the potential n has had to be estimated and annotations to the table explain the way this has been done. The large amount of missing responses (17%) for duration of current contraception is explored in **Appendix 4.2**, while the fact of *more* than expected responses regarding time since last pregnancy ended is explored in **Appendix 4.3**. For the remaining items the missing response rate was 2 to 7%.

The median age at starting oral contraception was 19 years old. In study women the contraceptive method in use was fairly stable, with median time on current method being 8 years. However 25% of women had used their current method for 3 years or less. The median total time taking the oral contraceptive pill was 7 years and the median time since stopping the pill was 10 years. The median time since female sterilisation operation was also 10 years and the median time since last pregnancy ended was 11 years.

4.3.3.v Health history

On MBQ women reported on past treatments for depression and anxiety. **Table 4.12** reports the prevalence of past treatment for these conditions, 20% for anxiety and 28% for depression. Statistics for the duration of longest treatment received are also presented. Over half of the women treated for depression had courses of treatment exceeding 6 months, and over half of those treated for anxiety had courses of treatment exceeding 3 months.

Table 4.11 Age at starting oral contraception, duration of use of current method of contraception and of oral contraception, time since stopping oral contraception and since sterilisation

Age/Duration (years)	Potential n*	n	Median (years)	Inter-quartile range	Range
Age started oral contraception	625[1]	609	19	17 to 21	11 to 46
Duration of current contraception	707[2]	590	8	3 to 13	0 to 28
Total time on oral contraception	625[1]	582	7	3 to 11	0 to 26
How long ago stopped oral contraception	757[3]	707	10	5 to 16	0 to 28
How long ago sterilised	276[4]	259	10	6 to 15	0 to 24
How long since last pregnancy ended	740[5]	750	11	6 to 17	0 to 28

* ***Potential n*** *is the number of respondents to whom the item applies (for example items addressing oral contraception can only be answered by those who have used it). The way in which potential n has been calculated/estimated is described in the notes below:*

1 *Calculated as the number completing MBQ who answered any item on oral contraception on MBQ or on CQ*

2 *Number completing MBQ*

3 *Calculated as the number completing CQ who answered any item on oral contraception on MBQ or on CQ (but given that some did not go on to complete MBQ, and there was therefore less opportunity to identify them as past pill users, this may be an underestimate by 20 to 30 patients) minus the 58 still using oral contraception*

4 *Calculated as the 299 completing CQ who were taken to have indicated that they themselves had been sterilised (by answering that consideration of their future fertility was 'not applicable – already sterilised'), plus the 2 who did not answer thus but on MBQ indicated female sterilisation, minus the 25 who on MBQ revealed that it was partner (male) sterilisation to which they were referring. As 79 of the 299 did not go on to complete MBQ, and so this potential for correction was not possible, the calculated denominator may be a slight overestimate (by about 8 individuals).*

5 *On CQ responding one or more to 'how many babies have you had altogether', and which may be fewer than those who have pregnancies.*

Table 4.12 Past treatments for depression and anxiety

Illness	n responding (potential n=707)	Ever treated for this by GP (%)	Duration of longest treatment (months)			
			n	Median	Inter-quartile range	Range
Anxiety	689	20.3	129	3	1 to 6	<1 to 60
Depression	686	27.7	174	6	2 to12	<1 to 84

There was a tendency for the same women to have been treated for both these conditions. Of the 681 women completing both items, 35% reported past treatment by GP for one or both of these conditions: 7% for anxiety only, 15% for depression only and 13% for both. The combination of treatments experienced was associated with deprivation (three bands), going from 26% of least deprived having had some treatment to 46% of most deprived (χ^2=20.8, 6df, n=674, p=0.002), and with relative frequency of treatment for depression increasing more with deprivation. The combination was strongly associated with comparative health, going from 20% of those reporting 'better' health having had some treatment compared to 59% of 'worse' (χ^2=66, 6df, n=674, p<0.001). Again, the gradient was more marked for depression.

4.3.3.vi Menstrual History

AGE AT MENARCHE, RECENT CHANGE IN PERIODS AND PREVIOUS EXPERIENCE OF PERIOD PROBLEMS

These data were obtained via MBQ. Age at menarche had median 13 years (IQR 12 to 14, minimum 9, maximum 18, n=692 out of 707 who completed MBQ). Women were asked if they had noticed any change in their periods recently. Up to two changes could be noted (as free text), and for each the respondent was asked to record how long ago the change had happened. In total 513 women reported at least one recent change. In order of prevalence changes were period heavier (32%), duration changed (22%), more irregular (10%), clots (8%), colour of blood (6%) and more frequent, increased pain and inter-menstrual bleeding (all 3%). The time since noticing the change was recorded as 9 months (IQR 6 to 18, maximum 96, n=487). The order of prevalence was virtually unchanged if both changes recorded were taken into account, so for simplicity only the first has been reported.

Table 4.13 shows the percentages reporting past history of any of four menstrual problems, firstly 'at all' and then 'severe'. While pain and heaviness were the most common past problems (about 90%), heaviness was the most common past *severe* problem (75%).

Table 4.13 History of menstrual problems, at all, and the subsets experiencing these severely (n's are numbers responding to items)

Menstrual problem	Had problem at all %	n	Had problem severely %	n
Period pain	89	692	58	689
PMS	77	691	50	685
Irregularity	62	698	41	691
Heavy periods	90	699	75	691

The generally high percentages, even for severe problems, indicate that many women had experience of more than one severe problem. The percentages reporting all/ 3/ 2/ 1 or none of these problems as severe in the past were 14%, 18%, 19%, 13% and 8% respectively. So a third of women had in the past had three or more of the menstrual problems, severely. **Figure 4.6** shows, for women subdivided into those aged less than 40 years of age, and those aged 40 or over, the distributions of ages at which the problems started and became severe. For each problem there are two box-plots, one for the age that problem started, the second for the age that problem became severe, if it did.

Only period pain (not necessarily severe) had onset predominantly in the teenage years, but there were also many women with onset later in life. *Severe* pain had a broader range of ages for onset. In general the younger group of women would be expected to have constrained age at onset or age at problem becoming severe, since the age specified has to be less than the current age, which is between 25 and 40 years. However, the plots for the older group of women show a wide mid-range of ages of onset (lower to upper quartile, the extent of the box) indicating that despite their older age at recruitment to the study, their problems are not generally new problems. Many have had the problems since they were much younger. Broadly speaking, the relative timing of onset of the menstrual problems in the group was pain at the youngest age, then PMS, then irregularity, and lastly heaviness.

Figure 4.6 Box-plots of ages at which problems started and at which became severe, separately for two age bands of study patients

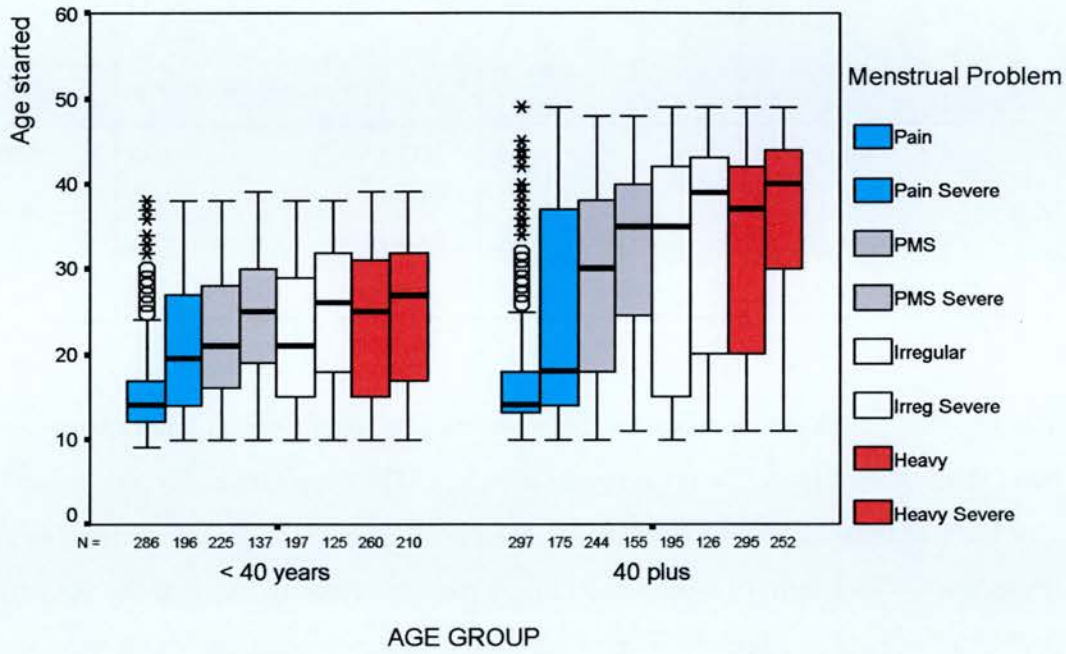
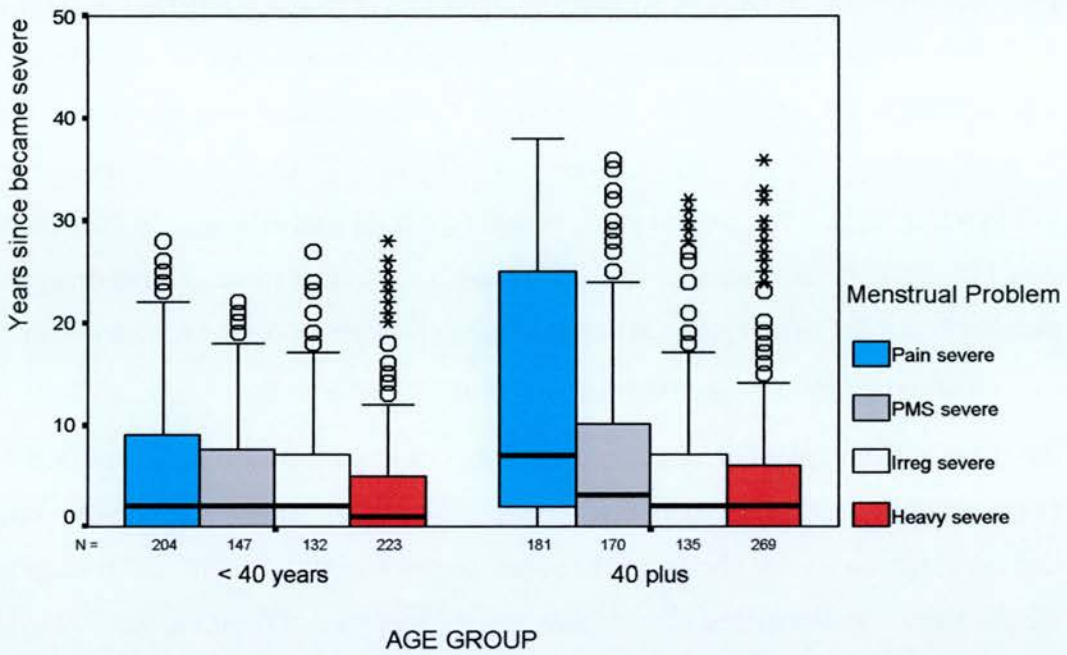


Figure 4.7 shows the distribution of times elapsed since onset of the most recent severe episode of menstrual problem, and this attendance at the clinic. Where women have reported more than one severe problem then it should be noted that it may be that only one of them is the referral reason, and/or the woman's self-stated reason. Assessed visually it appears that the shortest elapsed time is for women stating heaviness as (a) reason, with increasing elapsed times in order for women stating irregularity, PMS and pain.

Experience of past severe problems was strongly associated with self-reported poorer health. In terms of the number of the four period problems experienced as severe in the past, 65% of those with 'better' health had two or fewer past problems, whereas 58% of those with 'worse' health had three or all four. Considering the problems separately, the increase in reporting with worsening self-rated health was 11 percentage points for pain, 13 for heaviness, 21 for PMS and 27 for irregularity, the latter representing a two-fold increase. Irregularity was also associated with

deprivation, increasing 18 percentage points across three deprivation subgroups (1&2; 3&4; 5, 6 & 7). Reporting of problems with heaviness increased with parity (13 percentage points across three parity subgroups (0, 1, 2+)), whereas reporting of pain decreased with increasing parity, by 16 percentage points. There were no associations with age or work status.

Figure 4.7 Box-plots of years to clinic attendance, since severe problem started, separately for two age bands



PREVIOUS HEALTH-CARE CONSULTATIONS FOR PERIOD PROBLEMS

A third of women (301/952, 32%) stated on CQ that they had previously attended a hospital clinic for period problems, the majority of these (75%) for the 'same problem' as now. Of the 301 who had attended such a clinic before, 278 reported the time elapsed since that attendance, which had median 3.2 years (IQR 2 to 7 years, maximum 27 years). Of those who reported time elapsed (23 did not do so), 25 had attended such a clinic in the past year, this despite attendance in the past year being an exclusion criterion for this study (see Chapter 3). Only 19 had attended within the last 10 months (2% of the 952 participants).

From MBQ it was ascertained that the number of previous visits to GP for period problems was median 3 (IQR 1 to 6, minimum 0, maximum 70, n= 618 completing the item). Women were asked on MBQ if they had been seen before by a hospital doctor for period problems, and 41% responded that they had seen a hospital doctor (of 657 completing the item). The number of previous visits to a hospital doctor was median 2 (IQR 1 to 3, maximum 30, n=269 who had visited hospital doctor). The number of the four problems consulted for (pain, heaviness, PMS, irregularity) was predominantly one or two (70%), but 19% stated three of the problems and 11% all four (n=269). Overall the median age for first visit to hospital doctor was 31 years of age (IQR 24 to 39, n=244). Separately for the two age bands, less than 40 years and 40 years or more, the ages for first visit were 27 years (20 to 31, n=120) and 39 years (31 to 43, n=124). The proportion of women reporting past dilation and curettage was 31% (n=650 responding), with 4% having had three or more, the maximum number being 8. Current medications have already been reported (**4.3.3.ii**), with 16% of women (108/690) taking drugs for menstrual reasons.

Attendance before at a hospital clinic was associated with poorer self-rated health (increase of 9 percentage points from 'better' to 'poorer' health) but not with other demographic variables. The numbers of past appointments with GP and at hospital clinics were also associated with poorer health (Spearman rho =0.16, 95% CI 0.11 to 0.20 for GP and 0.10, 95%CI 0.09 to 0.14). The only other demographic variable associated with appointments was age which was inversely correlated with the number of GP appointments (Spearman rho= –0.13, 95%CI –0.17 to –0.09), which means that the younger women had had most GP consultations for periods.

EFFECT OF PAST ORAL CONTRACEPTIVE USE ON PERIODS

Respondents who had ever used oral contraception were asked in MBQ to comment on whether it had had an effect on their periods, in terms of pain, regularity, heaviness of loss and premenstrual symptoms. The judgements are presented in **Table 4.14**. For each aspect of periods there was a potential of 625 respondents (the number of ever-users of the pill completing MBQ), but one possible response was that the woman could not remember if there had been an effect. For all 4 aspects the number responding at all was fewer than 625 (n=585 to 548, i.e. 6 to 12% missing

responses), and the number able to make a judgement was even fewer (n=440 to 318, 70 to 50% of the potential 625 respondents). Period pain had the best response rate, but regularity had the best judgement rate, both within responders and overall. PMS had the lowest response rate and the lowest judgement rate both overall and within responders. The effects reported are presented as a percentage of those making judgements.

Table 4.14 Recalled effect of oral contraception on regularity and heaviness of periods, and on period pain and premenstrual symptoms (PMS)

	Regularity	Heaviness	Period Pain	PMS
n responding to item	573	567	585	548
n_r able to recall if effect	440	418	413	318
EFFECT OF PILL	% of n_r	% of n_r	% of n_r	% of n_r
Made better	72	68	55	38
Had no effect	26	31	43	50
Made worse	2	1	2	12

It is noteworthy that although the effect of oral contraception on regularity and heaviness, as observed by patients making judgements, was good (improved in 72% and 68% of cases), oral contraception had not been generally effective in terms of period pain (no effect or detrimental for 45% of cases). This is surprising given that the most common period-related reason for commencing the pill was *pain* (11% started for pain alone, and for a further 7% pain was a contributory reason, as reported in **4.3.3.iv**). If it is assumed that among those failing to respond, or unable to make judgements, there was very likely no discernible effect, then the proportions for which the pill had a noticeably beneficial effect on periods can be recalculated, using 625 as denominator. This gives 51% noticing the pill improved regularity, 45% for heaviness, 36% for period pain and 19% for PMS.

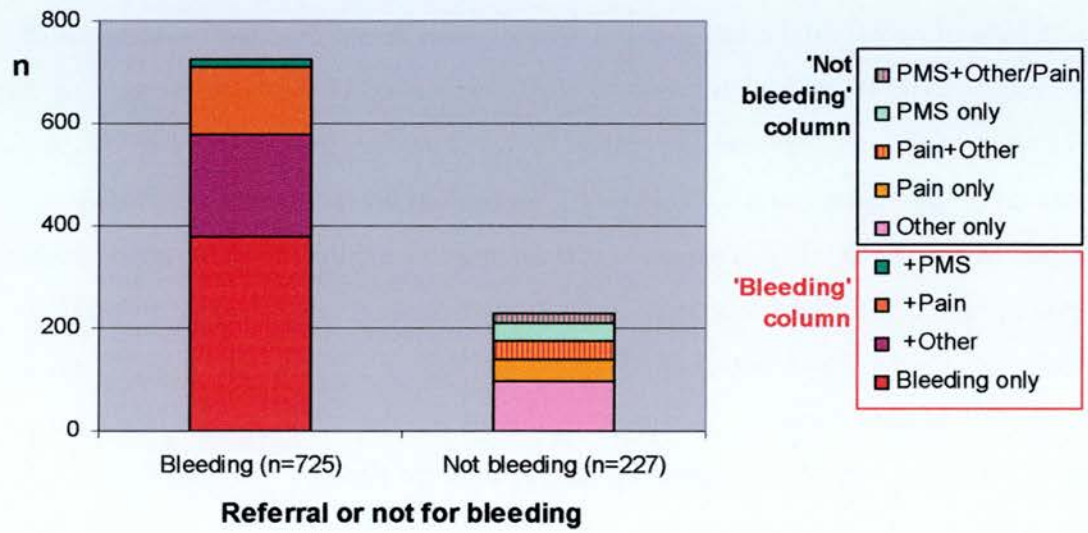
4.3.3.vii Referral

For 45% of the study sample only one referral reason was cited, and for the rest the first two were recorded. In a number of cases the two reasons cited were

subsequently coded into the same category (e.g. both bleeding or both 'other') so ultimately the percentage of women with only one *coding* for referral reason was 58%. Overall 725 of study participants (76% of 952) had menstrual bleeding problem mentioned as one of the first two referral reasons. With regard to other menstrual problems, 216 (23%) of all referral letters cited period pain as a reason, and 68 (7%) cited cycle-related symptoms or PMS. There were also 8 women (1%) with reasons for referral given as 'menstrual problem' (unspecified), 5 as the only reason, and one each in addition to pain, PMS and bleeding. Unspecified menstrual problem, and all remaining reasons not classified as bleeding, pain or cycle-related symptoms, were classified as 'other' reasons (e.g. intermenstrual bleeding/ discharge, fibroids, irregular periods, endometriosis, varied bleeding pattern, ovarian cysts). Altogether 342 women (36%) had 'other' as one or the only reason for referral.

There was considerable overlap between the referral reasons, and this is illustrated in **Figure 4.8**, with the participants divided into two subgroups (columns), those referred for bleeding and those not (n=725 & 227 respectively).

Figure 4.8 Numbers of women referred for bleeding (or not) and within each category the subsets referred (also) for the remaining referral reasons - pain, PMS and 'other'.

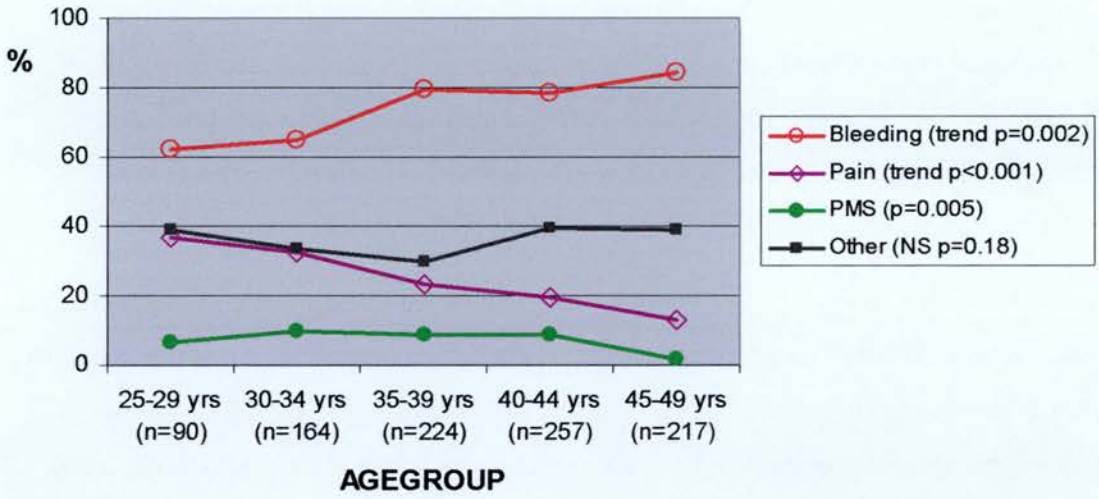


In the 'referral for bleeding' column over half the women were referred for bleeding *only* (52%), and the majority of the remainder were referred for bleeding with 'other' or with pain. By comparing thickness of slices between the two columns it can be

seen that women with pain or 'other' as referral reason were predominantly in the 'referred for bleeding column', that is, they were more likely than not also to have had bleeding as a referral reason. This is perhaps to be expected, given the prevalence of bleeding as a referral reason. It is all the more striking then that in the case of referral for PMS, it was more likely that bleeding would *not* be an adjunctive reason (53 without bleeding as reason v 15 with bleeding).

The association of four coded referral reasons with demographic variables were examined. **Figure 4.9** shows referral by age.

Figure 4.9 Prevalence by age of each referral reason separately (n=952)



There were significant trends for bleeding and, more strongly, pain. Bleeding referral increased with age, pain referral decreased (χ^2_{trend}1df =9.7 and 31.4 respectively, p<0.005 & p<0.001). PMS was also associated with age, but rather than a step-wise trend with age, 'PMS' referral was most common in women aged 30 to 44 years (χ^2=14.9, 4df, p<0.005). There were no detectable associations of referral for 'other' reason with age or the other demographic variables - parity, deprivation, extent of working, comparative health or single/cohabiting status.

For bleeding and pain referral reasons the only other associations detected were with parity, which were similar to those for age, shown in **Figure 4.9**. Referral for bleeding increased with parity, from 70% in nulliparous women to 80% in para 3+

(χ^2_{trend}=5.9, 1df, n=951, p=0.014). Referral for pain decreased with parity, from 34% in nulliparous women to 18% in para 3+ (χ^2_{trend}=13.4, 1df, n=951, p<0.001).

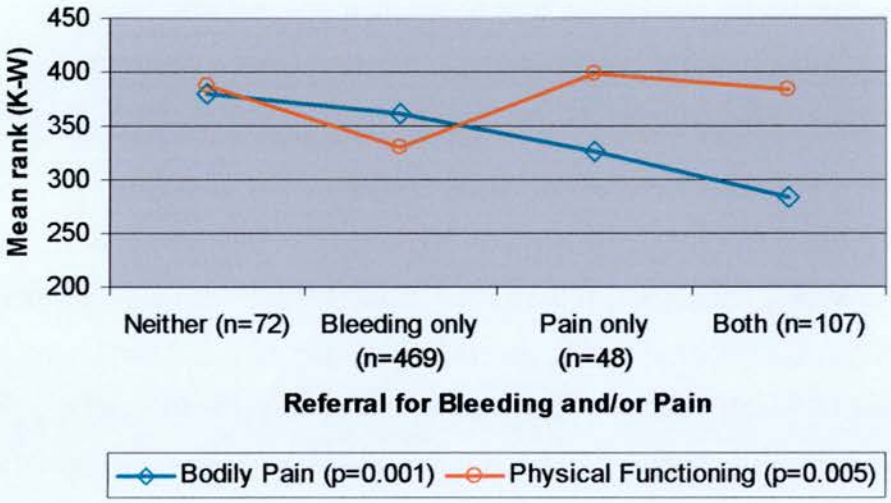
The association of referral reason with sterilisation was also examined and it was found that referral for bleeding was more common if sterilisation was the contraceptive method (as ascertained on CQ, meaning that either the woman herself or her male partner had been sterilised). Of those 'using' sterilisation 82% were referred for bleeding versus 71% among those not using sterilisation (χ^2=13.6, 1df, n=947, p<0.001). If association was examined in the subset who completed MBQ, enabling male and female sterilisations to be distinguished, then it appears that the effect was due mainly to female sterilisations, with 81% referred for bleeding among those not using sterilisation, 82% among women where it was the male partner who was sterilised, and 89% where it was the woman herself who was sterilised (n=365, 141 and 194 respectively). Referral for PMS seemed unrelated to sterilisation, but referral for pain and for 'other' reasons were slightly less common if there was sterilisation (respectively 21% v 25%, p=0.18 and 32% v 39%, p=0.25).

If referral for *two* reasons rather than one was examined there were no detectable associations with the demographic variables. The largest combination subgroup with clear definition was referral for both bleeding and pain (13.7% of 952). Given the trend for referral for bleeding to increase with age and parity, and the reverse trend for referral for pain, it is of interest to examine the demographic associations for the subgroup referred for bleeding and pain together. Referral for this combination decreased with age, from 17% to 9% (χ^2_{trend}=6.6, 1df, n=952, p=0.01), but no associations were detected with any other demographic variables, nor with sterilisation.

Referral reasons were also examined in relation to the SF36 quality-of-life scale scores. Those referred for cycle-related symptoms did not differ from those not referred in respect of any of the scales. With respect to referral for bleeding, pain and other reasons, the only scores for which differences were found, between those referred or not for one of these reasons, were for Bodily Pain and Physical Functioning. Physical Functioning was worse for those referred for bleeding

compared with those not referred, and similarly with respect to referral for pain. Effects were also seen for Bodily Pain by referral for pain or for 'other'. To ascertain the associations for the four combinations of referral reasons a new combined categorisation was computed (referral for neither, bleeding only, pain only and both reasons) and the scale scores were compared across these four subgroups. **Figure 4.10** shows the subgroup mean ranks calculated by the Kruskal-Wallis test (K-W) for these two scales.

Figure 4.10 Mean rank summaries of Kruskal-Wallis (K-W) tests comparing SF-36 Bodily Pain and Physical Functioning scores across the four subgroups determined by referral or not for bleeding and/or pain (lower score = worse functioning/status).



Bodily Pain scores were ranked lower, indicating worse pain, if there was referral at all for these reasons, even more so if it was for pain, and worst of all if there was referral for both pain and bleeding (K-W χ^2=16.0, 3df, n=696, p=0.001). However, Physical Functioning scores were ranked lower, indicating worse functioning, if there was referral for bleeding *alone* (K-W χ^2=13.0, 3df, n=696, p=0.006). This suggests Physical Functioning as a 'selecting in' factor for referral for bleeding, most notably in the subset who do not have pain.

4.4 DISCUSSION

4.4.1 Study design, recruitment and completion of measures

This research study, of measured menstrual loss in women with menstrual complaint, was designed to accommodate a low rate of agreement to menstrual collection. In the event the rate of agreement among women *eligible* for collection (in terms of having putatively heavy periods) was 26%. This rate is very close to what was anticipated based on the approximately 40% that had been achieved in the past in the context of clinical trials (Cameron et al. 1990). Patients invited to participate in treatment trials for heavy bleeding are probably more highly selected for severity of bleeding symptoms, than our unselected gynaecology clinic referrals with putatively heavy periods. Furthermore, the prospect of perhaps obtaining a new and effective treatment for their heavy bleeding, if consenting to menstrual loss measurement, would probably result in more highly motivated participants.

Many and varied theories have been advanced, as to aetiology of subjective menorrhagia complaint, especially of complaint that is not confirmed by menstrual blood loss measurement. Variables that have been implicated include demographic factors, personality, psychological health, general health, domestic and employment status, quality-of-life, health behaviours and obstetric, contraceptive and health history. This means that a wide range of data are required to allow elaboration of the contributions that the various factors make to the explanation of the association between subjective complaint of menorrhagia and measured menstrual loss. The present study has been the first to undertake this. However, questionnaire surveys can deter those with poor literacy who might find difficult, or impossible, the amount of reading involved in completion of all the questionnaires. This in turn runs the risk of a decrease in the proportion of women participating in the survey, or an increase in defaulting with respect to completion of questionnaires. Our study had a very high rate of agreement to participation (96%) but also a high default rate, with 28% of those recruited failing to return any questionnaires at all.

There was therefore concern that the design should maximise participation across the range of women referred for menstrual complaint. In order to achieve these aims it

was decided that the design should allow minimal participation, providing the basic demographic and menstrual complaint data. An extent of defaulting was anticipated, not least because of the relatively poor literacy skills of a substantial proportion of our population, so the aim of the very brief CQ was to ensure that at least that questionnaire could be completed at the clinic, prior to leaving. The nurses did try hard to ensure this was done. In reality though, a crowded and busy gynaecology outpatient clinic is a very difficult environment in which to undertake survey research of this type. No room was available for study use, so there was scant privacy to talk with prospective recruits about the study, and even if there had been there would probably have been anxiety on the patient's part that she may miss her earliest possible slot with a doctor. The patient may at any unpredictable point be called for her consultation with the doctor, interrupting any ongoing discussion or questionnaire completion. Many of the patients were stressed by the nature of the examinations they anticipated, by the need to take time out from work or family commitments to attend the clinic (for a problem that is felt by many in our society to be 'unmentionable'), and often by time pressures and transport or parking concerns. In the circumstances recruitment and completion rates achieved by the nurses were impressive.

The nurses would invite women to participate on the basis that minimal participation (CQ) was better than none, but that the more questionnaires that could be completed the better for the research study. The success of this strategy is shown by the numbers completing CQ compared to the number completing all questionnaires, 952 versus 714. It can be estimated that a further 25% of recruits would have defaulted, effectively, if participation had involved completion of *all* questionnaires. Furthermore, the brevity of the questionnaire used, together with research nurse support, ensured broad participation. The participants to the cross sectional survey were very similar to potential recruits who did not participate, in terms of age, deprivation code and referral reason.

Despite the number of questionnaires requiring to be completed, 75% of participants completed all the questionnaires required up to Research level 1, providing a wealth of data about themselves and their menstrual complaint. As intended these data have

enabled a very thorough evaluation of the characteristics of those agreeing to menstrual collection, compared to all referrals with menstrual complaint, and this is reported in Chapter 8.

4.4.2 Study sample

4.4.2.i Referral reasons

Referral reasons were extracted from general practitioner letters, ensuring naturalistic data. A disadvantage of this aspect of the study is that these data extractions and their coding into categories are with respect to free-text communications and hence subject to higher levels of unreliability than pre-specified responses. However, to have contacted each GP about the basis for referral of his/her patient would have escalated the workload, resources needed and logistic complications of the study beyond feasibility. The recording of two reasons when given, and the general brevity of the letters, minimised the need for subjective judgement, but these data should be interpreted with caution.

The study inclusion criteria were referral for any of the period problems heavy bleeding, pain, premenstrual symptoms or irregularity, or non-specific referral for 'menstrual problem'. The very high proportion of referrals where the GP gave bleeding as a reason for referral (76%) is therefore striking. It should be remembered though that the study focus was menorrhagia, and so gynaecology clinics targeted for attention by the part-time research nurses were those where more menorrhagia (than say cycle-related) referrals were to be found.

More than one referral reason was common, with 42% of women having two reasons coded to different categories (out of the four, bleeding, pain, cycle-related symptoms, other). The most common combinations were bleeding and 'other' (for example irregularity, or fibroids), bleeding and pain (14%), pain and other. Bleeding as reason increased with age while pain as reason decreased. A similar pattern was observed within parity subgroups. PMS as reason was most common in the middle age range, while 'other' reason was unrelated to age. Referral for bleeding was also more common if the woman had been sterilised. Referral for bleeding and pain combined

declined with age. These associations could with benefit be explored in terms of the more detailed nature of the complaints that are age-related, parity-related, or related to sterilisation.

4.4.2.ii Background data, health and quality-of-life

The majority of study participants were aged 35 to 49 years of age (83%) and were parous (78%), with 25% having had 3 or more babies. With regard to socio-economic status, years of education was ascertained and despite the fact that the detail required for rigorous determination of social class can not be gleaned by brief questionnaire, especially not for women, an attempt was made to classify social class from the woman's very brief description of her current or most recent employment. Deprivation codes derived from post-code of area of residence, and based on 1991 census data, were also utilised as a proxy for individual socio-economic status (Carstairs & Morris 1990). This was particularly valuable for comparison of those who were and were not recruited, among all eligible referrals, because social class or years of education could not be ascertained for those who did not complete CQ. As it turned out, deprivation proved to be the most useful socio-economic explanatory variable for all the study analyses, as reported in this and subsequent chapters.

Women in the study were well-dispersed across the range of deprivation codes. In Chapter 8 the deprivation distribution for study women will be compared to local populations, and between centres. The majority of women were working (75%), which may make menstrual symptoms less tolerable. While self-rating of general health as being 'about the same' as others the same age was common (64%), this was somewhat contradicted by what on the face of it seems a high rate of overweight/obesity (50%), chronic illnesses (59%) and experience of minor symptoms (half the women experienced 9 or more of the symptoms in the past two weeks). The proportions who had received treatment for depression and/or anxiety were 28% and 20% respectively, with 13% having been treated for both conditions. In terms of SF-36 quality-of-life scores, 36% rated their health as worse or much worse than a year ago. For the eight scaled scores, poorest quality of life (in terms of these scores being standardised on a 0-100 scale) was reported for Bodily Pain and

Vitality (median scores of about 50 or lower). In Chapter 8 we report comparisons with population data for SF-36, and between centres. Referral for bleeding was related to poorer scores on the Physical Functioning scale, albeit the scores were not necessarily low in an absolute sense. Referral for pain was associated with poorer scores for Bodily Pain and Physical Functioning. Therefore it would appear that SF-36 scores may reflect impact of menstrual problem on quality-of life, but that the heavy bleeding and pain are indistinguishable in their impact on physical functioning (Jenkinson et al. 1993). This will be examined further in Chapter 9.

4.4.2.iii Contraceptive history

In this group contraceptive method was fairly stable, with half the women having 'used' their current method (or no contraception) for 8 years or more. Nearly half the women were not actively using contraception because they or their partner had been sterilised, and a further quarter because they were not in a sexual relationship, were wishing to get pregnant, or with no explanation. Only 6% were using hormonal contraception of some sort, but the vast majority had used oral contraception in the past (86%). More than half the women had used the pill for 7 or more years and had stopped using the pill 10 or more years ago. It would be to interest to examine both these time-spans with regard to aetiology of complaint. Do women with recent prolonged use of the pill develop an unrealistic idea of 'normal' periods? Does prolonged uninterrupted menstruation lead to an 'ageing' effect on the endometrial/physiological process of menstruation, with problematic periods the consequence?

Among past pill users, 31% stated that they first started the pill for menstrual rather than contraceptive reasons, and the majority of past pill users felt the pill to have had a beneficial effect on period problems other than PMS. However, a high proportion of past pill users affirmed having had 'side-effects' while using oral contraception (38%). Furthermore, many study women would be precluded from taking it, because of obesity, smoking, or health history. Therefore many women referred to gynaecology clinics for period problems may be unsuitable for or unenthusiastic about the use of the pill to ameliorate menstrual symptoms.

4.4.2.iv Menstrual history

Although study patients were 'new' referrals for period problems there was evidence in the menstrual history data of considerable and diverse past menstrual morbidity, with 92% having had one or more of the four period problems (heaviness, pain, premenstrual symptoms (PMS) or irregularity) *severely* in past. Considering the problems separately, 75% of women had had *severe* problem with heavy periods before, 58% with pain, 50% with PMS and 40% with severe irregularity. Indeed, 32% had had *three or more* of these severe problems in the past. Another striking thing about the menstrual history data is the long duration of problems for many of these women, particularly so for pain. Ages of onset for the four problems showed a wide-spread but nevertheless consistent pattern, whether considering 'any problem', or the subset with *severe* problem. Pain had earliest onset, then premenstrual symptoms, then irregularity and slightly later heaviness. Therefore many women had long experience, often of more than one severe menstrual problem, with 'heavy periods' typically being the last to develop. This may partly explain the shorter time, compared to the other period problems, from onset of 'severely' problematic heavy periods, to referral to gynaecology clinic. However, it should be remembered that in this study group the strongest associations of past severe period problems with poor self-rated comparative health were for PMS and irregularity. So health impact and indication for referral may reflect differing rationales.

The history of severe period problems meant that a third of all study participants had attended gynaecology clinic before. Despite the picture of serial menstrual morbidity presented above (with respect to the four 'partitioned' period problems listed on MBQ), among those whose current clinic attendance was not their first, 75% had previously attended for 'the same problem as now'. This raises questions about the extent to which women conceptualise/recall their menstrual problems in the neatly partitioned way of gynaecology textbooks, GP referral letters, the majority of menstrual research, and the MBQ questionnaire.

4.5 CHAPTER SUMMARY

4.5.1 Recruitment and participation

- The 1320 women who consented to participate comprised 88% of the 1506 referrals logged who satisfied the inclusion criteria, but 28% of them did not complete and return the questionnaires. The remaining 952 women who participated comprised 63% of the eligible referrals.
- Those recruited to the first level were very similar to those not recruited, in terms of age, deprivation and referral reason.
- The study was designed to allow participation to varying levels, and 226 (24%) participated fully, by undertaking menstrual collection. Overall 48% of participants were given haemoglobin tests and 30% ferritin tests.
- With regard to case-note review, 665 women (70%) were followed up, comprising 89% of those recruited early enough to be eligible for follow-up.

4.5.2 Description of sample

- Up to two referral reasons were coded for each participant. Considering coded reasons separately, 76% of participants were referred for bleeding problem, 23% for pain, 7% for cycle-related symptoms and 36% for 'other' problems/conditions (with 42% having reasons mentioned which coded into two of these categories).
- Referral for bleeding increased with age and parity, and was greater if the contraceptive method was female sterilisation. Referral for bleeding and pain combined decreased with age.
- Participants tended towards the older end of the 25 to 49 age range, and the more deprived end of the deprivation scale, with modal age band was 40 to 44 years of age (27%), modal number of births was 2 (37%), and the modal deprivation codes were 4 and 5 (21% and 20% respectively).
- The most common 'methods' of contraception were sterilisation (46%) or none (26%), and while only 6% of participants were currently using hormonal contraception the vast majority had used oral contraception at some time (86%).
- Half the women were overweight or obese (BMI >24 kg/m^2). BMI increased with age, parity, deprivation and with worse self-rated health.
- Only 20% judged their health to be 'worse than other women the same age' but there was a fairly high level of chronic health problems, experience of minor symptoms,

overweight, past treatment for anxiety/depression and generally poor health status/ functioning on the SF-36 scales:

- In total 59% reported one or more long-term health problems (such as migraine, allergies, arthritis, asthma) and 53% were taking regular medication and 75% reported six or more minor symptoms (such as lack of energy, feeling sad, backache and bodily swelling).
- Past treatment by GP for depression was reported by 28% of women, and past treatment for anxiety by 20%, with 13% of women having been treated for both conditions.
- On the SF-36 quality-of-life scale, 54% of the sample judged their health much the same as a year ago, 36% as worse. Judged from the scale scores, the study sample recorded worst health status/functioning on the Vitality and Pain scales.

- Menstrual History
  - A third of women (32%) had previously attended hospital clinic for period problems, the majority (75%) for the same problem as this visit.
  - The majority of women completing MBQ had in the past had a severe problem with PMS (50%), period pain (58%), heavy periods (75%) and/or with irregularity (41%).
  - Recent changes noted in periods were heavier periods (32%), changed duration of period (22%), more irregular (10%), clots (8%) and colour of the blood (6%).

Chapter 5

STUDY SAMPLE:

DESCRIPTION OF MENSTRUAL PROBLEM AND CLINIC OUTCOME

5.1 INTRODUCTION

As has been explained in **1.4.2**, the four most common period problems (excessive periods, period pain, PMS and irregular bleeding) are on the whole similar to each other, in that:

- the characteristic symptoms are signs of potential clinical importance;
- the 'severity' of symptoms may warrant management in the absence of pathology; and
- there is often associated worry in the patient.

Each facet may impact on clinician behaviour (referral/ investigation/ therapeutic strategy) and on patient help-seeking behaviour. With regard to 'severity' of symptoms, the question is how this is judged, objectively in terms of pain intensity or measured volume of menstrual loss, or holistically and contextually, in terms of overall menstrual experience and impact of symptoms of daily-life and broader health. Clinicians and patients may be conceptualising 'severity' differently.

This bipartite (clinician/patient) and multifaceted (sign/severity/worry) model means that even where symptoms are not of themselves intolerable, referral to the gynaecology clinic may be necessary solely for exclusion of serious disease, for *clinical* reassurance on this score. For some women then, once pathology is excluded for her GP, nothing more needs to be done for her. In contrast, for many other referrals to gynaecology clinic, the symptoms, unexplained or not, are intolerable to the patient, and seriously diminish quality of life. Therefore even if serious pathology is excluded, such a woman will be hoping for some therapeutic intervention to relieve her suffering. This has been shown in **Table 1.1**.

It also means that a general practitioner's decision to refer may not be based primarily on severity of symptoms or concern about symptom-signs, but more because the patient is very anxious, and investigation and reassurance are judged to be potentially helpful to her. Therefore, anxiety is more likely to be apparent in the subgroup of patients referred with less severe symptoms, since they are more likely to have been 'selected' for referral on the basis of their anxiety. They are similarly more likely to be patients with new or recently exacerbated symptoms.

Therefore the themes for the menstrual data collection have been mainly 'severity' of symptoms (both objectively and holistically/subjectively), associated worry, and to a lesser extent the potential clinical meaning of symptoms (as may be reflected in referral by general practitioner and investigation by the gynaecologist.).

This chapter begins by reporting women's self-stated reasons for clinic attendance and a summary of data obtained on current menstrual symptoms, and of women's reports of how much of a problem they find various aspects of their periods. This is followed by a thematic analysis of responses regarding dealing with periods and feelings about this. Finally, there is a brief description of clinic outcome as ascertained from the case-note review follow-up i.e. the main findings for diagnosis, management (including results of iron status tests where undertaken) and outcome.

The results for the menstrual collection are held over until Chapter 6, with measurement issues being considered in more detail in Chapter 7. Chapter 8 examines the interplay of socio-demographic factors in the study groups, while in Chapter 9 integrative analyses and modelling will be presented to draw together the data reported in the preceding chapters.

5.2 METHODS FOR THIS CHAPTER

5.2.1 Patient's self-stated reason for clinic referral/attendance

In previous research some discordance had been found between reasons given for referral in the GP's letter to the gynaecology clinic, and the woman's reports of menstrual problem (Bancroft et al. 1993). Therefore in this study participants were also asked (on CQ) *their* (perceived) reason for clinic attendance: 'What problem, mainly, has brought you to this clinic?'. The free text responses were classified as for GP referral reasons (that is, as excessive bleeding, period pain, cycle-related changes or 'other': see Methods **3.8.5**). Also as for referral reasons, a maximum of two reasons were coded, the first two mentioned if more than two reasons were given. In **Chapter 4** the categorisation of GP referral reasons was reported (**4.3.3.vii**).

5.2.2 'Aspects of periods' and 'causes of clinic attendance'

5.2.2.i 'Aspects of periods' as problems

On CQ question 5 the woman was presented with 16 aspects of periods and asked to respond to each so as to indicate if this aspect occurred in her case, and if so, how much of a problem it was – not a problem or slight, marked or severe problem. The items were chosen to describe the range of aspects of menstrual experience, or attributions of impact of periods, rather than to partition pre-emptively into 'menorrhagia', 'dysmenorrhoea' and 'PMS', or lay versions of these terms. A count was made for each participant to ascertain how many aspects she had reported as a *severe* problem, and also how many aspects she had rated a *marked or severe problem.*

A further summary variable was derived, indicating whether a woman had noted as a severe problem *any* of the three aspects of volume of loss (lose too much blood, difficulty preventing accidents and periods going on too long, the latter being included because that is often part of the menorrhagia definition, particularly in the USA.). Similar summary variables were derived for pain (3 aspects, pain with and before periods, and pain all the time) and cycle-related changed (two aspects, mood

changes and other physical changes around periods). Another aspect which suggests a cyclic change in health/vigour attributed to periods is 'feeling unwell because of periods', so a fourth summary variable was derived, cycle/unwell (three aspects, cycle-related mood changes and other physical changes and feeling unwell).

5.2.2.ii Citing aspects of periods as 'cause' of clinic attendance

After indicating for each aspect how much of a problem it was for her, the woman was asked to note in order of importance up to three aspects that had been *the main cause of her coming to the clinic*. It was decided *in advance* that, if more than one cause had been cited, all should be taken into account, up to a maximum of three as specified on CQ. The rationale was that from the woman's point of view there might be little difference in importance between, for example, first and second causes cited. The causes cited were used to derive new variables, indicating separately for each aspect listed on CQ whether that respondent had cited it as a cause of coming to the clinic, regardless of whether first, second or third in order. For these variables, no cause cited at all (18 respondents) was taken as 'not cited', not as missing. The additional (non CQ-listed) causes cited, as reported above, could not be mapped reliably onto the CQ aspects, and so were ignored (135 citations out of a total of 2253).

As for 'aspects as problems', summary variables were also derived for volume, pain , cycle and cycle/unwell with respect to citations of 'cause' of help-seeking. (For the cycle groupings, 6 free-text citations of 'PMT' as cause could also be mapped and hence counted.)

5.2.3 Principal components analysis for data reduction

5.2.3.i Introduction

The way in which a woman experiences her periods, and finds them distressing, is likely to reflect a number of underlying processes. For example, some of these may be: the nature of her menstrual symptoms; the context of her daily life; her personal and practical resources for dealing with the symptoms; her tendency to be concerned

about her health; her past experience; and her emotional resilience. The various processes at work are likely to be reflected by differing degrees of affirmative responses to the broad range of items, describing adverse consequences of periods, presented in the Menstrual Evaluation Questionnaire (MEQ). Variables reflecting the same process should be highly correlated, and in the interests of parsimony it would therefore be helpful if they could be summarised into one score. In practice, specific variables might reflect more than one of the underlying processes. Nevertheless, there would be considerable advantage in being able to express the original variables in terms of a smaller number of dimensions of variability.

5.2.3.ii Aim of principal components/factor analysis

Principal components and factor analysis are multivariate methods which can be employed to reduce a large number of variables to a smaller number of factor scores that reproduce, to a sufficient extent, the correlations among the observed variables. Over and above data reduction there are two further advantages of these methods:

- the nature of the factors obtained provides insight to the underlying processes that may be operating to generate the observed data;
- when the factor scores are estimated for each subject, from the entire set of variables, they tend to be more reliable estimates of the underlying dimensions of variability, than any one of the original observed variables is of whatever it is that it measures (Tabachnick BG & Fidell 1996b).

Therefore these methods can offer both parsimony and precision. Important methodological issues are the number of factors to be retained in the solution, and whether or not the factor solution should be rotated.

5.2.3.iii Theoretical issues

There are a number of theoretical limitations to principal components analysis, and factor analysis. If there is much missing data its impact needs to be assessed. It is important that variables take a spread of values, and the solution is enhanced if the variables are normally distributed, which also implies linear relationships between pairs of variables. However, in the case of exploratory data analysis these assumptions are less constraining, and decisions can be made on a pragmatic basis

(Tabachnick BG & Fidell 1996b). It is also important correlations are reliably estimated, so a correspondingly large sample size is important. Three hundred cases is regarded as a practical minimum (Tabachnick BG & Fidell 1996b). In the present study the MEQ data have a sample size of over 700.

A number of reservations have been expressed about these methods, in particular that there is no criterion against which to test the solution (Tabachnick BG & Fidell 1996b). Also, there is an 'indeterminacy' due to the infinite number of rotations possible to achieve a final solution, all with differing interpretations, to a greater or lesser degree. However, neither of these is a serious concern when the aim is exploratory data reduction, as here.

5.2.3.iv Method used

As it is so specialised the detailed method is given in an appendix (**Appendix 5.2**) which will be referenced at the time results are reported, in section **5.3.1.iv**. The method steps covered are:

- Choice of extraction method – *principal components was chosen;*
- Extraction of components– *the approach taken by the SPSS software is described;*
- Deciding number of components- *a combination of scree plot, eigenvalue, and meaning of components was used;*
- Rotating the solution– *varimax rotation was used;*
- Estimating factor scores– *the approach taken by the SPSS software is described;*
- Checks with regard to solution– outliers and *single-variable 'factors' are discussed.*

5.3 RESULTS

5.3.1 Current menstrual problem

5.3.1.i Patient's self-stated reason for clinic attendance and duration of problem

For the 15 who did not respond at all to this free-text question, the classification for both reasons was set to 'missing'. For the remainder text responses were classified as per **5.2.1** and **3.8.5.ii**. Overall 56% of participants mentioned two (or more) problems, but in many cases both problems were coded to the same reason, so in terms of codes *assigned* only 31% of participants had two distinct reasons. (For example, 'periods going on too long' and 'heavy periods' would both code to 'excessive bleeding' reason.).

The breakdown of reasons stated by participants was 568 (60%) excessive bleeding, 283 (30%) period pain, 67 (7%) cycle-related changes, and 323 (34%) 'other'. The distribution of reasons coded to 'bleeding reason' was:

- heavy periods (72%),
- periods going on too long (12%),
- periods too frequent (7%),
- clots (6%) and
- continuous bleeding (3%).

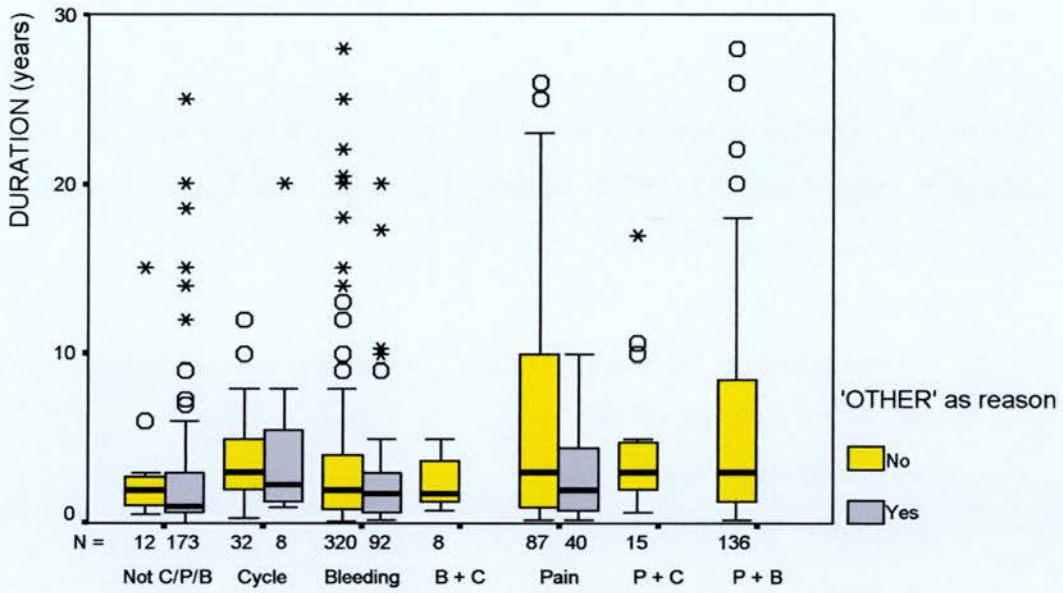
Intermenstrual bleeding, varied bleeding pattern and changed bleeding pattern were coded as 'other' (59, 6%), as was unspecified 'menstrual problem' (48, 5%). The most prevalent reason coded as 'other' was irregular periods (144, 45% of the 323 participants coded with 'other' reason).

The concordance between patients' self-stated reasons for clinic attendance and GP referral reason, and the association of self-stated reason with the various demographic, health and menstrual variables will be reported in Chapter 9.

The duration of the self-stated problem was ascertained via CQ: median 24 months (IQR 11 to 54 months, n=923). The question asked was 'How long has this been

bothering you?', referring to the 'problem, mainly, that brought you to the clinic'. Therefore, if more than one problem was cited it is not certain that the duration given applies to *both* problems cited. If pain was cited, either as the single reason or as one of two reasons, the median duration of 'problem' was 36 months (n=283), as it was if cycle-related changes was cited as reason (n=67). If bleeding was cited, median duration of 'problem' was shorter, at 24 months (n=568), and if 'other' was cited it was shortest of all, 16 months (n=323). **Figure 5.1** shows box-plots of duration of problem for the various combinations of self-stated reason for attending clinic.

Figure 5.1 Box-plots of duration of problem by the various combinations of self-stated reasons (cycle, bleeding, pain), sub-classified by whether 'other' has been stated as a reason.



This shows that the distributions are typically positively skewed, with durations of 10 years or more not uncommon, some being more than 25 years. **Figure 5.1** also shows that in all the reason-combination subgroups where there can be subdivision by 'other', durations tend to be shorter in the subgroup where 'other' was one of the reasons (or the only reason, 2nd box) .

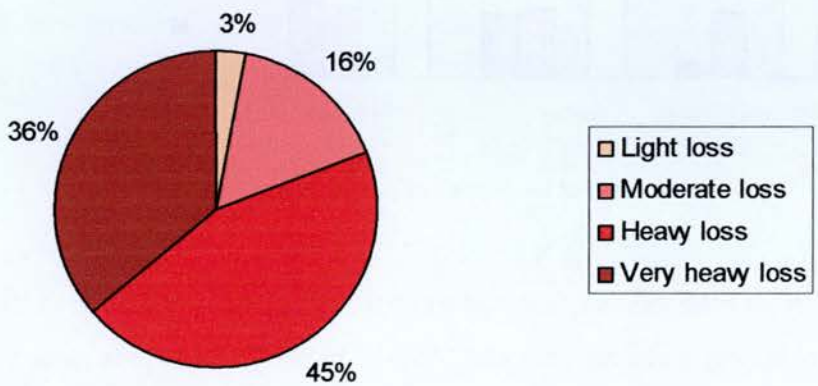
5.3.1.ii Subjective assessment of menstrual loss, pain and cyclic changes

Detailed data were obtained describing periods, both in CQ, and MEQ. These data are summarised in **Appendix 5.1 Tables A5.1.1 to A5.1.7**, and the main features are described here in a number of sub-sections addressing in turn: description of heaviness of loss; anticipation and planning for period; containment of period; pain associated with periods; and other cycle-related symptoms.

DESCRIPTION OF HEAVINESS OF LOSS

Appendix Tables A5.1.1 and A5.1.2 report variables describing heaviness of menstrual loss. **Figure 5.2** shows the distribution of subjective ratings of heaviness of periods in the last 6 months. The vast majority of women reported 'heavy' (45%) or 'very heavy' loss (36%). While these percentages are for almost the entire study sample completing CQ (except for 7 women who failed to complete this item, n=945), the subset of 818 who also completed MEQ had very similar distribution of ratings for 'heaviness' of loss, that is, 45% heavy and 38% very heavy.

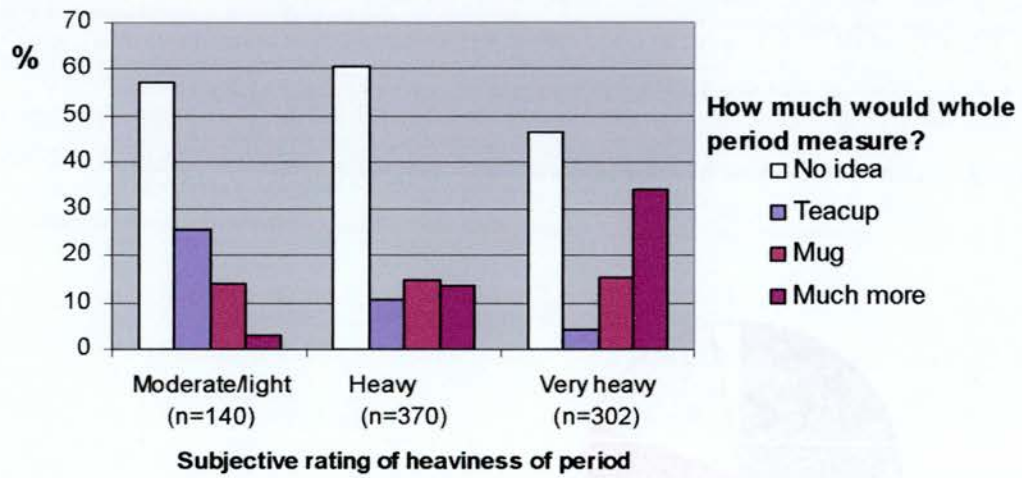
Figure 5.2 Distribution of subjective ratings of heaviness of periods (CQ data, n=945)



While almost all women were able to respond when asked to provide subjective ratings of 'heaviness' of their periods, as reported above, this was not the case when asked to respond in terms of volume of menstrual loss. As shown at the bottom of **Appendix Table A5.1.1**, when a woman was asked to select one of three options indicating how much she thought her whole menstrual loss would *measure*, she was

more likely than not to tick 'no idea' (55%) rather than one of the volumes offered. A teacup holds about 150mL and a mug about 270mL. Taking into account the blood and non-blood components of the menstrual loss, a period comprising 80mL blood would be expected to have a total fluid volume of about 180mL (Fraser et al. 2001). Therefore periods measuring 'mug' or 'much more' would be likely to exceed 80mL blood volume. These responses were given by only 30% of those completing MEQ. **Figure 5.3** shows the distributions of responses to this item for women subdivided into three groups on the basis of their subjective ratings of the heaviness of their periods. The heaviest group are most likely to hazard a guess as to the measurement of their period, but nevertheless 46% report they have 'no idea' as to volume.

Figure 5.3 Estimated 'measurement' of whole period, within subgroups determined by subjective heaviness of menstrual loss



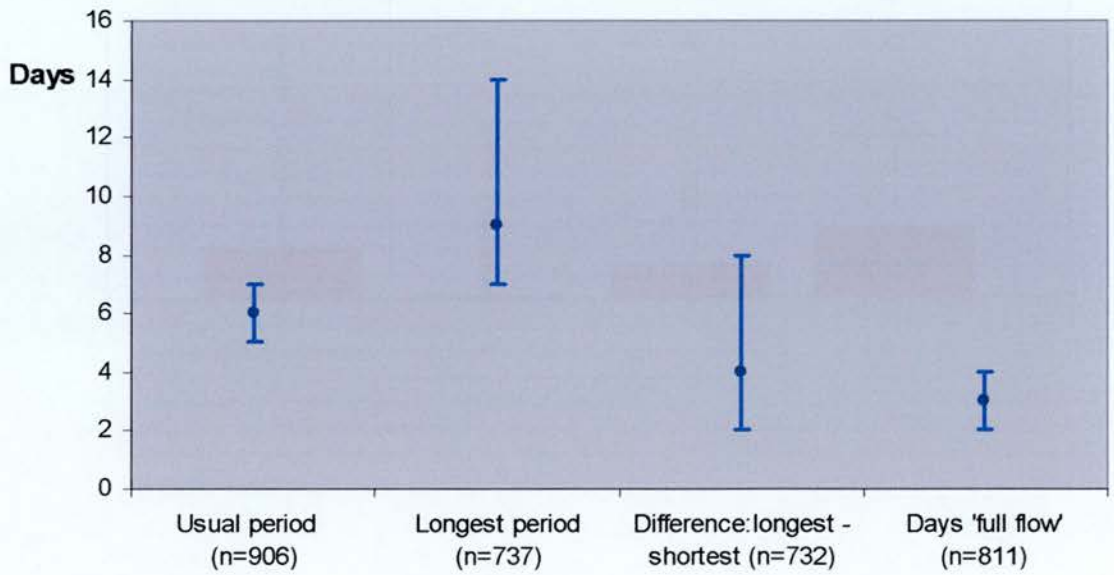
Nearly half of all respondents reported spotting between periods (46%), and a similar percentage bleeding 'between periods' (48%). 'In between periods' was defined as days separate from the woman's proper periods. The distinction between 'bleeding', as opposed to 'spotting', was defined in terms of whether the break-through bleeding was sufficient for sanitary protection to be required. When bleeding and spotting were considered in combination it was found that 59% of respondents reported bleeding and/or spotting either some, or nearly all, cycles.

Appendix Table A5.1.2 summarises count data for periods (duration of period, days full flow, days breakthrough bleeding/spotting or number of clots). The median number of days occurrence for each type of break-through bleeding was 3 days (n=307 & 272 respectively for break-through bleeding and spotting respectively). Roughly two-thirds of these women (n=198) reported *both* types of break-through bleeding/spotting.

On CQ the respondent was asked to report on duration of longest and shortest periods, if the duration of period varied from cycle to cycle. Approximately four fifths of the 906 women reporting on duration also reported duration of longest and shortest periods and for them the difference between the two durations was calculated. **Figure 5.4** plots the median and IQR for the usual and longest periods, as well as the difference, and also for the number of days 'full flow' as recorded on MEQ.

Figure 5.4 Days duration of usual period, longest period and 'full flow', and difference between longest and shortest periods (median & IQR)

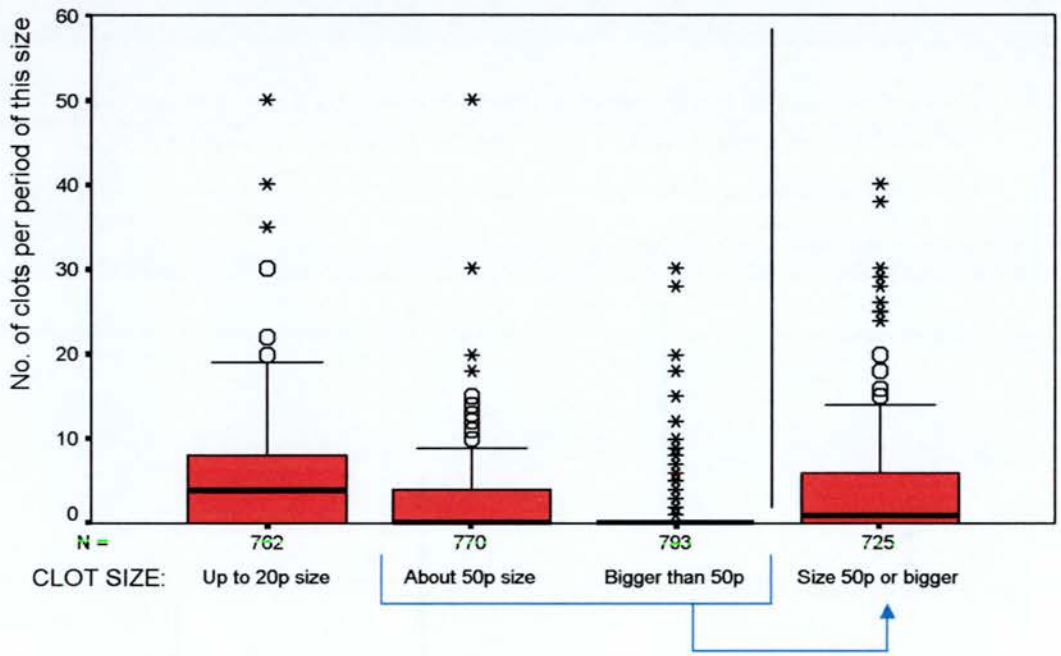
(The first 3 variables plotted are from CQ, the fourth from MEQ)



Although 819 women completed this item, for 8 their responses exceeded the usual duration quoted for the entire period, so their values for this item were set to missing. The median days 'full flow' was 3 days (IQR 2 to 4 days).

CQ data show that, for the entire study group, passing of clots was very common (90%), but large clots, that is, greater than the size of a 50p coin, were relatively uncommon (15%) (**Appendix Table A5.1.1**). In MEQ women were asked to state the usual *number* of clots of each of three sizes (up to 20p, 50p, or greater than 50p) that were passed per period. Combining counts for all three sizes of clots, 725 women had responded for all three sizes, and for them the median *total* number of clots per period was 6 (IQR 3 to 12). **Figure 5.5** presents box-plots of the three separate clot-size variables (counts of clots per period), as well as for a further variable, derived by adding together the number of clots recorded of size 50p or greater. This shows that the two larger sizes of clots were relatively uncommon.

Figure 5.5 Numbers of clots of the stated size, usually, in one period (MEQ data)

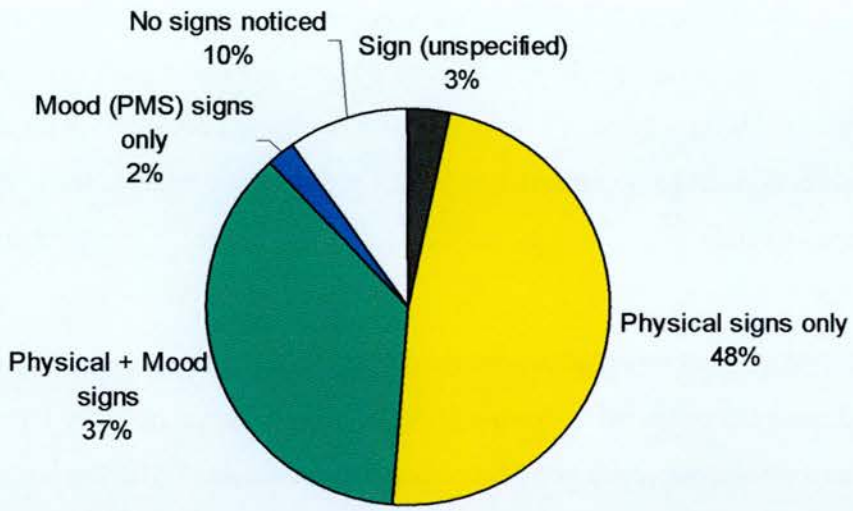


ANTICIPATION AND PLANNING FOR PERIOD

Appendix Table A5.1.3 summarises data from MEQ pertaining to timing and anticipation of bleeding. Success in containment of the period may depend on the suddenness of onset of flow. In this sample, 26% of women reported that their period started 'in a gush'. If a woman has a regular cycle she may anticipate the onset of her period by counting days from the previous one, and 65% (of those completing MEQ)

reported this was possible for them, although for only 42% was this the case 'most cycles'. However, 90% (n=741) responded that they knew by 'other signs' that a period was due to start in a few days. In total 714 women recorded the 'other signs' that alerted them to the imminence of a period, with 303 recording two signs. The signs were coded as physical signs (e.g. pain, bloating), mood signs (e.g. tense, irritable etc.), and 'PMS/PMT' (symptoms unspecified). Women were categorised according to the combination of signs recorded. **Figure 5.6** shows the distribution of responses to this MEQ item.

Figure 5.6 Distribution of responses regarding signs alerting to imminence of period (MEQ data, n=820)



CONTAINMENT OF MENSTRUAL BLEEDING

Appendix Table A5.1.4 reports on the women's description of containment of menstrual loss. On CQ, 946 women reported on the type of sanitary protection used. The most common type used was pads only (48%), but a further substantial proportion used tampons as well as pads to contain their periods (40%), whereas12% used tampons only. The proportions using high-absorbency protection (at that time typically labelled 'super plus') was 26% for pads only and 22% where pads and tampons were both used.

Nearly half of all women (46%) reported accidental leakage onto underclothes or bedding 'most periods' and a further 40% 'some periods'. Getting up at night to change sanitary protection was marginally less common: 42% 'most periods', 37% some periods. Use of double protection (two products at the same time) is indicative of concern about accidental leakage: 60% of CQ respondents reported having to use double protection at times. There was strong evidence of a positive association between use of double protection and reporting accidental leaks and getting up at night to change. Nevertheless, a quarter of the 441 who had leakage most periods did not use double protection, and nearly a quarter of the 131 who very seldom had leaks did use double protection. There was a very similar pattern for getting up at night to change.

When women were asked on MEQ 'how often do you have to change your pad/ tampon when you period is full flow?', 22% said every hour and 11% more often than every hour (819 responded). The subset of 821 women completing the CQ item on double protection, and also completing MEQ, were very similar to the entire study sample in terms of their prevalence of use of double protection as reported on CQ, 62% compared to 60%.

Use of double protection was also reported on MEQ, but this item offered three options for describing recourse to double protection - 'no/ some periods/ most periods'. There was strong evidence of a positive association of MEQ-reported frequency of use of double protection with frequency of accidental leakages and also with frequency of having to get up at night to change protection, as for the CQ item. However, only just over half of the 392 reporting leakages 'most periods' also reported use of double protection most periods, and one sixth of the 114 reporting leakages 'seldom', nevertheless reported using double protection most periods.

Appendix Table A5.1.5 reports count data with respect to containment. For the women completing the item on CQ (n=927) the median duration of use of double protection was 2 days (IQR 0 to 4 days). Only 3% of women reported more than 7 days use of double protection, and 41% reported zero days of double protection. As reported on MEQ, leakages onto underclothes were relatively common, with 75% of 781 women reporting 2 or more per period (median 3). Leakages onto outer-clothes

or bedding were less common, with the proportions reporting *no* such leakages being 61% and 32% respectively (medians 0 and 1 respectively, n= 796, 785).

In MEQ women quantified their usual usage of sanitary protection. The median was 30 products per period (IQR 20 to 40). For high absorbency products specifically the median was 10 products (IQR 0 to 24). For both these variables the maximum value was 164, a very high usage, but only 3% and 1% respectively used more than 85 products.

PAIN AROUND PERIODS

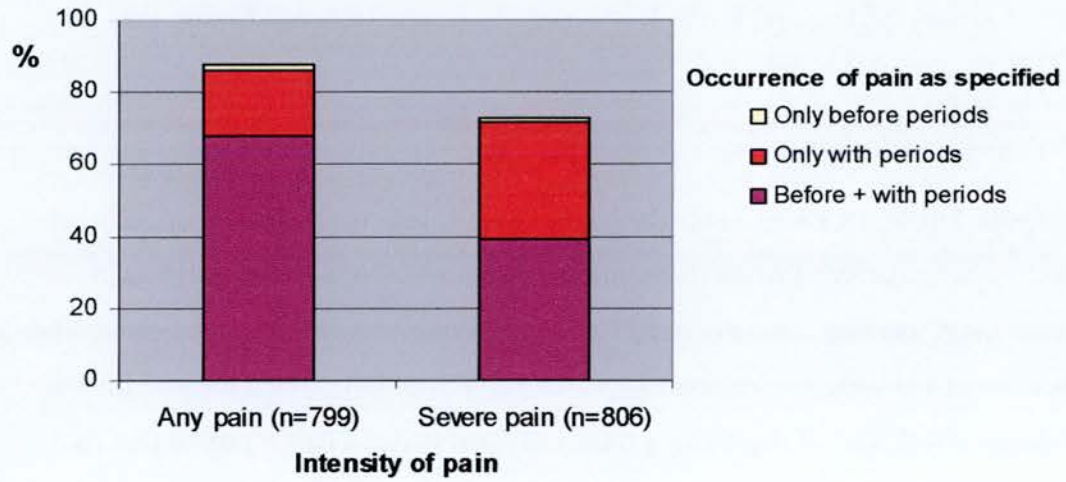
Appendix Table A5.1.6 presents data on women's reports regarding pain around periods. The majority of women completing MEQ (72% of 827) reported pain around 'most' periods and 59% of 829 used pain-killers for pain most periods. The pain-killers used were predominantly NSAIDs (98% of 710 giving a name for the pain-killer used), and of those using them only just under a half reported that the pain-killer used was effective most times (47% of 740).

Women were asked to record the numbers of days of period pain experienced, both before periods and with periods. Pain *before* periods was common, being reported by 70% of 812 women responding, but pain *with* periods was more common (86% of 803). To ascertain pain of an intensity that was likely to have adverse impact on daily life, women were also asked to record for each time phase the numbers of days that the pain experienced was *severe*. The corresponding percentages of women experiencing severe pain were 40% before periods, and 72% with periods (n=811 in each case). Therefore severe pain was proportionally less common before periods. This is illustrated in **Figure 5.7**. The relative heights of the columns shows that for vast majority of women who experience pain some of it was severe.

For *days duration* of pain there was greater separation between any pain and severe pain. The total number of days pain usually experienced around periods was obtained by adding the two together counts for before and during periods. This was done separately for (any) pain, and for *severe* pain. **Appendix Table A5.1.6** presents the distributions of number of days reported for total days of (any) pain, for total days of severe pain, and for number of days severe pain *with* periods. The median total

number of days of (any) pain was 5 days (IQR 2 to 8), whereas the median total number of days *severe* pain was 2 days (IQR 0 to 5).

Figure 5.7 Percentages of women reporting the various combinations of timings of pain around periods, separately for 'any pain', and for 'severe pain'.



CYCLE-RELATED SYMPTOMS AROUND PERIODS

Appendix Table A5.1.7 reports women's responses with respect to other cycle-related symptoms. In these questionnaire items the questions were all phrased in terms of cycle-related symptoms, and there was no requirement to affirm 'premenstrual *syndrome*'. Out of 797 women who completed the main item, 86% did experience cycle-related symptoms from time to time, 71% 'most periods'. Of those who experienced symptoms, 741 responded to the item ascertaining how troublesome the cycle-related symptoms were, and 76% reported they found the symptoms troublesome, with about a third of these rating the symptoms *very* troublesome. Women specified when their cycle-related symptoms were most troublesome, with nearly half (46% of 720) saying equally-troublesome before and during the period, and the remainder roughly evenly divided between 'before' and 'during' the period.

Women were asked to detail the cycle-related symptoms that were worst for them, separately for before and during the period. Backache/pain and tiredness were

commonly-noted troublesome symptoms both before and during the period, with backache/pain the predominant symptom during the period. The symptoms most often noted tended to differ by timing: before the period a greater range of symptoms was noted, including more emotional symptoms, with 'bloating/weight gain/breast tenderness' being most commonly reported as troublesome.

5.3.1.iii Aspects of periods, their occurrence and how problematic they are

DESCRIPTION OF ASPECTS, OCCURRENCE AND SEVERITY

The rationale for the aspects part of CQ has been explained in **5.2.2**. **Table 5.1** shows, sorted in order of prevalence, the percentages judging each aspect a 'severe problem' and the effective (non-missing) n for each percentage.

Table 5.1 Percentage of women judging each aspect of periods to be a severe problem

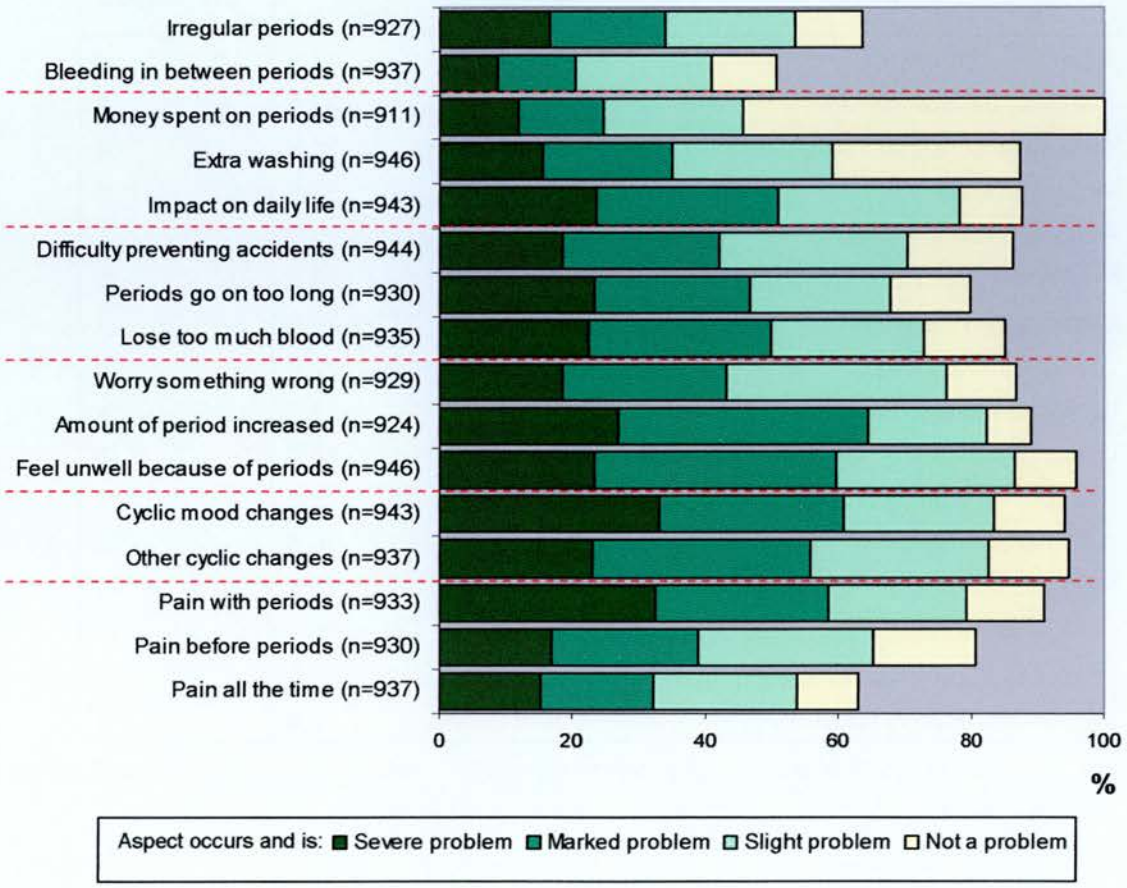
Aspect (précis)	n	%† severe problem	Rank in order of prevalence
Cyclic mood changes	943	33.2	*1*
Pain with periods	933	32.6	*2*
Amount of period more than used to be	924	26.8	*3*
Impact on daily life	943	23.6	*4*
Periods go on too long	930	23.3	*5*
Feel unwell because of periods	946	23.3	*6*
Other cyclic changes	937	22.9	*7*
Lose too much blood	935	22.5	*8*
Worry something wrong	929	18.5	*9*
Difficulty preventing accidents	944	18.4	*10*
Pain before periods	930	16.8	*11*
Irregular periods	927	16.5	*12*
Extra washing	946	15.3	*13*
Pain all the time	937	15.2	*14*
Money spent on pads/tampons	911	11.6	*15*
Bleeding in between periods	937	8.8	*16*

† *95% confidence intervals are, for prevalences ≥ 22%, within 3 percentage points either side of the figure reported, and for those < 22%, within 2 percentage points either side.*

Although 952 women completed CQ, each of these items had some missing responses, but for all except one item this was less than 3% (that is, 6 to 28 missing responses). For 'money spent on pads/tampons' there were 41 missing responses (4%). It can be seen that excessive volume of menstrual blood loss (23%) is only eighth in order of prevalence. The most prevalent 'severe problems' were cyclic mood changes, pain with periods, increased period and impact of periods on daily life (33%, 33%, 27% and 24%).

Given the 5-point response scale for the items, consideration just of *severe* problems (as in **Table 5.1**) loses some of the information in these data. **Figure 5.8** presents the full data as stacked bar charts. The response 'does not happen' is not plotted, but for each item would make the column up to 100%. The overall length of the bar as plotted therefore shows the total prevalence of occurrence of the aspect.

Figure 5.8 Distribution of degree of problem for aspects of periods (CQ data)



The bars have been organised into sets of related aspects (separated by dashed lines) – irregularity, impact, volume, concern, cyclic changes, and pain. The green-shaded slices represent degrees of problem – severe to slight – and the white slice 'happens but not a problem'. All women have to spend money on periods, so that bar (3rd) totals 100%, but it can be seen that relatively few find cost a severe or marked problem. Although far fewer women experience irregular periods (1st bar), relatively more, and indeed more in absolute terms, find this aspect a severe or marked problem (compared to 'money spent'). Even if severe and marked problem are considered together the relative ordering in terms of prevalence (of 'severe/marked problem') is little different to that for 'severe problem', with excess volume of periods remaining low in the ranking (7th). On the whole the binary variable of 'severe problem' (or not) gave a similar ordering in terms of prevalence of the various aspects.

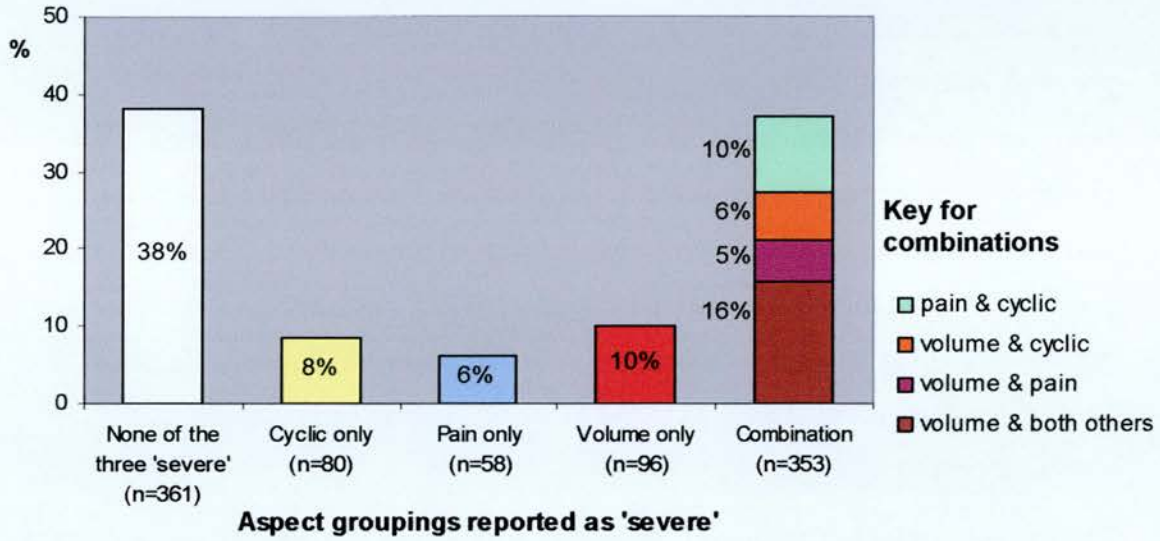
The median number of severe problems was 2 (IQR 0 to 5), with 285 women (30%) reporting no aspect severe and four (0.4%) reporting all 16 severe. The corresponding count for severe *or marked* problem, had median 7 (IQR 4 to 10), with 18 women (2%) reporting all 16 aspects severe. It was therefore decided that 'severe' was a more discriminating cut-off for creation of binary variables for 'problem'.

CATEGORISING ASPECTS INTO THREE GROUPINGS: VOLUME, PAIN AND CYCLIC CHANGES

Summary variables were derived as described in **5.2.2.i**, indicating whether a woman had noted as a severe problem *any* of the three aspects of volume of loss (3rd grouping on **Figure 5.8**), and similarly for pain (last grouping on the same figure) and cycle-related changed (5th grouping). Analysing these variables it was found that roughly equal proportions of women reported a 'severe' problem with some aspect of excessive volume, of pain, or of cycle-related changes (38%, 37% and 40% respectively for the three groupings), with considerable overlap between these. In total 62% of women reported at least one of these groupings of problems, 37% more than one, 16% all three (**Figure 5.9**). Of the 361 women who reported none of these

three aspect groupings a severe problem, 79% reported none of all the 16 aspects listed on CQ a severe problem.

Figure 5.9 Percentages of women experiencing as a 'severe problem' volume of period, pain around periods or cycle-related changes, and combinations of these
(all %s calculated out of total n=948)

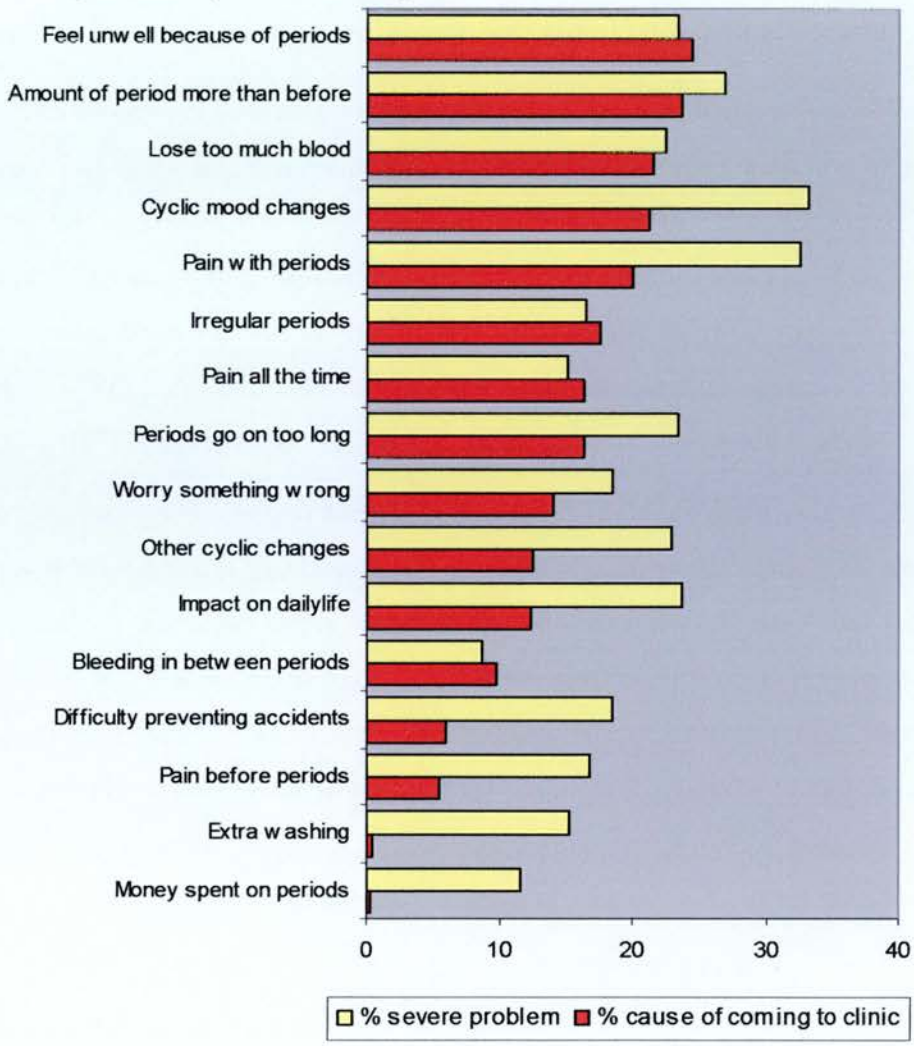


IDENTIFYING ONE OR MORE ASPECTS AS CAUSE OF CLINIC ATTENDANCE

After indicating for each aspect how much of a problem it was for her, the woman was asked to note in order of importance up to three aspects that had been *the main cause of her coming to the clinic*. The number citing no cause at all was 18, while 150 cited only one cause, 249 only two and 535 three causes. In some cases, causes other than the aspects listed were cited: overall 38 women cited clotting, 21 frequent periods, 5 discharge, 6 'PMT', 2 dyspareunia, 2 low haemoglobin, 3 endometriosis, 3 changed bleeding pattern and 55 cited reasons coded as 'other (non-menstrual)'. Therefore the total number of causes cited by the 952 participants was 2253, but the total number of causes cited that were also aspects listed on CQ was 2118, an average of 2.2 per woman.

As explained in **5.2.2.ii**, the causes cited were used to derive new variables, indicating separately for each aspect listed on CQ whether or not that respondent had cited it as a cause of coming to the clinic, regardless of whether first, second or third in order. The prevalences of citation of each listed aspect as a cause of help-seeking, as any of 1st, 2nd or 3rd most important cause for respondents, are shown in **Figure 5.10**, arranged in order of decreasing prevalence.

Figure 5.10 Prevalences of (i) citation of aspects as cause of coming to clinic (n=952 for all bars), and (ii) reporting aspects as 'severe problem' (n=911 to 946)



As on average the women cited 2.2 aspect-causes each the total of these prevalences is 222%, and women tending to respond expansively will have contributed more to the pattern of prevalences than women citing just one (main) cause. The prevalences of reporting the aspects as *severe problem* (as reported in **Table 5.1**) are also plotted in **Figure 5.10**, for comparison.

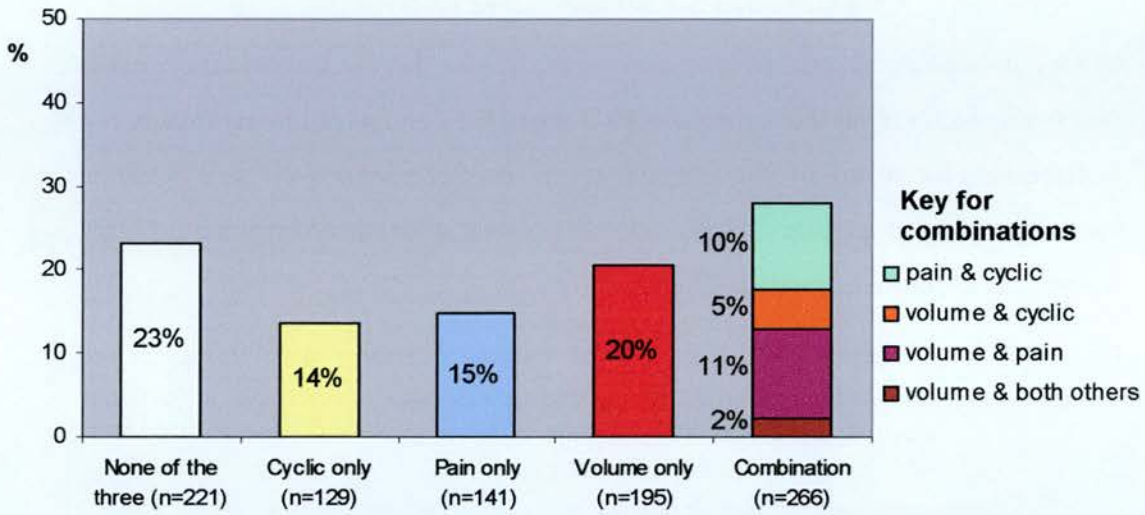
It can also be seen that for some aspects their prevalence as severe problems is not reflected in a corresponding prevalence as cause of coming to the clinic. This is indicated by disparity in length of pale and dark bars for the same aspect. This is the case particularly for pain (with and before periods), cyclic changes (mood and other) and the various impact variables (daily life, accidents, washing and cost).

CATEGORISING 'CAUSES' INTO THREE GROUPINGS: VOLUME, PAIN AND CYCLIC CHANGES

It is therefore of interest to examine the overlap in citation of *groupings* of causes (volume of bleeding, pain and cycle-related, described in **5.2.2.ii**), as has been done for severe problems in **Figure 5.9** above. On this basis, at least one of the 'pain' grouping (with periods/ before/ all the time) was cited by 360 women (38%) and at least one of the cycle-related aspects (mood/ other) was cited by 293 women (31%). Therefore, in terms of citation as cause, volume and pain are equal (38% each), but there are slightly fewer citations of cycle-related aspects as cause (31%).

Figure 5.11 shows that in total 77% reported at least one of these groupings of problems, 28% more than one, 2% all three.Compared to **Figure 5.9** for severe problems, this figure for 'causes' shows a flatter distribution across the categories, with relatively fewer women citing more than one of these causes, and fewer women citing none. Examining the 'none (of bleeding, pain or cycle-related)' subgroup, the first causes cited by these 221 women were predominantly: increased period (19%), irregular periods (17%), worry something wrong (15%), bleeding in between periods (15%), feeling unwell (10%) and 'non-menstrual reasons' (9%).

Figure 5.11 Percentages of women citing as a 'cause of help-seeking' excessive volume of period, pain around periods or cycle-related changes, and combinations of these
(all %s calculated out of total n=952)



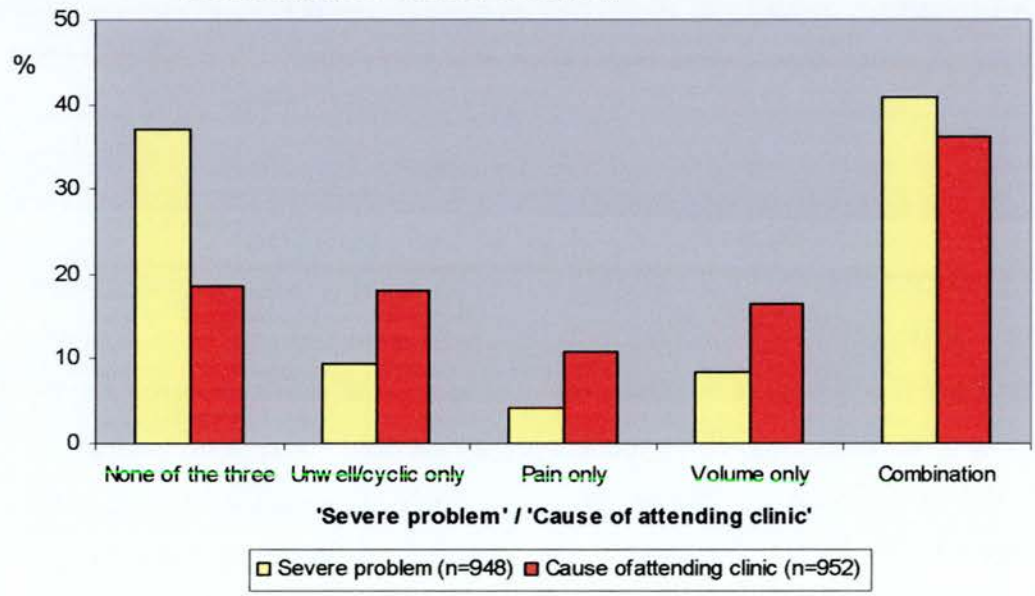
OTHER POSSIBLE GROUPINGS FOR ASPECTS

These relative percentages for the groupings, and the various combinations, do to a certain extent depend on the aspects grouped. It may seem that citation of 'amount of period more than it used to be' should have been counted in with volume, but it has not been, because strictly it is a relative judgement, and does not necessarily denote an excessive absolute volume (this can be related to ideas summarised in **5.1** and **Table 1.1**). Similarly, citation of clotting as cause was not counted in with 'volume', because clots are not necessarily an issue of absolute volume. (Checks revealed that of 38 citing clotting as a cause, 13 gave other cause(s) that meant that they were anyway classified as having cited volume of loss as a cause. Of the remaining 25 who did not cite any of volume aspects as cause, 14 reported at least one severe problem, this being predominantly pain with periods and/or cyclic changes. Therefore they do not appear to have been using clotting as shorthand for excessive loss. For the remaining 11, who did not cite volume causes and who reported no severe problems, if reporting of marked problems was examined it was found this was mainly increased period, mood changes and feeling unwell, so there is

no evidence even of 'restrained' reporting of excessive loss. Therefore it does not appear volume has been missed as a cause in women where clotting but not volume has been cited as a cause.)

As explained in **5.2.2.i**, 'feeling unwell because of periods' this does suggest a cyclic change in health/vigour attributed to periods, so a further cyclic summary variable was derived including this aspect/cause. **Figure 5.12** shows the difference in distributions for severe problems and causes when 'feeling unwell' is included in the cyclic grouping of aspects. That is, relatively more *severe problems* fall into the 'none' and combination categories.

Figure 5.12 Distributions of reports of 'severe problem' and 'cause of help-seeking' by the three aspect groupings: excessive volume of period, pain around periods or feeling unwell due to periods (including cycle-related changes)



A similar difference between distributions for severe problems and causes was seen when the cyclic grouping did not include 'feeling unwell'. (This can be ascertained by comparing **Figure 5.9** with **Figure 5.11**.)

Furthermore, by comparing **Figure 5.12** with **Figures 5.9** and **5.11** respectively, it is also possible to see how the patterns change when the cyclic grouping *includes feeling unwell*. When 'unwell' is included there are, for both severe problems and

causes, fewer in the 'none' category, and in 'pain only' and 'volume only', but more in the 'unwell/cyclic' grouping, and more with combinations of the three groupings.

5.3.1.iv Managing periods

In CQ assessment had been constrained to 16 aspects of periods, this being dictated by the need to have a very brief questionnaire for all participants. Not all respondents are happy to affirm something as a 'problem' because this has a connotation of failure to cope. To develop an assessment of menorrhagia it would be preferable to present women with a large pool of statements, and on the basis of responses and associations select from among these the ones that best encompass the scope of menstrual distress reported. Therefore in MEQ questions were asked addressing facilities at home for dealing with periods (question 20 (11 sub-items)) and facilities at work (question 21(17)), if the woman was in paid or voluntary employment. Question 22 addressed general experience of and strategies for dealing with periods (21 sub-items), and question 23 the woman's *feelings* about her periods and her managing of them (41 sub-items).

FACILITIES AT HOME

For the items on home facilities the prevalence of responses indicating adverse features are shown in **Table 5.2**. A score was calculated for facilities at home, by adding one point for each adverse feature reported, and in the case of the six items where two response options were offered ('very much so' or 'a little'), an extra point if the response was the stronger of the two. Using this rule the maximum score possible was 17. For the 807 respondents to MEQ who had completed all the sub-items of the score, the maximum score obtained was 15, and the median was 3 (IQR 2 to 5). The score was correlated with deprivation category, such that more deprived women were more likely to have more adverse scores for home facilities (Spearman rho= 0.21, n=792, 95% CI 0.14 to 0.27).

Table 5.2 Dealing with periods at home: adverse features reported

Adverse features of home facilities for dealing with periods	n responding	%
Others in home realise when having period	798	84
Nowhere suitable for soaking bloodstains	829	81
No toilet separate from bathroom	830	75
Periods inconvenience others in home *	822	32
Others in home complain about periods *	826	26
More than 4 people in home but only 1 toilet	832	23
Storage for supplies is not private enough *	830	22
Difficult to dispose of soiled pads/tampons *	832	20
Not enough space to store supplies of pads/tampons *	833	14
Difficult to get privacy to change *	829	14
No washing machine	830	1

** two degrees of affirmative response possible*

FACILITIES AT WORK

For the items on work facilities the prevalence of responses indicating adverse features are shown in **Table 5.3**. The number of days per period off work for heavy periods had median 0 (IQR 0 to 2, n=593). A workplace score for managing periods was calculated for facilities and attitudes at work. Scoring for this was the same as for the home score. The maximum score possible was thus 22. For 585 respondents to MEQ who had completed all the sub-items, the maximum score obtained was 21, and the median was 5 (IQR 3 to 9). The workplace score for period-management was weakly correlated with deprivation category, such that more deprived women were more likely to have more adverse scores for work facilities (Spearman rho=0.09, n=575, 95% CI 0.01 to 0.17).

Table 5.3 Dealing with periods at work: adverse features reported

Adverse features of work facilities for and attitudes to dealing with periods	n responding	%
Job involves standing for a lot of the time	633	59
Frequent trips to the toilet are noticeable	627	57
Job involves lifting/carrying	631	52
Absence from work because of periods is disapproved of *	610	50
Nowhere to store supplies of pads/tampons	630	39
Storage place is not private enough for you	577	38
Hard to get away from post to change *	626	35
Can not always get access to toilet if urgently needed *	628	35
Difficult to get at your supplies of pads/tampons *	627	29
Can not go to toilet whenever need to	633	25
Someone has to take place if going to toilet	628	24
Difficult to dispose of soiled pads/tampons at work *	629	22
Job requires white or pale uniform	631	20
Not enough toilets available at work	631	19
Frequent trips to the toilet are disapproved of *	625	18
Job is impossible to do during 'full flow'	628	7

* *two degrees of affirmative response possible*

DEALING WITH PERIODS

This section comprised 21 items all to the same format – '**How well do the following statements describe your periods...**?' with 5 response options ranging from 'not at all' to 'very much'. The main focus of the entire set of statements was dealing with bleeding, which included issues of predictability (regularity), but a number of statements could have been responded to in terms of severe period pain, for women who were suffering pain but not heavy periods. Examples of such statements are 'I feel unwell during my period' and 'If my period comes unexpectedly I have to cancel outings'. Therefore, interpretation of factor scores for components involving statements not specific to volume will need to take this into account.

The entire set of data was subjected to factor analysis, for which method an overview was given in **5.2.3**, and for which more detailed methods are described in **Appendix 5.2.** The initial principal component solution comprised 6 factors accounting for 68% of the variance, and this was subjected to varimax rotation to improve interpretability of factors. One of the items, 'My partner complains about interruption to our sex life' loaded on its own as the 6th factor. This item could be completed only by the subset of women with partners, and was therefore 'missing' for the remainder, so it was decided to drop it from the factor analysis, and report separately. The five factors remaining, accounting for 66% of the variance in the remaining items, comprised the following variables, mainly:

a) Avoidance of menstrual accidents by planning activities, cancelling arrangements, limiting what one does
b) Unpredictable/changed pattern of flow, uncertain when finished, going on too long, change from normal
c) Resource consequences such as cost, laundry, ensuring supplies of protection
d) Being unwell/irritable during period
e) Unpredictable onset, wearing protection before period starts.

A number of variables loaded to more than one component. Oblique rotation slightly improved this situation, but with the resulting components remaining very much as above, with respect to the main variables loading on them. Given that the interpretation is little changed, the varimax solution has the advantage of orthogonal components. Further analyses are required to refine the set of statements to provide purer components. The five factors could be interpreted as:

a) impact of volume on life
b) variable/unpredictable flow
c) resource consequences of heavy periods
d) loss of well-being
e) unpredictable onset/need for containment.

The varimax component scores for factors were saved for use in subsequent analyses (**Chapter 9**). The factor loadings are presented in **Appendix 5.2 Table A5.2.1**, together with box-plot graph of the distribution of component scores (**Appendix**

Figure A5.2.1). In response to the statement 'My partner complains about interruption to our sex life', 35% of the 694 women answering this item reported that this was the case, but only 11.5% responded 'a lot' or 'very much'.

FEELINGS ABOUT PERIODS

This section comprised 35 items all to the same format – 'How true are the following of **How you feel about your periods** nowadays ...?' with 5 response options ranging from 'not at all' to 'very much'. The main focus of the statements was feelings about dealing with bleeding, and about consequences of bleeding, but a number of statements could have been interpreted in terms of other menstrual symptoms, for example severe period pain. Statements of this more general type were 'I think my periods make me feel low/depressed' and 'No more periods would be a great relief'.

As for 'dealing with periods' (above), data reduction was achieved by means of factor analysis (for methods see **5.2.3** and **Appendix 5.2**). The initial principal component solution comprised 6 factors accounting for 71% of the variance, and this was subjected to varimax rotation to improve interpretability of factors. One of the items, 'I resent the interruption to my sex life caused by my periods' loaded on its own as the 7th rotated factor. This item could be completed only by the subset of women with partners, and was therefore 'missing' for the remainder, so it was decided to drop it from the factor analysis, and report separately. Furthermore, the third rotated factor comprised solely the two items regarding feelings about impact on work, and these also were completed only by the subset of women in employment. Therefore it was decided to remove them from the factor analysis and report separately. The analysis was rerun, and five factors accounted for 66% of the variance. After rotation the five components comprised the following variables, mainly:

a) emotional consequences of flow – embarrassment, annoyance, nuisance re accidents or having to change plans/limit activities, upset at failure to prevent accidents, feel overwhelmed by flow, always having to worry about changing, dread start of period

b) feeling bad re burden of periods (generally) on family/friends, feel upset by period and/or low/depressed, find periods intolerable
c) worry about change in periods and whether something wrong, wish periods back how they were
d) resent cost of protection and waste of money, feel embarrassed and/or abnormal buying so many supplies
e) no more periods would be a great relief, wish an end to them.

The majority of variables loaded onto more than one component. Oblique rotation improved this situation, but with the resulting components remaining very much as above, with respect to the main variables loading on them. Given that the interpretation is little changed, the varimax solution has the advantage of orthogonal components. Further analyses are required to refine the set of statement to provide more succinct components. The five components could be interpreted as:

a) Containment distress
b) Periods a burden, in particular for family/friends
c) Worry about change in periods
d) Resent resources used on periods
e) Had enough of periods.

The varimax component scores for factors were saved for use in subsequent analyses (**Chapter 9**). The factor loadings are presented in **Appendix Table A5.2.2**, together with graphs of the distribution of component scores (**Appendix Figure A5.2.2**).

In response to the statement 'I resent the interruption to my sex life caused by my periods, 60% of the 675 women answering this item reported that this was the case, but only 22% responded 'a lot' or 'very much'. In response to the two statements about work – 'I feel bad I have to miss work because of flooding' and 'It embarrasses me to have to miss work because of flooding' – the responses affirming these feelings were 34% for feeling bad, 30% for embarrassment, with 19% and 17% respectively responding 'a lot' or 'very much' (n=625, 626 respectively). There was very strong correlation between the responses on these two items (Spearman rho=0.86, n=624).

5.3.2 *Clinic outcome*

5.3.2.i Time-course of clinical encounter

Of the 665 patients followed up at 8 months after initial appointment, outcome was established for 663: 5% had been referred on to another specialty, 53% had been discharged, 15% had not been discharged but had failed to return for a further appointment, and 27% were still under care. Failure to return was strongly related to deprivation code, being more likely in disadvantaged groups. The median for number of clinic appointments up to 8 months after initial appointment and entry to study was 2 (IQR 1 to 3, maximum 9). The median time to discharge or referring on was 13 weeks (IQR 3 to 22 weeks, n=388).

5.3.2.ii Iron status

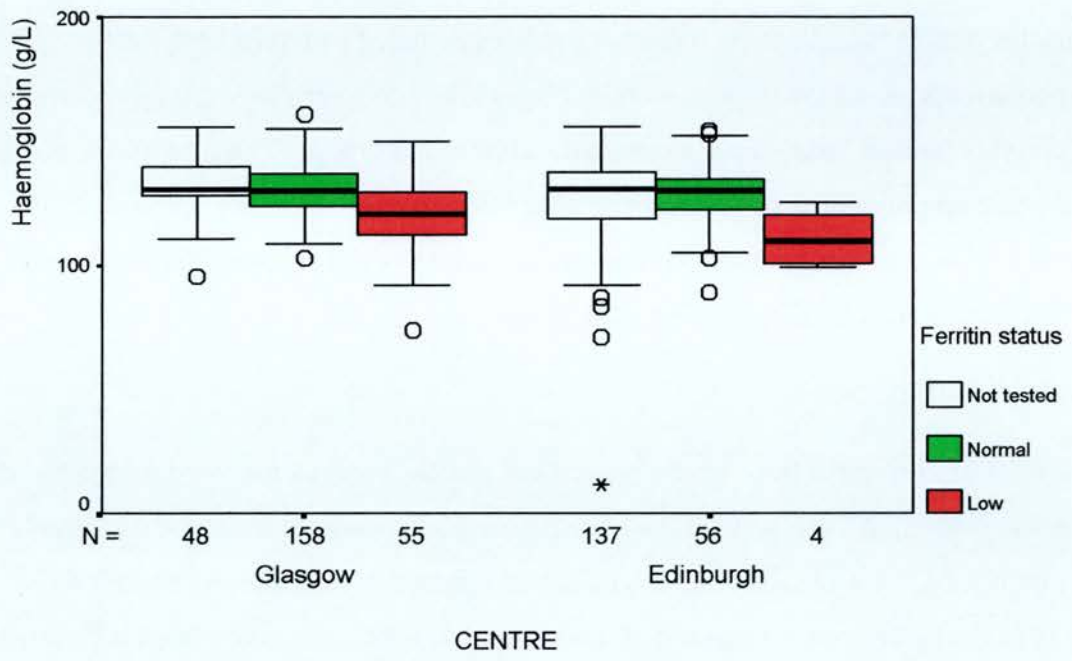
Results of iron status tests were obtained not just for patients followed up but for all patients who had these tests. 'Low' ferritin results, as defined for clinic and assay system used, were obtained for 6% (4/67) of Edinburgh women tested and 25% (56/221) of Glasgow women tested. Haemoglobin levels were correlated with ferritin levels (Spearman rho=0.51, 95% CI= 0.41 to 0.60, n=273). **Figure 5.13** presents haemoglobin results as box-plots separately by centre, with patients sub-grouped by ferritin status. Although haemoglobin levels look fairly similar across the two centres the proportions of low haemoglobin values (<120 g/L) were 17% (45/261) for Glasgow and 25% (49/197) for Edinburgh.

5.3.2.iii Other investigations

Apart from iron status, the most common test undertaken was biopsy, in 43% of patients (n=284), the vast majority of these being endometrial biopsy. The biopsy findings of potential interest were: irregular cyclical activity in 39 women, polyps 10, hyperplasia 5, perimenopausal endometrium 4, endometriosis/adenomyosis 3 and dyskaryosis 1, with no findings of malignancy. The other tests undertaken were ultrasound 33%, thyroid test 20%, hysteroscopy (theatre) 12%, hysteroscopy (outpatient) 11%, dilation and curettage 10%, laparoscopy 10%, colposcopy 1%, clot

screen 1% and suction curettage <1%. In addition 26% of patients had other assorted tests, for example hormone assay, smear, etc.

Figure 5.13 Box-plots of haemoglobin test results by ferritin status, separately by centre



5.3.2.iv Diagnosis

Up to two 'final' diagnoses (at 8 months) were to be extracted from the case-notes. (For some patients these may in fact have been *interim* diagnoses, given that they had not yet been discharged.) For 39 cases (6% of 665) no diagnosis could be found in the notes, and of the remainder, 626 had at least one diagnosis recorded, and 138 of these a second final co-diagnosis as well. There were only two malignancies, one ovarian cancer and one cancer unspecified. The distribution of diagnoses made is presented in **Table 5.4** after re-coding as 'other' the many and varied but very infrequent diagnoses (such as urinary, infertility, gastrointestinal, cancer and so on). Three patients had both first and second diagnosis recoded as 'other' (their first diagnoses being hypothyroidism, pelvic inflammatory disease and iatrogenic - IUCD), but have been included only once each in the table, under 'other'. This table

therefore presents percentages obtained by combining 626 first and 135 second diagnoses.

Table 5.4 Diagnosis made for patients followed up by case-note review

Diagnosis	n	% of 626*
Dysfunctional uterine bleeding (DUB) – regular cycle	180	29
DUB – irregular cycle	160	26
Fibroids	111	18
Endometriosis	48	8
Premenstrual syndrome (PMS)	46	7
Dysmenorrhoea	41	7
Polycystic ovary syndrome (PCOS)	25	4
Polyps	17	3
Peri-menopausal or menopausal	16	3
Anovulatory bleeding without evidence of PCOS	13	2
Other	90	14
No abnormality diagnosed	8	1
Symptoms settled by clinic visit	6	1

** percentages total 122% since 135 women contribute 2 diagnoses each*

Overall 54% of study women received a diagnosis of DUB (a diagnosis of exclusion, that no pathology, such as fibroids, has been found that *may* account for reported abnormal bleeding (Fraser 1994)). This diagnosis was common even if *no* volume aspect had been reported as a severe problem (50% of 399), if the women did *not* given bleeding as self-stated reason for clinic attendance (39% of 259), if the woman rated her menstrual loss as moderate or light (34% of 118), rather than heavy or very heavy, and if the GP had *not* referred her for bleeding (33%). Of the 340 women diagnosed with DUB, 97 had another diagnosis as well. The distribution of co-diagnoses (with DUB) was fibroids 24% (of 97), dysmenorrhoea 24%, PMS 12%, endometriosis 6%, peri-/menopausal 4%, PCOS 3%, polyps 3%, anovular bleeding without PCOS 1% and 'other' 23%.

If the percentages in **Table 5.4** were calculated just on the basis of the first final diagnosis extracted (626 diagnoses) then the percentage for each diagnosis was as would be expected slightly lower (for example 51% for DUB), but giving a pattern of percentages very similar to what has been shown. However there was relatively more reduction in the percentage for endometriosis, fibroids, dysmenorrhoea, PMS and 'other', reflecting the fact that these were more likely to be extracted as *second* 'final' diagnosis.

5.3.2.v Treatments

PREVIOUSLY TRIED BY GP

In the case note review it was recorded if the GP referral letter or notes mentioned treatments already tried for menorrhagia. Out of 665 notes reviewed, treatments already tried could be extracted for 343 women (52%). The main treatments that had been tried were progestogens (52% of 343), prostaglandin synthetase inhibitors (35%), anti-fibrinolytics (22%), oral contraceptive (17%), danazol/HRT (3% each). (Note that up to three treatments could be recorded per patient so the total of all the percentages (including those not presented here) add up to more than 100%.)

TREATMENTS TRIED/RECOMMENDED AT CLINIC

The follow-up data extraction form comprised a list of 11 types of drug treatment, plus hormone releasing IUCD and 'other drugs', 4 surgical treatments plus removal of IUCD, 'cancer treatment' and 'other'. The nurses were to record treatment given or suggested (to GP). Of the 665 notes reviewed, treatments *given* were recorded for 71%, and treatments given *or recommended* for 79%. The distribution of numbers of treatments given per patient in the 8 months was one (39%), two (22%) or three to five different treatments (10%). The corresponding percentages for treatments given or recommended were 43%, 25% and 11% respectively. The most recent treatment was also extracted (up to two). **Table 5.5** presents for each treatment type the percentages of women for whom this was the 'most recent treatment' and hence, for many, the final treatment. This information was missing for 4 women, and 91of the remaining 665 had two recent treatments recorded.

Table 5.5 Most recent treatments provided or recommended as ascertained from case-note review at 8 months after first clinic visit

Treatment	n	% of 661*
None	154	23
Drugs		
Anti-fibrinolytic	94	14
Hormone replacement therapy	81	12
Oral contraceptive pill	67	10
Progestogens	58	9
Hormone-releasing IUCD	47	7
Prostaglandin synthetase inhibitors	36	5
LHRH analogue	18	3
Other drugs	55	8
Surgical		
Hysterectomy	81	12
Dilation & Curettage	7	1
Endometrial ablation (3) & myomectomy (2)	5	<1
Removal of IUCD	9	1
Other	10	2

** percentages total 114% since 91 women contribute 2 treatments each*

As the case note review was undertaken towards the end of the study, for some of the early recruits more than 8 months had elapsed. In addition to review of the first 8 months, as described above, treatments since the 8 month cut-off were also recorded. A further 30 women (5%) had undergone hysterectomy by the time of actual case-note review and a further 11 (2%) had had a hormone releasing coil fitted, while a further 6 (1%) had had removal of coil. Dysfunctional uterine bleeding or fibroids were the most common indication for hysterectomy.

5.3.3 Reliability of data

In **Appendix 5.3** there is some consideration of issues of reliability in the questionnaire data on periods. The concordance of data obtained from more than one questionnaire was found to be satisfactory. There are concerns about some of the

high values, for days bleeding, days use of double protection, and for number of clots, all data intended to describe the usual count, per period, over the last 6 months. It is possible some women instead reported the total over 6 months, but the positively skewed data, some of which it is possible to corroborate, means that it can not be automatically assumed that all very high values must errors.

5.4 DISCUSSION

5.4.1 Presenting menstrual problem

Given the study focus on heavy bleeding, and the recruitment strategy, the 81% of women rating periods as *at least* heavy was perhaps to be expected. However, given the clinical definition of menorrhagia as excessively heavy bleeding, it is surprising that only 36% of referrals rated their menstrual periods as 'very heavy'. Furthermore, it appears that responses regarding heaviness were not based on judgements of volume, as 55% of women responded 'no idea' to an item offering various volumes of menstrual loss as response-options. Cycle-related changes were commonly-reported, with 71% reporting this occurring most periods, and 25% of the 741 women who ever experienced cyclic changes reporting them as very troublesome. Pain with periods, at the intensity of *severe*, was very common, with 40% of women reporting it before periods, and 72% with periods. Considering total days severe pain reported before and with the period, a quarter of women reported 5 or more days (25%) and fewer than half of the women who reported using painkiller found that they worked most of the time (47%). Yet when in questionnaire CQ women were asked *their* reason for attending the clinic, women were nearly twice as likely to state bleeding (60%) as pain or other reasons (30% and 34% respectively).

With regard to aspects of periods, it was striking that 'lose too much blood' was only the 8th most prevalent severe problem. The top two were cyclic mood changes and pain with periods, and fourth was impact on daily life. The most prevalent loss volume item (third overall) was 'amount of period more than it used to be', which strictly addresses the issue of *change* in periods rather than absolute volume.

Considering the partitioned view of menstrual problems, it was notable that when aspects were considered in groups corresponding to the main menstrual problems (bleeding, pain, cyclic), then the two biggest subgroups of women either had no severe problem with any of the three, or had severe problems with two or more. Very few had a clear-cut severe problem with just bleeding or cycle or pain (10%, 8% and 6% respectively). However, when aspects were considered as cause of help-seeking then the prevalence of 'lose too much blood' as cause was higher than expected on

the basis of reports of severe problems. The question arises as to whether women's indication of 'cause of clinic attendance' reflects more what they know of the basis and destination for their referral, rather than the severe problems they experience (and report on CQ). This is supported by the fact that GPs were more likely, than the women themselves, to attribute their clinic referral (attendance) to bleeding problems (76% (reported in chapter 4), compared to 60% for self-stated reason), and clinic gynaecologists were likely to diagnose DUB in the absence even of referral by GP for bleeding (33% nevertheless diagnosed with DUB), rating periods heavy (34% diagnosed with DUB), reporting a volume aspect of bleeding a severe problem (50% diagnosed with DUB).

To what extent then does volume emerge as a key problem for women in this study? Increase in amount of period has been top or next to top in the three rankings discussed so far, but as noted it does not indicate volume *per se*, and certainly should not be expected to be indicative of volume of blood loss in excess of 80mL. Women were asked (on MBQ) about any recent changes they had noticed in their periods. Examples given on the questionnaire were 'number of days, colour, flow' so this could have been suggestive. In order of prevalence changes noted were: heav*ier* period, duration changed, more irregular, clots, colour of blood, more frequent, more pain, inter-menstrual bleeding. Perhaps for many it is the recent *changes* in their periods that are the key to presentation at the clinic. It may be that these two constructs – change from normal pattern of bleeding, and absolute volume - have become blurred in clinical practice. As suggested in **5.1**, the former may be important mainly as a potential clinical sign of pathology, and/or as a cause of anxiety in the patient, whereas the latter reflects intolerable symptoms for which the woman wishes help, regardless of the issue of pathology. Recognition of the distinction between the two, in terms of need for intervention if serious disease is excluded, may improve the clinical management of patients presenting with problems around menstrual bleeding.

Women were also asked the age at onset for the current/most recent *severe* episode(s) of menstrual problem, if any were reported, so it was possible to calculate time elapsed from then to this clinic visit. Generally time elapsed was shortest for

excessive bleeding, and longest for PMS, and pain, particularly. This suggests that women have shorter-lasting tolerance of severe bleeding problems compared to pain and cycle-related symptoms, or that abnormal bleeding is viewed as a symptom that can or should be more swiftly referred to gynaecology clinic. If the latter, and if this tendency had become apparent to a woman suffering multiple menstrual problems, it is clear which problem she should present to her GP or gynaecologist. Many of the women (41%) had visited such a clinic before, so they were very likely to know the focus of interest. Clots were a very common occurrence, with 90% of women reporting some, the number per period being 3 to 12 (IQR), mostly up to 20p size. The significance of clots to women has not been researched, and the significance to doctors is not explicit in text books, guide-lines nor published papers. In this study group, 6% self-stated clots as reason for clinic attendance, and 4% cited clots rather than one of the listed aspects as cause of help-seeking. Perhaps clots are misinterpreted by women experiencing them. If so, this would suggest that clots could with benefit be addressed in clinical consultation.

5.4.2 Components of variation in menstrual experience

Women responded to two sets of items about their menstrual experience. The one set of items was about dealing with periods, a set matter-of-fact statements about what happens in their periods and what actions they take to deal with their periods. The other set of items covered similar territory, but in the sense of how the woman feels about her periods and about the efforts she has to make to contain with them. The components of variation that emerged from the factor analyses of these data sets were very interesting. The largest component of variation for *dealing with periods* was labelled, on the basis of the items involved, 'impact of volume' (21% of variation in the data accounted for), the next 'variable flow' (17%), then 'resource consequences' (13%), 'being unwell/irritable during period' (9%) and 'unpredictable onset' (6%). The items were devised with menorrhagia in mind, so focussed on volume, containment and similar issues. However, some items loading on 'impact' could reflect pain or cyclic symptoms, and so could the 'unwell/irritable' component. In this factor solution 'variability of flow' and 'unpredictability of onset' of period have loomed large.

For the items phrased to ascertain *feelings about periods*, a set of components was obtained that partly addressed similar facets to the first set, but from the point of view of emotional reaction to them. The largest component of variation was labelled 'containment distress' (23% of variation), the next was 'periods a burden' (17%), then 'worry' (10%), 'resent resources' (10%) and 'had enough of periods' (7%). 'Containment distress' and 'resent resources' would appear to be the *feelings* versions of two components in the 'dealing with periods' set – 'impact of volume' and 'resource consequences'. It is interesting to note that a 'worry' component is evident in the feelings set, as this lends weight to the hypothetical structuring of period problems in **5.1** and **Table1.1**.

Therefore, while 'heavy bleeding' is a common reason for referral and attendance at the clinic, the key issues for women are change from usual, containment of flow (often in the face of unpredictability), the practical consequences and the emotional burden of this challenge (and sometimes failure), and the impact on their lives and health. The question is whether these components will prove useful in understanding and modelling of menstrual complaint. This will be pursued in Chapter 9.

5.4.3 Containment of period

Duration of 'full flow' was 2 to 6 days (IQR), although there were many durations considerably longer than this. Women reported quite striking cycle-to-cycle variation in the total duration of their periods (IQR 2 to 8 days difference between shortest and longest reported periods), and this does seem to present a problem to many. Perhaps this explains the emergence of a dealing with periods component 'variable flow'. Furthermore, in items addressing *feelings* about periods there was also a 'worry' component capturing the anxieties arising from such a change in pattern. An important factor in successful containment of periods is knowing when the period will start, and when it does, that the onset should be staged, so appropriate action can be taken in time. Only about a quarter of women reported their periods starting 'in a gush' (26%) and overall 90% of women stated that they had signs warning as to imminence of period. Nevertheless, one component of variation for management of period was 'unpredictable onset' of period. Perhaps the period is anticipated in some

vague way, but not sufficiently precisely to allow timing of commencement of protection. Further analyses of these component scores, against signs indicating onset, will be informative (**Chapter 9**).

Protection used was compatible with heavy flow – nearly half of all women used only pads (48%) and a further 40% both pads and tampons. Approximately a quarter of these women were using the top (super plus) grade of absorbency. It is however intriguing that there were a number of women who never used double protection despite frequent accidents (about 110). The vast majority of women had to get up at night to change (79%), used double protection (69%), and experienced accidents (86%). A third of women reported having to change every hour or more often during full flow. The supplies and attention that need to be devoted to containment of period appears to be a burden for many women. A *dealing with periods* component of variation addressed the 'resource consequences' of heavy periods - maintaining adequate supplies, their cost, and the workload of dealing with laundry. In addition a *feelings* component of variation 'periods a burden' addressed the emotional consequences of problematic periods, and another, 'containment distress' addressed a sense of the relentless battle against accidents.

The difficulties expressed by women in the data discussed above, about frequency of changing, and dealing with accidents, is emphasised by the data pertaining to facilities at home for coping with periods: 75% of women have no toilet separate from the bathroom, and 81% have nowhere suitable to soak bloodstains. The home facilities deficit score is associated with deprivation, so further analyses of this against components and against severe problems with aspects of periods will be of interest. On the whole facilities at work seemed rather better, but a fairly high proportion of women had jobs that were unsuitable for women with problem periods: 59% involved standing, 52% lifting/carrying. It has been argued that when menstruation interferes with functioning at work, then either the menstruation must be 'abnormal' or the problem needs to be redefined as one of occupational health (Harlow 1986). In addition, 57% of women reported that frequent trips to the toilet were noticeable. As has been discussed, many women are embarrassed, or feel abnormal because of their periods, as in the *feelings about periods* component 'resent

resources'. It will be of interest to analyse this work facilities score against 'resent resources'. Further analyses in **Chapter 9** will clarify these issues.

5.4.4 Clinic outcome

Although the median time to discharge or referring on was 13 weeks, over half the women had only two or fewer clinic appointments in total. Although nearly half of all study subjects reviewed had endometrial biopsy (n=284) there was no finding of malignancy from these biopsies.

The low rate of diagnoses of dysmenorrhoea and PMS (7% each) contrasts strongly with the high rate of self-report of severe problems with these aspects of periods (37% and 40% respectively) and with the high rate of citing of these aspects as cause of help-seeking (38% and 31%). Neglect of these conditions was commented nearly 40 years ago (Dalton 1969), and it seems little has changed. It is not straightforward to compare complaint of excessive bleeding with corresponding diagnoses. Both fibroids (diagnosis for 18%) and polyps (3%) are considered to be potential causes of heavy bleeding, but making such a diagnosis does not constitute confirmation of the bleeding complaint. Similarly, diagnoses of peri-menopausal/menopausal (3%) and anovulatory bleeding without PCOS (2%) may be intended as an explanation for reported heavy bleeding, or may simply be a physiological observation. Apart from these diagnoses, 55% of women received a diagnosis of dysfunctional uterine bleeding, on its own far more than the 38% of women who found volume of bleeding a severe problems or the 38% who cited bleeding volume as cause for help-seeking. This diagnosis should be a diagnosis of exclusion, when no physiological explanation can be found for excessive bleeding (Fraser & Inceboz 2000). There are therefore two concerns about the prevalence of this diagnosis. Given that many women receiving this diagnosis did not seem to be complaining of bleeding, it seems it does not necessarily indicate the doctor's judgement that there is excessive bleeding (albeit unexplained). Secondly, the fact that this diagnosis is given in conjunction with fibroids or PCOS, for example, raises questions about what if anything this diagnosis means, when written in the notes. For remaining analyses the

diagnosis of DUB will be taken to apply only if it is the *first* 'final diagnosis' recorded (n=326, 51%).

5.4.5 Overview

There is substantial overlap in menstrual morbidity and, as we learned in **4.3.3.vi** many women have long histories of problems, in many cases of multiple menstrual problems. This questions the partitioned nature of menstrual problems as currently conceptualised. An integrated life-course view may be more helpful to women trying to maximise their 'lived health', and to come to terms with unexpected and sometimes frightening or very inconvenient and discomfiting changes in their private bodily rhythms and function.

The symptom, problem and component reporting of these patients, referred predominantly for menorrhagia, raises doubts about the clinical definition of menorrhagia, focussed as it is entirely on the volume of blood loss. It is therefore of considerable concern that the predominant clinic diagnosis is dysfunctional uterine bleeding, this diagnosis being common even where the woman's menstrual complaint and help-seeking does not seem to be focussed on volume of loss.

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5.5 SUMMARY OF CHAPTER

5.5.1 *Presenting menstrual problem*

- Despite the predominant referral reason of excessive bleeding (76%), relatively few women report 'very heavy' periods (36%).
- Problems with severe pain and cyclic symptoms were common. Cycle-related changes were reported by 71% as occurring most periods, a quarter of these women reporting them as very troublesome. Severe period pain was reported by 40% of women before periods, and 72% with periods. A quarter of women reported 5 or more days severe pain per period and fewer than half of the women who reported using painkiller found that they worked most of the time.
- Nevertheless the focus of the gynaecology clinic appears to be perceived as abnormal bleeding, by both referring clinicians and the women themselves. Women were more likely to state bleeding (60%) as reason for clinic attendance, compared to pain or other reasons (30% and 34% respectively).
- Reports of *severe problems* with aspects of periods were most commonly cyclic mood changes, pain with periods, 'amount of period more than it used to be' and impact on daily life. It was striking that the aspect of periods 'lose too much blood' was only the 8th most prevalent severe problem. So, where abnormal bleeding is a problem the issue is not specifically volume but instead appears to be based on concerns about change from normal and the strain of containment.
- Women's citations of which aspects had been the *cause* of help-seeking were in order of prevalence: feeling unwell, increased period, lose too much blood, cyclic mood changes, period pain and irregular periods.
- Clots were a very common occurrence, with 90% of women reporting some, the number per period being 3 to 12 (IQR), mostly up to 20p size, and 6% self-stated clots as reason for clinic attendance, and 4% cited clots rather than one of the listed aspects as cause of help-seeking.
- Time elapsed between onset of severe symptoms and clinic visit was shortest for excessive bleeding, and longest for PMS, and pain, particularly.

5.5.2 *Components of variation in menstrual experience*

- For *dealing with periods* the components of variation that emerged were: 'impact of volume' (21% of variation in the data accounted for), 'variable flow' (17%),

'resource consequences' (13%), 'being unwell/irritable during period' (9%) and 'unpredictable onset' (6%)..

- For *feelings about periods* the components that emerged were: 'containment distress' (23% of variation), 'periods a burden' (17%), 'worry about change' (10%), 'resent resources' (10%) and 'had enough of periods' (7%).

5.5.3 Containment of period

- Women reported cycle-to-cycle variation in the total duration of their periods (IQR 2 to 8 days difference between shortest and longest reported periods)
- A quarter of women reported their periods starting 'in a gush' (26%).
- Duration of 'full flow' was 2 to 6 days (IQR), although there were many durations considerably longer than this. A third of women reported having to change every hour or more often during full flow.
- Protection used was compatible with heavy flow – nearly half of all women used only pads (48%) and a further 40% both pads and tampons. About a quarter of these women were using the top (super plus) grade of absorbency.
- The vast majority of women had to get up at night to change (79%), used double protection (69%), and experienced accidents (86%).
- With respect to facilities at home for coping with periods: 75% of women have no toilet separate from the bathroom, and 81% have nowhere suitable to soak bloodstains. This score is associated with deprivation.

5.5.4 Clinic outcome

- Median time to discharge or referring on was 13 weeks, and half the women had only two or fewer clinic appointments in total.
- The low rate of diagnoses of dysmenorrhoea and PMS (7% each) contrasts strongly with the high rate of self-report of severe problems with these aspects of periods (37% and 40% respectively).
- Diagnoses that might be associated with heavy bleeding were fibroids (18%), polyps (3%), peri-menopausal/menopausal (3%) and anovulatory bleeding without PCOS (2%).
- Apart from these diagnoses, 55% of women received a diagnosis (first or second mentioned) of dysfunctional uterine bleeding. Diagnosis of DUB was made in the *absence* even of referral by GP for bleeding (33% nevertheless diagnosed with

DUB), rating periods heavy (34%), or reporting a volume aspect of bleeding a severe problem (50%).

- For remaining analyses the diagnosis of DUB will be taken to apply only if it is the first of the (up to) two 'final diagnoses' recorded (n=326, 51%).

Chapter 6

STUDY RESULTS:

QUANTIFYING MENSTRUAL LOSS

6.1 INTRODUCTION

For many decades menorrhagia has been the clinical descriptor for complaint of excessive heaviness of menstrual blood loss. In this chapter the data for the three methods of quantification of menstrual loss will be reported. These are:

- Measurement of menstrual blood volume from collected used sanitary products.
- Measurement of total menstrual fluid volume by weighing used sanitary products, which have been protected from evaporation as far as possible, and subtracting dry weight of products used to obtain directly from change in weight in grams the total volume of menstrual loss contained by the products. This total fluid volume can in turn be used to estimate menstrual blood loss volume.
- Prospective charting of menstrual period detailing experience and also number of products used and degree of soaking, with the aim of estimating menstrual loss volumes from product usage/soaking data.

The relationships between the methods will be evaluated and methodological concerns will be noted, but description of theoretical investigations and experiments undertaken to elucidate measurement issues, will be held over to **Chapter 7**.

6.2 METHODS FOR THIS CHAPTER

6.2.1 Objective measurement of volumes

6.2.1.i Principle

TOTAL FLUID VOLUME.

As explained in Chapter 3, the principle used for measurement of total volume of menstrual loss is that each millilitre of loss weighs one gram (Fraser et al. 1985). If all the menstrual protection used is collected in air-tight storage (to avoid evaporation), and if the dry weight of menstrual protection used is known, then all that is required is to weigh the used products, and subtract their dry weight prior to use. The difference in weight in grams can then be converted directly into millilitres for an estimate of total menstrual fluid loss.

This part of the study was essentially a feasibility trial of the use of the much more easily-measured total fluid volume, rather than menstrual blood loss, as an objective measure of 'heavy periods'. We particularly wished to develop a method that would be acceptable to women. Anecdotally, one of the aspects of menstrual collection (for measurement of blood volume) that women express distaste for is the idea of some laboratory worker handling their used sanitary products. Therefore it was believed a proposed method would be more acceptable if women could be reassured that the assessment of menstrual loss does *not* require handling of individual used products in the laboratory.

In the present study all used and collected products *had* to be handled for measurement of blood volume (see below), but we nevertheless wanted the total fluid measurement procedure to have the potential in the future to be a 'stand alone' method, if it proved a sufficient and clinically-useful quantification. In a future application of only the total fluid volume measurement procedure, women could be asked to collect used products sealed in opaque polythene bags, and record a count of the number and types of products used, on the basis of an undertaking that the collection would be weighed *unopened.*

With regard to the dry weights of the products used, we wished to avoid prior weighing of individual products, as had been used in other menstrual collection studies (Fraser et al. 2001; Fraser et al. 1985). Prior weighing would mean products had to be unwrapped, and then repackaged. In addition, it would have meant each product being supplied to the woman in a polythene bag labelled with the product's dry weight, and her being requested to track products by replacing each product once used into its original polythene bag, the one in which it had been supplied. Therefore individual pre-weighing of products would mean excessive demands on collectors, and may lead to defaulting or errors. The need to match wet to dry weights would also have made the goal of 'weighing unopened' very difficult to achieve. In the interests of acceptability therefore it was decided that individual products would not be pre-weighed, but instead the total dry weight of the products used would be *estimated* by means of previously established average weights for the various products used, by brand and absorbency grade.

This allowed the sanitary products to be provided to women still in their packaging as taken from retailer's shelf, thus avoiding any concern that their sanitary protection might have been 'contaminated' prior to use through handling by laboratory staff.

The intention was the woman would seal each individual used product in one of the airtight bags provided, without any wrappings or toilet paper, and all used products thus bagged were to be collected into an outer (strong) plastic bag. It would then be possible to weigh the entire collection in the outer bag, without opening any of the sealed bags. The menstrual chart would provide a count of products in the collection, and known average dry weights of these products, and of the plastic bags provided and used, would be used to calculate the expected dry weight of the collection. The method would have the further advantage of retaining, in the overall (wet) weight of the collection, the weight of any moisture that has evaporated from the products and condensed on the insides of the bags. The question is whether total fluid volume measurement would be accurate and informative enough for clinical purposes.

MENSTRUAL BLOOD LOSS.

The method to be used for measurement of menstrual blood loss was that initially described by Hallberg (Hallberg & Nilsson 1964). Our study pre-dated the trend towards making adjustments for spillages and clots, so such a potential was not allowed for in the design. However, a concern about the quality of life impact of menstrual accidents did ensure that the menstrual diary each collector completed for the period collected, asked about clots by size and about leakages (but without asking that 'size' of spillage be estimated). Therefore some examination of the potential bias due to under-measurement is possible.

The principle invoked is that if used sanitary products are soaked in sodium hydroxide (NaOH) then even dried blood will be dissolved, and the haemoglobin in the blood, and indeed most products resulting from degradation of haemoglobin, will be converted to alkaline hematine (Hallberg & Nilsson 1964). Spectrophotometric assessment of the soaking solution will determine the optical density (or 'absorbance') of the solution, that is the amount of light transmitted through the sample *relative to* a reference cell of pure NaOH (the reference cell being arbitrarily set at 100% transmittance). A particular compound in solution will produce a spectral-transmittance curve across the entire light spectrum that is characteristic for that compound. This feature can be used for identification of unknown compounds. However, in this application the part of the spectrum that is of interest is known; the absorbance range for heme chromogens is centred on 546 mμ, in the 'blue-green' range of the spectrum. For a particular band of the spectrum, the 'absorbance' is proportional to the concentration in the solution being assessed, of the compound of interest. This is generally the case for a range of concentrations, but the relationship may break down at extremes of concentration.

Provided proportionality holds, then the concentration of the compound in the solution can be obtained by relating the optical density of the solution with unknown concentration to that for a solution with standard concentration. In this application however it is not concentration as such that is of interest, but volume of blood in the menstrual collection. Furthermore, alkaline haematin is derived from haemoglobin,

and women differ from each other in terms of the concentration of haemoglobin circulating in their blood streams, and therefore also in terms of the concentration of haemoglobin in the menstrual blood collected. Therefore a 'standard' concentration of heme chromogens can not be used for spectrophotometric comparison. Instead, the comparator is a known dilution, in NaOH, of the woman's own blood, the venous sample taken around the time of menstruation. It is then possible to estimate for each collector the volume of *her* blood there must have been in her menstrual collection. This is done by taking the ratio of the optical densities (absorbances) of the two solutions in NaOH of her blood (venous and menstrual collection), each factored up by the dilution volumes of NaOH added.

6.2.1.ii Procedure for measurement.

TOTAL FLUID VOLUME.

The procedure used for ascertaining total fluid was:

- The woman was provided with standard brand products, still in their own packaging.
- Once used each product was to be sealed in an opaque nappy sack, and returned to the yellow liner bag, with no wrappings or toilet paper included.
- The woman was to record prospectively on the menstrual chart (MC) each new item of sanitary protection applied, and note any non-standard products used, including brand and type.
- At the laboratory the collection was to be weighed, still in the nappy sacks and yellow liner sack, giving the Total Weight for the Collection (TWC).
- The Total Product and Bag Weight (TPBW) was obtained by accumulating average dry weights of the products used, the average weight of the nappy sacks, and the weight of the yellow liner sack.
- Total weight of menstrual fluid collected was calculated by subtracting, from the total weight for the collection, the accumulated product and bag (dry) weight (TWC – TPBW).
- Total Fluid volume was obtained by a direct conversion from grams to millilitres: Total Fluid (mL) = [TWC – TPBW]g

The procedure described by Hallberg for ascertaining blood volume is detailed below (Hallberg & Nilsson 1964). (Some of the adaptations made for this study, or comments on Hallberg's method, are described in square brackets.)

- After weighing of entire collection for Total Fluid loss determination (as described above), and after cutting open the nappy sacks in which the products had been stored, the products were counted into a plastic liner bag within a container (bucket). (Any blood remaining on the inside of the bags was wiped off with a spare pad, which was added to the others, for extraction.)
- Sodium hydroxide solution (NaOH) was mixed at a strength of 160 NaOH pellets to 4 litres of water (5%).
- A measured amount of the NaOH solution was used to cover collected pads and tampons in the container Hallberg recommended 1 to 2 litres for up to 15 towels, and if there were too many to undertake the extraction in two halves (Hallberg & Nilsson 1964). (The solution was added in multiples of 2 litres until the products were covered).
- A measured amount of the venous blood sample was made up to a volume of 100mL with the prepared NaOH. Hallberg used a dilution of 1 in 100 (Hallberg & Nilsson 1964). (In Edinburgh the same dilution was used, for example, 1mL venous blood + 99 mL NaOH gives a 1 in 100 dilution. In Glasgow, according to their established practice, 0.5ml blood was made up to 100mL, giving 1 in 200 dilution.)
- The products soaking in the container, and the diluted venous blood, were left to soak/stand in the laboratory. Hallberg recommended a duration of soaking of at least 20 hours (Hallberg & Nilsson 1964). (In this study the duration of soaking was 48 hours or sometimes longer.)
- After soaking Hallberg recommended thorough squeezing and rubbing of each product to ensure all dried blood stains have disappeared, with rubber gloves for protection of hands. (This is not a pleasant activity, and would now also be considered an excessively hazardous task to request of laboratory

staff. This probably accounts for the introduction in recent years of stomachers, which undertake the mashing in an automated way, within the 'safety' of a heavy duty polythene bag.)

- A sample of the supernatant was then taken by dipping in a glass beaker. This fluid was filtered into a clean beaker. Hallberg recommends alkali-resistant filter paper (Hallberg & Nilsson 1964).
- The dilute venous blood and the filtered supernatant were each measured for haemoglobin by means of a spectrophotometer, measuring at the 546 mμ absorbency spectrum ('blue/yellow'), in the haematin range. (The optical density (OD, absorbance) was measured, without a conversion to haemoglobin.)

Hallberg does not in fact provide a formula for the calculation of blood loss volume, but comments only: "The amount of haemoglobin lost during menstruation was easily calculated from the extinction and the volume of the extract (Hallberg & Nilsson 1964). The menstrual blood loss was then calculated from the haemoglobin concentration of the subject." 'Extinction' (of light) is clearly an older term for 'absorbance' (Evenson 1994). (Most papers on this topic do not give the detail of the calculation/formula (Cole et al. 1971; Fraser et al. 2001; Hallberg et al. 1966; Higham et al. 1990; Rees 1991; Reid et al. 2000; Wyatt et al. 2001).) The formulae available at Edinburgh and Glasgow as 'the Hallberg method', undertake the calculation without an explicit need to specify haemoglobin concentration of venous blood. The formula applied in this study to calculate blood volume of menstrual loss collected was:

$$\text{Blood (mL)} = \frac{\text{Optical Density(products)} \times \text{Soaking Volume of NaOH}}{\text{Optical Density(venous blood)} \times \text{'Dilution' of venous blood}}$$

where 'dilution' is the volume *to which* 1ml venous blood is diluted. The advantage of this formula is that the same spectrophotometer is used to obtain haematin concentration (implicitly the haemoglobin concentration) for both the soaking solution and the venous blood solution. Therefore, where 4L of NaOH is used for soaking, and a 1 in 100 dilution of venous blood is used, the formula is:

$$\text{Blood volume (mL)} = \frac{\text{OD (products solution)} \times 4000}{\text{OD (venous blood)} \times 100}$$

There will be further discussion of the formula in the following chapter.

Although the optimum would have been to take the venous blood sample just prior to menses the timing for this would have been difficult to predict, and in all cases obtaining the sample would have been logistically very difficult, and an inconvenience for the women involved. Therefore it was decided that the blood sample would be taken when the menstrual collection was handed over, usually very soon after the end of the period. In a few cases (n=8) the woman and the research nurse did not meet up, and so no sample could be taken. In these cases the most recent clinic blood sample was used instead.

6.2.1.iii Preparatory work for measurement

TOTAL FLUID VOLUME.

For the calculation of total fluid volume, estimates were required of the average dry weight of the standard sanitary products to be used, of the nappy sacks for sealing each product, and for the yellow liner sacks. We undertook test-weighings of samples of products from a number of different packs of the brands/grades provided to the collectors. By calculating the means and standard deviations we would be able to estimate the error likely to be introduced into our measurement of total fluid loss by use of our 'overall' method.

Table 6.1 shows the average weights ascertained. In the case of sanitary protection these weights were free of wrapping and in the case of tampons free also of applicator. For nappy sacks the individual sack weights were very low, and in practice the majority of women would use 20 or more for one menstrual collection. These were therefore weighed in bundles of 25 sacks. There was highest variability in weights for the bundles of nappy sacks (coefficient of variation 9.7%). Our impression was that this was a production issue, resulting in an entire roll of nappy sacks tending to be heavier, or lighter, than the average given in the table, perhaps due to the temperature of the plastic fluid at the time of extruding into bags. For the

purposes of accumulating 'dry weight' of the collection, each nappy sack used was counted as weighing 46.79g divided by 25, that is 1.87g.

Table 6.1 Average weights of bags and products used in menstrual collection

	Mean weight (g)	Standard deviation (g)
Heavy duty yellow liner bag (each)	70.82	0.77
Nappy sacks (bundle of 25)	46.79	4.53
Bodyform superplus pads (each)	6.43	0.23
Tampax tampons (super, each)	3.30	0.08
Tampax tampons (super plus, each)	3.70	0.20

Although methodologically it would have been preferable to provide women with single bags randomly selected from different rolls, to average out the errors, it was decided that it would be easier and hence preferable for the women collecting, and the research nurses, if they could be given a single run (bundle) of 30 nappy sacks.

The purpose of this aspect of the study was simple provision of a clinically 'good enough' estimate of total fluid loss, which could form the basis for discussion between patient and doctor about the menstrual complaint, and strategies to manage it. For 68% of collectors the error introduced by the variability in weight of nappy sacks would be expected to be less than 4.6mL either side of the true value (which for a woman with menorrhagia as clinically defined, blood loss of 80mL or more would be anticipated to be, on the basis of past research, 180mL or more (Fraser et al. 2001)).

When the weighings of products were undertaken the opportunity was taken to check the scales at the two laboratories, and also to compare measurement reliability for the two research nurses. The weighings were undertaken by the study co-ordinator using both Edinburgh and Glasgow scales, and also in each centre by the local research nurse. At each centre there was good agreement between the two weighers (0.01g mean difference in Edinburgh between weighers for bundles of 25 nappy sacks,

0.06g difference in Glasgow for the same weighings, so less than 0.5% for the Edinburgh research nurse, less than 1.5% for the Glasgow research nurse). A small difference in weights between centres (scales) was observed across the range of weighings, with the Glasgow scale weighing, for example, bundles of 25 nappy sacks lighter by 0.42g, a discrepancy of less than 1% of the goods being weighed.

Where non-standard sanitary products had to be used, because of some emergency, it was requested that the brand and absorbency be recorded on the Menstrual Chart (MC). Once the data collection was underway, there was surveillance of Menstrual Charts returned, for any recording of use of non-standard sanitary protection. If this occurred a pack of equivalent products was purchased and weighings undertaken by the study co-ordinator to ascertain the appropriate average weight per product to be used for each recorded use of such a product, in summations of dry weight.

MENSTRUAL BLOOD LOSS.

The study design had specified that the established method of blood volume measurement would be used (Hallberg & Nilsson 1964). At the Glasgow centre blood loss determinations were already being used for assessment of some patients, so a measurement protocol was in use. Dr Mary Campbell Brown, the gynaecologist running the menstrual problem clinic, oversaw the service. She undertook to train the Glasgow research nurse, who would work in that laboratory for the purposes of the menstrual blood loss measurements. At the Edinburgh centre such determinations had been undertaken in the past, for research studies, and there was a technician who had been involved in the studies and could thus train the Edinburgh research nurse. At Edinburgh it had been the practice to use a 'stomacher' to mash the soaked products, sealed in a strong plastic bag designed for the equipment, to ensure speedy and efficient extraction of haematin into the NaOH solution. However, Glasgow revealed that they did not use a stomacher, but soaked only, for 48 hours, and that this worked well. Given that there was an established protocol in operation in Glasgow, and a wish to have homogeneity of methodologies across the centres in the study, it was decided that the stomacher would *not* be used Edinburgh, but instead the 'soaking only' method of Glasgow would be adopted. A further factor in making

this decision was that the research nurses were both part-time, and in the time budgeted also had to attend clinics to recruit patients, and undertake paperwork and administration to do with the study. So it seemed that the 'soaking only' approach would fit in better with their time schedules, since the collection could be set to soak at the end of one shift, and then left, needing only about 10 minutes attention two mornings later, for filtering and spectro-photometric analysis.

6.2.1.iv Objective measurement data

For measured menstrual blood loss the variables recorded were: date of analysis, volume NaOH used for soaking, secondary dilution factor (1 if no secondary dilution), optical density for soaking solution aliquot, venous sample dilution, optical density for venous sample aliquot, calculated menstrual blood volume.

For total menstrual fluid loss the variables recorded were: total wet weight of collection in yellow bag, weight of yellow sack given, number of nappy sacks used, numbers of study (super plus) pads, regular tampons and super tampons, numbers and weights of other non-study pads/tampons, calculated total dry weight of collection (including bags/sacks), calculated total fluid volume, numbers of pads and tampons stated as lost.

Blood as percentage of total fluid volume was calculated from menstrual blood volume and total fluid volume estimates.

6.2.2 Menstrual charting

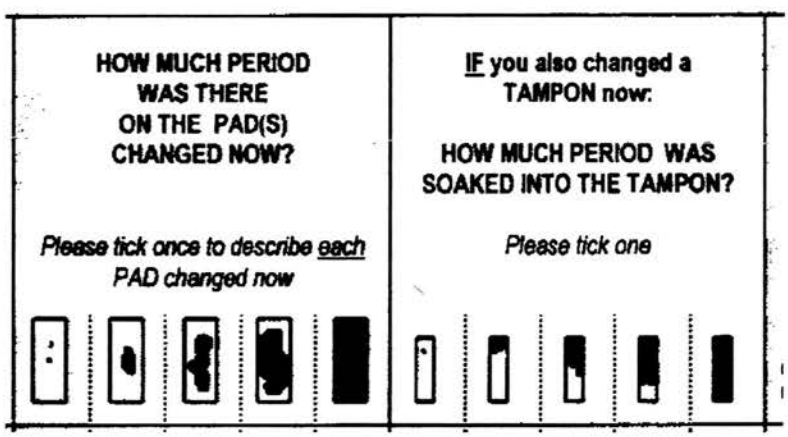
Two charts were published when we designed the study, (Higham et al. 1990; Janssen et al. 1995) but Higham's was chosen as the model. The two charts were actually almost identical. The chart requesting recording for each product used the extent of soaking/soiling of it, by matching to one of the pictograms of used menstrual protection provided (three each for pads and tampons) (Higham et al. 1990). The menstrual chart data in Higham's study enabled estimation of the volume of menstrual blood loss (Higham et al. 1990). Routine use of such a method of estimation would have the advantage of avoiding the need to collect used products, thereby preventing much of the discomfit of menstrual loss assessment. In the study

published, however, the products were collected, since as a methodological research study it was necessary to have objective measurement of blood loss alongside the charting, to enable development of the estimation formula.

6.2.2.i Rationale for adaptations to menstrual chart

For each type of protection, pad and tampon, Higham's menstrual chart (Higham et al. 1990) offered only three pictograms for recording extent of soaking/soiling, and none of them was suited to that stage of the period where the pad or tampon is used for reassurance mainly, when generally virtually no soiling occurs. It was felt that this over-simplification may have made it more difficult for women to complete the chart accurately, and certainly must have made it more difficult to estimate blood volume precisely. In addition, the pictograms for tampons were rather short and squat. Therefore, for the chart used in this study two pictograms were added to the sets for each of pads and tampons, one for very light soiling, and an extra one in the range of moderately heavy soiling. The tampon pictograms were also drawn to have a more realistic shape. The pictograms used are shown in **Figure 6.1**. The added pictograms are the first and fourth in each set.

Figure 6.1 Excerpt of menstrual chart showing pictograms for reporting of degree of soaking of used menstrual protection



The Higham chart (Higham et al. 1990) accumulated by day the numbers of products used with each of the three degrees of soiling, and the number of clots of various

sizes (compared to coins), with no indication of timing of product use. In the present study it was felt it would be helpful to understanding of the nature of complaint if the time-frame of changes could be captured. The chart was therefore adapted to become a log of changes of products (and degree of soaking of these) by time of day, as well as by day. This adaptation of the menstrual chart could give some insight to pattern of flow (and occurrence of clots) across the period (see **Appendix 3.5**). (When a research nurse analysed a menstrual collection in the laboratory she counted the products 'collected'. It was thus possible to check this number of products against product changes recorded in the chart.)

Thirdly, from discussions with women complaining of heavy periods (Warner & Critchley 1995), readings of the qualitative literature (Hodges 1989; Marshall 1998; O'Flynn & Britten 2000), and earlier research (Bancroft et al. 1993; Fraser et al. 1984), a picture was emerging that the main cause of complaining was not the volume of menstrual loss, but the impact on daily life, perhaps exacerbated by associated symptoms such as period pain. It was therefore decided that the menstrual chart should also capture the impact of periods. The log was elaborated to include use of double protection, accidents, and intensity of pain, by time of day, and to ask on a once per day basis about activities cancelled, use of pain-killers and use of other medication (see **Appendix 3.5**).

Finally, to be able to relate the period charted (and collected) to the reports of periods as already given in the questionnaires (CQ, MEQ), the woman was asked at the end of her period to compare it to periods over the last 6 months. The five aspects to be compared were: amount of loss, effect on daily activities, leakages, period pain, tiredness. For each the response had to be chosen from a five-point scale – much less, a bit less, much the same, a bit more, much more (than usual). This period review question can be found on the inside cover of the Menstrual Chart (see **Appendix 3.5**).

6.2.2.ii Development of the Menstrual Chart

To offset the quantity of information sought, great care was taken with the design and formatting of the chart to make it as user-friendly as possible. (See **Appendix**

3.5). The chart was laid out as an A5 landscape booklet, as it was expected women would have to carry it around with them if away from home. Both outside covers were blank, for discretion. Careful instructions were provided within the chart, together with the names and telephone numbers of the research nurses, in case any help was needed.

In previously published analyses, based on menstrual chart data (Higham et al. 1990), a score was assigned in advance to each of the possible pictograms, conveying degree of soaking (1, 5 and 10 were used for her tampon pictograms, and 1, 5 and 20 for pads). (For each of pads and tampons Higham's lightest and heaviest pictograms were almost identical to the 2nd and 5th pictograms used in the present study, while her middle pictogram was about half-way between the 3rd and 4th pictograms in the present study.) Higham's assigned scores were subsequently converted into total menstrual blood score (PBAC) by accumulating for each woman's period the relevant scores for each used product (pictogram) recorded (Higham et al. 1990). (In addition, the score was incremented for each clot reported - by 1 for clots size 1p, by 5 for clots sized 50p - but this would have been an adjustment for loss *not* collected.) If the final score was ≥ 100 this was deemed to be equivalent to a blood loss of $\geq$ 80mL. In contrast, the intention for this present study was to find by multiple regression the best score to apply for each pictogram, so as to achieve optimum estimation of menstrual blood volume and total menstrual fluid volume using a chart.

In order to be able to describe pattern of flow it was also requested that the time of changing be recorded. However, for the purposes of this initial analysis only the overall product use and soaking will be analysed, and related to the fluid volumes of interest.

6.2.2.iii Chart data

Menstrual chart variables recorded for analysis were: date and time of commencing protection; whether or not used tampons at all; total days charted; and, at end of period, comparison of period charted to periods in last 6 months, by means of a 5-point scale (much less/ less, about the same/ a bit more/ much more), in terms of five

features - amount of loss, having to stop activities, leakage onto clothes (and so on), severity of period pain and tiredness.

For each day the following summary variables were recorded: total number of changing times recorded; number of items changed; how many pads charted for each of 5 degrees-of-soaking pictograms; how many tampons charted for each of 5 degrees-of-soaking pictograms; whether pain was at any change in that day recorded as moderate; and whether at any change recorded as severe; how many clots were charted in that day of sizes 20p, 50p and 'bigger'; how many times in that day the respondent charted leakages onto underclothes, outer clothes and bedding/ furniture; whether any activities had had to be cancelled that day; how many pain-killers taken that day; and whether any other medication had been taken that day.

Further variables were calculated summarising the entire period: total pads, tampons and products (any) charted as used; total days where severe pain was charted and total days at least moderate pain; total numbers of clots of each size; total numbers of leakages of each degree; total pain-killers used; total days pain-killers used; maximum painkillers used any one day; maximum changes in any one day; and maximum items used in any one day.

6.2.3 Statistical methods

6.2.3.i Regression modelling of volumes

The menstrual blood and total fluid volumes have positively skewed distributions so for parametric analyses log transformation was used. For counts of products recorded in the menstrual chart, log transformation was also necessary for regression modelling. In this case, as some counts were zero, for which there is no 'log' value, 1 was added to every count prior to log transformation. For the estimation of blood volume from total fluid volume multiple regression was employed. For this regression the analysis was confined to women for whom there was a total fluid loss of 85mL or more. This was to avoid the excessive noise that was likely to pertain at lower total fluid losses, but would have been expected to retain in the analysis most women with menstrual blood losses of 42mL or more. The dependent variable was

blood volume, and the independent variable total fluid volume. This analysis was undertaken adjusting for centre (Edinburgh, Glasgow), and there was also examination of the effect of various other dependent variables, such as sanitary products used, and missing or extra products. Initially it had been intended to use two-thirds of the data as a training data set, and then to evaluate the prediction on the remaining data. However, this plan was changed because of a finding of between-centre differences in blood loss measurement, which will be reported in **6.3.1.iii** (and further examined and discussed in **Chapter 7**). It was felt it would be better to use all the data for modelling, in an effort to better understand the measurement differences between centres, and to have better scope to derive informative models adjusted for centre.

Multiple regression was also used to model menstrual blood loss and total menstrual fluid loss volumes in terms of diary data. As explained already, this had to be undertaken adjusting for centre. There was no prior specification that analysis would be confined to women with total fluid loss over a specific threshold, as had been done for the analyses for Fraser's study (Fraser et al. 2001), but it was anticipated this may be necessary for pragmatic reasons.

6.2.3.ii Confidence intervals for regression modelling

For regression estimates two confidence intervals can be calculated for the predicted value. For example, if estimating blood volume from total menstrual fluid volume, the first confidence interval is analogous with the commonly understood confidence interval for a mean or other summary statistic. It is the confidence interval for the true *mean* value for blood volume for collectors with that total fluid volume. Since there is greater confidence in prediction near the 'centre' of the data the intervals will be narrowest near the mean for the x-values (total fluid volumes), and widest towards the extremes of the x-values. The tendency for closer limits at the centre will be more noticeable for sparse data sets with a wide range of x-values. The line formed by joining the upper end points of all possible confidence intervals across the range of x-values therefore forms a diagonal arc, closer to the regression line in the 'centre' of the data. Similarly, but in reverse, for the lower limits. This is essentially the

confidence interval for the regression *line* predicting blood volume from total fluid volume.

The second form of confidence interval is that which applies to an *individual* prediction. That is, for an individual collector with a certain measured total menstrual fluid volume, the 95% confidence interval for *her* blood volume as predicted (estimated) by the regression model. For a specific measured total menstrual fluid volume, the 'predicted' blood volume will be the same regardless of whether it is an individual prediction being made, or an estimation (prediction) of the true mean value for collectors with that total menstrual fluid volume. However, the confidence interval for an individual determination, has to allow for the substantial between individual variability that bedevils clinical measurement, and so will always be considerably wider than the confidence interval described first, for the true *mean* blood volume. The confidence interval for an individual prediction is sometimes called the *prediction interval*, to distinguish it from the confidence interval for the true mean value.

In fact the regression analyses of blood volume on total fluid volume were undertaken with both variables log transformed, to deal with skewed distributions. In such a situation the definitions above for the two forms of confidence interval apply to the data and predictions *on the logged scale*. However the predictions and prediction intervals obtained by regression modelling on the logged scale can be back-transformed to the original scale, and can then be plotted with the original data. The process of back-transformation will however change the shape of the lines. For example, the regression line will be curved rather than straight after back-transformation, although this may be imperceptible.

6.2.4 Reporting results for log transformed menstrual volume variables

Menstrual loss volumes were log-transformed prior to parametric analysis by means of the t-test for independent groups. Group means (and confidence intervals) calculated for these logged data can be back-transformed and reported on the original scale as geometric means, with confidence intervals. (A geometric mean of n values

is the n^{th} root of the product of all values multiplied together.) However, in such comparisons the preference would be to report the *difference* between groups, with confidence interval for the difference. This is not possible given analysis on the logged scale. A back-transformed difference between group means of logged data is effectively a *ratio* of *geometric* means. Fortunately this ratio has a meaningful interpretation, as 'how many times bigger one geometric mean is than the other'. For example, a ratio of 1.8 would imply the one group's geometric mean is 1.8 times the other, or 80% bigger. If the ratio is 1 or very close to it then the means are (approximately) equal. Since the analysis of the logged data provides a difference with confidence interval for the difference, all three quantities (mean, lower limit and upper limit) can be back-transformed to give on the original scale a ratio of means with 95% confidence interval for the ratio. It is this strategy that has been used in this thesis.

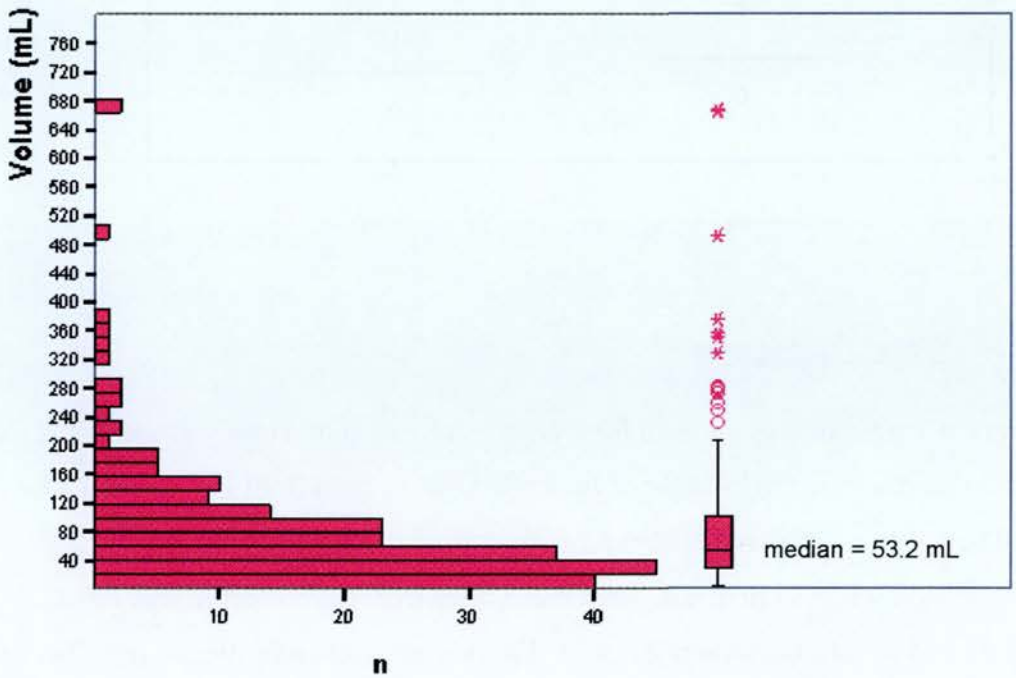
6.3 RESULTS

6.3.1 Findings for measured menstrual loss

6.3.1.i Measured blood volume

The distribution of measured blood losses for the 226 women who collected is shown in **Figure 6.2**; the median loss was 53mL (inter-quartile range 27 to 101mL) and 34% had losses of 80ml or more. Blood volumes in Glasgow were generally higher than in Edinburgh. The median, inter-quartile range (IQR) and maximum for blood volume in Edinburgh were 41.4 mL (IQR 22 to 77mL, maximum 351mL), and in Glasgow these were 64.7mL (IQR 31 to 119, maximum 668mL).

Figure 6.2 Histogram of measured blood losses, with superimposed box-plot (total n=226)



The positively skewed distributions for blood loss volume mean that log transformation is appropriate prior to use of parametric analysis methods, and so the natural logarithm transformation (Ln) was applied. **Figure 6.3** shows box-plots of Ln(blood volume) by centre. It can be seen that after transformation the distributions

Figure 6.4 Histogram of measured total fluid volumes, (total n=225)

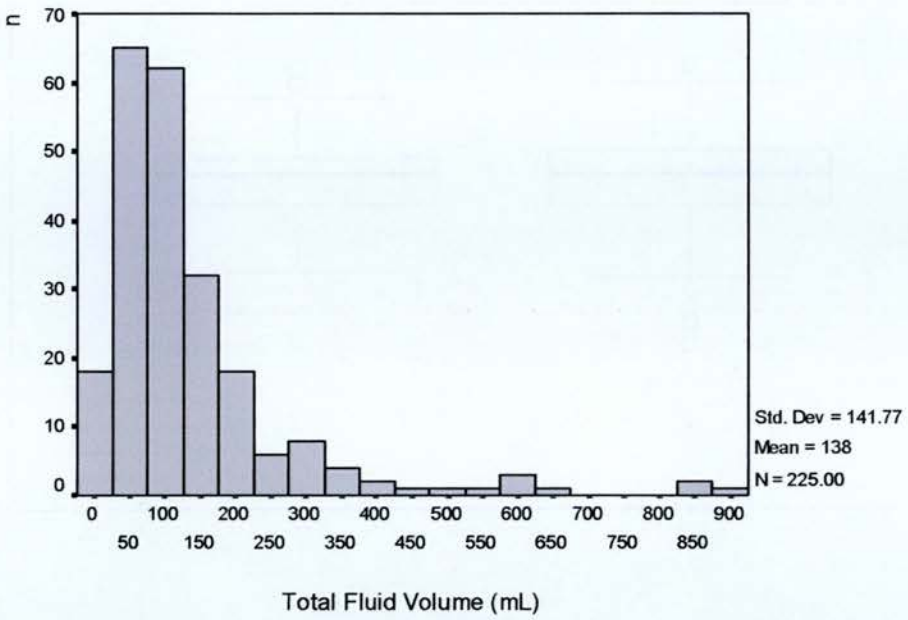


Figure 6.5 shows box-plots of Ln(total fluid volume) by centre. It can be seen that the resulting distributions are fairly symmetrical and the central location is almost equal. That is, Edinburgh total menstrual fluid volumes are very similar to those in Glasgow (medians 102.6mL and 103.4mL respectively).

The blood component of the menstrual loss can be calculated as a percentage of the total volume of menstrual loss. The median and inter-quartile range (IQR) for percentage blood by volume in Edinburgh were 44.3% (IQR 33 to 55%,), and in Glasgow these were 68.8% (IQR 53 to 86%). This difference in percentage blood loss was unexpected, based on earlier research work, so led to the various experiments and theoretical work to try to explain the differences (for example, to try to ascertain whether blood measurements in Glasgow were biased upwards, and/or total fluid volume measurements biased downwards, or *vice versa* in Edinburgh). These will be described in **Chapter 7**.

loss. This strategy also eliminates from analysis women with low menstrual volumes, where there are proportionately greater errors in total fluid measurement. The results of the analysis are shown in row 2 of **Table 6.2**. The residual error mean square was lower for the second analysis, and this allowed identification of an extreme outlier, with a standardised residual of –4.18.

Table 6.2 Linear regression analyses of logged menstrual blood volume on logged total menstrual fluid volume: data inclusion criteria and analysis of variance statistics

Analysis	Collectors included in analysis	N	R^{2+}	Residual EMSq^{++}	F ratio	df	p
1	All with data for x,y	225	0.742	0.276	319.7	2, 222	<0.001
2*	Total fluid ≥ 80mL	140	0.665	0.154	135.8	2, 137	<0.001
3 ~	Total fluid ≥ 80mL & case is *not* the extreme outlier*	139	0.704	0.134	165.3	2, 136	<0.001
4 (E)	Edinburgh collector & total fluid ≥ 80mL	56	0.647	0.142	98.0	1, 54	<0.001
5 (G)~~	Glasgow collector & total fluid ≥ 80mL & case is *not* the extreme outlier*	83	0.678	0.130	170.8	1, 81	<0.001

+ *R^2 is the proportion of the variance of (log) blood volume that is explained by the regression on log total menstrual fluid volume and, for analyses 1,2,and 3 only, centre.*

++ *Residual Error Mean Square from the analysis of variance table for the regression model*

* *One extreme outlier A was noted in analysis 2, with standardised residual –4.18. (Details of this and subsequent outliers are given in* ***Appendix 6.1 Table A6.1.1****.) Examination of this case found very high fluid:blood ratio, and that the woman had used all non-study (and heavy) pads. This case was excluded for subsequent analyses involving Glasgow collectors, that is, 3 and 5.*

~ *One new outlier B was noted in analysis 3, with standardised residual –3.08. Examination of this case found high fluid:blood ratio, but that the woman had used all standard pads. This case was retained.*

~~ *Two outliers were noted in analysis 5, B again, and a new case C, with standardised residuals –3.16 and –3.03. C had high fluid:blood ratio and had used a large amount of sanitary protection, about a third of which were non-study pads. These were retained.*

Given the size of the standardised residual, and the fact that the woman had used for her menstrual collection all non-study pads (for which a very heavy dry weight was assigned in the calculation), it was decided that the analysis should be re-run excluding this data point. The results for the analysis excluding this extreme outlier are shown in the third row of the table. This model also was a very good statistical fit, but the R^2 of 70% was not quite as good as that for the first analysis (74%). This is a result of the reduction in range of x-values in the model, due to excluding those with total fluid volume <= 80mL, since this allows the model less scope (range) to display it fit. However, it can be seen that by focussing on the upper range of total fluid volumes, and excluding the one extreme outlier, the Residual Error Mean Square, the residual error used to calculate confidence intervals for estimates, has been halved compared to the first analysis.

A further analysis was undertaken to explore the interaction between centre and slope, but there was no improvement in the model. The implication of this is that the best (parsimonious) model for these data has parallel regression lines for Edinburgh and Glasgow (on the log scale). For interest, analyses were also undertaken separately within centre, and these are presented in rows four and five of the table (Edinburgh and Glasgow respectively). The regression coefficients for all five analyses are presented in **Table 6.3**.

Table 6.3 Linear regression analyses of logged menstrual blood volume on logged total menstrual fluid volume: regression coefficients

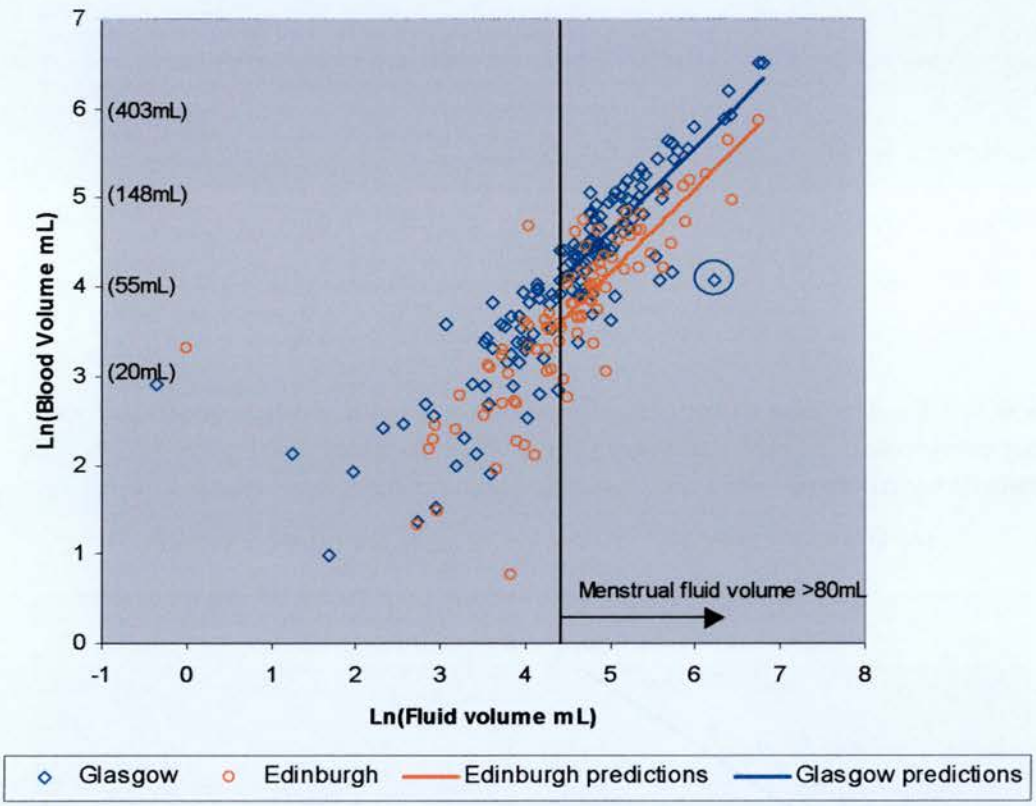
Analysis *	Regression Coefficients					
	a	(95% CI)	b_{centre}	(95% CI)	$b_{ln(total\ fluid)}$	(95% CI)
1	0.44	.05 to 0.82	–0.451	–.59 to –.31	0.907	.84 to 0.98
2	0.54	–.11 to 1.19	–0.439	–.57 to –.31	0.900	.78 to 1.00
3	0.34	–.27 to 0.95	–0.457	–.58 to –.33	0.946	.83 to 1.10
4 (E)	-0.42	–1.3 to 0.5	*n.a.*		0.916	.73 to 1.10
5 (G)	-0.23	–0.9 to 0.5	*n.a.*		0.967	.82 to 1.11

** See Table 6.2 for details of data cases used, n and regression ANOVA results.*

A scatter plot of all the menstrual fluid by blood volume measurements (logged) is presented in **Figure 6.6**, together with the parallel regression lines obtained for

Edinburgh and Glasgow from analysis 3 (see **Tables 6.2 & 6.3**). For each centre the regression line represents the predicted (logged) blood volume across the range of (logged) total menstrual fluid volumes.

Figure 6.6 Scatter plot of blood volume by total fluid volume (both logged) by centre, with superimposed lines for blood volume regressed on fluid volume.



To ease interpretability the logged values on the y-axis (blood component of menstrual loss) have been annotated with corresponding volumes on the original scale. Points plotted to the left of the solid black line on the x-axis (total fluid volume ≤80mL) were excluded from the regression modelling (analysis 3 in **Table 6.2**). All but one of these points had logged value for blood volume less than 4.2 (that is, measured blood volumes between 2 and 63mL). However, one Edinburgh point thus excluded had blood volume of 107mL, despite an 'impossible' *total* fluid volume of only 57mL - presumably the result of procedure (evaporation) and/or measurement errors giving a lower than true total fluid volume and/or a higher than true blood volume. As explained for analysis 3 (**Table 6.2**), one point initially included in the

analysis was subsequently excluded as an extreme outlier: this point, on the right of the line, is circled. All remaining points to the right of the line were included in the analysis. It can be seen that predicted menstrual blood volumes were higher for Glasgow collectors compared to Edinburgh collectors, across the range of total fluid volumes.

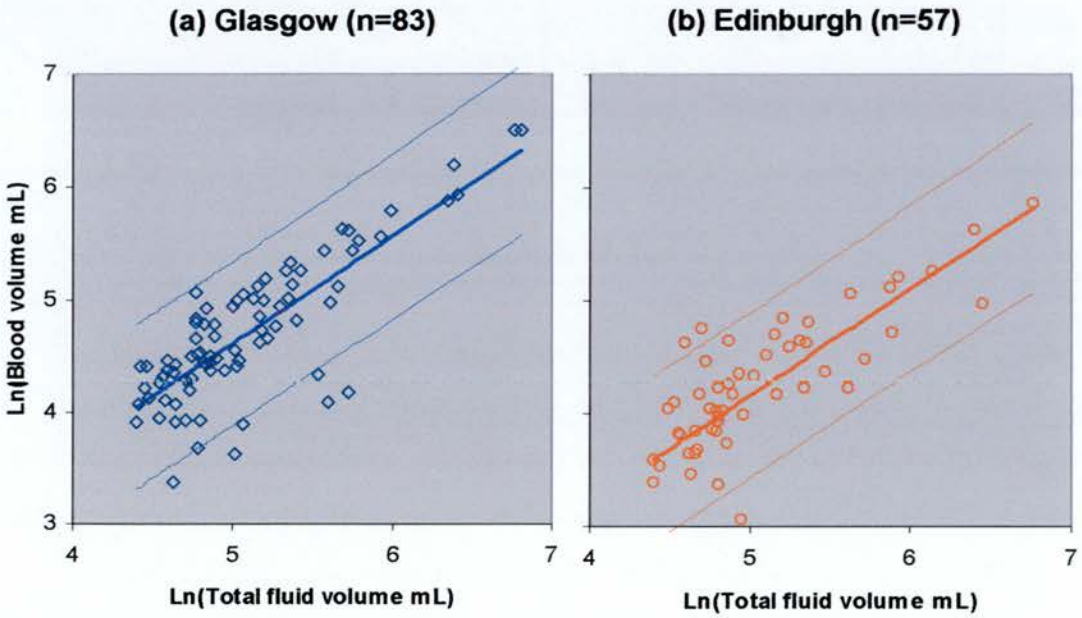
The regression equation was

$$\ln(\textit{blood volume}\ \text{mL}) = 0.34 - 0.457 \times \textit{centre} + 0.946 \times \ln(\textit{total menstrual fluid}\ \text{mL})$$

where *centre* =1 for Glasgow or 2 for Edinburgh.

Considering solely the data used in the analysis, **Figure 6.7** shows the logged data points and the regression lines and individual prediction intervals separately for each centre (second type of confidence intervals described in 6.2.3.ii).

Figure 6.7 Scatter plot of blood volume by total fluid volume (both logged), with superimposed regression lines (and 95% individual prediction intervals), separately by centre.

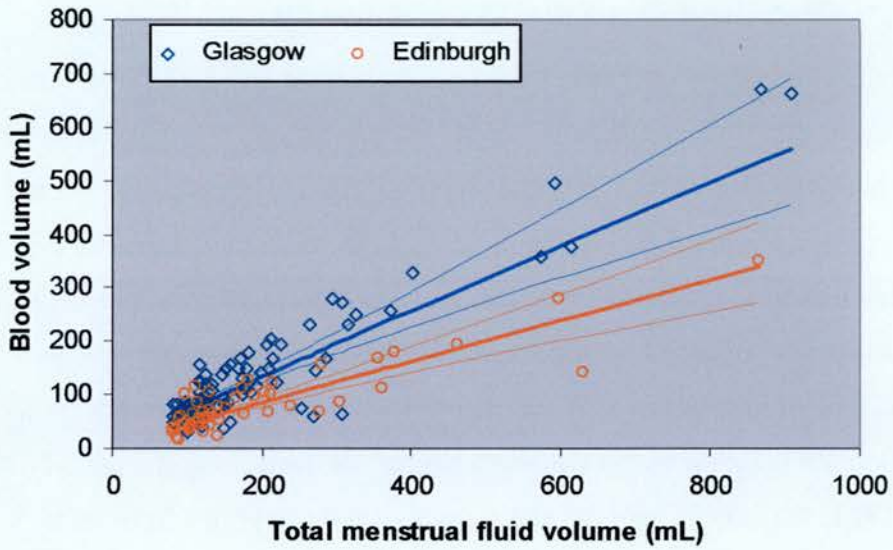


This shows that in Edinburgh prediction is fairly reliable for logged fluid volumes greater than 5 (that is, volumes > 148mL). For Glasgow there are 7 noticeably low estimates, plus the excluded outlier (not plotted here but shown in **Figure 6.6**), but otherwise estimation appears reliable. However, with the two plots being on the same

scale it is very clear how much higher the blood volume estimates are in Glasgow compared to Edinburgh.

The log transformation of the data was a mathematical contrivance to allow linear regression analyses of these data, but is not otherwise helpful to assessment of the clinical utility of the model. The real clinical interest lies in the predicted blood volumes converted to the original scale. The original data points have therefore been plotted in **Figure 6.8**, together with the regression lines for each centre and the confidence intervals for the regression lines (means), all anti-logged to the original scale.

Figure 6.8 Scatter plot of blood volume by total fluid volume by centre, with superimposed regression lines (and 95% confidence intervals) for mean blood volume on fluid volume (anti-logged from model derived on logged data).



These graphs show only the data included in analysis 3. The (thicker) regression lines are identical with those shown in **Figure 6.7**, except back-transformed. The (lighter) confidence intervals however are those pertaining to the regression lines (means) and are not back-transformations of the individual prediction limits shown in **Figure 6.7**. The confidence intervals plotted in **Figure 6.8** are the first type of confidence interval defined in Statistical methods (62.3.i), those for the true *mean* blood volume the hypothetical group of collectors with that total fluid volume.

It can be seen that once anti-logged the regression lines of **Figure 6.7** (on the logged scale) are no longer 'parallel'. (They will also be slightly curved, but this is hardly perceptible.) The interpretation of this plot is that on the original scale the amount by which a predicted blood volume in Glasgow exceeded that in Edinburgh, for the same total fluid volume, was greater for greater total fluid volumes. The regression equation can be re-written in the original scale as:

$$\textit{Blood volume}\ (\text{mL}) = 0.890 \times \textit{Total Menstrual Fluid(mL)}^{0.946} \text{ for Glasgow}$$

$$\text{or} \quad = 0.563 \times \textit{Total Menstrual Fluid(mL)}^{0.946} \text{ for Edinburgh.}$$

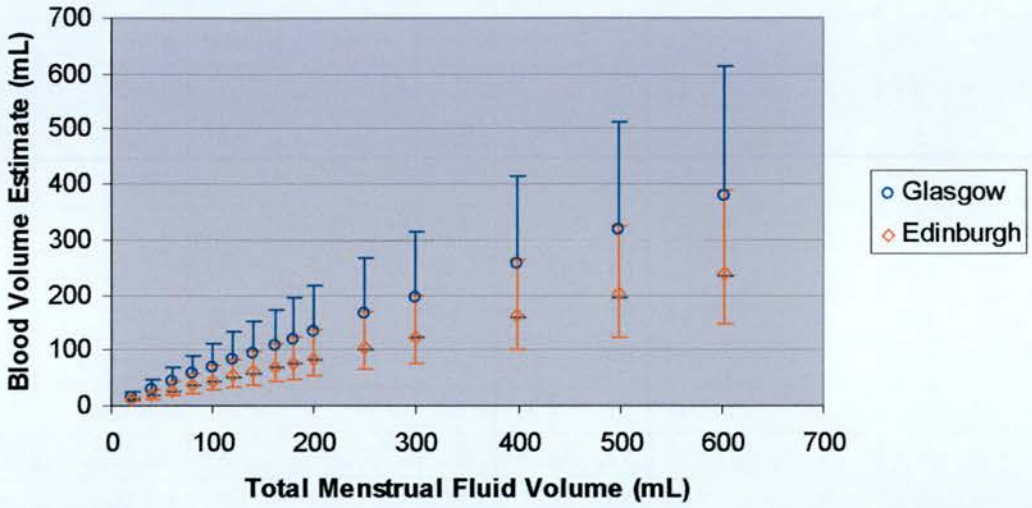
Therefore across the range of total menstrual fluid volumes the estimated blood volumes for Edinburgh were smaller than the Glasgow volumes by a factor of 0.563/0.890, that is 0.63. This means blood volume estimates in Edinburgh were lower by 37%, and confirms the visual impression from **Figure 6.8**.

The clinical utility of using total menstrual fluid volume to estimate blood volume depends on the width of the prediction interval expressed on the original scale. The width, once back-transformed, of the (narrower) confidence intervals for the means (regression lines) in **Figure 6.8** gives some idea of the width that would be expected for the much wider 95% prediction intervals, once back-transformed. However, in place of no estimation of blood volume at all, the usual clinical scenario, some prediction may be preferable, even if less than 95% confident. **Figure 6.9** shows the 80% prediction intervals for blood volume estimates derived using the model of analysis 3 (**Table 6.2**) for a range of total menstrual fluid volumes from 20 to 600mL. (It should be noted that the first three total fluid volumes (20, 40 and 60mL) are out-with the range of total fluid volumes used to derive the model (>80mL), that is, are extrapolated.)

On the log scale the prediction interval is plus/minus approximately 0.5 either side of the estimated log blood volume, across the whole range of (logged) total fluid volumes. The marked widening of the prediction intervals with increasing total fluid volumes, seen in **Figure 6.9**, is almost entirely due to the arithmetic process of back-transforming from the log scale. However, in the range where the widest prediction

intervals are found, total fluid volumes of more than 400mL, for each x-value the entire interval of blood volume estimates is on the whole 'extreme' (>100mL, say), regardless of whether at the top, middle or bottom of the prediction intervals.

Figure 6.9 Blood volume estimates and 80% prediction intervals for a range of total menstrual fluid volumes, separately by centre.



For easier reference **Table 6.4** presents prediction intervals in tabular form for the same range of total menstrual fluid volumes. In Glasgow the blood volumes are high relative to total fluid volumes, so the upper limits of the 80% prediction intervals for estimated blood volume exceed the total fluid volume in every case. Since the blood volume is a sub-part of the total fluid volume it is a physical impossibility for the blood volume to exceed the fluid volume. However in these data both the fluid volume and blood volume are measured with error. The width of the prediction interval reflects that fact and does not imply that the *true* blood volume could be greater than the *true* total fluid volume.

The predicted blood volumes are demarcated with a solid line denoting the separation between fitted values (with total fluid volume >80mL) and extrapolated (where total fluid volume <80mL). The blood volume estimates have been classified tentatively as light, moderate, heavy, very heavy and extreme.

Table 6.4 Linear regression predictions of blood volume separately by centre, with 80% individual prediction intervals (PI).

Menstrual Fluid Volume (mL)	GLASGOW			EDINBURGH		
	Estimated Blood Volume (mL)	80% PI	*	Estimated Blood Volume (mL)	80% PI	*
20	15	10, 25	L	10	6,16	L
40	29	18, 47	L	18	11, 30	L
60	43	26, 69	M	27	17, 44	L
80	56	35, 90	H	36	22, 57	M
100	70	43, 112	H	44	27, 71	M
120	83	51, 133	VH	52	32, 84	H
140	95	59, 153	VH	60	37, 97	H
160	109	68, 175	VH	69	43,111	H
180	121	79, 174	E	76	47,123	VH
200	134	83, 215	E	85	53,136	VH
250	165	102, 265	E	104	65,168	VH
300	195	121, 315	E	124	77, 200	E
400	257	159, 415	E	163	101, 263	E
500	317	196, 513	E	200	124,325	E
600	379	234, 615	E	240	148,390	E

** KEY: Possible classification of blood volume- L = light (<35mL), M = moderate (35-50mL), H = heavy (50-75mL), VH = very heavy (75-115mL), E = extreme (>115mL)*

6.3.2 Description of periods by prospective charting

6.3.2.i Completion of charts and description of prospectively charted periods

In total 295 women completed menstrual charts. Of the 226 women undertaking menstrual collection 19 did not provide completed menstrual charts. **Table 6.5** summarises the prospective record on the period collected for the 207 women who completed a chart. The number of changes of protection will in some cases be fewer than the number of products used because some women use double protection and hence may use one 'change' to replace two or more products. The timing of 'onset' of periods (defined as the time of day when use of sanitary protection commenced) was relatively unlikely to be overnight, that is between 7pm and 6.59am, with only 2% of women per hour on average commencing their periods during this time. The

most common time to start wearing protection was 7am to 9.59am (average 11% of women per hour), whereas the rate of commencing protection for the remainder of the day was a fairly even 5% per hour.

Table 6.5 Description of collected period in terms of prospectively collected menstrual chart data (n=207 women, missing data n=19).

Prospective record of period	Mean	Median (IQR)	Maximum
Duration of period (days)	5.6	5 (4,6)	27
Changes of sanitary protection:			
Total no.	22.6	21 (16,27)	68
Most in a day	6.4	6 (5,8)	13
Number of products used:			
Total no.	25.1	23 (17,31)	78
Most used in a day	7.7	7 (5,9)	23
Clots:			
Total no. size 20p	6.1	4 (1,8)	71
Total no. size 50p	2.2	0 (0,3)	35
Total no. bigger than 50p	0.6	0 (0,0)	15
Leakages:			
Total no. onto outer clothes	0.6	0 (0,1)	6
Total no. onto bedding, furniture	1.1	1 (0,2)	6
Cancelled activities:			
Total no. of days	0.7	0 (0,1)	4
Days with period pain:			
Total days moderate/severe pain	2.6	2 (1,4)	12
Total days severe pain	1.2	1 (0,2)	6
Use of pain-killers:			
Total no. of days	2.3	2 (1,4)	9
Most no. taken in a day	3.6	4 (1,6)	12

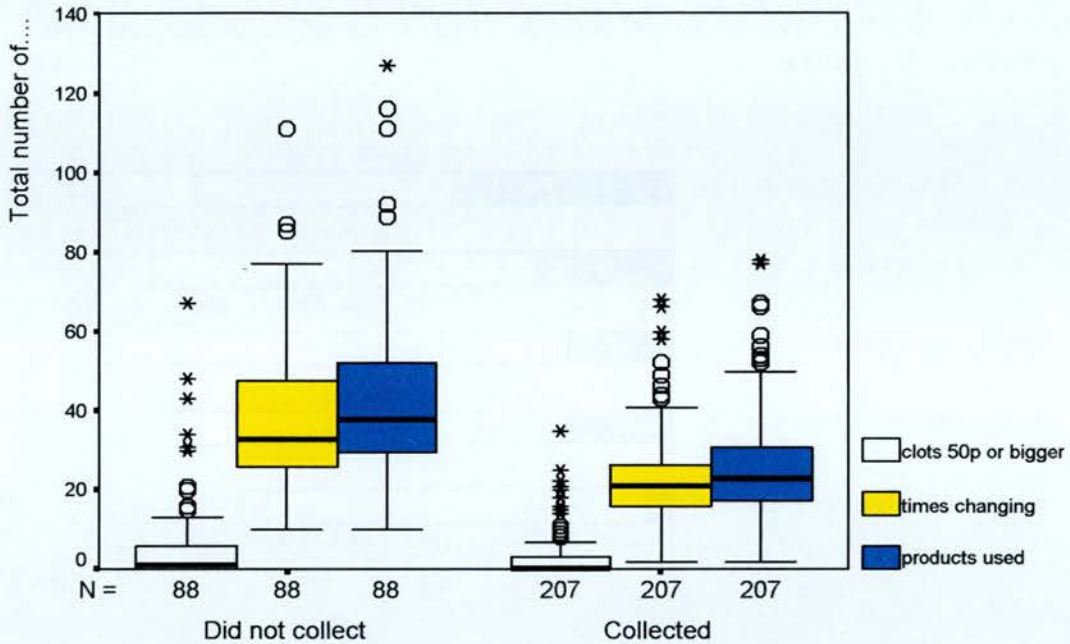
The 19 women who collected but did not complete charts, despite agreeing to do so, were compared with the remainder of collectors. The collectors who did not complete charts were predominantly of lowest socio-economic status (Carstairs deprivation categories 5,6 &7, 84% v 43%) (Carstairs & Morris 1990). These women were more likely to have rated their periods as *less than* 'very heavy' (68% v 46%),

so it may seem that their menstrual loss was not extreme, which is supported by the fact that they were slightly more likely to have measured blood loss less than 50mL (53% v 45%). However, they were also more likely to have given bleeding problem as their self-stated reason for clinic attendance (79%v 70%), to have responded that 'losing too much blood' was a marked/severe problem for them (84% v 64%), and to have identified one or more aspects of excessive bleeding as the reason for coming to the clinic (58% v 41% cited as reason one or more of losing too much blood, difficulty in preventing accidents and periods going on for too many days).

The periods of the subgroup collecting (already shown in **Table 6.5**) were for some variables different to the periods described by the women who agreed to complete charts but who did not collect (n=88). This latter subgroup comprised some women who agreed to collect but in the event did not manage to achieve this, although they nevertheless completed the menstrual chart. Other women were clear from the outset that they would not or could not collect, but offered to complete the chart to describe their experience of an actual period. The charted periods of women who did *not* collect tended to last about a day longer, with mean 6.8 days and median (IQR) of 6 (5,8) days, and they were more likely to use tampons (63% v 43%, using tampons solely or in addition to pads). The other variables that seemed to differ between the two subgroups have been presented in **Figure 6.10** as separate box-plots for the two subgroups.

It can be seen that the charting women who did not collect reported more of the larger two sizes of clots, and also considerably more changes of sanitary protection, and a greater total number of products used. For all the other variables in **Table 6.5** the two subgroups were very similar, in particular for the maximum number in any day of products used and changes required. They were also similar in terms of timing of 'onset' of periods.

Figure 6.10 Amongst all women completing menstrual chart, comparison of those undertaking menstrual collection with those who did not



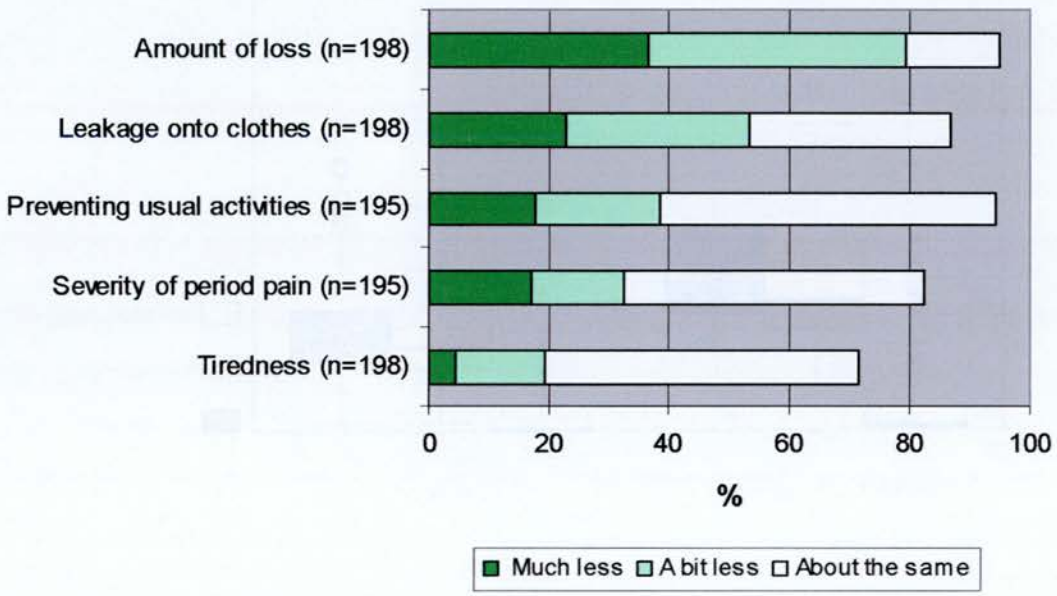
6.3.2.ii Comparison of period collected to 'usual' periods

At the end of the period the woman was asked to complete a summary page on her chart, indicating how the period charted compared with her periods over the last 6 months (the time frame for reporting on periods in CQ and MEQ). Comparisons were requested for amount of period, leakage, impact of period on activities, pain and tiredness. Responses offered were the same, a bit less, much less, a bit more and much more. **Figure 6.11** plots the percentages of collectors responding 'the same' or either degree of 'less'. Those responding more and much more are not plotted but would make the total bar length up to 100%.

It can be seen that nearly 80% of collectors (who completed charts) felt the period charted (and collected) was less or much less in volume than their usual periods, and over 50% experienced less leakage. For the other three items (tiredness, pain and impact of period on activities) over 50% of collectors felt the period charted was the same as usual periods. Women finding their periods not 'the same as usual' in these respects, were relatively more likely to experience less (rather than greater)

curtailment of activities, but relatively less likely to experience less tiredness rather than more.

Figure 6.11 Comparison of period charted (and collected) with periods over the previous 6 months

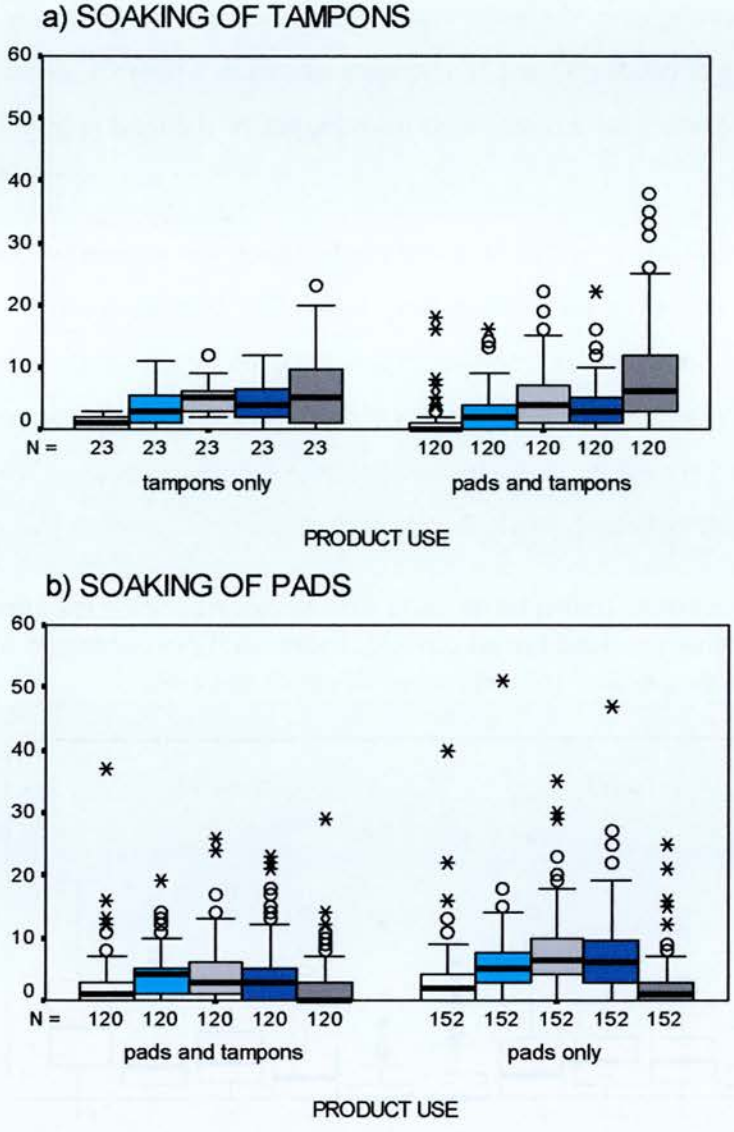


The equivalent summary for the 82 women who charted periods but did not collect showed a very similar distribution of responses, except for amount of loss. Only just under 50% reported the period charted as less than usual in amount (compared to 80% for collectors) and more reported the period as more than usual (19% v 5%).

6.3.2.iii Product use by degree of soaking

Women were asked to categorise for each product changed its extent of soaking by rating it against pictograms showing degrees of soaking (there were two separate sets of 5 pictograms, one set each for pads and tampons). For each woman, for each day of her period, counts were accumulated against each of the 'soaking' pictograms, of number of products used in this way. The daily counts of each type were then totalled over the whole period. The summarised counts of product use/soaking are plotted in **Figure 6.12** as two graphs, one for tampons used and one for pads used.

Figure 6.12 Separately for (a) tampons and (b) pads: number of products used by degree of soaking, separately by combinations of products used
('degree of soaking' is as represented by pictograms, with the 5 columns left to right representing in order none/minimal to completely soaked)



Women were categorised in terms of combination of sanitary protection used, as users of tampons only, pads only, or both types of product. For the 23 women who used only tampons, all their product use is reported in graph (a), and for the 152 using pads only, all their product use is reported in graph (b). However for the 120 women using both types, their total product use is reported partly (that is, with respect to tampons) in graph (a) and the rest, pads, in graph (b). It can be seen that

women using tampons tend to report a relatively high number of completely soaked tampons, even more so if they use pads as well. In contrast, in the case of pads, completely soaked pads are relatively seldom reported.

The counts summarised in **Figure 6.12** give an idea of the numbers of products with each degree of soaking, over the study group, but do not give an insight to individual profiles of soaking of products used. To achieve this each woman's reported product/soaking counts were expressed as percentages of the total number of products she used.

Figure 6.13 is a box-plot summary of these percentages, for women who used both pads and tampons. It can be seen that in most individual profiles completely soaked pads were relatively uncommon (median 0%) but completely soaked tampons were the most common (median percentage of total products used, 20%). However, there were women with different profiles, for example the woman with over 70% of all her products categorised as heavily soaked pads.

Figure 6.13 For women using both pads and tampons, box-plot summary of individual profiles of product type/soaking: individual percentages of each product-type/soaking out of total number of products used

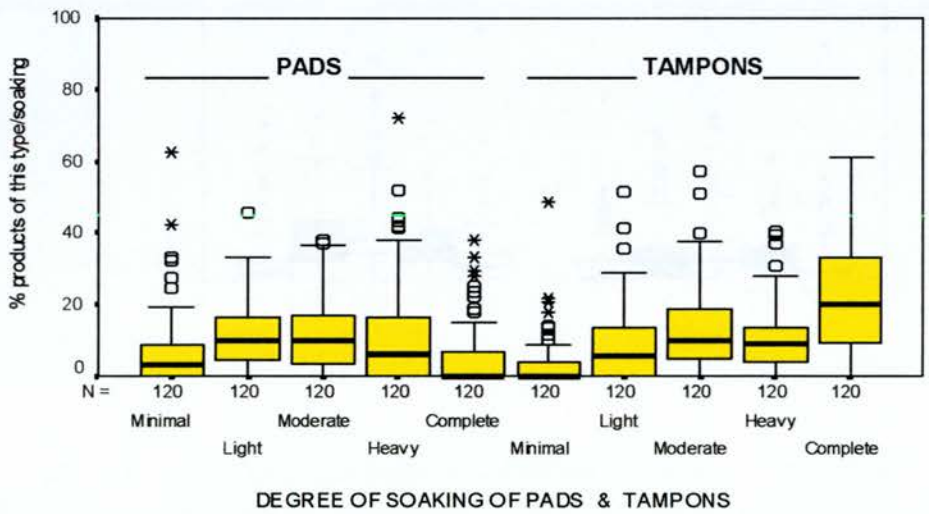
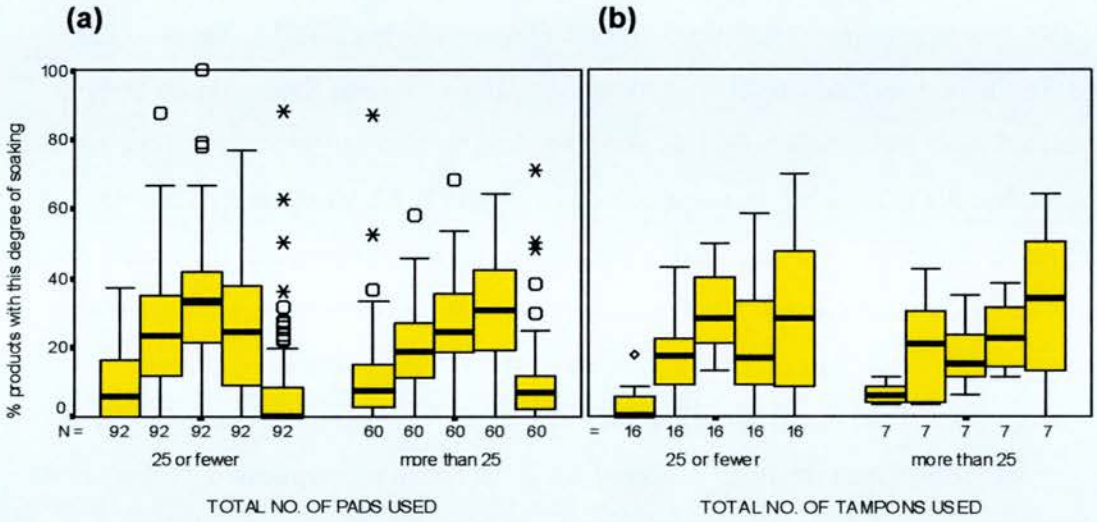


Figure 6.14 shows the corresponding product-use profiles separately for women using pads only or tampons only. It can be seen that among women using pads *only* there are also relatively few pads that are completely soaked (**Figure 6.14a**) - median 0% for those using fewer than 25 pads, and median 7% among those using more.

Figure 6.14 For women using (a) pads only or (b) tampons only: box-plot summary of individual percentages by degree of soaking, out of total number of products used, plotted separately for those with total number of products 25 or less, and more than 25. *(For each cluster of five 'boxes' the degree of soaking goes, left to right, from none/minimal to completely soaked.)*



There were a number of women with profiles differing from the group average, in particular a number with very high percentages of completely soaked pads (including two over 60% and one over 80%). There was also one woman who reported every pad she used as corresponding to the middle pictogram (moderately soaked), giving a percentage of 100%. For women using tampons only, the most common degree of soaking recorded was 'completely' – median 28% for those using 25 or fewer tampons, 34% among those using more than 25 tampons.

Comparison of **Figures 6.13**, **6.14a** & **6.14b** shows that the profiles of product soaking differ according the combination of product types used – pads only, tampons only or both product types. For pad only and tampon only users, **Figure 6.14** shows that the median profiles were very similar between the subgroups of women using fewer or more products. The same was observed for women using a combination of pads and tampons (not shown). The profiles of product use/soaking were also similar between the two centres (not shown).

6.3.3 *Estimating menstrual volumes from chart data*

6.3.3.i Predicting total menstrual fluid volume from chart data

Linear regression analysis was undertaken to examine the potential for prediction (estimation) of total menstrual fluid volume (logged) from chart data on products used. In the first instance all 206 women with values for total fluid volume and the menstrual chart were included in the analysis, and numbers of products of each of the various degrees of soaking, as summarised in **Figure 6.12**, were entered into the analysis as they were. For this analysis there was no improvement in the model due to including centre in the model. The only product-usage data required in the model to predict total fluid volume were the counts for the three 'most soaked' pad categories (out of the five offered) and the counts for the two most soaked tampon categories. Subsequent analyses revealed what the box-plots suggested, that it would be better to log transform the counts to deal with skewness in the data. When the regression analysis was rerun using the logged product data the same variables were needed for the model, but the F statistic increased from 35.7 to 40.2 (df 5,200 and $p<0.001$ for both). The analysis results for this are shown as the first analysis column of **Table 6.6**. The model was a good statistical fit, but only just over 50% of the variance in logged menstrual fluid volume was explained by the regression on product use/soaking data from the menstrual chart.

Since it was possible that the pictograms for pads used as *secondary* protection (in addition to a tampon) may denote a different absorbed volume of fluid/blood than for a pad used as the sole protection, further analysis was undertaken to explore the relevance of tampon use to the modelling. This found that the value to the model of some product use did differ by whether the woman was a tampon-user or not, in particular that use of the second-most soaked category of pads contributed additionally to the model if the woman was not a tampon user. (In effect there was an interaction between use of pads only and the 'value' of the count of products with this degree of soaking in predicting total fluid volume of menstrual loss.) Using this model 57% of the variance in logged menstrual fluid volume was explained by the regression on product use/soaking data from the menstrual chart. In this model the

significance of regression coefficient b_{pads3} was p=0.18, but for consistency across models it has been retained in the model.

Table 6.6 Linear regression analyses of logged total menstrual fluid volume on logged product use data from the menstrual chart

	Analysis 1#		Analysis 2*	
n (included in analysis)	206	(all with data)	204	(all except 2 outliers#)
R^2 +	0.502		0.566	
Residual Error MS ++	0.479		0.365	
F	40.2		42.7	
df	5, 200		6, 197	
p	<0.001		<0.001	
Regression coefficients	**Coeff.**	**(95% CI)**	**Coeff.**	**(95% CI)**
a	3.203	2.94, 3.46	3.169	2.92, 3.42
b_{pads3}	0.149	0.01, 0.28	0.097	-0.03, 0.22
b_{pads4}	0.332	0.20, 0.46	0.211	0.06, 0.35
b_{pads5}	0.385	0.20, 0.47	0.326	0.20, 0.45
$b_{tampons4}$	0.252	0.03, 0.47	0.261	0.07, 0.46
$b_{tampons5}$	0.550	0.29, 0.60	0.534	0.38, 0.68
$b_{pads4 \times non\text{-}tampon\text{-}user}$	*n.a.*		0.227	0.08, 0.38

\+ *R^2 is the proportion of the variance of (log) total menstrual fluid volume that is explained by the regression.*

++ *Residual Error Mean Square from the analysis of variance table for the regression model.*

\# *There were three outliers in this analysis, A, D and E (standardised residuals -3.7, -5.5, and -3.6. It was decided to exclude A (as previously excluded, see **Table 6.2**) and D (as standardised residual so extreme). (Details of all outliers are in **Appendix 6.1 Table A6.1.1**.)*

* *Three outliers were noted in analysis 2, but retained: E again (standardised residual for this analysis= -4.2) and two new outliers F (-3.6) and G (+3.1). G had very high fluid and blood volume (total fluid 593mL), but contained on only24 products, whereas F had very low volumes (18mL fluid) contained on 17 products.*

The regression equation for estimating total menstrual fluid volume (TMF) using analysis 2 is, after back-transformation:

$$\text{TMF(mL)} = 23.8 \times (pads3)^{0.097} \times (pads4)^{0.438} \times (pads5)^{0.326} \quad \text{if using pads only}$$

$$= 23.8 \times (tamp4)^{0.261} \times (tamp5)^{0.534} \quad \text{if using tampons only}$$

or, if user of both pads and tampons

$$= 23.8 \times (pads3)^{0.097} \times (pads4)^{0.216} \times (pads5)^{0.326} \times (tamp4)^{0.261} \times (tamp5)^{0.534}$$

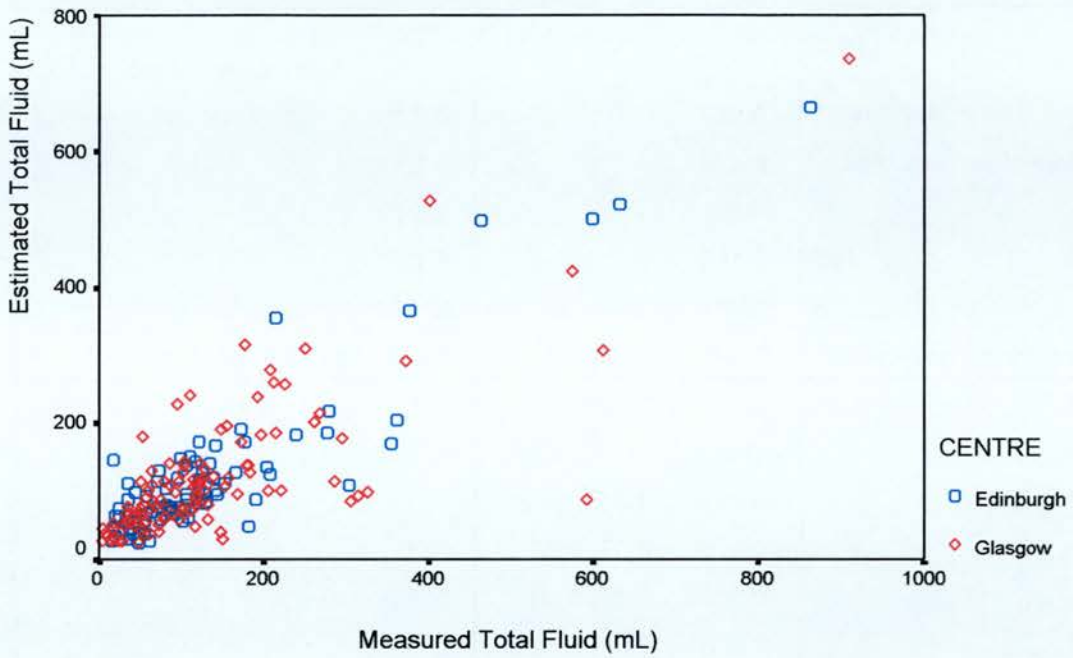
where *pads 3* = 'count' of pads rated as third pictogram of soaking degree, *pads 4* = 'count' of pads rated fourth pictogram of soaking degree, and so on, and *tamp4* and *tamp5* similarly correspond to the fourth and fifth pictogram ratings for tampon soaking.

'Count' is in fact the recorded count of products *plus 1*, to allow log transformation (see methods **6.2.3.i**). However, since the back-transformed equation is multiplicative rather than additive, if for a particular pictogram there is *no* usage recorded, the zero count plus 1 is just 1, and so regardless of the power indicated in the equation the multiplier due to that term in the equation is just one. Hence in estimation for such a period there is no change to the predicted volume due to products of that type and that degree of soaking, despite the zero count having been increased to 1. This arithmetic fact also explains the simplification of the equation in the case of women using pads only or tampons only. Note that the power to which *pads4* is raised differs depending on whether tampons are used or not.

Examination of the formulae shows that for women using pads only the key determinant of the estimated volume is the number of pads almost soaked, and to a slightly lesser extent the number of completely soaked pads. For women using tampons only by far the most important predictor of volume is completely soaked tampons. For women using both types of products the key predictor is the number of soaked tampons and to a lesser extent the number of completely soaked pads.

Figure 6.15 shows for analysis 2 of **Table 6.6** a scatter-plot of the total fluid volumes as estimated from chart data, plotted against the volumes as measured.

Figure 6.15 Scatter plot of fluid volumes estimated from chart data, against measured fluid volume, for all collections included in analysis 2 (n=204)



6.3.3.ii Estimating menstrual blood volume from chart data

Linear regression analysis was also undertaken to examine the potential for prediction (estimation) of menstrual blood volume (logged) from the chart data on logged counts of products used for each of the various degrees of soaking, as summarised in **Figure 6.12**. In the first instance all 207 women with values for blood volume and the menstrual chart were included in the analysis. For this analysis it was necessary to include centre in the model to improve fit. The product-usage variables required in the model to predict blood volume were the same as those required for the prediction of total fluid volume (**Table 6.6** analysis 2), plus *pads3* (which in the total fluid prediction was not statistically significant at conventional levels of significance, but was retained in the model). The interaction term was also required. The regression statistics and coefficients are presented in the first analysis column of **Table 6.7.**

Table 6.7 Linear regression analyses predicting logged blood volume

	Independent variables for regression analysis			
	Chart data only #		Including Total Fluid volume ~	
n (included in analysis)	207	(all with data)	204	(all except 1 with missing fluid volume & 2 outliers*)
R^2 +	0.577		0.821	
Residual Error MS ++	0.478		0.188	
F	38.7		187.5	
df	7,199		5,198	
p	<0.001		<0.001	
Regression coefficients	**Coeff.**	**(95% CI)**	**Coeff.**	**(95% CI)**
a	2.892	2.5, 3.3	0.217	-0.17, 0.61
b_{centre}	-0.415	-0.61, -0.22	-0.403	-0.53, -0.28
b_{pads3}	0.143	0.004, 0.28		
b_{pads4}	0.198	0.03, 0.36		
b_{pads5}	0.359	0.22, 0.50	0.085	-0.004, 0.17
$b_{tampons4}$	0.316	0.09, 0.54		
$b_{tampons5}$	0.600	0.43, 0.77	0.205	0.104, 0.304
$b_{pads4 \times non\text{-}tampon\text{-}user}$	0.314	0.14, 0.48	0.158	0.071, 0.245
$b_{ln(total\ fluid\ volume)}$	*n.a.*		0.860	0.768, 0.951

+ *R^2 is the proportion of the variance of (log) total menstrual fluid volume that is explained by the regression.*

++ *Residual Error Mean Square from the analysis of variance table for the regression model*

*There was one outlier in this analysis, G again (see **Table 6.6**). It had standardised residual 3.37 and was retained. (Details of all outliers are given in **Appendix 6.1 Table A6.1.1**.)*

* *Two outliers were excluded and the analysis re-run - D (again, see **Table 6.6**), with std. residual here of 5.6, and H (std. residual -3.7) which had an extremely low blood: fluid ratio, possibly because the very low optical density for menstrual solution was an error.*

~ *There was one outlier in this analysis, K (standardised residual 3.19). It was retained.*

It can be seen that the model was a good statistical fit, and 58% of the variance in logged menstrual blood volume was explained by the regression on centre and product use/soaking data from the menstrual chart. The regression equation for estimating menstrual blood volume for Glasgow is, after back-transformation:

$$\text{Blood}_G\,(\text{mL}) = 11.9 \times (pads3)^{0.143} \times (pads4)^{0.502} \times (pads5)^{0.359} \quad \text{if using pads only}$$

$$= 11.9 \times (tamp4)^{0.316} \times (tamp5)^{0.600} \quad \text{if using tampons only}$$

or, if user of both pads and tampons

$$= 11.9 \times (pads3)^{0.143} \times (pads4)^{0.198} \times (pads5)^{0.359} \times (tamp4)^{0.316} \times (tamp5)^{0.600}$$

where *pads 3* etc. are logged counts as explained above.

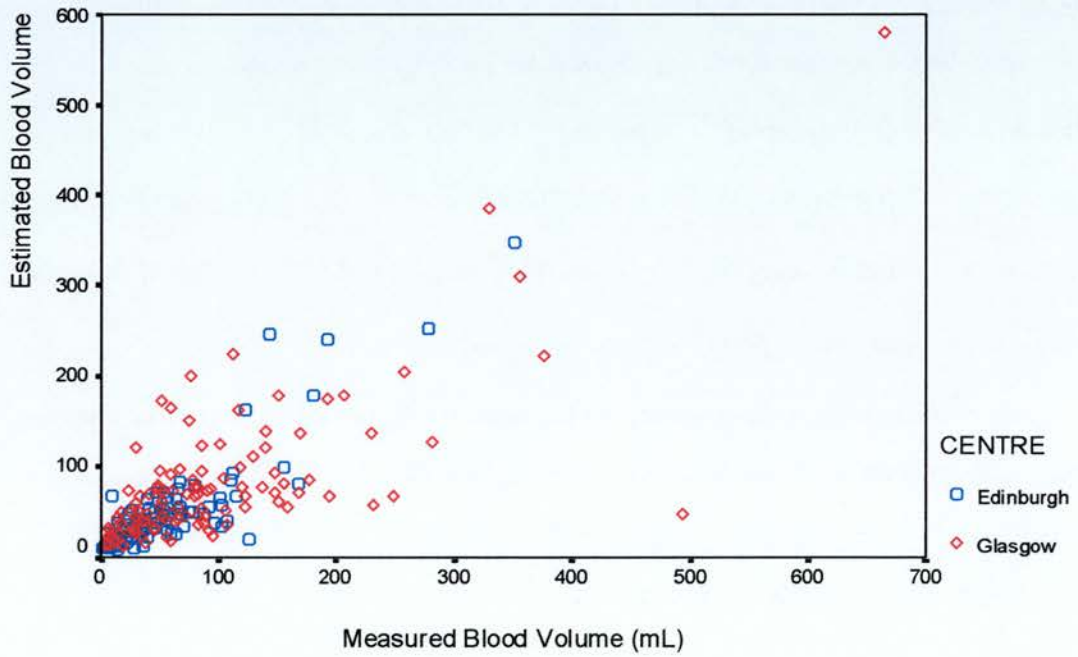
The term in the regression equation for centre, additive on the logged scale, back-transforms to a multiplicative term in the original scale. So the corresponding equations for Edinburgh, for all three product-type-usage groups, can be obtained directly from the Glasgow formulae above, by multiplying by the (back-transformed) factor indicated by the regression model. That is,

$$\text{Blood}_E\,(\text{mL}) = 0.66 \times \text{Blood}_G\,(\text{mL})$$

That is, for the same product use/soaking, an Edinburgh estimate of blood volume is 66% of the corresponding Glasgow estimate.

Figure 6.16 shows for the first analysis of **Table 6.7** a scatter-plot of the blood loss volumes as estimated from chart data, plotted against the measured blood volumes.

Figure 6.16 Scatter plot of blood volumes estimated from chart data, against measured blood volume (n=207)



6.3.3.iii Estimating menstrual blood volume from chart data *and* total fluid volume

Since both the total menstrual fluid volume and the menstrual chart record are easier to obtain than the measured blood volume, further linear regression analysis was undertaken to explore the possibility of using these in combination to predict (estimate) menstrual blood volume.

Initially all 206 women with values for blood volume, the menstrual chart and total fluid volume were included in the analysis. For this analysis also it was necessary to include centre in the model to improve fit, but with total fluid volume included in the model the only product-usage variables required were the counts of completely 'soaked' pads and tampons, and the interaction term that had been included before, *pads4* for women using pads only. The regression statistics and coefficients are presented in the second analysis column of **Table 6.7**. The model was a very good statistical fit, with 82% of the variance in logged menstrual blood volume explained by the regression on centre, logged total menstrual fluid volume and product use/soaking data from the menstrual chart. The regression coefficient for completely soaked pads (*pads5*) just missed statistical significance at the conventional level (p=0.06) but has been retained in the model.

Using the second analysis model of **Table 6.7**, the regression equation for estimating menstrual blood volume for Glasgow is, after back-transformation:

$$\text{Blood}_G\,(\text{mL}) = 0.8 \times (pads4)^{0.158} \times (pads5)^{0.085} \times (total\ fluid)^{0.860} \quad \text{if using pads only}$$

$$= 0.8 \times (tamp5)^{0.205} \times (total\ fluid)^{0.860} \quad \text{if using tampons only}$$

$$= 0.8 \times (pads5)^{0.085} \times (tamp5)^{0.205} \times (total\ fluid)^{0.860} \quad \text{if using both}$$

where *pads 3* etc. are logged counts as explained above.

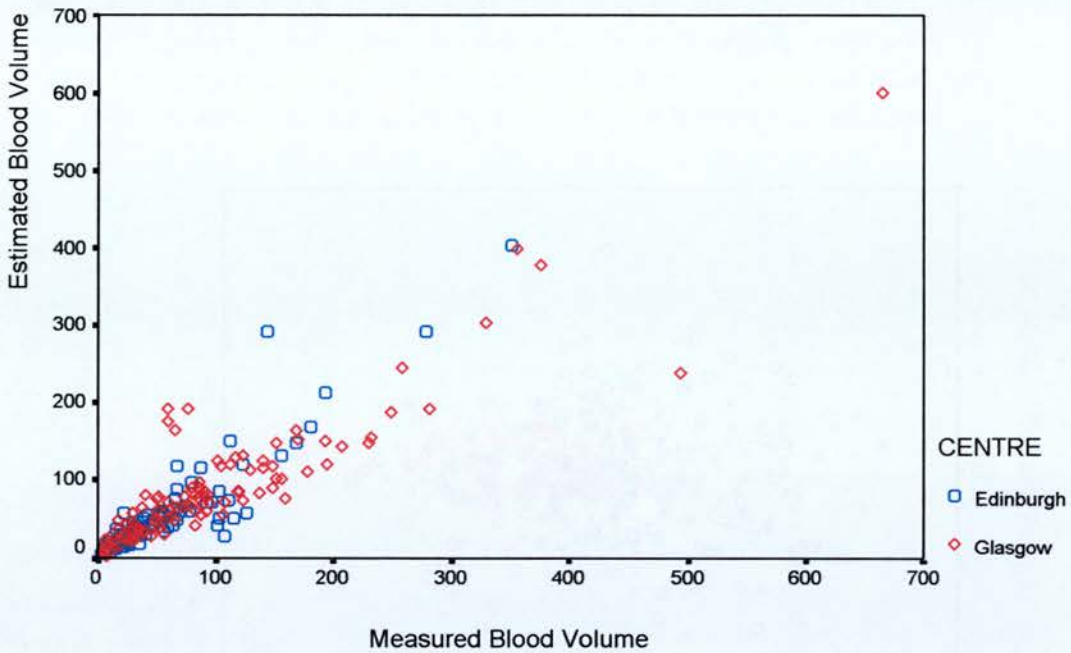
As before, the corresponding equations for Edinburgh, for all three product-type-usage groups, can be obtained by multiplying by a factor derived by back-transformation, for this model 0.668 (rather than 0.660 in the preceding model):

$$\text{Blood}_E\,(\text{mL}) = 0.668 \times \text{Blood}_G$$

Therefore, for periods with the same measured total fluid volume and the same profile of use/soaking of sanitary protection, Edinburgh estimates of blood volume are 67% of Glasgow estimates.

Figure 6.17 shows, for the second analysis of **Table 6.7,** a scatter-plot of the blood loss volumes as estimated from chart data and total fluid data, plotted against the blood volumes as measured.

Figure 6.17 Scatter plot of blood volumes estimated from chart and total fluid data, against measured blood volume (n=204)



6.3.4 Comparison of models estimating menstrual blood volume

For the three models for estimating blood volume, from total fluid alone (**Table 6.2**), chart data alone (**Table 6.7** column 1) and from both (**Table 6.7** column 2) can be compared in terms of R^2, the proportion of the variance in logged blood volume explained by the regression. For the three models R^2 was 74%, 58% and 82% respectively. The interpretation of this is that total fluid volume is the best predictor of the volume of the blood component of the period, but prediction can be improved by including prospective menstrual chart data. Considering use of predictive models in the case of individual patient, the models can also be compared in terms of the

residuals of the observed values minus the fitted (estimated values). **Figure 6.18** presents the residual by predicted value plot, overlaid for the three models. The residuals for the model predicting blood from fluid only were derived from the model using only data points with total fluid volume greater than 80mL. The residuals for the model using only chart data are most dispersed about the zero line. It can be seen that when both chart data and total fluid data (including data points with total fluid ≤80mL) are used the residuals are closer to the zero line, and fairly evenly dispersed on either side for the line for the range of predicted values.

Figure 6.18 Plot of residuals versus predicted values (both on the log scale) for three regression models for predicting ln(menstrual blood volume): (i) Total fluid >80mL (n=139), (ii) chart data (n=207) and (iii) both total fluid (any volume) and chart data (n=204).

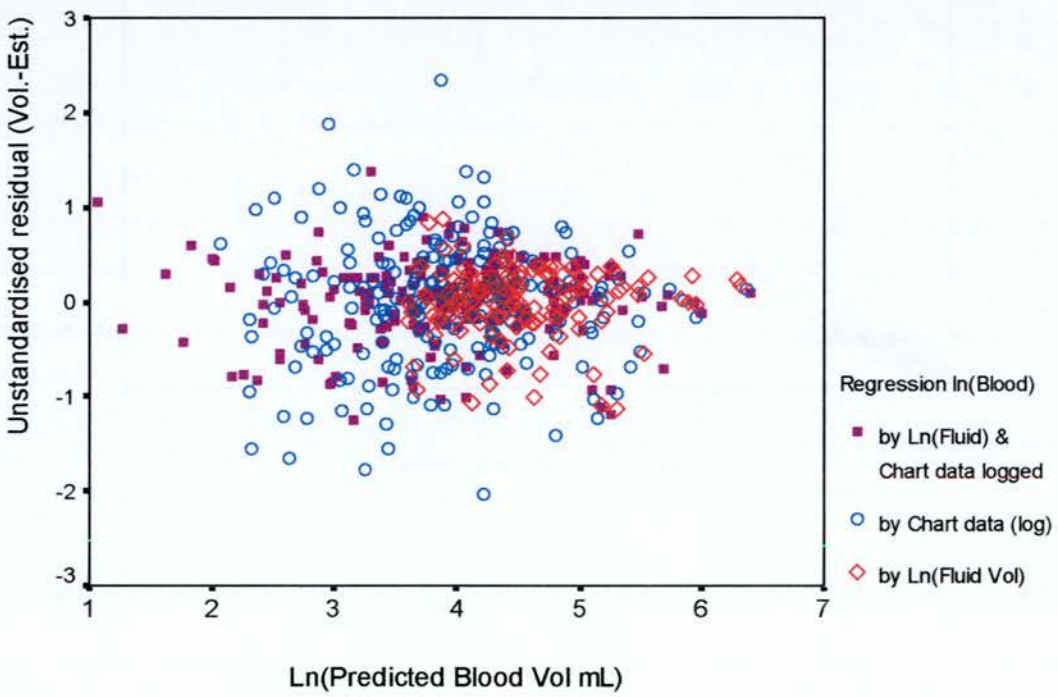
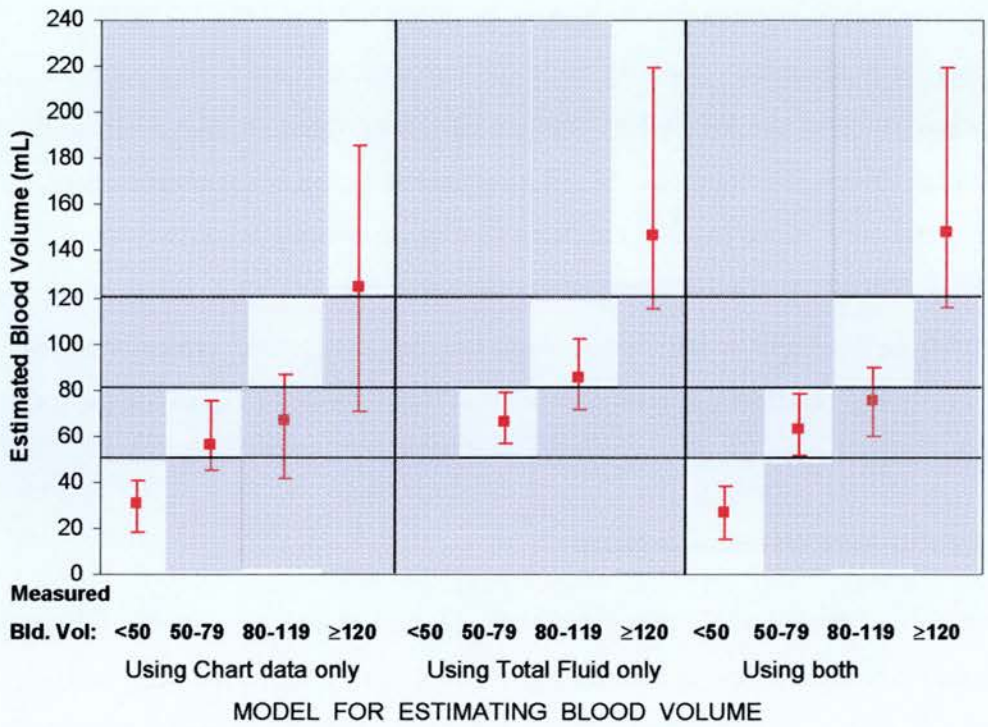


Figure 6.19 presents separately for the three models, the median and inter-quartile range for the estimated blood volumes for periods with measured blood volumes categorised into four subgroups: <50mL, 50 to 79mL, 80 to 119mL, ≥120mL. The blood volume bands are demarcated for estimated volumes by the horizontal lines. In each case the unshaded area is the region within which all estimates would fall, for a

perfect model. For the fluid only model, no median (IQR) estimate is plotted for the lowest blood loss grouping, as the relevant total fluid loss volumes were on the whole excluded from that model. If estimates were made they would be unlikely to be unbiased or precise. However, the two models using chart data provide accurate estimates in this grouping. For the next blood band up the 'chart data only' estimate is fairly good, but the estimates are even better when total fluid volume data is used. For the 80mL to 120mL band the estimates are on the low side for all models, but considerably better for the fluid only model. For the highest losses estimation is best by models involving total fluid. These judgements are possibly over-optimistic as the estimates pertain to the same data as was used to derive the models.

Figure 6.19 Median (IQR) for estimated blood volumes, for periods grouped by measured blood volume, separately for the three models



Considering the 80mL criterion for menorrhagia, the total fluid model correctly estimates 97% and 79% respectively of the first two blood loss groups as being less than 80mL, and 67% and 91% of the second two groups as being over 80mL. For the combined model the corresponding percentages are 99%, 79%, 44%, 92%. The same caveats apply for this summary.

6.4 DISCUSSION

6.4.1 *Quantification of menstrual loss*

Our study is the first to measure menstrual loss in routine patients referred to a clinic with heavy periods, rather than women selected for clinical trials. Collectors' periods have been quantified in three ways. Firstly, total menstrual fluid volume was measured by weighing of menstrual collection (and subtracting dry weight of menstrual products used). Secondly, the volume of the blood component of the period was obtained by laboratory assay, involving soaking of the collection in sodium hydroxide (NaOH), spectro-photometric assessment of the optical densities of the soaking solution and a solution of venous blood, and calculation of blood volume from the optical densities and the volumes of NaOH used. Finally, prospective reporting, in a menstrual chart, of products used and their degree of soaking, against 5 pictograms each for pads and tampons, offered a third approach to quantification of menstrual loss. Chart data are easiest to obtain, total menstrual fluid volume is next easiest to obtain, and blood loss determination is a resource intensive laboratory procedure. Since the clinical definition of menorrhagia involves the volume of the blood component of the menstrual loss (>80mL), the gold standard for assessment of menorrhagia is laboratory blood volume assessment, typically by the method of Hallberg (Hallberg & Nilsson 1964). It was intended to evaluate the total fluid and the chart data as alternatives to determination of blood loss volume.

6.4.2 *Blood loss determinations*

It was therefore of considerable concern that the blood volumes obtained in Glasgow were substantially higher than in Edinburgh (medians 65mL and 41mL respectively), when both laboratories were evaluating blood loss by the Hallberg method (Hallberg & Nilsson 1964). While the difference in average blood volumes could have been a true difference in the patient populations, this was thought to be unlikely, because of the similarity in total fluid volume distributions between the two centres, and in product use/soaking profiles. Experimental and theoretical research was undertaken to seek a methodological explanation of the difference in blood loss volumes, and

this work will be reported and discussed in **Chapter 7**, together with a general consideration of measurement issues for all three methods. For the purposes of the present chapter all regressions were undertaken in the first instance with centre as an independent variable in the model, to allow for adjustment for between-centre effects in the relationship between the dependent variable (blood volume say) and the independent variable(s). Centre proved to be necessary in all models involving blood volume.

6.4.3 Estimating blood volumes from other measures

6.4.3.i Using total fluid volume

The model for predicting blood volume from *total fluid volume* was a good fit, although the percent of the variation explained by the regression (70%) was less than in Fraser's analysis (86%) (Fraser et al. 2001). However, that study involved weighing of every product prior to use, whereas the present study sought to use methods that could feasibly be employed in routine clinical assessment.

6.4.3.ii Using chart data

The model for predicting blood volume from the *chart data* did not capture as much of the variation in blood volume (58%). Interestingly, to enable prediction of blood volumes the counts of products used by degree of soaking needed to be log transformed. This means that a simple summation of scores for each product recorded, as has been used in other published research, would be sub-optimal (Higham et al. 1990; Hurskainen et al. 1998; Janssen et al. 1995; Wyatt et al. 2001). This is possibly why Higham's chart does not in fact claim to estimate blood volume itself, but simply provides a PBAC score which is increasingly biased/unreliable at higher volumes (Higham et al. 1990). The utility claimed for the method is that if the PBAC score is ≥ 100 this 'predicts' a blood volume greater than 80mL, but if the volume is greater than 80mL the PBAC does not inform in any interpretable way as to the whether the volume is, say, around 90mL, over 160 mL, or over 240mL. A validation study was undertaken with Higham's chart and it was found to perform poorly compared to the founding study, with generally high chart scores which did

not agree with the measured blood volume (Reid et al. 2000). Higham's original study involved patients referred to a gynaecology clinic being assessed with a view to participation in a treatment trial, whereas the validation study involved volunteers recruited by advertising, and patients referred by GPs who had been informed about the study (Higham et al. 1990; Reid et al. 2000).

There were two further features of interest in the analysis. The first feature was that the model presented here took no account of the first two pictograms. One was an extra pictogram relative to the Higham chart (Higham et al. 1990), denoting minimal spotting, so its irrelevance to prediction was expected. However, products categorised thus remain 'products used', so this finding does confirm the difficulty for clinicians in trying to estimate menstrual blood loss by enquiring as to total number of sanitary products used in a period. The second pictogram not required in the model was one that would have scored 1 per product in PBAC (Higham et al. 1990). As some women recorded many such products these could have made a big difference to the total score if PBAC was being implemented. However the present analysis found they make no useful contribution to volume estimation. The second feature of interest was the need for an interaction term in the regression model. That is, the relevance of 'heavily soaked' pads differed depending on whether the woman used pads only, or pads with tampons, with the contribution being more if she did not use tampons. A possible explanation for this is to do with the relationship between the surface area of the blood stain, and the volume of blood. When blood leaks out around a tampon it may spread more across the surface of the pad, rather than soak down, and so may represent a smaller volume of blood for the same (size) pictogram, than if it was a pad worn as the only protection. That is, it would not be as 'heavily soaked' as it appeared from the surface staining. This, the size of the 'stain' (as represented by the pictogram) relative to the volume of blood involved, raises a broader measurement issue. Even a fully-soaked pad may vary hugely in the volume of blood it contains, depending on whether it is a regular absorbency pad or, say, a special 'night-time' pad. This will be discussed further in the next chapter.

6.4.4 Estimating total fluid volume from chart data

This leads to a further reflection, on the ability of the chart data to predict the *total menstrual fluid volume*. There may be no logical need to estimate in this way, since blood is the key volume and that can be obtained directly from the menstrual chart. However, in a future re-consideration of menorrhagia complaint it could be that there is realisation that total menstrual fluid volume itself might be the menstrual volume of importance, representing as it does the woman's containment challenge. If that was the case though, total fluid volume is relatively easy to obtain by weighing, so it would be preferable to assess it directly.

A further issue is that the pictograms of the chart denote the extent of *blood* staining, if viewed two-dimensionally, so it is unclear how women would categorise products which were soaked but not with dark blood. However, the prediction of total fluid volume by chart was attempted for interest, mainly to see if this could throw some light on the differing distributions of blood volume at the two centres. In the event, the best model for predicting total menstrual fluid volume accounted for 57% of the variation in total fluid volume, so this was almost as successful as the prediction of blood volume. The relative sizes of the coefficients for the pictograms were very similar to those for the blood volume model, with slightly more weight given (than in the blood volume model) to heavily and completely soaked tampons. However, a striking difference was that there was no need for a coefficient for centre, since total fluid volume could be predicted from product use/soaking by exactly the same formula in both centres. This gives support for the growing impression that in this study the implementation of the Hallberg (Hallberg & Nilsson 1964) method at the two centres yielded centre-specific bias or biases in the blood loss determinations. This will be addressed further in the following chapter.

6.4.5 Reflection on utility of menstrual charts

In the present study if both chart data and total fluid volume were used to predict blood volume then the model was considerably improved, with 82% of the variation in blood volume accounted for by the regression model. The major contributor to the prediction is however the total fluid volume, with the only chart data required for the

model being completely soaked tampons or, for women using pads only, heavily soaked pads. This raises the question of whether the menstrual chart is worth the resources and the additional albeit modest imposition on the patient? However, the menstrual chart has the potential to do more than quantify the menstrual loss as it collects, in addition to numbers, types and degree of soaking of products used, information on other aspects of the period – time-course, leakages, clots, curtailment of normal activities, pain and use of pain-killers. This could provide useful prospective description of the period for the clinical encounter. However it should be remembered that menstrual charting requires a high level of commitment from the woman, and to do it conscientiously is a challenging task. We found that the women least likely to produce charts to go with their menstrual collections were the more deprived women.

Some of the experiences described are extreme – for example a quarter of women who collected changed 8 or more times on their worst day, one woman 13 times. Half of all collectors used 23 or more products for their period, representing a considerable financial outlay, especially if using higher absorbency products, and one woman used 78 products. Product usage was even higher for the 88 women who charted their periods but did not collect, with a quarter of them using over 50 products, five over 80 products, and the maximum being over 120. Leakages and cancellations of activities were not as prevalent as might have been expected, but perhaps women planned their lives in anticipation of periods, and avoided accidents by frequent changing. Absence of accidents does not necessarily denote absence of containment challenge (nor absence of adverse impact on daily life).

6.4.6 *Cycle-to-cycle variation in menstrual loss*

The comparison for the collected period against usual periods in the last 6 months, unique to this study, was very helpful to interpretation of the research data, but this information would possibly be useful also clinically. For 80% of collectors the period collected was less or much less than usual, and it is statistically very unlikely that by random variation period-to-period one would observe such a high percentage of women with periods less or much less than usual on the period that happened to be

collected. One obvious explanation is regression to the mean, since symptoms may have been at their peak at the time of consulting their GP, but by the time they attended the gynaecology clinic, symptoms may have been subject to spontaneous improvement. However, for periods that were charted but not collected (n=82) the proportion experiencing periods less than usual in amount was under 50%, and these periods should have been equally subject to this phenomenon. Another explanation may be commencement of medication, since we could not ethically require women to delay commencing medication prescribed by the clinician at the first appointment, for the sake of the menstrual assessment for our research purposes. In the case of menorrhagia, if therapeutic effect or regression to the mean was at work then it was more evident for collectors than women charting their periods but not collecting, and this difference was confined to amount of period, and was not seen for leakage, curtailment of activities, and so on. This does therefore raise the issue of reliability of reporting. Are women more circumspect in their judgements of the amount of their menstrual loss when they know there is to be objective validation of the volume (the purpose of the collection)? If so, then this does not augur well for the validity of menstrual chart estimations in the absence of menstrual collection, the purpose for which they have been developed.

A further possible explanation is the effect of the process of charting on the woman's experience of her period. It was observed in PMS research that when women kept menstrual diaries to assess their premenstrual symptoms they often reported at the next clinic appointment that in the cycle just recorded their symptoms had not troubled them nearly so much as before. A commonly accepted interpretation of this phenomenon was that the process of diary-keeping was therapeutic for some women, by giving them some semblance of 'control' over their symptoms. It is possible that some similar mechanism may operate in menorrhagia, especially with respect to the emotional response to the menstrual flow. If this is the case then there may be potential to capitalise on this psychological effect in clinical management of the complaint. The question would remain as to why the effect was not so apparent in non-collecting women who charted their periods. Many did wish to be helpful but had a strong aversion to undertaking collection, and they are undoubtedly a self-

selected subgroup. They may differ psychologically in a way that gives a different outcome (periods judged as heavy as usual) despite the process of charting. Future analyses in combination with the psychological questionnaire data may elucidate this point.

6.4.7 Menorrhagia and blood loss volume

Higham added scores to the total PBAC score for each clot recorded, although there has been no empirical assessment of the true blood volume equivalent to clots (Higham et al. 1990). There have recently been attempts to further improve the measurement of blood volume by adjusting for blood lost to the collection, because of clots or blood leaking into the toilet, or onto clothes or bedding (Hurskainen et al. 1998). Among 154 women recruited into a menorrhagia treatment trial the average adjustment to volume judged necessary, based on diary recording of uncollected menstrual loss, was an increase of 20mL. For many women the adjustment made was a surprisingly high proportion of the blood successfully collected, 57% in one case. The validity of the adjustments made was not demonstrated, so reassurance is required as to the rigour of this approach (Hurskainen et al. 1998). It is difficult to imagine a scenario whereby a woman with moderately light menstrual blood loss could manage to lose over half of it into the toilet or onto her clothes.

However, there is a further fundamental flaw to this activity. That is that the clinical definition of menorrhagia is statistically-derived, based on a population distribution of menstrual blood volumes measured *without any adjustments for clots or leakage* (Hallberg et al. 1966). Taking as given the conceptual validity of the original clinical definition, it defined menorrhagia as the cut-off for the extreme 4% of the population distribution of menstrual blood volume *as measured from that successfully collected on sanitary protection.* Therefore the only valid way to implement that definition is to continue to apply it to measurements made *in the same way.* If in that seminal study the measured blood volumes been adjusted up in accordance with reported clots (and possibly also leakages) then the distribution of blood volumes they would have obtained would have been shifted to the right, and the resulting menorrhagia

definition, using the same reasoning, may have been 100mL, or more. Calibrating *adjusted* blood volumes against the *un*adjusted threshold (80mL) is meaningless.

6.4.8 Overview

In this chapter there has been examination of estimation of blood volume by three regression models, using total menstrual fluid volume or chart product use/soaking data separately, and in combination. In-depth consideration of the relative merits and demerits of these models must wait until the measurement issues have been considered, in **Chapter 7**. However, one issue could be addressed now. That is the disparity in prediction precision possible for the overall model for the data, and the prediction possible for an individual patient. Very little of the published work confronts the unreliability inherent in individual estimations (Higham et al. 1990; Hurskainen et al. 1998; Reid et al. 2000; Wijma et al. 1982; Wyatt et al. 2001), although there is one exception (Fraser et al. 2001). Generally, well-fitting regression models can be obtained, as has been the case in the present study (R^2 74% or 82%). This summarises the entire model, and reflects the fact that the model is successful at estimating the 330mL menstrual blood volume to somewhere in that region (give or take 100mL), and the 20ml blood volume as somewhere in that region (give or take 15mL). However, the high degree of between women variability means that generally the individual prediction limits for a specific patient with a particular product use/soaking profile, or a particular total menstrual fluid volume, are very wide. Therefore, in the region where it matters clinically, by tradition around 80mL, imprecision can render such estimation for the individual as almost pointless. Is it clinically helpful to know that a patient's menstrual blood volume is with 95% confidence between 40 and 120mL? Yet this is the reality behind chart-estimated blood volume. This matter will be further addressed in Chapter 10.

6.5 CHAPTER SUMMARY

6.5.1 Measured menstrual loss volumes

- Total fluid loss estimations were similar in Edinburgh and Glasgow (median (IQR) 103mL (55 to 156), n=225).
- Overall 226 women had blood loss volume determinations: 91 Edinburgh collections had median 41mL (IQR 22 to 77) and 135 Glasgow collections had median 65mL (31 to 119).
- The between-centre difference in blood volumes but not total fluid volumes was of concern, and led to a series of experiments/theoretical reflections which will be reported and discussed in Chapter 7.

6.5.2 Menstrual chart completion

- Overall 295 women completed menstrual charts but 8% of collectors failed to complete the menstrual chart.
- Collectors who did not chart were of lower socio-economic status (85% deprivation category ≤ 5 compared to 43% for collectors completing chart).
- Women who declined to collect their used sanitary protection, but completed charts (n=88), used almost twice as many products as those who charted and also collected.

6.5.3 Menstrual chart description of period

- Chart data provided details of products used and degree of soaking, number and size of clots, number and degree of leakages, prevention of usual activities, associated pain and use of pain-killers, and provided a comparison of the period charted to periods in the last 6 months, in terms of amount of loss and other features.
- Women were most likely to commence use of sanitary protection between 7am and 10am.
- Overall 8% of women charting their periods used tampons only, 52% used pads only and 40% used both types of products.
- Over 50% of women reported that pain, curtailment of activities and tiredness were 'the same as usual'.
- Nearly 80% of collectors reported the charted period as less or much less than usual in amount, and over 50% experienced less leakage.

- In contrast, fewer than 50% of those who did *not* collect, but charted periods, reported the charted period as less than usual in amount

6.5.4 Prediction of blood volume from total menstrual fluid volume

- Blood volume could be predicted within centre using total fluid volumes (both volumes logged, R^2= 70%, F=165, df 2,136, p<0.001).
- However, the between-individual variability meant that the individual prediction limits were wide. This was exacerbated, at higher losses especially, by the need for back-transformation from the log scale. Total menstrual fluid volume of 100mL gave an estimated blood volume in Glasgow of 70mL (80% PI 43 to 112mL) and a total fluid volume of 200mL gave an estimated blood volume of 134mL (80%PI 83 to 215mL).
- The estimation formulae obtained for the two centres were, after back-transformation:

  Glasgow Blood volume (mL) = $0.890 \times (\text{Total fluid volume mL})^{0.946}$

  Edinburgh blood volume (mL) = $0.563 \times (\text{Total fluid volume mL})^{0.946}$

- For the same total fluid volume, blood volume estimates were therefore 37% lower in Edinburgh than in Glasgow.

6.5.5 Prediction of menstrual loss volumes from chart data

- Both total menstrual fluid volume and blood volume could be predicted by chart data after applying log transformation to volumes and product counts.
- The product-use information needed in the model for *total fluid volume* (R^2 = 57%, **Table 6.6**) was only for pads and tampons matching the two most soaked pictograms. No coefficient for centre was required, so estimates of fluid volume would be the *same in both centres* for the same profile of product use/soaking.
- The model for *blood volume* (R^2 =58%, **Table 6.7** col. 1) required the same variables as the total fluid model but also needed the count for pads corresponding to the third-most soaked pictogram. A coefficient for centre *was* required, so for the same profile of product use/soaking estimates of blood volume would be 34% lower in Edinburgh estimates than Glasgow.
- Prediction of blood loss volume from a combination of chart data and total fluid volume resulted in a much better fitting model (R^2 =82%, **Table 6.7** col. 2). The product-use information required was reduced to only counts for completely soaked

pads and tampons and, for women using pads only, counts for pads corresponding to the second-most soaked pictogram. A coefficient for centre was required, giving Edinburgh estimates of blood volume 33% lower than Glasgow estimates.

- The residuals (observed – predicted) were best behaved for heavy losses (over 80mL blood volume), for predictions using just total fluid, and for lighter losses, for prediction by the model including chart data and total fluid.

Chapter 7

STUDY RESULTS:

ISSUES IN THE MEASUREMENT OF MENSTRUAL LOSS

7.1 INTRODUCTION

An important issue is the reliability and validity of the available methods for quantification of menstrual loss. Some errors are inevitable, but the scale of errors (precision) determines their utility for clinical assessment of menstrual loss volumes, particularly with regard to management of individual patients. Furthermore, if implementations of the same method at different clinics can lead to disparate results, then this undermines the entire notion of a universal clinical criterion for menorrhagia in terms of absolute volume, such as the 80mL. Such a situation would also make very difficult the synthesis of research findings across studies, and hence of consolidation of the evidence base. In the first instance there is a need to explore the extent to which there may be errors or biases affecting the fluid volume determinations in the present study. If there are systematic biases then efforts must be made to try to establish whether they could be a result of factors operating at the collection stage or in the laboratory. In addition there is a need to extrapolate from findings in this study to consider menstrual loss measurement generally.

Care was taken to avoid errors at the collection stage by the nurses providing women with explanation of the requirements of the collection, with written instructions, and with a contact telephone number in case extra guidance was needed. In an effort to obtain a broad description of the woman's experience of her period and its containment, the menstrual chart requested a detailed record of both usage and changing of menstrual protection, and of associated symptoms. Cross-referencing the menstrual chart to the collection would enable some check of individual success in collecting and recording the collection. Findings for these checks will be reported in this chapter. Efforts were also made to minimise errors arising at the laboratory measurement stage. Glasgow had a blood loss measurement protocol in operation, and a protocol also following the Hallberg method (Hallberg & Nilsson 1964) was set up in Edinburgh. The study nurses were appropriately trained to comply with these protocols. Quality checks were undertaken to assess the measurement of tests collections. The findings for these will be reported in this chapter.

In **6.3.1.iii** it was reported that Glasgow collectors tended to have higher blood volumes than Edinburgh collectors. This may not have been a result of measurement bias, as it could have been due to the referral case mix of the main Glasgow clinics involved in the study, which may have comprised more women with excessive menstrual blood loss. However, the regression model fitted Edinburgh blood volumes at 37% lower than Glasgow, across a range of observed total menstrual fluid volumes (*see **6.3.1.iii***). The percentage that blood comprised of the total menstrual fluid volume of each collection was higher in Glasgow than had been found in previous research, whereas in Edinburgh it was lower, with mean percentages blood by volume of 69% and 46% respectively. Previous research had found that the mean percent blood loss varied only marginally, from 48% to 50%, over the range of menstrual losses from moderately light to very, very heavy, (at the upper limit, with blood volumes greater than 600mL) (Fraser et al. 2001). Taking the constancy of average percentage blood in menstrual loss as a given, there was thus a need for investigation as to the possible causes of the difference in percentage blood loss estimates at the Edinburgh and Glasgow centres. The blood percentage could be biased upwards if either the total fluid measurement was biased downwards, or the blood volume measurement was biased upwards. It was felt that the latter (more complex) measurement process was more likely to have resulted in between-laboratory differences. A further indication that the problem lay with blood loss determinations was that the regression model estimating total menstrual fluid volume from chart data required no coefficient for centre, whereas the model for estimating blood volume form the same chart data did require a centre coefficient. (*see **6.3.3.i** & **ii***).

Discussion established that there were a number of ways in which the methodology used in this study differed from that detailed by Hallberg (Hallberg & Nilsson 1964), and in addition that there were a number of differences between the two centres in the interpretation/adoption of the Hallberg method. There were two methodological concerns:

- To what extent might methodological variants explain the disparity between the two centres in percent blood determinations?

- To what extent does the method actually used at either centre qualify as blood loss measurement 'by the Hallberg method' (Hallberg & Nilsson 1964)?

This chapter will report a number of investigations and experiments that were undertaken to try to elucidate the between centre differences in percentage blood loss.

7.2 METHODS FOR THIS CHAPTER

7.2.1 Procedure for measurement.

7.2.1.i Menstrual Blood loss.

The procedure described by Hallberg for ascertaining blood volume has been described in **6.2.1.ii**. Hallberg's paper (Hallberg & Nilsson 1964) recommended calculating menstrual blood volume via circulating haemoglobin and haemoglobin in the collection. However the formula used in the two centres undertaking blood loss determinations for this study is the much more widely-used one, calculating directly from optical densities (Newton 1977). For each collector the volume of her blood there must have been in her menstrual collection is calculated by taking the ratio of the optical densities (absorbances) of the two solutions in NaOH of her blood (venous and menstrual collection), each factored up by the dilution volumes of NaOH added. The formula most usually applied to calculate blood volume of menstrual loss collected is:

$$\text{Blood (mL)} = \frac{\text{Optical Density(products)} \times \text{Soaking Vol. NaOH} \times \textbf{Dilution factor}}{\text{Optical Density(venous blood)} \times \text{'Dilution' of venous blood}}$$

where 'dilution' is the volume to which 1ml venous blood is diluted, and 'dilution factor' is the factor by which 1ml of supernatant solution is (secondarily) diluted up with NaOH. For example, if the factor is 10, then 1mL of supernatant is diluted to 10mL with additional NaOH. This addition to the standard formula involves a simple proportioning up of the calculated volume to compensate for the dilution of supernatant prior to spectro-photometry. In Glasgow, there was in most cases secondary dilution of the soaking supernatant, prior to spectro-photometric assessment.

Reflection and detailed discussion of the blood loss measurement protocols in the two centres identified the following differences in method between the centres:

a) Different tubes were used to collect the venous blood sample – orange cap (standard) or purple cap (heparinised tube).

b) Different dilutions of venous blood were used prior to measurement of optical density (absorbance) of venous blood – Edinburgh used 1 in 100 (as per Hallberg) whereas Glasgow used 1 in 200.

c) Collections waiting to be measured were stored in a freezer in Edinburgh but in a refrigerator in Glasgow.

d) Different methods of filtration were used for the supernatant soaking solution – in Edinburgh two standard filter papers and in Glasgow one stiffened filter paper.

e) Glasgow further diluted the supernatant prior to measuring optical density (absorbance), but this was only relatively seldom the case in Edinburgh. The rationale for secondary dilution is that provided no bias or random error is introduced in the dilution stage, estimation via photometric measurements will be more accurate if the two samples being tested are of similar concentration. (There was at the time no explanation for this, but as has since been established (and will be described in **Appendix 7.6**) this would avoid distortion due to any non-proportionality in the relationship between concentration and optical density). Other factors pertinent to the need to dilute the supernatant would be the volume of blood in the collection, and the initial volume of NaOH used to soak the collection.

In addition it was established that on occasion pressure of workload meant that products were left soaking longer than 48 hours. This may have been more the case in Glasgow than Edinburgh.

7.2.1.ii Total Fluid loss.

The procedure for measurement of total fluid loss has been described in **6.2.1.ii**. Total fluid volume is obtained by subtraction of dry weight of sanitary products from the wet weight. Where non-standard pads were used their type was ascertained, and individual products weighed to obtain a dry weight per product to use in calculations.

Menstrual blood volume and total fluid volume were two independent measurements, and total fluid volume was known to be potentially error-prone. Possible contributors

to measurement error and/or bias for total fluid volume could be envisaged as follows:

- Unpredictable errors - variability in dry weight of products as manufactured; failure in calibration of weighing scale used; transcription error when recording the weight displayed on the scale used; error in recording count of products used on the menstrual chart; and use of unknown non-standard products.
- Biasing fluid measurements upwards - accidental wetting of products (for example by showering); and incorporation into collection bag of any wrappings or toilet paper.
- Biasing fluid measurements downwards - evaporation due to imperfectly sealed bags.
- Bias in unknown direction – change over the time course of the study in manufacturing specification for standard products.

7.2.1.iii Menstrual Chart.

The menstrual chart provides a prospective record of the woman's experience of her period, including the number of sanitary products used and the degree of soaking of each. The number of sanitary products in the collection was checked against the number of products recorded in the chart.

7.2.2 Laboratory and theoretical exploration of methodological issues in measurement of blood and total fluid volumes

7.2.2.i Quality check on measurement of blood and total fluid

Quality checks on the volume measurements were undertaken at the two centres. This was a considerable organisational and laboratory exercise. 'Test' collections were initially created using out-of-date stored blood from the Blood Transfusion Service. However, this simulation failed because the haematocrit of stored 'blood' is typically 50 to 60%, relative to a standard haematocrit of 35 to 40% for women of reproductive age. Further discussions with the Blood Transfusion Services established that there was the possibility of obtaining sufficient fresh 'whole blood' to run a quality check. There were patients who attended regularly because they

needed therapeutic venesection, and some of these had consented for their blood to be used for research purposes. This enabled the first Quality Check to be made; this described in **Appendix 7.1**.

7.2.2.ii Experimental evaluation of factors related to blood volume measurement differences by centre

Two factorial experiments were designed to try to evaluate the relevance to blood loss determinations of the method variants identified above (except refrigerator/freezer storage). Experiment 1 evaluated the effects of venous sample tube and dilution, and soaking time, and Experiment 2 evaluated the impact of actual menstrual blood loss volume, volume of NaOH used for soaking, filtration method, and subsequent dilution of filtrate on *determination* of menstrual blood volume. These are described in **Appendices 7.2 and 7.3** respectively.

7.2.2.iii Repeated quality check on blood and total fluid volume measurement

The second Quality Check is described in **Appendix 7.4**.

7.2.2.iv Reflection on impact of menstrual loss volume on accuracy of estimation of menstrual blood loss

A further methodological error was detected by my examination of the formula for calculating blood volume. The method as described by Hallberg (Hallberg & Nilsson 1964) assumes that the used sanitary products have been allowed to dry out. The formula derived from Hallberg's work (Hallberg & Nilsson 1964), and widely-used in menstrual collection studies, makes no correction for the *volume* of the menstrual blood loss contained by the sanitary products. This may have minimal effect if the collection has dried out, although this has probably not always been the case in past research studies, as the best way to avoid odour is to keep the collection in a tightly sealed container or bag, right up until covering with NaOH, if possible in a fume cupboard. Where there was an intention to avoid evaporation altogether, as in the present study, the conservation of the full menstrual loss volume has the potential to render the estimation formula inaccurate for purpose of calculating menstrual blood loss, giving a bias towards underestimation of blood volume.

Appendix 7.5 shows that if the menstrual collection has been stored so as to prevent evaporation, then to allow for the volume of menstrual blood loss added to soaking solution, the formula used to calculate blood volume should be (formula (v)):

$$\text{Blood vol.}_{\text{adj. for bld. vol.}}\ (\text{mL}) = \frac{OD_{\text{menstrual solution}} \times V_m \times s}{[OD_{\text{venous}} \times V_v] - [\mathbf{OD_{menstrual} \times s}]}$$

where V_m = initial soaking volume of NaOH, V_v = volume to which 1mL of venous blood is diluted with NaOH, s = secondary dilution factor (the volume to which 1mL of soaking supernatant is further diluted with NaOH), and the ODs are the optical densities of the venous and menstrual solutions. The term printed in bold in the denominator is the elaboration of the standard formula to adjust for the menstrual blood volume in the collection.

The fact of underestimation due to wet blood volume has since been confirmed by reading Eijkeren, who noted the effect when undertaking methodological studies on pads directly after adding known amounts of blood (that is, while still wet) (van Eijkeren et al. 1986). However the adjustment formula provided can be used only for known amounts of blood added to products, and not for wet menstrual collections of unknown blood volume (van Eijkeren et al. 1986). Furthermore, with wet menstrual collections blood is not the only liquid volume added, since the menstrual blood volume comprises on average only half the total fluid loss volume for the period, as has been shown by Fraser (Fraser et al. 2001). The formula taking total period into account would be, as shown in **Appendix 7.5** (formula (vi)):

$$\text{Blood vol.}_{\text{adj. for total vol.}}\ (\text{mL}) = \frac{OD_{\text{menstrual solution}} \times V_m \times s}{[OD_{\text{venous}} \times V_v] - [\mathbf{2 \times OD_{menstrual} \times s}]}$$

Since the adjustments to the denominator are not included in the standard formula, blood loss measurement of 'unevaporated' menstrual collections using the standard formula will underestimate the blood loss volume. **Appendix 7.5** derives formulae for the extent of underestimation of the blood volume, and the formula expressed in terms of total menstrual fluid volume (formula (ix)) is:

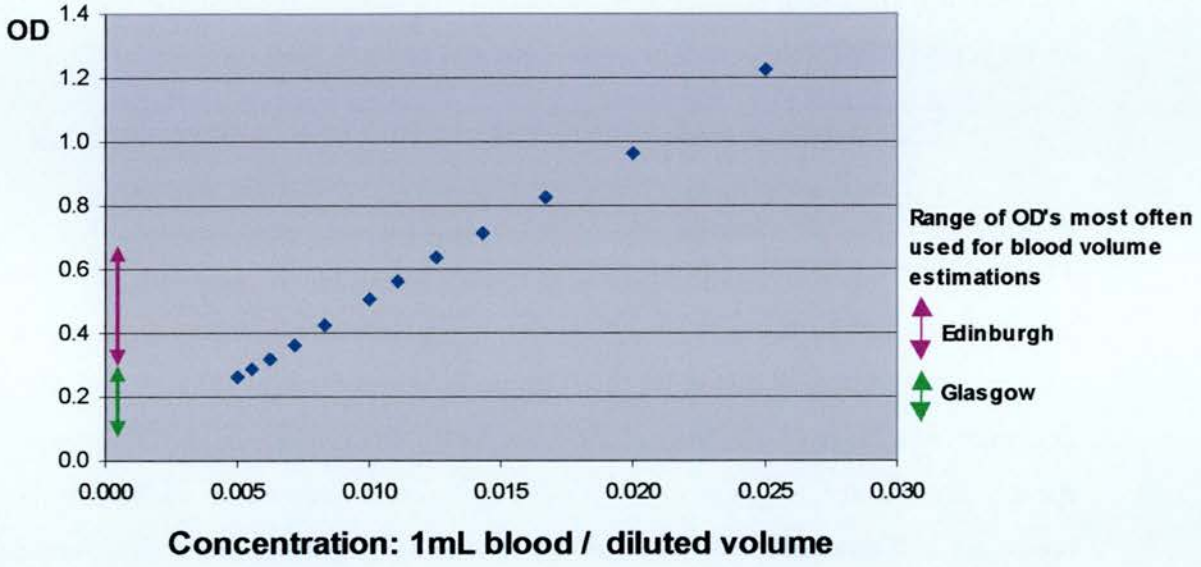
$$\text{Underestimation of blood (\%)} = \frac{\text{TMF mL}}{[\text{TMF} + V_m]\ \text{mL}} \times 100\%$$

It can be seen that this formula has no term involving the secondary dilution factor **s**, and that only the initial soaking volume of NaOH (V_m) and the liquid volume of the entire period (TMF) are pertinent to the extent of underestimation.

7.2.2.v Importance of proportionality to accuracy of menstrual blood loss estimation formula

The formula for calculation of blood loss volume depends for its accuracy on the assumption of proportionality of optical density against concentration of haematin. This is a more stringent condition than simple linearity. **Figure 7.1** plots optical densities for a range of dilutions of the same blood, undertaken on the Glasgow spectro-photometer. Regression of optical density on concentration shows that the points are best modelled by a regression line with a non-zero intercept. This is the case even if the modelling is confined to concentrations 0.005 to 0.010. The fact of this non-proportionality has been noted before, in Experiment 1 (**Appendix 7.2**). The two dilutions (1 in 100 and 1 in 200) tested for each of the blood samples in Experiment 1 should have yielded optical densities that were in proportion, that is in a ratio of 2:1. Yet as was shown the mean ratio at 48 hours standing was 2.07. For the data plotted in **Figure 7.1**, different regressions were obtained for different ranges of concentration. The concentration used for venous blood in Glasgow was 0.005, and in Edinburgh 0.010. Modelling ODs for the lower range of concentrations (0.005 to 0.01), as used at Glasgow, the regression model had *intercept* a=0.012 and *slope* b=49.3. However, if a higher range was used, 0.007 to 0.017, as common in Edinburgh, the regression model had a=0.022 and b=48.5. We needed to establish what impact these non-proportional linear relationships would have had on blood volume estimation.

Figure 7.1 **Optical density (OD) by blood concentrations, for a range of dilutions** (double-headed arrows have been added as annotation to indicate the prevailing OD values –operating ranges- in the two centres)



Appendix 7.6 derives a formula for the error in estimation of blood loss volume, when the relationship between optical density and concentration is non-proportional, but the standard formula (that does not make allowance for non-proportionality) is used.

$$\textbf{Estimation Error}_{\text{standard -allowing for non-proportionality}}(\text{mL}) = \frac{a \times (OD_v - OD_m)}{OD_v \times [OD_v - a]} \times \frac{sV_m}{V_v}$$

This can also be written as (formula (v)):

$$\textbf{Estimation Error}_{\text{std. -adj. for non-proportionality}}(\text{mL}) = \frac{a}{OD_v} \times \left[\frac{sV_m}{V_v} - M\right]$$

In **Appendix 7.6** it has been shown the extent of estimation error, ignoring sign, will be related to the size of **a** and to the amount by which the ratio of effective NaOH solution volumes, $\mathbf{sV_m / V_v}$, differs from the true menstrual blood volume **M**. The error will also be inversely related to $\mathbf{OD_{venous}}$. That is, the error will be bigger for lower optical density. For situations where intercept **a** is positive, then where the specific dilutions used lead to $\mathbf{sV_m / V_v}$ being greater than **M**, there will tend to be

over-estimation, and *vice versa*. If **a** is negative the pattern of over- and under-estimation is reversed.

To demonstrate the joint effect of the differing dilutions a graphical simulation will be plotted. Taking the OD by concentration data reported in **Figure 7.1**, a perfect line was fitted between concentrations 0.005 and 0.02, beginning and ending on the same ODs as had been found in that experiment. (The reason for doing this was to eliminate, for the purposes of this explanatory graphing exercise, the perturbations to calculations arising from the random error in the OD measurements of **Figure 7.1**.) This line had a=0.026, b=47.

Next, using these fitted values for ODs, the standard formula could be used to estimate blood loss volume for a range of simulated collection solutions. All simulations had haematin corresponding to 80mL blood, but diluted in various volumes of NaOH. Therefore the true (correct) estimation in every case would be 80mL blood volume. For the venous blood ODs the appropriate fitted values for these dilutions were used, 0.496 (for 1 in 100 as used in Edinburgh) and 0.261 (for 1 in 200 as used in Glasgow). Using the relevant volumes of NaOH solutions and corresponding fitted ODs, the blood loss volumes were estimated.

7.2.2.vi Reflection on impact of laboratory error on estimation of blood volume

The measurement of blood loss involves a number of steps of laboratory work that are at risk of simple technical error. If such technical errors are random then they would tend to cancel each other out at the group level, but would contribute to an inflated experimental error. However, there is also the possibility of bias. The latter may occur, for example, if the technician consistently dispenses aliquot volumes wrongly, in the same direction, as might occur if there was a consistent misreading of the meniscus. For example, the 0.5mL of venous blood, for the venous solution, may be dispensed consistently at under the nominal volume, perhaps under by 0.02mL (4%). The laboratory errors that would lead to a biasing upwards of the blood loss estimate would be:

- Adding less than the nominal volume of soaking NaOH.

- Dispensing less than the nominal aliquot of venous blood (0.5mL in Glasgow, 1mL in Edinburgh).
- Diluting the venous blood up to more than the nominal venous dilution (100mL in both centres).
- If secondary dilution is used, dispensing more than the nominal aliquot of supernatant and/or diluting it up to less than the nominal dilution volume. For example if diluting 1 to 5 this could be, instead of dispensing exactly 10 mL of supernatant and diluting it up to 50mL with further NaOH, inadvertently dispensing 10.2mL of supernatant and/or diluting it up to 49.8mL. If both these occur the effective dilution is more concentrated than the nominal dilution by almost 5%.

If all these errors occurred in the same blood loss determination in the directions indicated, at the level of 5% error, the effect would be multiplicative, leading to an overall error of 22% over-estimation.

Simulation analyses will be undertaken of the effects of various hypothetical laboratory errors on blood loss determinations.

7.2.2.vii Experimental evaluation of effect, on blood volume measurement, of rubbing/wringing

Hallberg advocated rubbing and squeezing the products after 20 hours soaking (Hallberg & Nilsson 1964). The main reason for physical 'work' on the products was to extract dried blood, which would be common feature in fully dehydrated collections. The requirement in the present study to store used products in air-tight bags after use, in order to avoid evaporation before weighing, means that the used products in this study would have been subject to less evaporation/drying. However there would still have been some, because this tends to happen anyway during wearing of pads, due to body heat. The method advised by the Glasgow laboratory was that longer soaking (48 hours instead of 20) obviated the need for the use of a stomacher to mash the products. It was therefore some surprise to be told, when further deliberating the discrepant blood loss measurements for Edinburgh and Glasgow, for Quality Check 1 (**Appendix 7.4**), that Glasgow used manual squeezing

and rubbing of products to ensure maximal extraction of blood. Therefore Experiment 3 (described in **Appendix 7.8)** was designed to enable the Edinburgh nurse to ascertain the improved extraction that is possible with squeezing and rubbing products.

7.3 RESULTS

7.3.1 Measurement of menstrual blood volume

7.3.1.i Completeness of collection and compliance with procedure for measurement

Altogether 246 women agreed to collect, but 20 (8%) failed to do so, or provided collections that were too incomplete. There was a fairly high rate of use of non-study pads and tampons, with 34% the 226 collectors having used non-study products in the period collected, either pads, tampons or both (median 5 (IQR 1 to 18, maximum 47, n=77)). Overall for 14% of Glasgow collectors and 21% of Edinburgh collectors *more than a quarter* of the products used were non-study products. In addition, 11 (5%) reported pads lost (and therefore incomplete collections): the number of pads lost ranged from 1 to 9, with median 4 (IQR 2 to 9). Out of 95 collectors who used tampons, 3 women (3%) reported tampons lost to the collection: two women lost 4 each, and one lost 6. With regard to the requirements for calculation of blood loss volume, for 8 women no blood sample was obtained, so a standard value had to be used for calculation of blood volume. For one woman the blood sample was taken later i.e. not at the time of collection. We have already reported (**6.3.2.ii**) that 80% of women reported that the period collected was 'less or much less than usual'.

7.3.1.ii Treatments potentially affecting menstrual blood volume or iron status

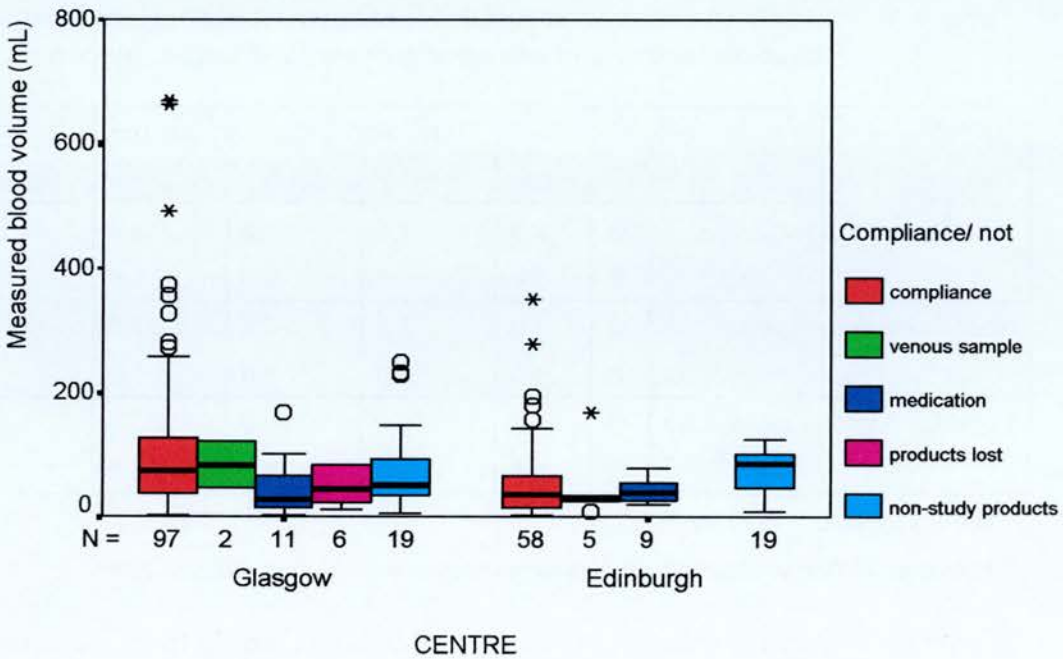
While not strictly speaking a measurement issue for the blood loss volume of the period collected, use of medication is of concern with respect to quantifying *the presenting complaint*. Some collectors were taking medication for their periods by the time of the collection: 10 tranexamic acid, 5 mefenamic acid, 2 each norethisterone, goserelin acetate and iron supplement, and 1 each oral contraceptive pill and warfarin. The numbers were very small, and we do not know what their blood loss volumes would have been if not medicated. Visual inspection ascertained that the one patient taking Warfarin, one each of those taking tranexamic acid, norethisterone and goserelin acetate, and two of those taking mefenamic acid, had

measured blood volumes in the low range for their centre (less than 30mL). On the section of the menstrual chart where women recorded the amount of the charted period 'compared to usual', nearly all women taking these medications reported the period collected, compared to 'usual', as less or much less in amount (17 out of 21, excluding two women on mefenamic acid who did not complete this part of the chart). However, as shown in **Figure 6.10** this is very similar to the proportion of all 198 collectors (completing this part of the chart) who judged the collected period to be less or much less than usual. (nearly 80%).

7.3.1.iii Evaluation of effects of deviation from procedure

The distributions of blood volume for subgroups of collections classified in respect of compliance, or not, are presented in **Figure 7.2**.

Figure 7.2 Distribution of measured blood volume by centre and compliance or not with measurement procedure



Non-compliance was sub-classified in terms of various aspects of the procedure (2nd to 5h columns) as problems with venous sample (not obtained, so standard value used in calculation), taking of medication which may render volume non-representative of complaint (albeit this was not 'non-compliance' as such), more than two products

lost, or more than a quarter of products used being non-study products. Three collectors from Glasgow who were both taking medication and using non-study products have been classified into the latter category. They had blood volumes that were higher than the overall average.

It can be seen that collectors classified as users of non-study products tended to have high blood volumes, and this may be why they resorted to their own tried and tested methods of containment, often very high absorbency 'night time' pads.

7.3.1.iv Exploration of methodological issues in measurement of blood and total fluid volumes

DESCRIPTION OF DILUTIONS AND OPTICAL DENSITY DISTRIBUTIONS IN THIS STUDY

As has been explained in Methods (**7.2.2.iv & v**) the NaOH dilutions used are important to the accuracy and potential for bias in the determination of blood volume. The distributions for these are given in **Table 7.1**.

Table 7.1 Soaking volumes of NaOH for menstrual collection, secondary dilution factor, and effective menstrual dilution, by centre.

Centre*		Min.	Lower quartile	Median	Upper Quartile	Maximum
Soaking volume NaOH (L)	G	0.9	1.5	2.0	2.5	4.0
	E	3.8	3.9	3.9	5.8	9.9
Secondary dilution factor	G	1.0	3.5	10.0	11.0	40.0
	E	1.0	1.0	1.0	1.0	2.0
Effective dilution volume # (L)	G	1.0	6.0	15.0	25.0	140.0
	E	3.8	3.9	3.9	5.9	19.8

** G= Glasgow, E = Edinburgh*

 # Effective dilution volume = Initial soaking volume × Secondary dilution factor

Higher initial soaking volumes were used in Edinburgh, nearly twice the volumes used in Glasgow. On the other hand, secondary dilution was rare in Edinburgh compared to Glasgow (6% versus 91% of determinations). The strategy for secondary dilution in Glasgow was to achieve a haematin concentration in the menstrual solution that was very close to that of the venous solution. Therefore the

majority of collections were subjected to secondary dilution, with more than half the dilution factors being 10 or more. The high secondary dilution factors in Glasgow meant that the effective dilutions were much greater than in Edinburgh (50% being 'effectively diluted' in 15L or more NaOH (up to a maximum of 140L), compared to 3.9L in Edinburgh (max. 19.8L)).

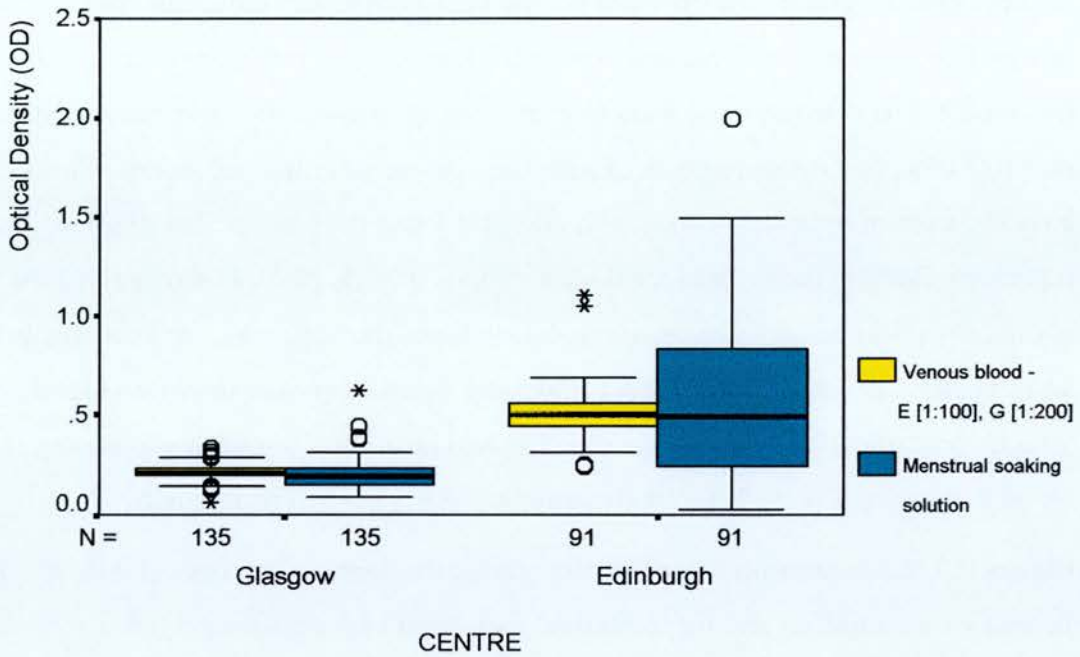
Secondary dilution was adopted in Edinburgh very late on in the study, and only for collections where the optical density for the menstrual solution would otherwise be greater than one (where there is a danger of unreliability in optical density measurements). There were 12 blood loss volume determinations with menstrual optical densities greater than 1, these having been processed before this change. For a further five soaking solutions, secondary dilution was undertaken, in each case by a factor of 2. The data recorded from four of these spectro-photometric measurements plus two other test measurements of solutions, before and after secondary dilution, gave six pairs of optical densities with one over 1 and the other a 50% dilution. The regression fitted to these data (R^2=0.68, F=10.85, df=1,5, p=0.03) showed that the undiluted optical density was on average 1.98 times the 50% dilution. This enabled an estimate to be made of the impact of optical densities greater than 1 on blood volume determination; the *average* effect would have been to underestimate the blood volume by 1% (95% CI 'underestimate by 9%' to 'overestimate by 7%').

Figure 7.3 shows separately for the two centres the distributions optical densities for venous blood dilutions and for 'effective' menstrual soaking solution (after secondary dilution). The menstrual optical densities reflect the effective menstrual dilutions, as shown in the bottom row of **Table 7.1**.

The menstrual optical densities had a much narrower inter-quartile range in Glasgow because of a deliberate policy to choose the secondary dilution to ensure the menstrual optical density was as close as possible to the venous optical density. The between-centre difference in the central locations of the distribution of *venous* optical densities was due to the 1 in 200 dilution of venous blood in Glasgow, compared to 1 in100 in Edinburgh. However, the Glasgow distribution of venous optical densities was also more compact, despite the fact that the range of haemoglobin test results in the two centres was similar. This is partly because of greater dilution. If the

Edinburgh venous optical densities are halved, to what they would be expected to be if a 1:200 dilution had been used in Edinburgh, then the Edinburgh and Glasgow distributions are much more similar (Edinburgh median 0.25 IQR 0.22 to 0.28, Glasgow 0.22 IQR 0.20 to 0.24). It can be seen that the Edinburgh venous optical densities are marginally higher. Regression of optical densities on haemoglobin results confirmed that the regression lines in the two centres are parallel, with Edinburgh optical densities higher by 0.03 for the same haemoglobin.

Figure 7.3 Box-plots of optical density readings for venous and menstrual solutions, separately by centre.



FIRST QUALITY CHECK ON MEASUREMENT OF BLOOD AND TOTAL FLUID

The first Quality Check is described in **Appendix 7.1**. The fluid loss volume measurement was satisfactory, but the blood volume measurements were anomalous. A possible explanation was the settling of the blood in the pack, leading to successively higher haematin concentrations in later drawn test samples. The check would have to be re-run.

Experiment 1 (described in **Appendix 7.2**) showed that tube type had no bearing on optical densities. Optical densities did differ markedly by centre and standing time to measurement, but when the within-sample optical density *ratios* (1in 100 dilution : 1 in 200) were considered there was no detectable effect between centres nor across time. There was a trend for decline in optical density ratio with time, albeit not statistically significant in the small experiment undertaken. Optical density ratios varied quite markedly between individual readings, such that an 80mL blood loss collection requiring spectro-photometric assessment of two dilutions of blood (equivalent to 1 in 100 and 1 in 200) would in 95% of such determinations estimate the blood volume as between 65mL and 98mL. These results do not inform as to the situation at solution concentrations outside the range of 1:100 to 1:200 dilution of blood of normal haemoglobin content, nor in situations where very similar concentrations for venous blood and soaking solution are compared spectro-photometrically (say 1:150 to 1:150).

Experiment 2 (described in **Appendix 7.3**) showed that the double filter paper used in Edinburgh resulted in slight underestimation of the blood volume. Since this affected only the collection optical density, the extent of underestimation is multiplied up if greater effective volumes of NaOH are used, from 1mL underestimation at 4L of NaOH to 5.2mL if the volume of NaOH is increased by a factor of 5. In Edinburgh, where the double filter paper was used, the majority of determinations had 4L of NaOH, but for heavier losses the underestimation would have been greater. This experiment also highlighted the importance of NaOH volumes for the menstrual soaking solution being sufficient to ensure low enough concentrations of haematin for reliable spectrophotometer readings. For the purposes of photometric readings the upper limit of acceptable blood concentration is 80mL blood in 4L NaOH.

REPEATED QUALITY CHECK ON BLOOD AND TOTAL FLUID VOLUME MEASUREMENT

The second Quality Check is described in **Appendix 7.4**. The total fluid measurements using standard pads and average weights were on the whole satisfactory (within 4% of actual fluid volume). There was one aberrant estimation, which was possibly due to a transcription error, the sort of error that could occur for fluid or blood loss volume measurements. The blood loss measurements on the other hand were anomalous. Blood volumes were *underestimated* in Edinburgh (by 5 to 16%) and *overestimated* in Glasgow (by 13 to 35%).

REFLECTION ON IMPACT OF MENSTRUAL LOSS VOLUME ON ACCURACY OF ESTIMATION OF MENSTRUAL BLOOD LOSS

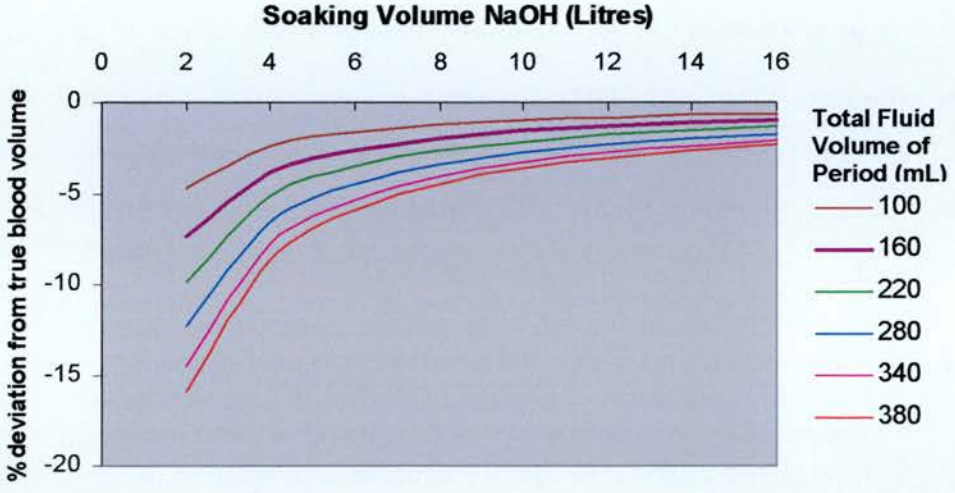
The key formulae are presented in Methods (**7.2.2.iv**) based on the algebraic proof presented in **Appendix 7.5**. The formulae show that the important volumes in judging the extent of this bias are:

- the liquid volume of the menstrual loss contained in the products at the time of commencing soaking, and
- the initial volume of NaOH used for soaking.

The extent of secondary dilution has no bearing on this bias. The theoretical underestimation is illustrated in **Figure 7.4**, for a range of volumes of total menstrual period (blood and non-blood).

It can be seen that the greater the total volume of the period, the more marked the underestimation (separate lines). For all lines underestimation is less marked the greater the volume of NaOH used for initial soaking. The thicker line represents a total period volume that would, on Fraser's data (Fraser et al. 2001), comprise a blood loss volume of approximately 80mL. For a menstrual period such as this, underestimation of blood volume is less than 2% if a minimum of 8L of NaOH is used for initial soaking, and less than 4% if a minimum of 4L is used. It should be noted that if, despite air-tight storage, there has been some evaporation of the menstrual loss from the products, then the underestimation will not be as much as indicated by **Figure 7.4**.

Figure 7.4 Percentage underestimation of menstrual blood loss volume against volume of NaOH used for *initial* soaking, separately for a range of total fluid volumes of the menstrual period.

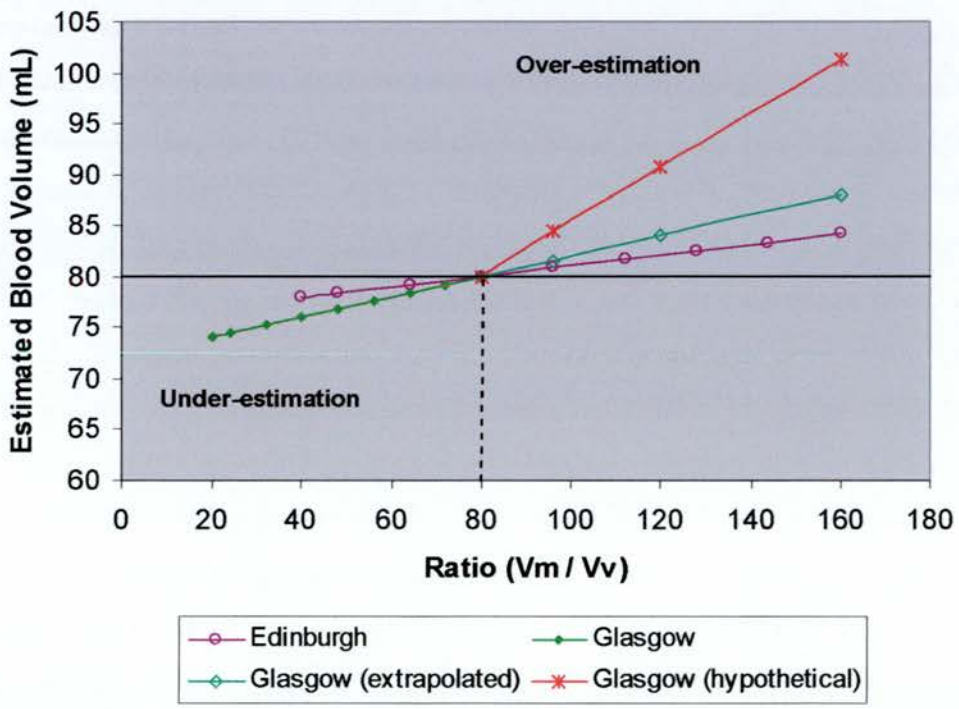


Even when there is no adjustment for total menstrual loss volume, if initial soaking volumes are at least 20 times the total menstrual fluid volume then the estimation error will not be substantial (that is, will be less than 5%). For example, calculating the underestimation applying for Quality Check 2 (**Appendix 7.4**), the difference in estimation in Edinburgh, if using the standard formula rather than one adjusting for menstrual loss volume, would be to under-estimate the test collections of 70, 120 and 190mL blood volume, by only 2.8, 8.1 and 13.2mL respectively. However, for Glasgow the under-estimation would be by 5.6, 12.4 and 26.4mL respectively. The greater under-estimation in Glasgow is because the menstrual fluid volume has had more impact given the generally lower initial soaking volumes of NaOH. The soaking volumes used in Edinburgh were 3.9, 3.9 and 6L respectively, compared to 2L, 2.5L and 3L respectively in Glasgow. The initial soaking volumes in Edinburgh were 24, 15 and 14 times the total menstrual fluid volumes. In contrast, in Glasgow the initial soaking volumes were approximately half the corresponding Edinburgh volumes, so the soaking:blood volume ratios also were approximately half what they were in Edinburgh.

The formula for calculation of blood loss volume depends for its accuracy on the assumption of proportionality of optical density against concentration of haematin.

Using the relevant volumes of NaOH solutions and corresponding fitted ODs, as described in Methods (**7.2.2.v**), the corresponding blood loss volumes were estimated. These are shown in **Figure 7.5**, plotted against the ratio of NaOH solution volumes, $\mathbf{V_m / V_v}$, since in this case no secondary dilution was involved.

Figure 7.5 Estimated blood loss volume when non-proportionality applies (with positive intercept), using Edinburgh and Glasgow approaches for venous blood sample (V_v = 100 and 200mL respectively), for a range of simulated collections, all with haematin corresponding to 80mL blood loss, but with differing volumes of soaking NaOH (V_m)



For the green and purple lines the ODs used are derived from the same model and so have the same (positive) value for intercept **a**. For the Edinburgh data points, the menstrual soaking volumes of NaOH go from 4L to 16L, left to right, and for the

Glasgow data, the soaking volumes for the 'solid diamond' data points are 4 to 16L, and for the 'open circle' data points 19.2 to 32L.

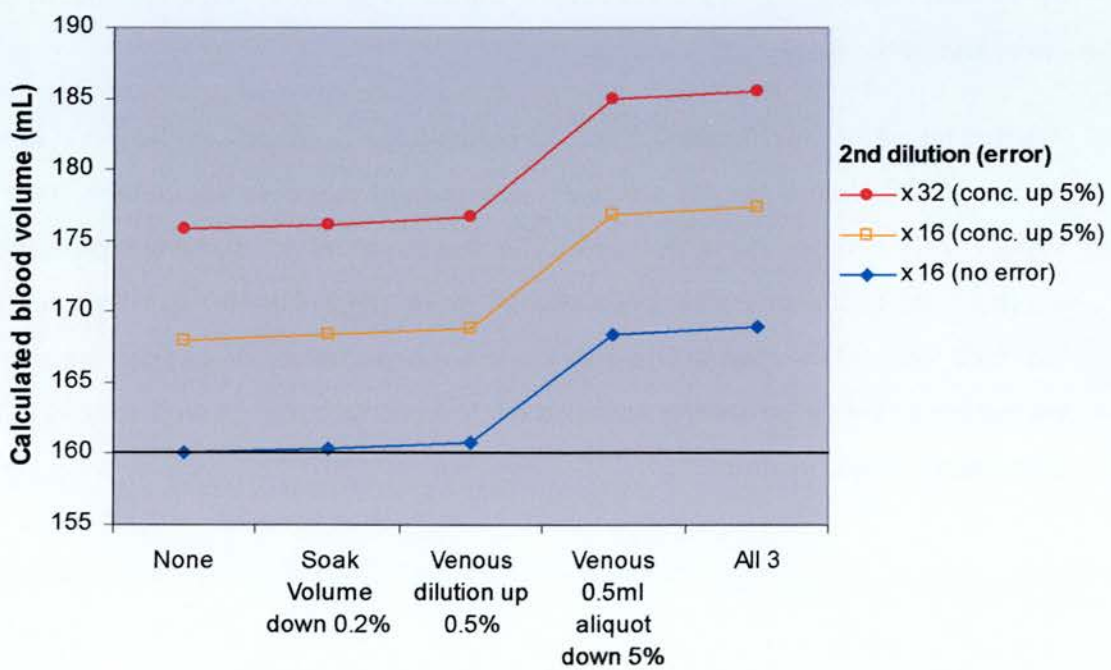
As would expected from the formula for *Estimation Error* above, where the ratio of NaOH solution volumes $\mathbf{V_m / V_v}$ is greater than the menstrual blood volume **M** (that is, 80), there is over-estimation, and conversely where $\mathbf{V_m / V_v}$ is less than **M** there is under-estimation. For both Edinburgh and Glasgow processes, assuming no random error, the estimate is exactly correct, despite non-proportionality, if the dilutions are such that the ratio of NaOH solution volumes $\mathbf{V_m / V_v}$ is *equal* to **M** (dotted line). If $\mathbf{V_m / V_v}$ is approximately *equal* to **M** then the blood concentration is approximately the same in both solutions, so the optical densities also should be approximately equal. This therefore confirms that approximately equal ODs should be advantageous to estimation. It can also be seen that, for equal ratios $\mathbf{V_m / V_v}$, estimates made using the Edinburgh process are closer to the true value of 80mL (the solid black line), than Glasgow estimates. Hence Edinburgh estimates would also be closer to the true value for equal differences between this ratio and **M** (or, if using the OD formula, between $OD_{menstrual}$ and OD_{venous}). This is because of the lower venous dilution used in Edinburgh and the higher OD_{venous} as a consequence. Apart from this, the estimates made by either the Edinburgh or Glasgow processes deviate more where the ratio of dilutions $\mathbf{V_m / V_v}$ deviates most from the menstrual blood volume **M**, to either end of the plotted green and purple lines.

Further reflections on **Figure 7.5** and the methodological issues can be found in **Appendix 7.7**. In practice the errors due to non-proportionality are unlikely to be large. For the determinations in Quality Check 2 (**Appendix 7.4**), taking the intercept **a** as 0.01, the under-estimation in Edinburgh would range from 0.8 to 1.5mL across the three 'collections', and in Glasgow the mis-measurement would range from over-estimation by 1.8mL to under-estimation by 2mL. If the intercept were instead 0.02 these biases would be doubled.

In Methods (**7.2.2.vi**) there has been reflection on the laboratory errors that could, hypothetically, occur. The impact of errors on estimated blood volume is presented in **Figure 7.6**, where the true blood loss volume of 160mL is shown by a black line. The contribution of laboratory errors at the various stages of the blood loss determination is shown by the extent of deviation of the estimates (coloured lines) from the true value (black line).

The errors modelled along the x-axis are 0.2% for soaking volume (error of 4mL in 2000mL), 0.5% for venous dilution (erroneously diluting up to 100.5mL rather than 100mL), 5% for the venous blood aliquot (dispensing 0.48mL rather than 0.50mL), and a combination of these. Two of the three lines model the effect of a 5% error for the secondary dilution (using slightly more of the supernatant and/or slightly less of the additional NaOH, similar to the example given in Methods (**7.2.2.vi**), so that the effective blood concentration is 5% more than intended).

Figure 7.6 Impact of laboratory errors for hypothetical volume determinations of blood loss of 160mL (initially diluted in 2L NaOH, then second dilution by a factor of 16 or 32), measured against a venous blood sample diluted 0.5mL to 100mL (1 in 200).



Part of the rationale for this examination was to ascertain a mechanism for the higher than expected blood volumes in Glasgow, so the figure models only errors in the direction that would increase the blood volume estimate. A marked impact can be seen due to under-sampling of blood in the venous dilution (last two columns of points). These calculations use the optical density data of **Figure 7.5**, derived from the observed data of **Figure 7.1**. For the blue line the (error-free) secondary dilution is such that, provided there are no other laboratory errors, the venous and menstrual ODs are identical, avoiding the problems of non-proportionality. For the other two lines, where there is an error in the secondary dilution, the deviation from the true value of 160ml is partly due to the error and its impact in the formula, but is also partly due to non-proportionality. The combination of under-sampling of venous blood in the venous blood dilution, a high secondary dilution factor (32), and an error in secondary dilution that gives an effective concentration of menstrual blood that is 5% higher than intended, results in a blood volume estimate of 185mL. This is up by 16% from the true value of 160mL.

EXPERIMENTAL EVALUATION OF EFFECT, ON BLOOD VOLUME MEASUREMENT, OF SQUEEZING PRODUCTS

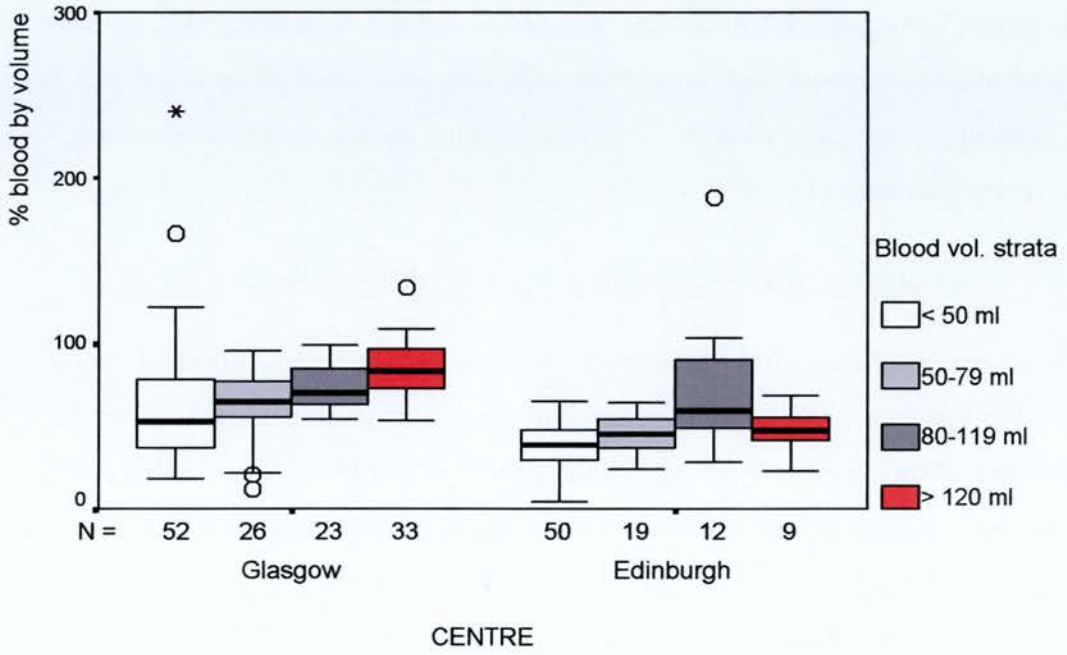
Experiment 3 (**Appendix 7.8**) showed that failure to mash or squeeze the products did lead to underestimation of blood volume in Edinburgh, and it is possible this is exacerbated for very heavy losses. This varied across the five tests but averaged out at an under-estimation by 14%.

7.3.1.v Exploration of measurement effects on study collection data

In this section analyses will be undertaken to explore the potential effect on blood loss determinations of the factors theoretically and experimentally explored in the earlier part of the chapter. While the main concern is that blood loss volume appears to have been subject to a centre bias, so that Edinburgh determinations were lower in volume than those in Glasgow, there is also the question of whether within each centre the blood loss measurements are correct in a relative sense. The true blood loss volume is of course unknown, but two approaches will be taken to obtain insight to the possibility and extent of any biases or errors that may have occurred. Firstly,

findings will be presented within-centre by four groupings based on *measured* blood loss volume: <50mL, 50 to 79mL, 80-119mL, ≥ 120mL. Secondly, the percentage blood will be used as an indicator of the relative accuracy of the blood volume estimation. The underlying assumption is that the true percentage should be around 50%, as per Fraser's data (Fraser et al. 2001). However, it should be remembered that perturbations of the percentage can arise from either of both of the numerator (the measured blood volume) and the denominator (the total menstrual fluid volume, which is also subject to measurement error). **Figure 7.7** shows the percentage blood loss by centre and blood loss volume. The aim of such a plot is to examine variation in percentage blood across the subgroups. In fact, for 6% of Glasgow and 4% of Edinburgh collectors the calculated percentage blood exceeds 100%, a logical impossibility and thus clearly due to measurement error with respect to one or both volumes. However, the absence of a centre effect in the regression model predicting total fluid volume from chart data suggests that total fluid volume determinations are subject only to random error and not centre-specific bias.

Figure 7.7 Percentage blood by volume of total menstrual loss, by centre and blood loss volume stratum.



One interpretation of the graph is that subgroups with higher average percentage blood loss have *relative* over-estimation of blood volume, while those with lower average percentage blood loss represent *relative* under-estimation. So in **Figure 7.7** Glasgow collections with measured blood volume of 80mL or over appear to have over-estimated blood volume relative to all other (Glasgow and Edinburgh) subgroups, while Edinburgh collections with measured blood volume less than 80mL appear to have under-estimated blood volume. If it can further be assumed that the 48 to 50% blood by volume established in Fraser's study is the true proportion, then an *absolute* judgement can be made, that subgroups with average percentage notably less than 50% indicate under-estimation of blood volume, and subgroups with average percentage >50% over-estimation. This would suggest Edinburgh collections with measured blood volume <50mL may have been subject to under-estimation, and Glasgow collections > 50mL to over-estimation, with the extent of over-estimation increasing with greater measured blood volume.

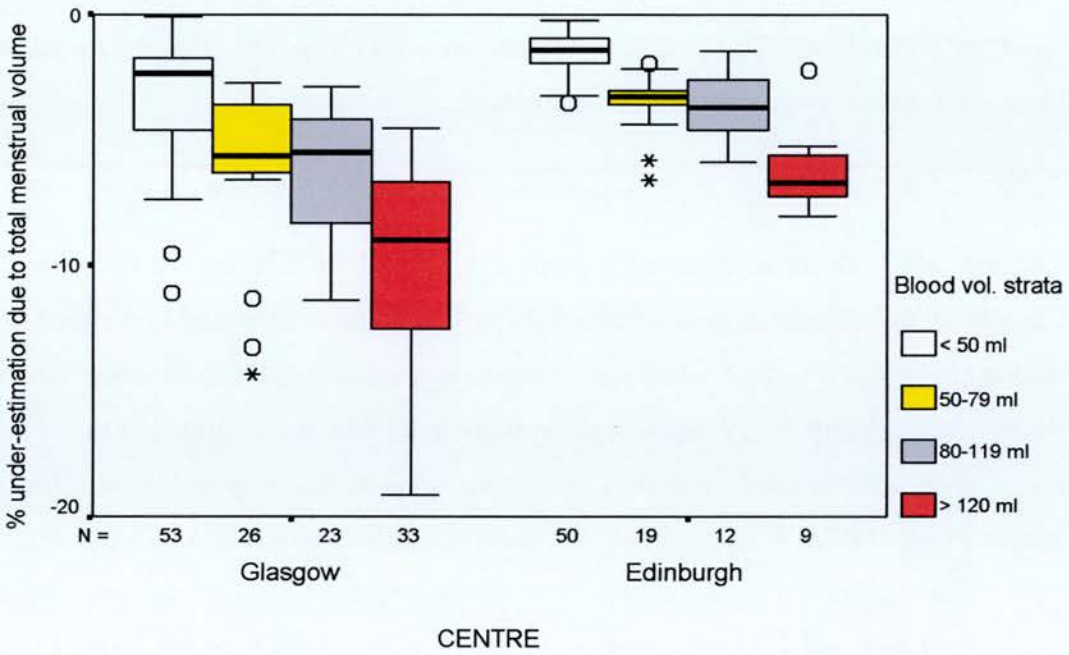
IMPACT OF WET VOLUME OF MENSTRUAL COLLECTION ON ESTIMATION OF BLOOD VOLUME

The potential underestimation in the study data, due to the fact that the blood volume calculation formula takes no account of the volume of the menstrual loss added to the soaking solution, was calculated, assuming no evaporation prior to soaking. To make the correction, formula (ix) derived in **Appendix 7.5** was used, adjusting in accordance with the total menstrual fluid volume, ascertained by weighing. This is shown in **Figure 7.8**. It can be seen that because of the lower initial soaking volumes of NaOH the extent of underestimation would be expected to be greater in Glasgow than Edinburgh, and in both centres it would be greater for greater menstrual blood volumes. This latter effect is because it is algebraically greater for greater *total menstrual fluid* volumes (formula ix in **Appendix 7.5**), and there is a strong association between the total menstrual fluid volume and the volume of the blood component of the menstrual loss.

The underestimation shown in the figure would be the maximum that would apply. Inevitably some evaporation would have occurred from the products into the airspace in the sealed plastic bags containing them, so that once the bags were opened this

'moisture volume' would have been lost. If after opening there had been the opportunity for part or complete evaporation of the remaining moisture in the sanitary products collected, the underestimation would have been less marked or nil. However the menstrual loss determination protocols in both centres involved weighing of sealed collection, opening, counting and initiation of soaking all occurring within a short space of time, so evaporation should have been minimal. Collections were sometimes stored prior to processing (still sealed, in a refrigerator in Glasgow, in a conventional freezer in Edinburgh, so no marked difference in evaporation anticipated).

Figure 7.8 Anticipated percentage underestimation in blood volume due to failure of formula to take account of total menstrual fluid volume.



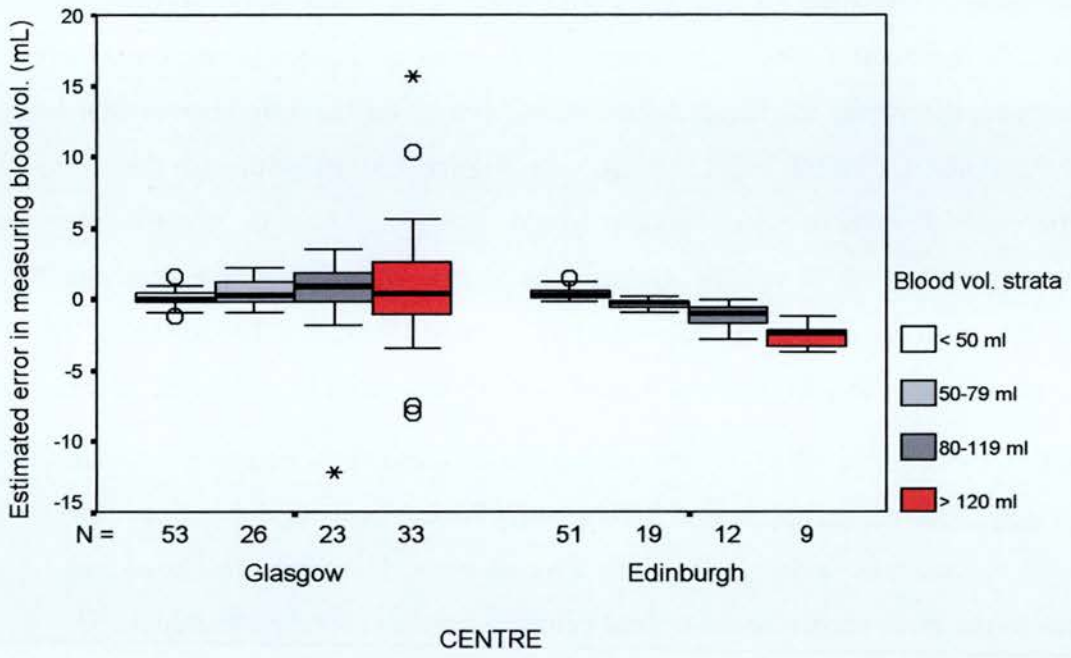
These calculations may help explain some of the apparent underestimation of the higher blood volumes in Edinburgh, but are contrary to the observed between-centre disparity. This pattern of underestimation would have led to Edinburgh blood volume measurements being on the whole *higher* than in Glasgow, for similar total menstrual fluid volumes.

It has been shown that the difference in optical densities of the menstrual and venous solutions has a bearing on estimation error when there is non-proportionality. There was a deliberate aim to avoid substantial differences in Glasgow, which was largely achieved, the overall median and inter-quartile range for the difference in ODs being –0.02 (IQR –0.07 to 0.03, n=135). (See also **Figure 7.3**) In Edinburgh the differences were more marked and, as would be expected from the statistics reported above, varied by blood volume stratum. The median optical density differences, for the lightest to heaviest blood volume strata, were -0.19, 0.25, 0.39 and 0.68 (IQRs –0.3 to –0.1, 0.17 to 0.41, 0.2 to 0.7 and 0.4 to 0.9 respectively, n=51, 19, 12 and 9).

Since the combined effect of these various factors on estimation error is difficult to envisage, formula (iii) presented in **Appendix 7.6** has been used to estimate the blood volume measurement error for each collection. The actual menstrual and venous dilutions used, and the optical densities obtained for the menstrual and venous solutions, have been substituted into the formula. The value for **a** used was 0.01, the value obtained by modelling the data from the dilution experiment on the Glasgow spectrophotometer, as presented in **Figure 7.1**. The estimated errors in measurement due to that degree of non-proportionality are shown in **Figure 7.9**, separately by centre and blood volume strata.

As anticipated from the theoretical deliberations, if non-proportionality applied (with positive intercept) Edinburgh would have tended to under-estimate the heavier blood volumes (due to the menstrual optical densities being on the whole substantially bigger than the venous). Also as anticipated, Glasgow would have had, on the whole, larger errors (due to factoring up by the greater dilution ratio) in both directions, which would have been most apparent in the heaviest losses, where greater dilution factors were needed. Furthermore, assuming the positive intercept applied, these errors would have tended to be *over*-estimations (due to the high proportion of menstrual optical densities that were less than corresponding venous optical densities).

Figure 7.9 **Estimated error in blood volume measurement, due to failure of proportionality** (using actual dilutions and optical densities, and non-proportionality observed on Glasgow spectrophotometer)



In absolute terms these non-proportionality errors were on the whole within 5mL, but if, for example, the non-proportionality applying was greater than that represented by the **a** used (0.01), then the errors would be greater. So for example, if in Edinburgh intercept **a** was actually 0.02, double the value used, then the errors pertaining would be double those shown in **Figure 7.9**. Similarly, if the non-proportionality applying, in the lowest range of the Glasgow spectrophotometer, was not the same as that found in the higher range for which test successive dilution data were available, but more marked, then the *over*-estimation for Glasgow would be more extreme than shown in **Figure 7.9**. (This effect has been illustrated hypothetically in **Figure 7.5**.)

7.3.1.vi Overview of measurement of menstrual blood loss volumes in this study

For the present study **Table 7.2** summarises the features of the method, as specified by Hallberg, and as applied in the Glasgow and Edinburgh centres. Some of the errors and biases that have been considered are summarised in **Table 7.3** in terms of the likely effect on blood volume determination.

Table 7.2 Detail of methods used for blood loss measurement: comparison between Hallberg (Hallberg & Nilsson 1964) and the two centres in the present study

Hallberg Procedure	Edinburgh	Glasgow
Evaporated collection	Not usually	Not usually
Add 2L 5% NaOH per 12/15 products	3.9L, or more as needed, for entire collection	2L to start, but more added if necessary
Soak 20 hours	48 hours plus	48 hours plus
Rub, wring and squeeze products	No, stirring and prodding only	Yes
Filter through alkali-resistant filter paper	Double ordinary filter-paper	Yes, stiffened filter-paper
Read against 5% NaOH at 546mμ	Yes, but latterly dilute further and re-test if first OD>1*	Yes, but dilute further first, judged visually to an OD of ± 0.2
"From the OD reading of haemoglobin lost at menstruation, calculate menstrual blood loss volume using the woman's haemoglobin concentration."	Equivalent formula missing out haemoglobin step, but requires proportionality. Uses venous blood diluted 1 in 100.	Equivalent formula missing out haemoglobin step, but requires proportionality. Uses venous blood diluted 1 in 200.

** This secondary dilution was introduced only near the end of the study.*

Table 7.3 Observed or hypothesised under-estimation/ over-estimation of blood volume at Glasgow and Edinburgh

	Edinburgh	Glasgow
Unknown effect(s), as evidenced in Quality Check 2 (Appendix 7.4)	– 5 to –16%	+13 to 35%
Menstrual loss volume unaccounted for in formula (Appendix 7.5)	– 4 to –7%	– 8 to –14%
Use of double ordinary filter paper (Appendix 7.3)	– 2% approx.	*n.a.*
Failure to squeeze/rub products (Appendix 6.3)	– 14%	*n.a.*
Hypothetical systematic dispensing errors (as in section 7.3.1.vii)	*not considered*	+16%

The undefined errors encompassed by the 2nd quality check (row 1) were very similar in degree and direction to what might be expected from both use of double filter

paper and failure to squeeze products in Edinburgh, and some systematic dispensing error in Glasgow.

Effects due to failure of proportionality are not included in **Table 7.3** because if proportionality fails the direction of the effect depends on the sign of the intercept. The sign of the intercept may vary for different ranges of the optical density (concentration) scale, from run to run, and certainly between centres (equipment).

7.3.2 Measurement of total menstrual fluid volume

7.3.2.i Compliance with procedure for total fluid collection

The percentage of those agreeing to collect who succeeded in providing a collection has been reported above, as has completeness of collection (**7.3.1.i**). Use of non-study pads and tampons is a particular issue since the accuracy of the estimation of fluid volume depends on the accuracy of the calculation of the dry weight. Overall, 19% of the 95 users of tampons in the period collected (which use may be in addition to sanitary pads) used non-study tampons (median 13.5 non-study tampons (IQR 2 to 24, maximum 43, n=18)). Of the 205 collectors who used sanitary pads at all in the period collected, 32% used non-study pads (median 4 non-study pads in the period collected (IQR 1 to 17 pads, maximum 43, n=65)). Where the non-study product type was, as requested, identified by the collector, similar products were purchased so that a weight could be ascertained for the product to use in the calculation of total fluid volume. However, 25 women used one or more pads of unknown type, and 7 used one or more tampons of unknown type. Of particular relevance to the measurement accuracy is the proportion of non-study products used.

In addition 16 women used one or more non-study plastic bags for the products. (The research nurses weighed these.) Despite clear instruction to include only products in the collection, 12 women included wrappers and 10 included some toilet paper. Weights were obtained per sheet of toilet paper and included in the calculation. The research nurses reported that in the case of 4 collections (all Glasgow) there was urine evident on the products, and for these the percentages blood by volume were on the low side, 21%, 31%, 33% and 58%, compared to median 68% (IQR 53% to 86%)

for all 135 Glasgow collections. They also noted 7 collections where the bags were not tightly sealed to prevent evaporation (5 Glasgow and 2 Edinburgh) but for these the percentage of blood in the collection was not high compared to the remainder of the collections (being 27% to 71% for Glasgow, 47% to 48% for Edinburgh).

7.3.2.ii Evaluation of effects of deviations from procedure

The regression analysis of blood volume on total fluid volume (analysis 3 of **Tables 6.2** and **6.3)** was re-run excluding collections where there were potential measurement issues for total fluid volume. That analysis had been confined to collections where total fluid volume was $\geq$ 80mL so this restriction was maintained for the re-run analysis. The extreme outlier excluded from that analysis was no longer an issue as that collection was now pre-excluded on the basis of 100% use of non-study products. A further 39 collections were now excluded because they had a high proportion of non-study products (>0.25), or used unknown products, either of which could affect measurement of total fluid volume. This left 100 collections for re-analysis. The regression analysis results were very similar to before, but with evidence of a better fit to the regression model - increased R^2, increased F, and diminished mean square error. The exclusion criteria were further extended to exclude collections for which the research nurses coded the collection as smelling of urine or to have had unsealed bags (so subject to evaporation), or where the patient had already commenced medication (which might have affected the proportion of blood in the menstrual loss). A further 14 collections were excluded on this basis, and the regression analysis rerun. The 'goodness of fit' to the model improved further, marginally, in terms of R^2 and mean square error (n=86, F=173.6, df 2,83, $p<0.001$, Residual Error Mean Square = 0.112, R^2 = 81%). It was noteworthy that for both these re-run analyses the coefficient for centre was *increased*, meaning that the better-fitting model revealed a greater between-centre disparity in predicted blood volume, for the same total fluid volume. The coefficients for the model were such that the predicted blood volume was 70% of total fluid volume in Glasgow but 37% of total fluid volume in Edinburgh.

7.3.3 Measurement issues in menstrual charts

7.3.3.i Compliance with procedure

In total 315 women agreed to complete a menstrual chart for their next period. However, 20 (6%) did not manage to do so, or provided charts that were too incomplete to use for analysis. The use of non-study products has been reported above (**7.3.2.i**) and is clearly an issue for calculation of total fluid volume. This is because the calculation involves subtraction, from wet weight of collection, of as good an estimate as possible of the dry weight of products used and collected. However, it may also be an issue for menstrual chart estimation of blood volume. Categorisation of a used sanitary pad as 'completely soaked', by indicating it as matching the most extreme pictogram for pad soaking, is likely to represent a rather different volume of menstrual loss if that pad is a regular absorbency pad, compared to if it is 'super plus' 'night time' absorbency, or even, as occurred, an incontinence pad used for menstrual containment.

7.3.3.ii Evaluating effect on estimation of blood loss volume of use of non-study products

Collections with more than 25% non-study products, or using special night-time or incontinence pads (with more than double the capacity of study pads), were excluded (n=40) and the analyses of **Table 6.7,** predicting blood volume from chart data, and from both chart data and total fluid volume, rerun. For the prediction from the chart data only there was modest improvement in fit to the regression model, with R^2 increasing from 58% to 64%. The change in coefficients showed that in the model derived from collections not including night-time pads, greater value was given to pads rated as corresponding to the two most soaked pictograms. If total fluid volume was also included in the model (with the same two outliers excluded as was noted for the corresponding analysis in **Table 6.7**) then again there was modest improvement in the fit to the model (R^2 increasing from 82% to 84%). There was little change in the coefficients for product use, but a slight increase in the coefficient for total fluid volume (presumably because the reliability of measurement of total fluid was also

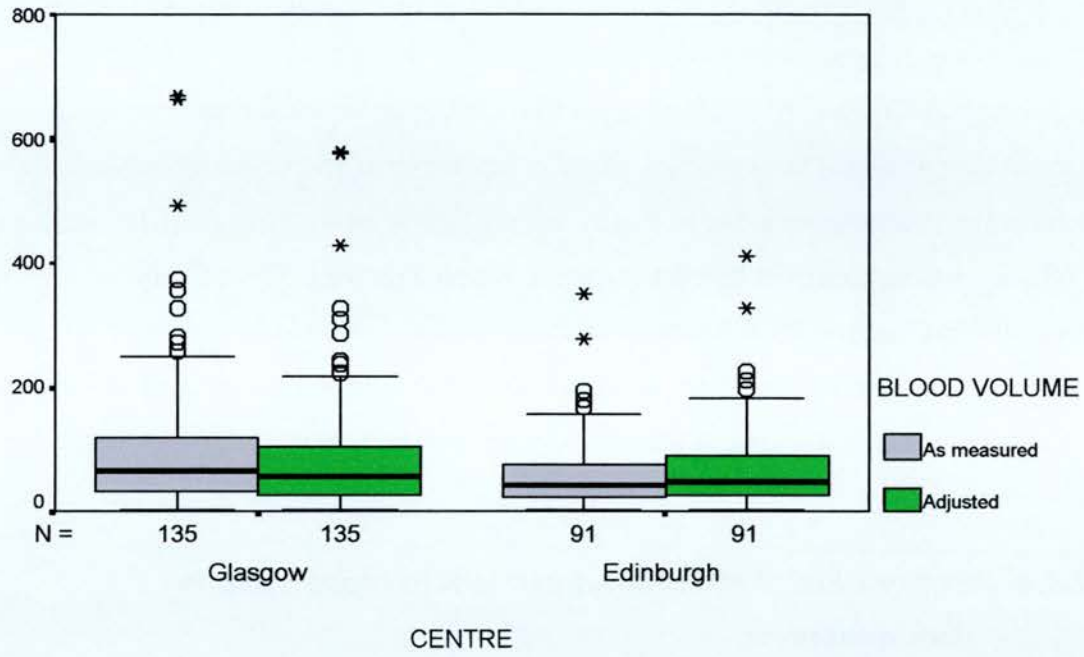
better in the subgroup selected for this analysis, with low use of non-study pads, and no use of very absorbent, and hence heavy, products). Again it was noteworthy that for both these re-run analyses the coefficient for centre was increased, so that the 'chart data only' and 'chart plus fluid data' models predicted blood volume for Edinburgh at 63% and 61% of the prediction for Glasgow, for the same product use/soaking and total fluid profiles. (This is indicative of less disparity between the centres than was shown in the re-run model predicting blood from fluid data only (**7.3.2.ii**), where predicted blood volumes in Edinburgh were 52% of volumes predicted in Glasgow for the same total fluid volume. It should be remembered that that analysis was confined to collections where total fluid volume exceeded 80mL, so this is yet further confirmation that the between centre disparity is greater at greater volumes.)

7.3.4 Exploration of effect of adjustment to blood volume determinations

7.3.4.i Adjusting blood volume determinations for potential laboratory errors and biases

The potential estimation errors summarised in **Table 7.3** can be used to inform potential adjustments to blood volume estimations. An adjustment was made on the basis that Edinburgh had under-estimated blood volume by 15%, and that if there was no secondary dilution, Glasgow had over-estimated by 6%, or if secondary dilution had been undertaken, that Glasgow had overestimated by 15%. The presumed scenario was that Edinburgh's underestimation had arisen mainly from non-mashing of soaked products, and Glasgow's overestimation from some unspecified technical process around venous dilution (6%), or from that and in addition some unspecified error around secondary dilution (15% in total). The adjusted blood volumes were as shown in **Figure 7.10**.

Figure 7.10 Blood volumes by centre, as measured and after 'adjustment'



It can be seen that as would be expected the central location for the Glasgow distribution has become lower (median 56.2mL IQR 27 to 103mL) as have the outlier volumes, whereas the distribution for Edinburgh volumes has shifted higher (median 48.7mL IQR 25 to 90mL). The percentage blood is also more similar in distribution across the two centres; 60.2% in Glasgow (IQR 47 to 75%) and 52.1% in Edinburgh (IQR 39 to 65%), compared to medians of blood percentage of unadjusted data of 69% and 44% respectively.

No adjustment was made for the failure of the formula to account for the wet volume of the menstrual collection. The difference in initial soaking volume practices would have meant an adjustment that increased Glasgow blood volumes relative to Edinburgh. However, this effect would be included in the overall estimate of measurement error provided by Quality check 2 (**Table 7.3**). If the true (relative *and absolute*) over-estimation in Glasgow is as found in Quality check 2 (**Appendix 7.4**), despite the greater under-estimation theoretically likely in Glasgow because of the addition to the smaller soaking solutions of the wet volume of the collection, without any allowance for this in the formula, then the implication must be that factors

producing a systematic (relative and absolute) over-estimation in Glasgow must be more extreme than the 6% or 15% modelled.

It has also been explained above (**7.3.1.vi**) that without knowledge of the intercepts applying at the time of the photometric reading it is not possible to anticipate the direction of mis-estimation due to failures of proportionality. Therefore it is not possible to make informed adjustments for non-proportionality.

7.3.4.ii Effect on regression models of adjusting blood volume determinations for potential errors

When the adjusted blood volumes were regressed on total fluid volume, on chart data and on both chart data and total fluid volume (all variables logged), the regression results were almost identical to what was reported in Chapter 6 (**Tables 6.2, 6.3 & 6.7**), except that the regression coefficient for centre was much reduced. Whereas use of actual measurements for the regression gave a model where the Edinburgh volumes were 34% lower than Glasgow (for corresponding values for the other dependent variables), the *adjusted* volumes give Edinburgh predictions only 14% lower than Glasgow, if modelled only on total fluid volume, or 12% and 10% lower if using chart data, or chart data and total fluid. In the latter two models the coefficient for centre was no longer statistically different from zero. (The two models involving chart data involved (almost) all collections whereas the model for prediction of blood volume from total fluid was confined to collections for which total fluid volume exceeded 80mL. These would have been the collections with generally higher blood loss volume, where the between centre disparity has been observed to be more extreme.)

7.4 DISCUSSION

7.4.1 Between-centre differences in blood loss volume determinations

As has been explained in the Introduction (**7.1**), the main driver for this chapter considering measurement issues in menstrual loss, was the finding reported in **Chapter 6**, that the blood loss determinations in Glasgow were higher than in Edinburgh. Concern was heightened because the percent by volume of blood in the menstrual loss was also considerably higher, with mean percentages 69% versus 46%. This emerging concern was reinforced by regression modelling analyses after the end of the study. Whereas the regression models to predict blood volume from chart product-use data required a coefficient for centre (**Table 6.7**), the regression model based on the same data, to predict total fluid volume from chart data (**Table 6.6**), did not need centre in the model. Unless some mechanism could be envisaged, whereby Glasgow patients are more prone to menstrual loss with a higher proportion of blood by volume, then the unavoidable conclusion is that measurement biases have reduced Edinburgh measured blood volumes and/or inflated Glasgow blood volumes. Furthermore, measurements for test collections created for a quality check, provided quite startling evidence of discrepancy. Three collections were made up with 70, 120 and 190mL blood, to be processed at each of the two centres. The Edinburgh volume determinations were under-estimated by 5 to 16%, while the Glasgow volumes were *over*-estimated by 13 to 35%.

Examination of the blood volume measurement protocols revealed disparities in method that might have contributed to the differences between centres in percentage blood by volume. In particular, Glasgow used more dilute venous blood samples, lower soaking volumes of NaOH, and much more secondary dilution of supernatant, while Edinburgh used different blood sample tubes and different filter paper. Experiments were devised to test some of these factors. Use or not of heparinised tube was found not to be important, and *relative* optical densities were robust to dilution (1:100 or 1:200) and standing time of 'soaking', but type of filter paper used was shown to lead to slight underestimation of Edinburgh volumes. Some of the

value of these experiments was forfeited by the use of blood concentrations that were too high for reliable photometric reading of optical densities. In particular the possibility that secondary dilution introduced a between-centre bias could not be fully explored.

7.4.1.i Inappropriateness of formula for 'wet' collections

The quest for an explanation, and consideration and manipulation of the formula for calculation of blood volume, led to some theoretical insights. One was that the formula made no allowance for the wet volume of the collection. Application of the formula derived to make allowance for the 'wet' collection volume showed that underestimation would have been greater in Glasgow than Edinburgh, because in the context of the higher initial soaking volumes in Edinburgh the added volume of collection would have had proportionally less impact. This finding would produce a disparity between centres that is counter to what was observed. So, while the finding that the standard formula applies only to completely dehydrated collections is theoretically interesting, it rather exacerbates the concern about some mechanism producing a disparity in percentage blood between Edinburgh and Glasgow. Nevertheless, the finding regarding the formula does raise concerns about comparability of other research into measured menstrual blood loss.

7.4.1.ii Importance of proportionality

A further theoretical insight was obtained through examination and manipulation of the formula describing the linear relationship between optical density and haematin concentration. The size of the measurement error arising from non-proportionality depends partly on the absolute size of the intercept (the degree of non-proportionality), partly on how low the venous optical density is, and partly on the difference between the blood volume and the ratio of the effective soaking volume of the menstrual collection (taking into account secondary dilution if it is undertaken), to the dilution volume of the venous sample. Glasgow tended to use a greater venous dilution and therefore to have lower venous optical densities, but Glasgow also had a strategy of ensuring the dilution ratio was as close as possible to the blood volume. If successful and error-free, this does avoid problems of non-proportionality. However

it also revealed that the Glasgow practice of more dilute venous blood samples (1:200) will mean that any random error occurring in optical density readings will have a far greater impact on the calculated blood volume. Furthermore, it is likely that secondary dilution provides an extra opportunity for the introduction of measurement/dispensing errors.

The problem with non-proportionality is that the direction of error depends on whether the intercept is positive or negative, and it is not possible to know what situation pertained at specific readings. Furthermore, the non-proportionality is unlikely to be the same in both machines, and within machine is very unlikely to be constant over the full range of optical density readings. The between-centre difference in practice regarding venous dilution and secondary dilution of supernatant meant that almost all Glasgow photometric readings were in the range 0.1 to 0.3, whereas Edinburgh readings were centred on 0.5, and about a quarter of menstrual collection readings were over 0.75. Therefore, in Glasgow the secondary dilution strategy would lead us to expect a tendency to errors in both directions, depending on the sign of the intercept and on whether the ultimate dilution of the menstrual solution was more or less than the venous sample. Where secondary dilution was high or venous optical densities very low these errors would be more marked. Therefore it would be better to use a 1 in 100 dilution for venous blood and use sufficient soaking NaOH at the start to ensure a blood dilution in the supernatant also of about 1 in 100. That would mean 8L NaOH for an 80mL blood loss.

Assuming the same positive intercept obtained in Glasgow as was found for test serial dilution readings between optical densities 0.26 and 0.96, non-proportionality might explain some underestimation in Edinburgh, but even in the highest losses would be unlikely to account for underestimation exceeding about 5mL. In Glasgow however, non-proportionality could not be the explanation for systematic over-estimation.

Realisation of the importance of proportionality, to the accuracy of the blood volume determination, confirmed a theoretical basis for the practice in Glasgow of using secondary dilution of the supernatant to achieve a menstrual optical density that was very close to the venous optical density. However, the interesting feature of this story

is that the practice of secondary dilution was implemented via a 'steps to be undertaken' rule, without the theoretical basis being understood/known. Therefore staff involved in the laboratory work would have been unlikely to be aware of the potential dangers of the practice: that minute measurement errors could have substantial impact once factored up; or that any advantages may be more than offset if the achieved optical densities were below the optimum operating range. Similarly, laboratory staff at the other centre had no sense of the need to ensure optical densities were not above the optimum operating range. This situation may also pertain in other laboratories where such measurements are undertaken, which again raises concerns about comparability of menstrual blood loss measurements across different research laboratories.

7.4.1.iii Maximising extraction of blood from products

The foregoing has given some theoretical explanation for modest underestimation in Edinburgh, and for some instability in volumes in Glasgow where there were heavy losses, but not for the extent of disparity between Edinburgh and Glasgow, nor for the disparity in blood percentages, compared to Fraser's data (Fraser et al. 2001). A potential explanation for the latter was the discovery that in Glasgow the soaked products were rubbed, squeezed and wrung to ensure maximal extraction of blood. Previous provision for blood volume determinations for research in Edinburgh had involved the use of a stomacher to mash products safely while ensuring extraction of blood into the supernatant. However, when resurrecting the laboratory service for this study it was decided, for the sake of homogeneity of procedures, *not* to use of the stomacher in Edinburgh, because that was not the practice for the established blood loss measurement service in Glasgow. Unfortunately it was not realised until too late that the Glasgow practice of 'just soaking for 48 hours' also involved subsequent manual rubbing/wringing of products. So, a decision that was made with the express purpose of increasing homogeneity in measurement across centres, had in all likelihood contributed to some of the disparity. To gain some insight to the size of the blood extraction deficit, the Edinburgh nurse was asked to undertake her remaining five blood loss determinations by her usual method, and also by subsequently rubbing/wring the products to ensure maximal extraction. It was found

that the average underestimation, without rubbing/wringing, was 14%. Fortunately this was likely to be a pro rata effect, so that within Edinburgh determinations would be ordered correctly, in a relative sense.

7.4.1.iv Possible technical error in laboratory practice

In the present study the outcome of all the experiments and deliberations around measurement issues in menstrual loss was that there were possible explanations for 4 to 20% underestimation in Edinburgh (filter paper, not mashing, and collection volume unaccounted for in formula). For Glasgow there was some theoretical expectation of 8 to 14% *under*-estimation effect (collection volume unaccounted for in formula) but *no* explanation for a systematic *over*-estimation effect. Yet as has been summarised in **Table 7.3**, the simulated collections with known blood volumes provided evidence of *over*-estimation in Glasgow *relative to Edinburgh* of 35% to 45%, and of over-estimation against a known blood volume of 13 to 35%.

The only mechanism that could be imagined to account for this was some technical procedure error(s), say in dispensing/diluting venous blood, or in undertaking the secondary dilution. It is conceivable that this could be a laboratory (equipment/pipette) or operator specific (judging meniscus) characteristic, occurring at only one site. Furthermore, this could be exacerbated by differences in procedure at the two sites, since the same absolute error in dispensing the required amount of venous blood (0.5mL in Glasgow, 1mL in Edinburgh) for the venous solution, would result in a doubled percentage error in Glasgow. Another difference in procedure between centres was the frequency of use of secondary dilution, which was far greater at Glasgow than Edinburgh (91% v 6%), so if a bias was introduced at this stage it would have been essentially a Glasgow-specific effect.

Adjustments were made to the measured blood volumes at the two centres, based on a supposed underestimation of 15% in Edinburgh, and over-estimation by 6 or 15% in Glasgow, depending on whether there was *not* secondary dilution (9% of collections), or *was* (the remaining collections). This caused no change to the regression models predicting blood volume (adjusted) from total fluid volume and/or chart data, other than in markedly reducing the coefficient for centre. This is what

would be expected in modelling terms given that what has been imposed by the adjustment is in effect a pre-emptive centre 'term'. Furthermore, for the adjusted blood volume data there was no longer statistical need for a 'centre' term in the model for prediction involving chart data (with or without total fluid). The results for Quality check 2 (**Table 7.3**) showed over-estimation against a known true value of up to 35% in Glasgow, which suggests that a more extreme adjustment, than the 6 or 15% used here, may be warranted for Glasgow data. If a more severe adjustment had been applied to Glasgow data then the distributions of adjusted blood volumes in the two centres would have approached each other even more closely, even for the higher reaches of the distributions.

7.4.1.v Overview and implications for menstrual research

For this study our intention had been to use the Hallberg method for blood loss determination (Hallberg & Nilsson 1964), the established method applied in the vast majority of past menstrual research involving quantification of blood volume. The blood loss measurement service was to be provided for the study by laboratory personnel experienced in applying the Hallberg method for clinical assessment and for previously published research studies. However, subsequent examination of the protocols in use in Edinburgh and Glasgow showed that the protocols differed from each other in small but potentially important details and that they did not replicate closely the method described by Hallberg (Hallberg & Nilsson 1964). It was also noted that Hallberg did not in fact provide the formula used to calculate blood volume. With the benefit of hindsight, and of my own post hoc engagement with the laboratory processes, which were initially left to laboratory personnel, it could be argued that Hallberg used rather low NaOH volumes for soaking, so would have tended to have high optical densities, with attendant unreliability. Hallberg does not advise on dilution for venous sample nor on secondary dilution (Hallberg & Nilsson 1964).

The measurement problems that beset this study became apparent only because total fluid volume was measured and disparities were observed between the centres with respect to percentage blood in total fluid volume. It is very likely that in past research

ostensibly using the Hallberg method (Hallberg & Nilsson 1964) similar measurement problems have pertained, but they have been undetected. Furthermore, it is unclear how Hallberg's method has been applied in other published studies, since it is not usual for detail to be reported of dilution strategies, formula, pre-soaking drying, timing (Fraser et al. 2001; Higham et al. 1990; Wyatt et al. 2001). Use of automated extraction methods (equivalent to the stomacher) have been specified in some research reports (Fraser et al. 1985).

This lack of technical clarity as to exact procedure for measuring blood volume makes it difficult to compare findings with other research studies and raises concerns about the actual comparability across other studies. Adaptations of the procedure are many and varied (Stomacher to mash products (van Eijkeren et al. 1986), direct calculation from optical density (Fraser et al. 2001; Haynes et al. 1977; van Eijkeren et al. 1986)). There have even been reinterpretations of the definition, perhaps only implicitly, such as: menorrhagia being defined as average blood volume for *more than one period* over 80mL (inclusion criteria for trial (Bonnar & Sheppard 1996)); and by addition to the measured blood volume of an amount to compensate for lost blood and clots ((Hurskainen et al. 1998; Wyatt et al. 2001)). All these issues give cause for concern about comparability of findings across studies.

7.4.2 General measurement issues for blood loss volume

Considering further one aspect of random measurement error, the experiments also revealed the unreliability of optical density readings. Experiment 1 (**Appendix 7.2**) found that for an 80mL blood loss the individual prediction interval, taking into account only the variability of optical density readings, was from 65 to 98mL. That is, from under by 19% to over by 23%. Previous research reporting menstrual blood loss volumes, including our own ((Fraser et al. 2001; Warner et al. 2004a; Warner et al. 2004b)) tends to refer to 'measured blood loss'(Gannon et al. 1996; Haynes et al. 1977; Hurskainen et al. 1998; van Eijkeren et al. 1986; Wyatt et al. 2001). This term should perhaps be abandoned as misleading. No direct measurement is made. The volume is calculated using a formula where both the numerator and denominator involve *predicted* haematin concentrations obtained from linear regressions of

haematin on optical density. Such predictions are very likely to have wide prediction intervals, and for the ratio of two such quantities even greater imprecision will prevail.

No previous research provides precision limits for individual blood loss determinations, but considering the multiple sources of variation that pertain the intervals are likely to be considerably wider than ± 18%. While there may be some value in before-and-after blood loss 'measurement', in clinical trials of therapies for reducing menstrual blood loss, in order to be able to estimate *group* effects, it is difficult to see how blood loss measurement can be useful for clinical management of individual patients. If a patient's blood loss is 'measured' to be 61mL (with 95% prediction interval 43 to 101mL, say), is she deemed to have menorrhagia? All else being equal, should the management of that patient differ from another with measured blood volume of 91mL (95% prediction interval 57 to 134mL), given that the prediction intervals for their likely true blood loss volumes overlap (57 to 101mL) more than they discriminate?

This leads us on to reflect that in practice the clinical definition of menorrhagia presumes a distinction between patients with measured blood volumes of 79 and 81mL! Yet in our study we have exposed methodological problems in blood loss determinations, and the high risk of accumulating errors in these measurements. We have also noted the general omission in published research of important methodological detail about the blood loss estimation undertaken. Taken together these raise strong doubts about the rationality in the 21st century of persisting with a menorrhagia definition based on laboratory blood loss measurements made in 1966 on a Swedish population(Hallberg et al. 1966).

7.4.3 Measurement issues for alternatives to blood loss measurement

7.4.3.i Menstrual charts

There have been efforts to find simpler ways to quantify menstrual blood loss, using pictorial charts (Higham et al. 1990; Janssen et al. 1995; Wyatt et al. 2001), or measurement of total fluid volume ((Fraser et al. 2001)). On the whole this work has

been undertaken in the context of basic science research and validation studies (Higham et al. 1990; Wyatt et al. 2001), or of clinical trials of new and promising treatments ((Bonnar & Sheppard 1996; Irvine et al. 1998), etc). The participants are therefore likely to be (self-)selected and/or highly motivated. Ours is the first study to attempt to undertake quantification in a more pragmatic way, with routine gynaecology clinic referrals whose clinical care is not linked to the collecting.

COMPLIANCE WITH PROCEDURE

We did provide study products, and indicated our wish that these be used as far as possible, but this was not an absolute requirement. (It should be remembered that the study was measuring blood volume, total fluid volume, and asking for charting of periods, so the demands on the participants were fairly high.) It was noteworthy then that over a third of women used at least one non-study product, and for between 14 and 21% more than a quarter of the products used were 'non-study'. Given the goodwill evidenced by these participants, in terms of their substantial efforts on behalf of the study (extensive questionnaires completed and a menstrual collection undertaken), it seems likely that some deviations from optimal procedure, such as use of non-study products, were unavoidable. For a woman with intolerably heavy periods it must be extremely difficult to superimpose the study procedure onto an already challenged menstrual daily life. That is, to ensure one has menstrual chart, spare products and nappy sacks to hand at all times, and to transport home in nappy sacks any used products changed while out. Furthermore, the strategy a woman uses to contain her periods will evolve over months and years. Successful containment, and confidence that this will be achieved, depends on a sense of the body's usual pattern of flow, and of the capacity of the sanitary products usually used. (Indeed this may be part of the reason why many women find it disturbing to have a change in their periods (**5.3.1.iii** and **5.3.1.iv**).) In such circumstances, a request to use only 'study products' for an entire period is likely to have significant adverse impact on the serenity and confidence with which the collector can go about her daily life during her period.

It was noteworthy that exclusion of collections where the very substantial 'night-time' or even incontinence pads had been used not only improved model fit but also

resulted in a change in the regression coefficients to be applied to products classified in terms of the pictograms. This refinement was tried on the basis that use of such products might make for unreliable measurement of total fluid volume, given their substantial dry weight and the likely variability in this. Also, the pictogram representation of a 'fully soaked' pad of this type would denote a very different volume of menstrual blood compared to, say, a fully soaked study pad, albeit 'super plus' absorbency. Therefore the chart development to include specification of the type of study product in addition to the pictogram rating, should on the face of it improve measurement (Wyatt et al. 2001). However, such an addition to the menstrual charting task would make it much more laborious, and would only improve measurement if women complied with the requirement to use the study brand and range of products, which as we have shown is not a trivial imposition, and recorded fastidiously which pictogram related to what absorbency of product.

OPTIMISING PREDICTION OF BLOOD FROM CHART DATA

With respect to chart assessment, this is the only study where the 'score' per product used is derived from the data for product use and soaking. The model obtained for predicting blood from chart data required the log transformation of the counts of the numbers of products used by the various degrees of soaking. This means that the optimal estimation of blood volume is not by means of a *sum* of scores per degree of soaking. Yet this is the approach that has been taken (Higham et al. 1990; Janssen et al. 1995; Wyatt et al. 2001). This may explain why all three charts produce scores that deviate systematically from measured blood volume, to a greater extent for greater volumes (or for greater numbers of products used).

CLINICAL UTILITY

It has been remarked that one validation study of the original chart found very poor performance (Reid et al. 2000). Possible explanations are less highly selected complaint, than women referred to gynaecology clinics, and possibly also lower motivation. However, even if charting performs relatively well against measurement, where both methods are applied, we need to be cautious of the potential for different responding patterns depending on whether the chart is the sole record of menstrual

loss, or supported by objective measurement. In our study a sub-group of 88 women who did not want to collect but nevertheless agreed to chart their periods, differed in some intriguing ways from the remainder of women who collected and charted their periods (n=207). They recorded a far higher usage of products, and more clots of size 50p or bigger, and many fewer noted the period charted to have been less or much less than usual in amount (<50% v 80%) (**6.3.2.ii**). It is known that women with complaint of 'heavy periods' are less focussed than their doctors on the volume of loss (Marshall 1998; O'Flynn & Britten 2000) and that women acknowledge that heaviness is difficult to judge, given the societal constraint on discussion of menstrual loss even among female family members. Furthermore, in the present study we asked a specific question about volume of period, and over half of respondents chose 'no idea' over various specified volumes offered as alternatives. In these circumstances there is a strong possibility that in the face of accompanying objective measurement it would be only human nature to be cautious about declaring on the menstrual chart that the current period is representative of the presenting complaint of 'heavy' or 'very heavy' periods. For the women who charted but did not collect, and whose accounts could not therefore be evaluated in objective terms, the finding that so many fewer rated the charted period as less than usual, suggests that they may have felt less need to be cautious in their responding. The possibility of such a mechanism would need to be borne in mind if moving to assessment of menorrhagia by chart only.

7.4.3.ii Total menstrual fluid

Restrictions on the data used in the modelling analyses, to exclude data where the measurement quality was suspect, resulted in better fitting models, but still with total fluid being the best predictor (**7.3.2.ii** & **7.3.3.ii**). Of course in routine clinical use less than optimal measurement conditions such as these may apply to the patient being assessed, and if a measurement deficit is picked up, clinical judgement as to loss will have to be made instead. In general terms the estimation of blood volumes would be more accurate if total fluid volume were more accurately measured. If prediction of blood volume from total fluid were to be used in the future then it would probably be most acceptable if women were allowed to use their usual

products. The brands and absorbency grades would need to be specified at the recruitment stage, and sufficient packs of the relevant products purchased and weighed, before being given to the participant for the collection. If she were to return the unused products (even if just temporarily) these could be weighed as well as the collection of used products. This would enhance the accuracy of the total fluid loss determination, as the exact dry weight of the products actually used could be obtained by subtraction (from the weight of the products originally provided). It would have the further advantages that the imposition on the patient would be reduced, leakages would be minimised, and compliance would be more likely, because each women would be using her usual products.

The methodological issues discussed above do raise the question as to whether the true percentage that blood comprises of the total fluid volume is as found by Fraser (48 to 50%) (Fraser et al. 2001). This hinges on whether products were thoroughly dried prior to soaking in NaOH, and on concentrations of solutions subjected to spectrophotometry. (Mechanical extraction was used.) However, the finding of fairly constant percentage blood over the range of loss volumes is probably secure.

Perhaps this methodological wake-up call could be the stimulus for a paradigm shift in thinking about menorrhagia. If menorrhagia was to be conceptualised as the volume of the period to be dealt with, rather than volume of blood loss, then total fluid volume is all that would need to be measured, and the objective assessment of 'menorrhagia' would be vastly simplified. Furthermore, measurement would be much more precise, since there would no longer be the need for the regression estimation of blood from fluid. However, the same cautions apply to total fluid volume measurements as for charts, that the validity of the measurement depends on the compliance with collection protocol by the patient. If she adds tampons that have become soaked during bathing (by bath water rather than menstrual fluid loss), or wraps products in toilet paper, or uses an extra 'emergency' product and forgets to notify that this has happened, then her measurement of total fluid volume will be biased upwards.

7.4.4 Overview

The observed disparity in blood volumes must arise from a centre-specific mechanism. It is likely to be greater than is apparent on inspection of the data, as it will have been masked, to an extent, by the wet volume/formula anomaly, which will have reduced calculated blood volumes in Glasgow, relative to Edinburgh, for equal total menstrual fluid volumes.

It is impressive how many women achieved collections, and charting, but a question remains as to just how feasible any of these quantification methods are in routine clinical care. It was noteworthy that although those who ultimately collected were representative in socio-demographic terms of those eligible to collect, those collectors who failed to also provide a completed chart were twice as likely to be living in areas of most deprivation (**6.3.2.i**). It needs to be remembered that although charting may seem less of an imposition on patients than menstrual collection, and less distasteful (in not requiring collection of used products), it may be more problematic for some women. In addition, many of these women were attending the clinic because they were finding their periods unmanageable, so they may have some difficulty with the extra demands imposed by menstrual loss measurement, to use only standard products and/or to collect all used products. Menstrual collection and menstrual charting both require a degree of conscientiousness that is undoubtedly much harder to accommodate in some life-styles than others.

7.5 CHAPTER SUMMARY

7.5.1 Compliance with collection and menstrual blood loss measurement

- For 14% of Glasgow collectors and 21% of Edinburgh collectors more than a quarter of products used were non-study products.
- Glasgow used lower initial soaking volumes of NaOH and higher secondary dilutions for menstrual solution. Glasgow used higher dilution of venous blood samples. This meant optical densities were lower in Glasgow than Edinburgh (about 0.22 versus 0.5).
- The consequences of the disparities in implementation of the method at the two centres have been discovered to be:
  - Under-extraction of blood into NaOH at Edinburgh due to non-squeezing of soaked products.
  - Potential underestimation of blood volume in both centres due to failure to correct for menstrual volume in soaking solution.
  - If there is non-proportionality of OD to haematin concentration for the relevant spectro-photometer then there will be either *under*- or *over*-estimation of blood volume, depending on the sign of the intercept (positive or negative) and on whether the menstrual optical density is greater or less than the venous optical density.
  - If the non-proportionality of OD to haematin concentration in the relevant range for concentration has intercept *greater than zero*, then in Edinburgh there would tend to be *under*-estimation of blood loss volume, whereas in Glasgow there would tend to be *over*-estimation, but not by large amounts. Procedure in Glasgow would also mean more marked errors in both directions
- The measurement check showed that Edinburgh underestimated blood volume by 5 to 16% and Glasgow over-estimated by 13 to 35%.
- Unknown laboratory error (bias), such as systematically under-dispensing the venous aliquot, would be a possible explanation for some of the overestimation apparent in Glasgow.
- The differences found in blood loss determinations between centres means that all analyses involving blood volume need to be checked stratified for centre.

7.5.2 Total menstrual fluid volume measurement

- Re-running of the regression analysis excluding cases with sub-optimal data resulted in a better-fitting model for estimating blood from total fluid volume.

7.5.3 Measurement by menstrual chart

- Women who did not manage to complete a Menstrual Chart were more likely to be from deprived areas.
- Re-running of the regression analysis excluding cases using more than 25% non-study products (which were often 'night-time' pads), resulted in a slightly better-fitting model for estimating blood from chart data, and a change in the weight given to completely soaked pads.

Chapter 8

STUDY RESULTS:

EXPLORING COMPARABILITY AND CONFOUNDING

8.1 INTRODUCTION

There are well-known socio-economic, religious and general health disparities between the two cities contributing participants to this study. Such factors may have an important bearing on experience of menstrual symptoms, on the extent to which such problems can be discussed in lay networks to obtain support and information that may aid self care, on access to information from other sources such as books or web-sites, and on the initiation and conduct of consultations with the general practitioner. These factors can therefore have a profound albeit indirect influence on the outcome of an individual's symptoms. Furthermore, there may be differences between the two centres in local clinical practice with respect to menstrual problems, possibly affecting the referral culture and management of problems. This in turn can permeate back to the woman consulting her general practitioner, or referred to gynaecology clinic, who builds up an understanding of how best to negotiate her menstrual health care needs.

Therefore, before we move on to the modelling analyses of chapter 9, it is important to examine the study data with respect to the interplay of socio-demographic factors, and the differences in these factors between the two centres. In addition it would be salutary to examine the study recruits in relation to the local health board populations.

The study design outlined in Chapter 3 is characterised by nesting, with even the cross-sectional survey involving nested levels of participation, in terms of extent of questionnaires completed. Also nested within the questionnaire survey were:

- a survey of iron status (among those for whom the gynaecologist deemed an iron status test necessary);
- a case-note review follow-up study (among all those recruited more than 8 months before the end of data collection); and
- a prospective menstrual charting and menstrual loss volume measurement study (among those with 'putatively heavy' periods, all questionnaires completed, and who consent to menstrual collection)

It is therefore important, for interpretation of findings, to ascertain the comparability of participants across the various levels of the questionnaire survey, of those receiving iron tests or not, undertaking menstrual collection or not, and being subjected or not to case note review.

In the present chapter the analyses outlined above are reported, prior to the final results chapter (chapter 9) which draws on the multi-faceted study data to undertake modelling analyses .

8.2 METHODS FOR THIS CHAPTER

8.2.1 Homogeneity of centres

The patients recruited in Edinburgh are compared to those recruited in Glasgow. Where differences are found associations reported in Chapter 4 are reviewed after stratification by centre.

8.2.2 Representativeness of populations

For a clinic population there is not any expectation that they should be epidemiologically representative of the background population. However, for each centre patients are compared to the local general populations, in terms of deprivation code and age. This gives some insight to the demographic characteristics of patients referred with menstrual problems, and some indirect opportunity to assess whether there appears to be similarity in the referral filters operating in the two centres.

8.2.3 Comparability across levels of participation

Not all women recruited to the study were in fact eligible for Full participation (collection of loss). As stated in methods (**3.4.4**), to be eligible to collect the woman needed to have putatively heavy periods. That is, to have been referred by her doctor for heavy bleeding or, on CQ, to have reported her periods as heavy or very heavy or to have stated that she was attending the clinic for bleeding. Out of the 952 recruited 87 were not eligible for collection.

The questionnaires comprising participation to level Research 1 and beyond were intended mainly for the purposes of making sense of the measured menstrual loss (ascertained at Full participation), in relation to complaint ascertained at recruitment via the questionnaire CQ. Therefore, the nurses were instructed *not* to pursue completion of the Research level 1 and 2 questionnaires if it was already evident from CQ and referral letter that the woman was ineligible for collection. In some cases all the questionnaires including CQ were completed together, so it would not be until after completion of these that the research nurse would know that the participant was not eligible for menstrual collection, and therefore should not be

asked. It follows then that some differences between those participating to various levels may be expected merely because of imposed criteria for eligibility to collect. These would be observed:

(a) between those recruited but stopping before Research 1 (i.e. completing Basic only) and those proceeding to Research 1 (and/or beyond) – due to non-pursuance of completion for Research 1 questionnaires; and

(b) between those completing up to levels Research 1/2 but not collecting and those proceeding to collection – due to ineligibility.

The characteristics of patients participating to a greater or lesser extent in the study are compared. In addition, patients having iron status tests are compared to those not having tests, and participants having case-note review to those not reviewed.

8.3 RESULTS

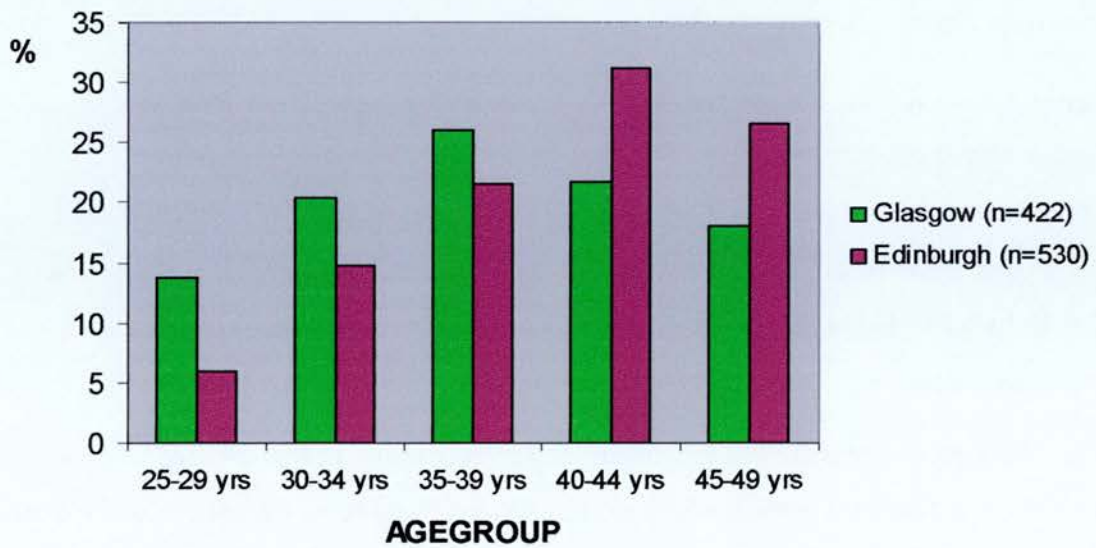
8.3.1 Comparisons between Edinburgh and Glasgow recruits

8.3.1.i Socio-demographic variables

AGE AND RELATIONSHIP

The Edinburgh and Glasgow centres recruited patients that differed quite markedly in demographic characteristics. The Edinburgh participants were older, as shown in **Figure 8.1**. The proportions of women who lived with a partner or husband were similar across the two centres (72% Glasgow versus 79% Edinburgh) but of the remainder, the Glasgow participants were more likely to be single (51% versus 33%) and less likely to be separated or divorced (45% versus 64%). To some extent this is likely to be because of the age differences.

Figure 8.1 Age distributions within centre.

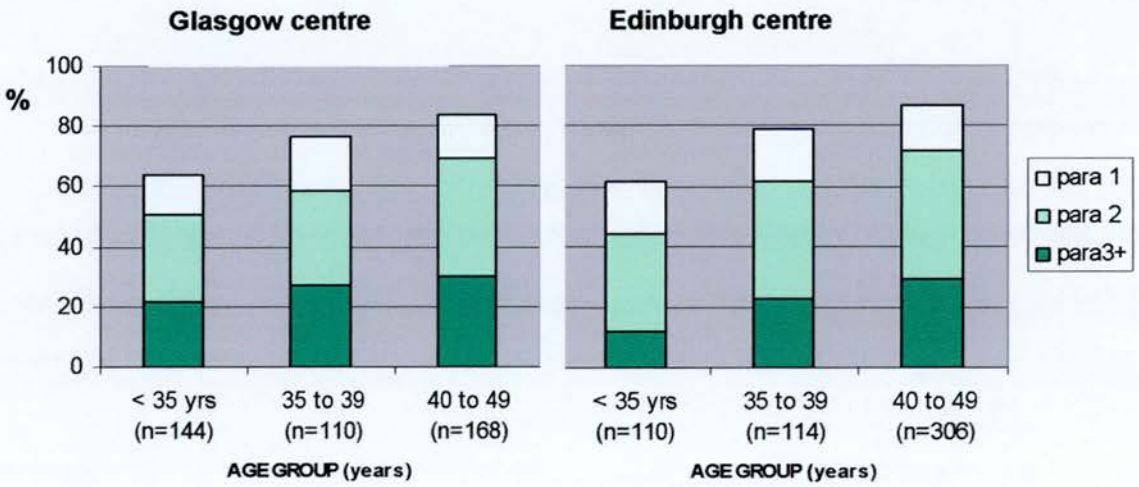


PARITY

Parity was similar across the two centres, with 25% of Glasgow and 20% of Edinburgh participants being nulliparous, and 26% of Glasgow and 24% of Edinburgh participants having three or more children. The pattern of accumulation of

children by age did differ somewhat between the two centres. **Figure 8.2** shows for each centre the percentage of parous women in each of three age bands (overall height of columns) with the columns subdivided into slices to show actual parity.

Figure 8.2 Parity distribution by age group within centre

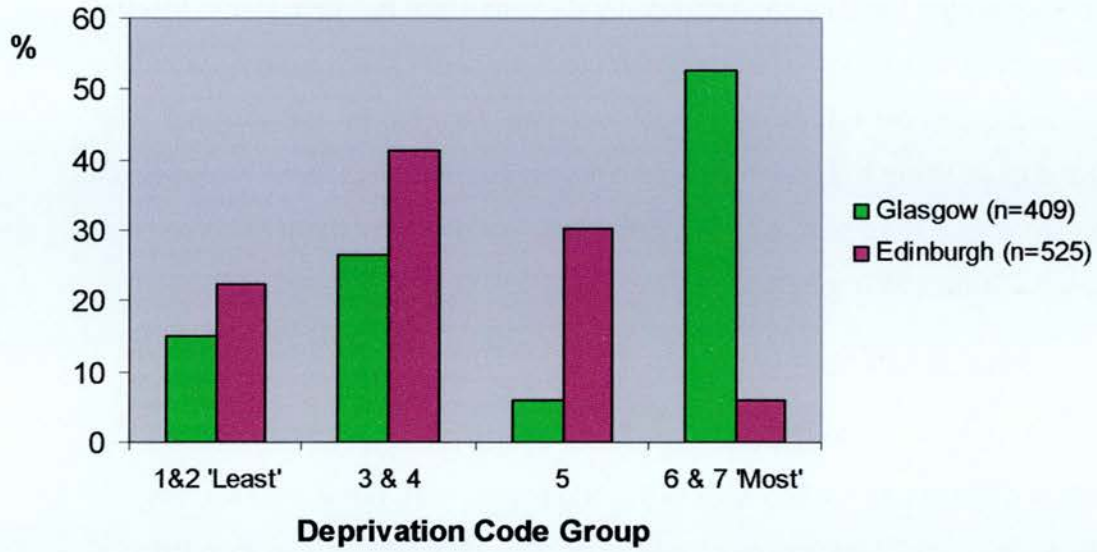


SOCIO-ECONOMIC STATUS

Figure 8.3 shows that the centres differed markedly by deprivation code, with Glasgow having a preponderance of participants living in areas designated deprivation code 6 or 7 (53%). Overall deprivation was negatively correlated with age, so that the most deprived women were the youngest (rho= –0.24, n=934, 95% CI 0.18 to 0.30). However, if the data were stratified by centre then the correlation was found to be confined to Glasgow (rho= –0.292, n=409, 95% CI 0.20 to 0.38).

There were moderate differences with respect to education, in that 24% of Glasgow and 32% of Edinburgh participants had college/university level education, while 64% of Glasgow and 54% of Edinburgh participants left school at 16 years of age. Social class could be classified for only 860 women (368 Glasgow and 492 Edinburgh). The difference in social class between the two centres was also less marked than for deprivation: 35% Glasgow compared to 41% Edinburgh participants in social classes I and II, while 21% Glasgow compared to 19% Edinburgh participants were in social classes IV and V.

Figure 8.3 Deprivation distributions within centre.



EMPLOYMENT

Those in part-time work were most likely to be living with husband or partner (86%), and those in full-time work or unemployed least likely (71% and 74% respectively). Extent of working was negatively correlated with deprivation, so that the most deprived were working least (rho=-0.19, n=924, 95% CI 0.13 to 0.25). It was also associated with age, such that full-time working was most common in the youngest and oldest age-bands (55% and 52% respectively), and unemployment was most common in women aged 30 to 34 years (39%) and least common in the oldest age band (18%) (χ^2=33, 8df, n= 942, p<0.001). Therefore, as would be expected, the centres also differed by employment (χ^2=23, 2df, n= 942, p<0.001), with more Glasgow compared to Edinburgh participants *not* working (33% v 20%), and fewer Glasgow participants reporting full-time working (39% v 49%). This pattern was evident within both the nulliparous and even more strongly in the parous subgroups (among nulliparous 21% v 11% not working, 69% v 81% working fulltime, n=208; among parous, 37% v 22% not working, 29% v 41% working full time, n=733). The nulliparous group was too small to explore further, but within the parous group the relevance of deprivation and time since last pregnancy were examined. For parous women, in the most affluent group (codes 1&2, n=140) there was no detectable

difference in extent of working between Edinburgh and Glasgow (overall 15% not working, 31% part-time and 54% full-time). The remaining parous women (deprivation codes 3 to 7) were stratified by the time since last pregnancy (less than 10 years since pregnancy (n=261) or 10 or more years (n=327)). In those with more recent pregnancies the Edinburgh women were less likely to be 'not working' (28% v 52%) and more likely to be working part-time (51% v 31%). In those whose last pregnancy was over 10 years ago, the Edinburgh women were more likely to be working full-time (53% v 38%).

8.3.1.ii General health

The height, weight and BMI were very similar across the two centres. However, there were quite marked differences in general health, with Edinburgh women judging their health comparatively more favourably than Glasgow women ('better than others the same age'18% v 12%, n=526 v 418, 'worse' 15% v 26%). This difference arose partly because the association of self-reported worse health with younger age was accentuated in Glasgow, and Glasgow had a younger group of participants.

Given the differing age and working profiles in the two centres it is not unexpected that the prevalence of long-term health problems tended to be higher in Glasgow than Edinburgh participants, differing by more than 4 percentage points for 'other' (11%: predominantly gastro-intestinal, nervous system, musculo-skeletal, urogynaecological and haematological conditions), arthritis (7%), high blood pressure (6%) and migraine (4%).

Glasgow participants tended to report having experienced more of the common symptoms in the last two weeks than Edinburgh participants. The specific symptoms which differed most in prevalence between the centres (Glasgow exceeded Edinburgh by more than 4 percentage points) were: craving for particular foods (14%), diarrhoea/constipation (13%), swelling of parts of the body (12%), difficulty in concentrating, nervous tension and aches/stiff joints (all 11%), feeling sad (8%), dizzy spells (7%), lack of energy and rapid heartbeat (6% each), and upset stomach, headaches, shortness of breath, backaches and sore throat (all 5%).

8.3.1.iii Quality-of-life

There was no evidence of an association of SF-36 Health Transition item with demographic variables, but the scale scores were on the whole associated with demographic variables, as shown in **Table 8.1**. The strongest correlation was with deprivation, in that more deprived participants had poorer scores on all scales, in particular mental health. Better scale scores were related to greater extent of working. Physical Functioning was less favourable with increasing age, but the other scales showed better scores with increasing age.

Table 8.1 Non-parametric correlations of SF-36 scale scores with age, deprivation and extent of working (none, part-time, full time)

Scale	n	Age rho$^{\rho}$	Deprivation rho$^{\rho}$	Working rho$^{\rho}$
Physical Functioning	689 to 696	** –0.088	** –0.218	** 0.227
Social Functioning	691 to 698	** 0.114	** –0.244	** 0.157
Role-Physical	682 to 689	0.012	** –0.140	** 0.122
Role-Emotional	683 to 690	0.053	** –0.186	** 0.140
Mental Health	690 to 697	** 0.098	** –0.295	** 0.165
Vitality	690 to 697	* 0.080	** –0.229	** 0.150
Bodily Pain	689 to 696	** 0.144	** –0.251	** 0.165
General Health	686 to 693	** 0.120	** –0.235	** 0.249

$^{\rho}$ *Spearman's rho – positive value means better health status/functioning with increase in demographic variable.*

** *p<0.01*, * *p<0.05*

Given the correlation of scale scores with deprivation, and the previously reported associations in this sample of deprivation with age and working, there was a possibility that the correlations of scale scores with age and working reported in **Table 8.1**, may be a result of confounding by deprivation. The study sample was stratified by deprivation and then the correlations of scale scores with age and working were calculated separately within the three strata. For the most affluent stratum (deprivation codes 1 and 2) the *only* correlation persisting was Bodily Pain which had more favourable scores with increasing age (rho =0.193, n=141). Within

the middle stratum (deprivation codes 3 and 4) also, few correlation persisted: these indicated that in this group extent of working increased with favourable scores for General Health, Physical Functioning and Role-Physical (rho= 0.177, 0.164 and 0.127 respectively, n= 245 to 248).

In contrast, within the most deprived stratum (deprivation codes 5,6 and 7), extent of working remained correlated with all scale scores (rho= 0.279, 0.231, 0.160, 0.206, 0.240, 0.200, 0.217 and 0.289 for the scales in order listed in the table, n= 290 to 296). These correlations were stronger than for the group as a whole (as reported in the Table 4.14) and showed that among deprived women reduced or non-working is associated with poor quality-of-life scale scores. In addition in this group Physical Functioning deteriorated with age, also more strongly than for the group as a whole (rho= –0.195, n= 299).

Distributions of responses for the SF-36 Health Transition item were similar in the two centres but for all the scales except Vitality Edinburgh participants had more favourable scale scores than Glasgow participants. However, after stratifying by the three-level deprivation variable, only a few differences remained. Within the middle deprivation group, there were differences in Role-Physical and Social Functioning, with Edinburgh participants having better scores. Within the most deprived group there were differences in Bodily Pain and Social Functioning, again with Edinburgh participants having better scores. The differences were not however large in absolute terms, the biggest difference between the median scores for the two centres being 13.

8.3.1.iv Contraceptive and obstetric history

The prevalences of abortions, miscarriage/still birth and multiple births were similar in the two centres. Differences between centres in contraceptive usage were to be expected because of its strong association with age, which differs between centres. As is shown in **Table 8.2**, the current method of contraception differed between the centres, mainly due to excess sterilisation in Edinburgh, and excess 'None' and 'Other' in Glasgow. Controlling for age group all but eliminated the differences between the centres, with only a borderline significant difference remaining in the oldest age band (40 to 49 years, n=470, p=0.063), mainly due to excess sterilisation

in Edinburgh (61% v 48%) and excess 'none' in Glasgow (27% v 19%). On the other hand, controlling for parity revealed that there was a difference between centres only in the para 0/1 stratum (n=358, p=0.011), due mainly to excess sterilisation in Edinburgh (21% v 11%) and excess hormonal methods (13% v 5%) in Glasgow.

Table 8.2 also shows there were differences between Glasgow and Edinburgh in rates of sterilisation (any) and female sterilisations.

Table 8.2 Comparison of contraceptive characteristics by centre

	Glasgow % of n	Edinburgh % of n	p
Current contraception (n=420, 527) [a]			0.014[1]
None	30	22	
IUD	2	2	
Sterilisation	41	50	
Hormonal	8	5	
Other	20	20	
Sterilisation, male or female (n=420, 527) [a]	41	50	0.004[2]
Female Sterilisation (n=262, 439) [b]	20	32	0.001[2]
Years on oral contraception (n=215,367) [b]	Median (IQR) 6 (3 to 10)	Median (IQR) 8 (4 to 12)	0.001[3]

Statistics - 1: χ^2 4df, 2: χ^2 1df, 3: Mann-Whitney U

Data source - a: CQ data, b: MBQ data

Rates of male sterilisations did not differ between the centres (18% v 19%). For *all sterilisations*, if age, parity or deprivation were controlled for, detectable differences between centres, in terms of fewer sterilisations in Glasgow than Edinburgh, remained only in subgroups age 40 to 49 years (48% v 61%, n=166, 304), deprivation '5,6&7' (43% v 56%, n=237, 190) and para 0/1 (11% v 21%, n=167, 191).

Ever having used the pill was similar in the two centres (84% Glasgow and 87% Edinburgh), and remained so after controlling for parity and age. There were no detectable differences between the centres in reason for starting the pill (contraception only or menstrual-related reasons), nor in observed effect on pain, heaviness, regularity and PMS. However, age starting oral contraception was younger in Edinburgh, and age stopping older, so total number of years using oral contraception was greater for Edinburgh participants.

8.3.1.v Health history

There was no detectable association of past treatment for anxiety with current age, parity or domestic status (single/cohabiting). However there were trend associations with comparative self-reported health (increasing from 14% in those with 'better' health to 35% in those with 'worse', χ^2_{trend}=16.8, 1df, n=682, p<0.001), deprivation (increasing from 13% in the least deprived to 29% in the most deprived, χ^2_{trend}=10.0, 1df, n=682, p=0.002) and extent of working (increasing from 16% in those with full-time work to 29% in those not working, χ^2_{trend}=11.0, 1df, n=683, p=0.001).

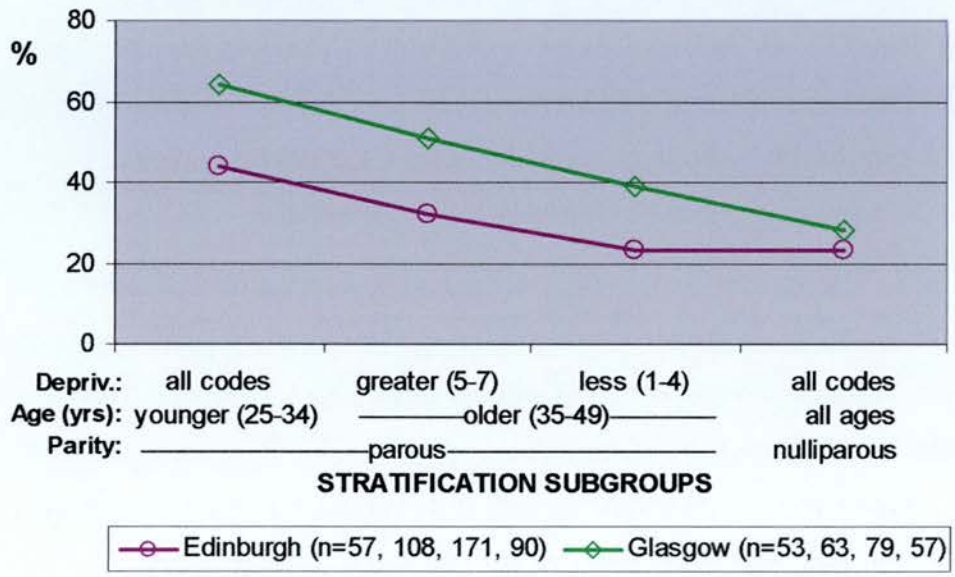
There was no detectable association of past treatment for depression with domestic status (single/cohabiting), and only a non-significant trend for past treatment for depression to be slightly less prevalent in nulliparous women. However there were trend associations with comparative self-reported health (increasing from 14% in those with 'better' health to 54% in those with 'worse', χ^2_{trend}=51.9, 1df, n=681, p<0.001), deprivation (increasing from 19% in the least deprived to 46% in the most deprived, χ^2_{trend}=23.0, 1df, n=679, p<0.001) and extent of working (increasing from 22% in those with full-time work to 44% in those not working, χ^2_{trend}=22.7, 1df, n=680, p<0.001).

As would therefore be expected then there were marked differences between patients at the two centres in terms of past treatment by GP for depression or anxiety, with more Glasgow participants having had some treatment (45% compared to 28%), this increase being in all combinations – anxiety only, depression only and both. It would be expected that in the population the prevalence of past treatment for depression and/or anxiety would be higher in older women because of the longer time during

which the woman may have succumbed to either of these conditions and sought help from her GP.

Given the demographic differences between the centres it is necessary to make a comparison between them in past treatment taking age, deprivation and parity into account. Considering the simple binary variable of treatment (of either or both sorts) or not, it was found that overall the prevalence of a past history of treatment was 30% in those aged 35 to 39 years (n=156) and 32% in those aged 40 to 49 years (n=355) compared to 45% in the youngest women, those aged 25 to 34 years (n=170). A similar age pattern was observed within both centres, but when subdivided by parous state, only within the parous subgroup (n=534). The centres were compared in terms of prevalence of past history of treatment, stratified as subgroup sizes permitted by parous state, deprivation (codes 1 to 4 versus codes 5 to 7) and age (under 35 years or 35 years or older). The prevalences in the four resulting strata are shown in **Figure 8.4**, separately by centre.

Figure 8.4 Comparison between Glasgow and Edinburgh of prevalences of past treatment for depression and/or anxiety within subgroups resulting from stratification by parity, age and deprivation



It can be seen that past treatment was least common among nulliparous women, and most common among younger parous women. Within the older parous women it was

possible also to stratify by deprivation, and past treatment was more common among women living in greater deprivation. In all three parous subgroups there was more past treatment in Glasgow women compared to Edinburgh. There was no detectable difference between the centres in duration of longest treatment for either depression or anxiety.

8.3.1.vi Referral

More of the Edinburgh participants had been referred for bleeding (80% v 71%) and fewer referred for PMS (3% v 12%). Even if age was controlled for (three strata) the differences for bleeding persisted in the two older age bands, and even if deprivation was controlled for (three strata), the differences for PMS persisted in the two more deprived strata.

8.3.2 Comparisons with population data

8.3.2.i Socio-demographic characteristics

The age and deprivation distributions of Edinburgh and Glasgow participants differed, so the question arose whether this reflected background populations. The distribution of age and deprivation score as at the 1991 census was obtained for women aged from 25 to 49, for the Glasgow and Lothian Health Boards. The age distributions of the populations in the two areas were very similar. **Figures 8.5a** and **8.5b** show for each health board the age distribution for the 1991 population, compared to participants in the study (during 1996 to 1998).

It can be seen that the age distribution of participants showed a different pattern to the population, with a lower proportion of women aged under 35, particularly women under 30 years, and a higher proportion of women aged 35 years or older. This is likely to reflect the epidemiology of menstrual complaint. However, the extent of discrepancy between population and participant distributions differed between the two centres. It was less marked in Glasgow, with the modal age group for participants being 35 to 40 years. The trend for participants to be towards the older end of the age range was most marked in Edinburgh, with very few participants aged under 30 years of age, and the majority aged 40 years or older.

Figure 8.5a Age distributions of Glasgow Health Board 1991 female population and Glasgow study participants

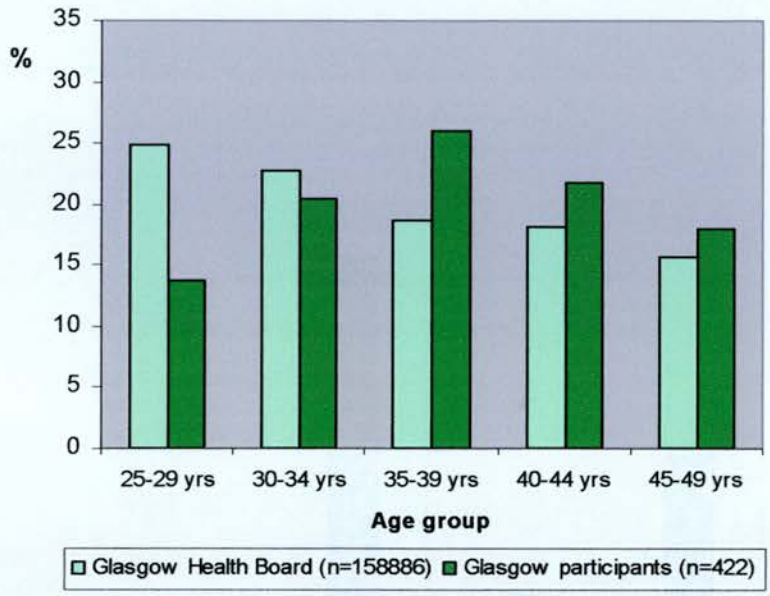
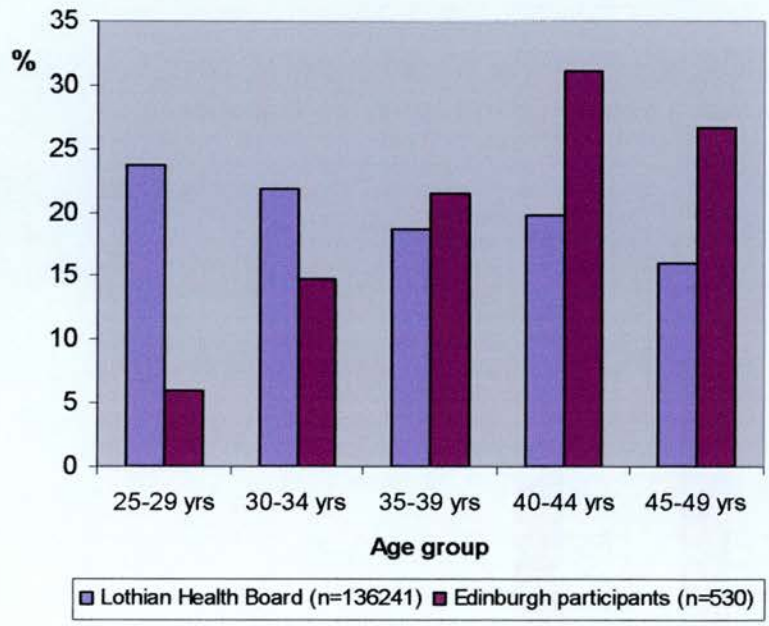


Figure 8.5b Age distributions of Lothian Health Board 1991 female population and Edinburgh study participants



Figures 8.6a and 8.6b show that in each health board the deprivation distribution for participants was fairly similar to the background population. Comparison of the two

figures shows that the deprivation distribution for Glasgow Health Board differed markedly from Lothian, with the majority of Glasgow women living in areas with marked deprivation (scores 6 or 7).

Figure 8.6a Distributions by deprivation score of Glasgow Health Board 1991 female population and Glasgow study participants

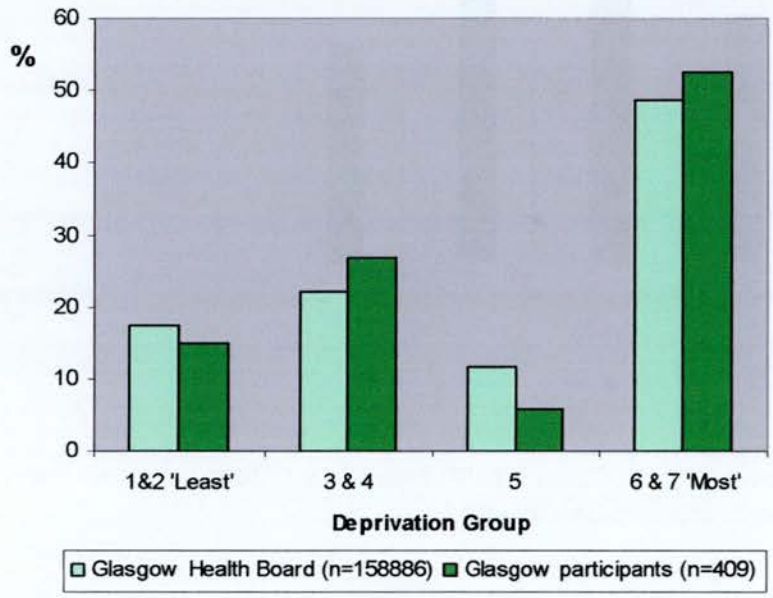
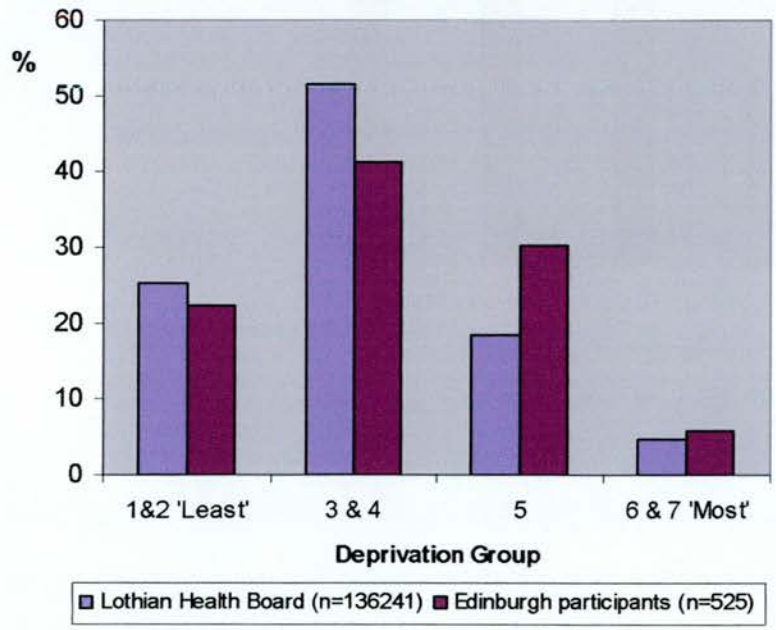


Figure 8.6b Distributions by deprivation score of Lothian Health Board 1991 female population and Edinburgh study participants

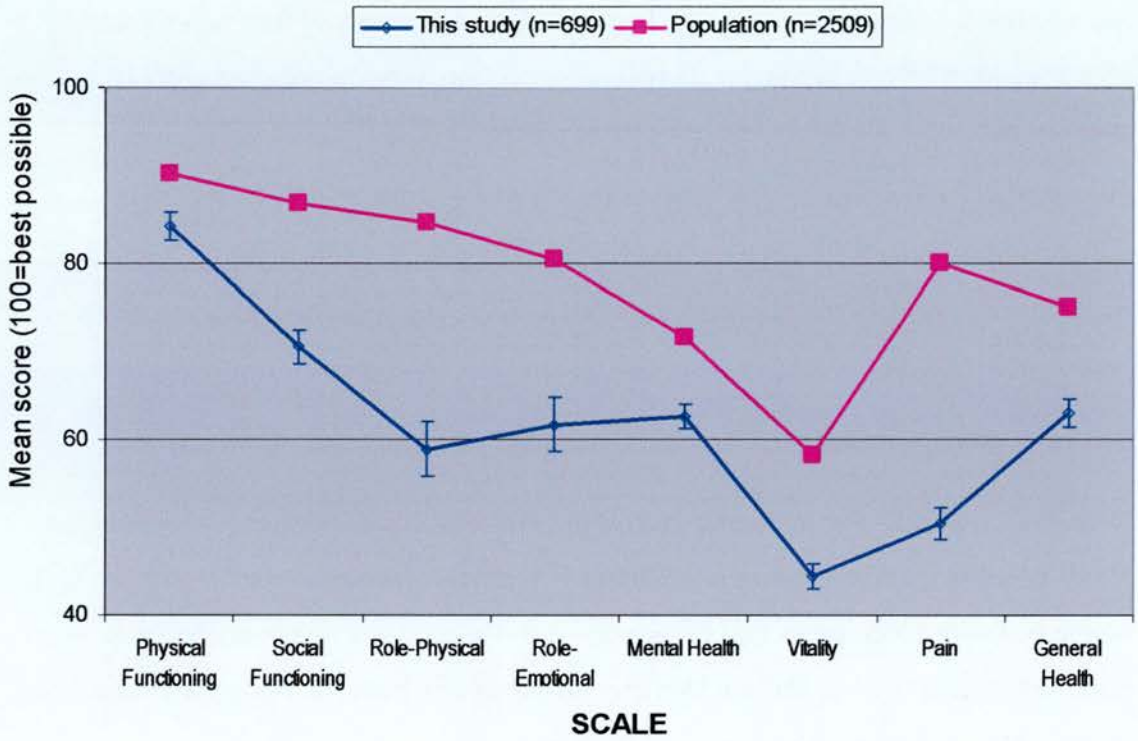


In **4.3.3**.i it was reported that in the study participants overall there was a correlation between young age and deprivation. In **8.3.3.i** it was established that this correlation was confined to the Glasgow centre. To ascertain whether such a correlation exists in the background populations the above data were plotted as stacked histograms of age within deprivation. In neither the Glasgow nor Lothian Health Board data was there evidence of a younger demographic within the more deprived areas.

8.3.2.ii Quality-of-life

Figure 8.7 presents the means and 95% CIs for participants in the present study, and population means (weighted to reflect the age profile of study participants).

Figure 8.7 Comparison of population normative data$^{\phi}$ for SF-36 with mean (and 95% CI) of scale scores for study participants



$^{\phi}$ *Jenkinson, Coulter and Wright BMJ 1993*

Normative data for the SF-36 in the UK was obtained using a sample of 13042 randomly selected subjects aged 18 to 64years, residing in Berkshire, Buckinghamshire, Northamptonshire and Oxfordshire (Jenkinson et al. 1993). The

response rate for females was 77%, providing 5103 respondents. Scale scores were presented by age band, two of which were 25 to 34 years and 35 to 54 years (n=1299 and 1210 respectively) (Jenkinson et al. 1993). The scale means for these age bands have been combined into a weighted mean reflecting the relative sizes of the nearest corresponding age bands in the present study - 25 to 34 years (n=176 completing SF-36) and 35 to 49 years (n=523). Our outpatient sample had lower scores on all scales, in particular Pain, Role-Physical and Role-Emotional.

8.3.3 Comparability of women participating to a greater or lesser extent

8.3.3.i Socio-demographic variables

Age distribution was very similar across levels of participation, albeit with very slightly fewer young women proceeding to Full participation. If the analysis was restricted to women eligible for menstrual collection by virtue of putatively heavy periods then there was even less shift in age by level of participation.

Distribution of deprivation was very similar across participation levels, overall and within centre. Social class distribution was similar across levels within Glasgow. Each of parity, employment and living with a husband/partner was similar across participation levels.

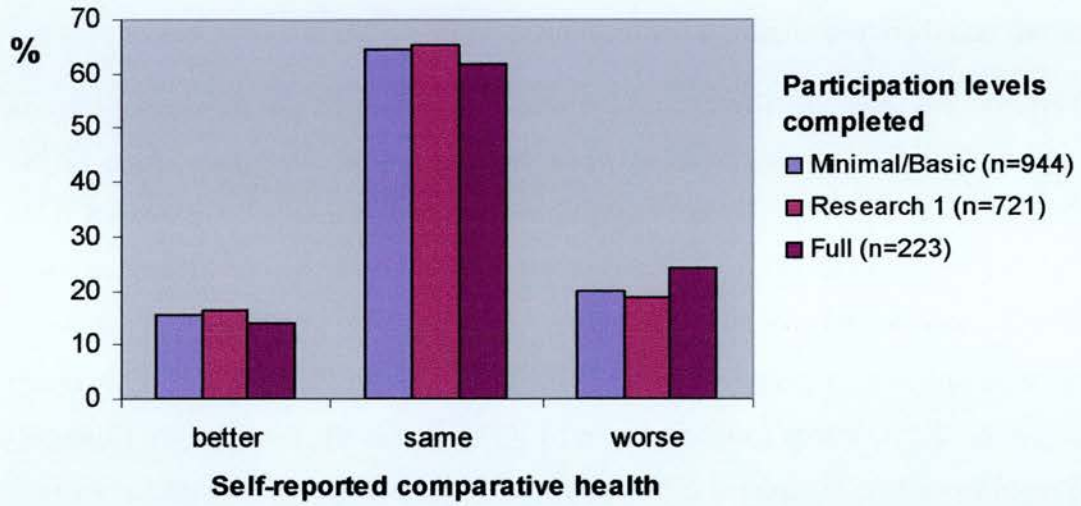
8.3.3.ii General health

Distribution of self-reported comparative general health was very similar across levels of participation, as shown in **Figure 8.8**, albeit with slightly more women with worse health proceeding to Full participation. If the analysis was restricted to women eligible for menstrual collection by virtue of putatively heavy periods then there was slightly less shift in health by level of participation.

BMI were very similar across the levels of participation and for long-term illnesses there were no differences in prevalence exceeding 4 percentage points. For minor symptoms the differences exceeding 8 percentage points were all in the direction of those proceeding to Full participation being more likely to have reported symptoms

in the last two weeks. The differences were backaches (11%), diarrhoea (10%) and feeling sad (9%).

Figure 8.8 Self-reported general health by participation levels completed.



8.3.3.iii Quality of life

Women completing the SF-36 may have stopped at Research 1 (n=473) or proceeded to Full participation (menstrual collection, n=225). There were very similar Health Transition and scale scores in the two subgroups, except for Bodily Pain and Social Functioning. For both these scales those proceeding to menstrual collection had better scores, with the medians differing between the participation subgroups by 10 scale points in each case.

8.3.3.iv Contraceptive and obstetric history

There was a significant difference in the prevalence of sterilisation between Basic only and 'Research 1 or more' participants (39% v 48%, n=235 v 712, p=0.018). However, if analysis was confined to participants *eligible* for Full participation then the difference in prevalence of sterilisation between Basic and Research 1 disappeared (44% v 49%; n=172, 689; p=0.26).

There were no differences detected for (any) sterilisation nor current contraceptive method from Basic to Full nor from Research 1 to Full. However, with respect to *female* sterilisation there were significantly fewer sterilised women proceeding from Research 1 to Full participation (31% v 22%, n=476 v 225, p=0.033) and this was essentially unchanged if analysis was confined to women with putatively heavy periods and therefore eligible for collection.

There was a significant difference in the prevalence of current or past use of the oral contraceptive pill, between Basic only and 'Research 1 or more' participants (78% v 88%, n=238 v 714, p<0.001) and this difference persisted even if only women eligible for full participation were considered. However, the fact that there were no differences detected between Basic and Full, nor Research 1 and Full suggest the above finding may be partly artefactual, due to the greater likelihood of ascertaining pill use via the Research 1 questionnaire MBQ. Fortunately, the observed difference between those who completed Basic only (n=238) and those who completed more does not translate into marked differences when comparing all who have completed Basic (n=947) versus the sub-groupings who have completed more.

8.3.3.v Health history

There was no detectable difference in prevalence of past treatments for depression or anxiety between women completing MBQ only and those proceeding to full participation (menstrual collection).

8.3.3.vi Referral reason

Given the criteria for eligibility for 'full' participation a higher proportion of full participation would be expected in the 'bleeding' referral categories. This was indeed the case, as 76% of women overall were referred for bleeding, whereas 81% of those who completed Research 1 were referred for bleeding, and 86% of those participating fully. Referral for pain was very similar regardless of level of participation, but referral for bleeding and pain together was slightly more common among those participating fully (14% overall, 13% of those completing Research 1 and 19% of those participating fully). Referral for PMS and 'other' reasons was less common among those participating to a greater extent.

8.3.4 *Among women eligible for menstrual collection, comparability of those collecting or not collecting*

Table 8.3 shows the socio-demographics of collectors, and of those who were eligible but did not collect.

Table 8.3 Description of women who undertook menstrual collection (and of non-collectors)

	Collector n=226 %	Declined= / defaulted n=639 %
Socio-demographic factors		
Age Group		
25-29y	8	9
30-34y	15	16
35-39y	27	23
40-44y	33	25
45-49y	17	26
Deprivation Code	(n=222)	(n=630)
Least deprived: 1 & 2	19	19
3 & 4	35	35
5	16	21
Most deprived: 6 & 7	31	25
Parity		
no births	20	21
1-6 births	80	79
Employment status		(n=632)
no job	28	24
part-time work	31	30
full-time work	41	46
Factors used to determine invitation to collect		
Referral for excessive bleeding	87	83
Patient believes referral is for excessive bleeding	71	64
Subjective Heaviness of Periods	(n=225)	(n=634)
moderate	3	14
heavy	49	49
very heavy	48	37
Total 'heavy'	97	86

= *declined to complete further questionnaires, or completed questionnaires but then declined to undertake menstrual collection*

The 226 women who collected their used sanitary protection comprised 26% of all 865 eligible women (with putatively heavy periods), 32% of the 691 who had also completed the necessary questionnaires. The two subgroups are well-matched, except for a slight deficit of collectors aged 45 to 49 years. The remainder of the table gives the prevalence of the criteria for eligibility to 'collect', and shows collectors were somewhat more likely to judge their periods *very* heavy. Among women eligible to collect (n=865), those collecting or not were compared in terms of the prevalence of reporting the various aspects of menstruation as a severe problem. Pain with periods, mood changes, and increased amount of period were consistently most problematic. (This was the case even if all women in the study were considered (n=952), or the subset referred for bleeding (n=725)). The prevalences for the group who collected were in general slightly higher but the relative ordering of problematic aspects was very similar. The aspect closest in meaning to absolute volume ('lose too much blood') was fifth in order of prevalence in the group of all eligible women, and fourth among collectors. Among collectors a severe problem with some aspect of volume of period was reported by 50%, of pain around periods by 43%, and of cycle-related changes by 45% (3, 3 and 2 items respectively, see methods).

8.3.5 Characteristics of participants undergoing iron status tests

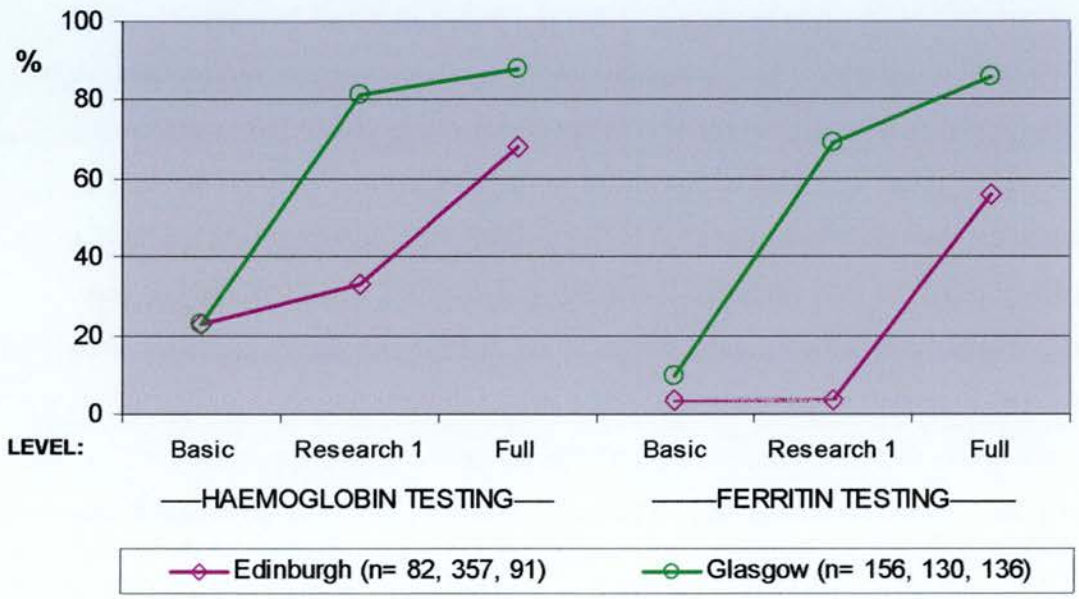
The disparity in haemoglobin and ferritin testing rates between Edinburgh and Glasgow centres has already be reported (**4.3.2.ii**). Comparison of the demographic characteristics and referral reasons of those tested compared with those not tested therefore runs the risk of confounding by demographic factors associated with centre, in particular age, deprivation and self-rated health. The initial overall analyses were therefore checked by stratifying by centre, and where findings differed between centres these are reported separately.

Haemoglobin testing was more likely if there had been referral for bleeding (overall 52% v 35%) and less likely if there had been referral for 'other' reason (overall 41% v 52%). Haemoglobin testing increased with age in both centres, most strongly in Edinburgh (25% to 49%) but also borderline in Glasgow (59% to 64%). In Edinburgh there was a marked increase in haemoglobin testing with increasing parity

(29% to 42%), and in Glasgow there was a moderate decrease in testing with greater deprivation (72% to 59%). Ferritin testing also was more likely if there had been referral for bleeding (overall 33% v 21%) and borderline less likely if there had been referral for 'other' reason (overall 26% v 33%). However ferritin testing rates were not found to be associated with age, deprivation or any of the other demographic variables.

Haemoglobin and ferritin testing rates were found to be strongly associated with extent of participation in the study. **Figure 8.9** shows the prevalence of haemoglobin and ferritin tests by extent of participation, separately for the two centres. In Glasgow those proceeding to research level 1 participation or more were about four times as likely to have a haemoglobin test and seven to eight times as likely to have a ferritin test. In Edinburgh there was modest excess likelihood of iron status testing if the woman participated to Research 1 level (that is, completing in addition the MEQ, quality-of-life, personality and psychiatric health questionnaires), but if she participated fully then there was two to three times the likelihood of haemoglobin testing and thirteen times the likelihood of ferritin testing.

Figure 8.9 Prevalence of haemoglobin and ferritin testing by extent of participation in the study (level), separately by centre.



8.3.6 Characteristics of participants subject to case-note review

The demographic characteristics of those followed up by case-note review (n=665) were compared with those not followed up (comprising 83 whose notes could not be obtained and 204 who were recruited too late). The distributions for the demographic variables other than comparative self-reported health were as expected very similar in the two groups followed up/not. There was no detectable association of follow-up (or not) with any of the referral reasons, nor with any of the SF-36 scale scores.

For comparative health there was a weak trend for follow up to be more likely in those with better self-reported health, going from 77% in those judging their health better to 69% in those judging it the same and 67% in those judging it worse (χ^2_{trend}=4.03, 1df, n=944, p=0.045). This was examined further within centre, and it was found the effect was confined to Edinburgh. Furthermore, within Edinburgh the trend was more strongly evident, with follow-up rates going from 82% to 63% (χ^2_{trend}=8.6, 1df, n=526, p=0.003). Those not followed up comprised 136 ineligible due to their recruitment being too recent and only 20 who should have been reviewed but were missed. As far as could be judged (given the unequal division) the distributions of comparative health ratings in these two subsets were very similar. That the finding for comparative health reflected the population of referrals, and was not an artefact of bias due to missed follow-up, was confirmed by examining participants' comparative health reports across the time-course of recruitment. Age group, deprivation group and referral or not for bleeding and/or pain were also examined by time. Considering the entire study sample there were no detectable differences, between those recruited before and after the follow up cut off date, in the distributions of the four variables listed above. However, when the analysis was repeated separately within centre, it was found that for comparative self-reported health in Edinburgh there was a difference between those recruited before the cut of date and those recruited afterwards, with the former subgroup reporting 14% worse health than others, 66% same and 20% better, compared to 19%, 69% and 12% respectively in the latter subgroup (χ^2_{trend}=5.9, 1df, n=526, p=0.015).

8.4 DISCUSSION

8.4.1 Levels of participation

The design of this research study embedded the menstrual collection within a cross-sectional questionnaire survey of the background clinical population. One aim of the design was to ensure that the background population of women with menstrual complaint and specifically with putatively heavy periods could be well described. Another aim was it to enable checks as to the comparability of women participating to the various levels in the study. Key to this latter aim was the wish to be able to check the representativeness of the subset agreeing to menstrual collection, something that has never before been achieved.

On the whole those participating to a greater extent were very similar to those participating minimally, at least for the data initially reported in Chapter 4. The initially broad recruitment, including any menstrual complaint, was to ensure no covert complaints of heavy bleeding were missed. It was always intended that menstrual collection would be sought only from women with putatively heavy periods (referred for or stating clinic attendance to be for bleeding problem, or reporting menstrual loss as heavy or very heavy). This meant that there had to be exclusion from full participation of those with*out* putatively heavy periods. There was therefore some increase, with greater participation level, in those referred for bleeding (from 76% overall to 86% among those collecting) and some attrition among those not referred for bleeding (which was found for PMS and 'other'). However there was no reduction in the proportion referred for pain, and indeed there was an increase in the proportion referred for both bleeding and pain (14% to 19%). This suggests pain with periods may have been a motivating factor to full participation in the research, and raises the question of whether pain is an important part of the complaint of heavy periods.

Other factors associated with greater participation were having been sterilised, reporting experience of minor symptoms in the last fortnight and having poorer SF-36 Bodily Pain and Social Functioning scale scores. Among women with putatively heavy periods there was a higher prevalence of female sterilisation in those

undertaking menstrual collection, compared to those who stopped at level Research 1 (31% v 22%; n=454, 225; p=0.017). The possible scenarios explaining why sterilised women appear to be over-represented in those participating to a greater extent are that they are likely to have commenced recurrent 'natural' menstruation from the time of sterilisation, and that they are likely to be of higher parity than other women in the sample. Association of female sterilisation and menstrual blood loss volume will be examined in chapter 9.

8.4.2 Case-note review follow-up and iron status testing

Although time-constraints meant follow-up was confined to the first 79% of women recruited, it was not expected that this could introduce any sample bias. However, it was found that the comparative health of Edinburgh women differed between those followed-up or not, although fortunately only a weak trend. This was established as resulting from a change in case-mix with time.

There were marked differences between centres in the proportions being tested for iron status, and the factors associated with testing. Therefore test results can not be interpreted as indicative of iron status for the population of women referred for menstrual complaint and participating in the study. The main interest in iron status was as an indicator of clinical menorrhagia, which can only be established by menstrual blood volume measurement. Fortuitously, iron status testing was markedly more frequent among those undertaking menstrual collection, so these data nevertheless allow some examination of iron status in relation to measured menstrual blood loss volume.

8.4.3 Comparisons between centres

There were many differences between the participant groups in two centres. The most striking were in terms of the demographic factors age and deprivation. While the differences in deprivation appeared to reflect a difference between the two local populations, the differences in age were despite similar age distributions in the local populations of women. Furthermore, in Glasgow participants there was a correlation between deprivation and young age that was not evident in the health board

population. This may result partly from the fact that the Glasgow centre recruited from two hospital clinics, one serving a deprived area and running a specialist menstrual problem clinic (dealing with problems across the age range including a good proportion of young women), the other serving a more affluent catchment and offering a standard gynaecology outpatient clinic (which typically tends to have an older referral population). That recruitment was predominantly from the first of these two clinics may explain the younger demographic of Glasgow participants.

Many of the other differences between Edinburgh and Glasgow participants were likely be a direct consequence of the differences in age and deprivation. For example, the younger age distribution in Glasgow may well explain the fact that among women not living with a partner, Glasgow women were more likely to be single, Edinburgh women separated/divorced. Another finding was that relatively more of the Edinburgh women were working (80% v 67%), and working full-time (49% v 39%). It may be thought that this too was due to differences in age, since older women would tend to have older offspring and therefore would be freer to undertake employment, and more extensive employment. However, the difference in extent of working was also evident among nulliparous women, albeit not as strongly as among parous women. Among parous women there was no detectable difference between centres in extent of working in the most affluent women (codes 1&2, n=140). The observed differences suggest that among less affluent and deprived women there may be some fundamental difference between the centres in employment tendency or opportunity. This reminds us that there may well be other ways in which the two localities differ, for example in general practitioner referral style, and gynaecologist management of menstrual complaint.

These findings demonstrate the complexity of the inter-relationships between age, age at child-bearing and deprivation, and also alert to the need to check all comparisons for demographic and reproductive differences. Differences that persisted after adjusting for deprivation and age were higher prevalence of female sterilisation and greater duration of use of oral contraceptive pill in Edinburgh.

However, even where differences can be explained in terms of underlying differences in deprivation, as for example self-reported comparative health in

Glasgow women, they may remain of relevance to complaint, and to management in the outpatient clinic. That is, a woman suffering indifferent health, perhaps largely because of the deprivation of her circumstances, may very reasonably find heavy periods less tolerable, and it may well be that her menstrual condition warrants more radical treatment, because of her multiple morbidity. Other health deficits among Glasgow women that were very likely explained by deprivation were greater prevalence of past treatment for depression or anxiety, more long-term illnesses, more minor symptoms, and poorer scores for all SF-36 quality of life scores other than Vitality and Health Transition. The impression gained from these early descriptive analyses is that for many women living in considerable deprivation and suffering poor health, their menstrual complaint must be almost the least of their problems. Perhaps though it is the only aspect of their lives that is amenable to remedy.

8.4.4 Overview

There were concerns at the design stage regarding the difficulties in recruiting women to undertake menstrual collection purely for research purposes, and to complete such a battery of questionnaires. It is therefore reassuring that those recruited to the study differ so little from those who were not – as reported in Chapter 4 -, and that the subgroups participating to a lesser or greater extent within the study differ in relatively few ways from each other.

Those subject to case note review, essentially those recruited before February 1998, were as expected on the whole similar to those not reviewed. However, iron status tests should be interpreted with caution as both rates of and the indications for testing appear to have differed markedly between centres, and across participation levels in both centres. The most striking finding was the difference between Edinburgh and Glasgow participants in terms of demographic and health characteristics.

This is of concern because of the potential association of these factors with menstrual complaint, and with the management possibilities for such complaint. Some of the differences reflected the background population, but this may have been exacerbated by the client specialism of the main recruiting clinic in Glasgow, and perhaps also by

general differences in referral practice between Edinburgh and Glasgow. Therefore great care needs to be taken in all analyses to check for confounding by centre and/or by associated factors.

8.5 CHAPTER SUMMARY

8.5.1 Comparison between participants recruited in Edinburgh and Glasgow

There was a difference between centres in referral reason, with more Edinburgh recruits having been referred for excess bleeding (80% v 71%), and fewer for PMS (3% v 12%). The two centres were similar in terms of parity, height, BMI, past use of the oral contraceptive pill, abortions and miscarriages, but they differed as follows:

- There was considerably more deprivation among Glasgow women (53% in codes 6&7, compared to 6% of Edinburgh women).
- The Glasgow women were younger, with fewer women aged 40 to 49 years (40% in Glasgow v 58% in Edinburgh), and more under 30 years of age (14% v 6%).
- The parity distributions were very similar in the two centres, despite the age difference, because in general childbearing occurs at a younger age in Glasgow.
- Relatively more of the Edinburgh women were working (80% v 67%), and working full-time (49% v 39%), this being evident among nulliparous women and even more strongly among parous women.
- Glasgow women had poorer self-reported health (26% v 15% rating themselves in 'worse' health than other women their age), more long term illnesses (mainly arthritis, high blood pressure and migraine) and reported more minor symptoms.
- In terms of the SF-36 quality-of-life measure, Edinburgh women had more favourable scores for all scales except for Vitality and Health Transition but these differences largely disappeared if there was stratification by deprivation and long-term illnesses.
- More Edinburgh women were sterilised (32% v 20%) and even if age, parity or deprivation were controlled for, a difference in female sterilisation rate persisted in the oldest age band, in the most deprived women, and in the least parous (para 0/1).
- Edinburgh women reported a greater duration of use of the oral contraceptive pill (on average two years).
- Glasgow women were more likely to have had past treatment for depression and/or anxiety (45% v 28%), with overall rates highest in parous women, particularly young parous women.

8.5.2 Representativeness

8.5.2.i Sample recruited

- Compared to local health board population data participants tended to be aged nearer 49 than 25 years, suggesting that referral for menstrual complaint is associated with age over 34 years. However, this effect was much more marked in Edinburgh than Glasgow.
- In each centre the deprivation distribution of participants was very similar to local health board population data.
- Compared to Lothian (Edinburgh) the Glasgow *population* deprivation distribution was skewed to the deprived end of the range. Therefore the differences in deprivation between the two centres reflect differences in the background populations.
- As would be expected for an outpatient population, the SF-36 quality-of life scale scores for participants showed poorer health status/functioning than population norms for women the same age, for all scales but most markedly for Pain, Role-Physical and Role-Emotional.

8.5.2.ii Participation to a lesser or greater extent

- Given the attrition in numbers participating through the study levels, from Basic (n=952) to Full participation (menstrual collection, n=226), there was surprisingly little shift in the characteristics of the study sample, in terms of the background data summarised in chapter 4.
- The eligibility criterion for Full participation, having 'putatively heavy periods', meant that referral for bleeding increased from 76% for the entire study sample to 86% of those participating fully. Referral for PMS or 'other' decreased, but there was no reduction across levels in referral for pain. Referral for bleeding and pain, jointly, *increased* from 14% in the study sample to 19% of those undertaking menstrual collection.
- With regard to the remaining characteristics checked, women participating 'fully':
  - were more likely to have reported experiencing minor symptoms in the previous two weeks (backaches, diarrhoea and feeling sad differed by ≥ 8 percentage points), and had worse SF-36 Bodily Pain and Social Functioning scores (difference in medians of 10 scale points for both).

- Were less likely to be sterilised (22% v 31%) and had been using their current method of contraception for a slightly shorter period of time (median 7 v 8 years).

8.5.2.iii Iron status blood testing

- Iron status testing was more likely if there had been referral for bleeding (haemoglobin 52% v 35%, ferritin 33% v 21%) and was more common in Glasgow than Edinburgh (62% v 37% for haemoglobin and 52% v 13% for ferritin).
- Iron status testing rates among those participating fully were higher, and were much more nearly equal across the two centres than they were for the entire group of participants. For haemoglobin testing rate, the difference between centres of 37% v 62% overall, improved to 68% v 88% in those participating fully, and for ferritin the change was from 13% v 52% to 56% v 86%.

8.5.2.iv Case-note review

- Rates of follow-up review were similar in Edinburgh and Glasgow (70% & 69%).
- There were no detectable differences between those reviewed or not reviewed, except in respect of self-reported comparative health in Edinburgh participants. Those who judged their health 'better' than others were more likely to have been reviewed (82% v 68%), but this reflected a change in study population over the time-course of recruitment.

Chapter 9

STUDY RESULTS:

MODELLING MENORRHAGIA

9.1 INTRODUCTION

In Chapters 4 to 6, the study participants have been described, in terms of the basis for referral to gynaecology clinic, their current menstrual symptoms, background characteristics, health history, menstrual history, current quality-of-life, an extensive menstrual assessment, clinical management and outcome, and quantification of menstrual loss. All 952 participants provided data on referral reason and presenting complaint, and successively smaller subsets completed the additional measures, with 226 ultimately having measured menstrual loss. In Chapter 8 it was shown that those recruited were representative of all referrals, and that those participating to further levels of the study were representative of those who would have been eligible to do so. In the present chapter integrative analyses will be reported, linking together background information, presenting complaint, subjective report of periods, menstrual assessment and quantification of menstrual loss.

9.1.1 Pathway through research study

We can envisage the pathway to the gynaecology clinic (and hence involvement in the study) to have 'stages' as shown below:

i. The woman judges her periods to be intolerable and so consults her GP.

ii. The GP refers her to a gynaecology clinic – giving ***referral reason(s)***.

iii. The woman attends clinic and is recruited into study:

a) completing CQ, which ascertains basic details of periods, including:

heaviness
her account of the ***reason for clinic attendance***
how ***problematic each of 16 aspects of periods is***, and
which of these had been the ***cause of help-seeking*** (up to three coded).

b) If agreeable to further participation, she completes MEQ, MBQ, SF-36.

c) If she has 'putatively heavy periods', has completed the above questionnaires, and is agreeable to doing so, she undertakes ***menstrual collection*** and ***menstrual charting***.

Across these stages a rich set of data variables has been collected, giving diverse 'assessments' of subjective rating of heaviness of period, perception of problems experienced with aspects of menstruation, which of these have been cause of help-seeking, and both externally-judged (GP) and self-stated reasons for clinic attendance now. These data can provide insights to complaint of menorrhagia and to menstrual problem more broadly.

9.1.2 Research questions

It is has been reported that menstrual problems often occur in combination (Bancroft et al. 1993). Therefore the first question to be asked of the data (in **9.3.1**) is:

How concordant are the GP referral reason and patient's self-stated reason for clinic attendance?

The remaining questions to be asked of these data address measured menstrual loss, that *sine qua non* of menorrhagia thinking, and subjective menorrhagia complaint. Regarding measured menstrual loss, the questions to be addressed first (in **9.3.2**) are:

What factors are associated with measured menstrual blood volume?

Can measured blood loss be predicted from features of the clinical history?

Is measured blood volume over 80mL important in identifying complaint and determining management?

Regarding subjective menorrhagia complaint, loosely defined, questions to be addressed (in **9.3.3**) are:

What factors are associated with reporting of periods as 'very heavy'?

What factors are associated with citing volume of periods as 'cause' of help-seeking?

From the GP and patient perspectives, what patient factors are associated with referral to gynaecology clinic for excessive bleeding?

These three questions may seem similar but they are distinct, as will be discussed further in conjunction with the results. An alternative conceptualisation of subjective menorrhagia complaint is in terms of the principal component scores derived from

responses to MEQ questions 22 and 23. Therefore the final questions, to be addressed in **9.3.4**, are:

What are the associations of subjective menorrhagia complaint, defined in terms of menstrual experience component scores, with demographic, health and other factors?

To what extent is measured menstrual fluid volume associated with principal component scores?

9.2 METHODS FOR THIS CHAPTER

9.2.1 Key variables

Key menstrual variables ascertained along the pathway can be cross-referenced to the list outlined in **9.1**, as follows:

Stage (ii) **GP referral reasons**, coded as four separate binary variables reflecting whether one of the two reasons extracted from the letter was (or was not) each of heavy bleeding, pain, cyclic symptoms, or 'other' (see **3.8.5.i**).

Stage (iii a)

Self-stated reasons for clinic visit, coded as four separate binary variables reflecting whether one of the two reasons for clinic attendance given by the woman in free-text item on CQ was (or was not) heavy bleeding, pain, cyclic symptoms, or 'other' (see **3.8.5.ii**).

Extent of problems with 16 aspects of periods, as they are, as 5-level response variables, and also re-coded (see **5.2.2.i**) as:

- 16 separate binary variables for each aspect indicating severe problem reported (or not);
- four separate variables indicating *how many* severe problems have been reported around excessive bleeding (maximum of 3 possible), pain (maximum 3), cyclic mood and physical symptoms (maximum 2), or cyclic symptoms including feeling 'unwell/tired because of periods' (maximum 3);
- count variable as to how many of the 16 aspects have been rated as a marked or sever problem.

Aspects that have been cause of help-seeking, cited in response to the prompt 'Which of these has been the main cause of your coming to this clinic?'and coded (see **5.2.2.ii**) as:

- 16 separate binary variables for each aspect indicating whether (or not) that aspect has been cited as a cause of help-seeking;

- four separate variables indicating *how many* 'causes' have been cited (same maxima as above for severe problems) that could be categorised as excessive bleeding, pain, cyclic mood and physical symptoms, or cyclic symptoms including feeling 'unwell/tired because of periods'.

Stage (iii b) **Managing periods** (see **5.3.4.i**).

- one score each for *home and work facilities* for dealing with periods;
- 5 principal component scores each for *dealing with periods* and for *feelings about periods*.

Stage (iii c) **Quantification of menstrual loss**

- ***Measured menstrual blood loss*** and ***total fluid volume*** (see **6.2.1.iv**);
- ***Menstrual chart data*** (see **6.2.2.iii**).

Other menstrual demographic, health and quality-of-life data, were ascertained via CQ, MEQ, MBQ and SF-36 (stages iiia & iiib on the pathway list in **9.1**).

9.2.2 Operationalising 'subjective menorrhagia complaint'

Variables considered as potential indicators of subjective menorrhagia complaint are listed below, the main ones being given distinguishing 'complaint' labels:

- referral for excessive bleeding
  - GP reason for referral *(stage ii)* – ***'GP-judged complaint'***
  - self-stated reason for clinic attendance *(stage iiia)* – ***'lay complaint'***
- 'very heavy' periods *(stage iii)* – ***'subjective judgement of heaviness'***, *not* complaint
- citing volume aspect(s) of periods as cause of help-seeking *(stage iiic)*
  - specifically relevant, theoretically: citing 'lose too much blood' (n=205)
  - more broadly: citing as cause any one or more of three volume aspects 'losing too much blood', 'difficulty avoiding accidents' and 'periods going on too long' (n=365) – ***'volume complaint'***.

In addition, the principal component scores of **5.3.1.iv** will be considered as potential descriptors of degree of complaint.

9.2.3 Summarising association

The data to be analysed in this chapter comprise continuous variables with approximately normal distributions, other continuous variables with skewed distributions, and ordinal variables for which the methods suited to continuous data can not be used. It was therefore decided that the univariate summary of association to be applied to all pairs of variables would be the Spearman rank order correlation. This method has been described in **3.8.3**.

9.2.4 Logistic regression

To explore the association of binary outcome variables with the various menstrual variables, socio-demographic variables and principal component scores, logistic regression was used (Kirkwood & Sterne 2003) (pg189).

Potential binary outcome variables are: subjective report of menstrual loss as 'very heavy', versus the rest; citing an aspect of volume of loss as reason for help-seeking, or not; referral by GP for excessive bleeding, or not; self-stating that the reason for clinic attendance is excessive bleeding, or not; measured blood loss in excess of 80mL or not.

Potential explanatory variables were offered to the logistic regression model using 'inclusive' entry and removal criteria: entry criterion ($p<0.15$) and removal criterion once in the model ($p>0.20$). The aim was to obtain a relatively stable model where succinctness was not the main goal but rather a model that was descriptive in the sense of including contending variables rather than excluding them. Iterative runs were undertaken to check the linearity of multi-level variables, and where necessary variables were re-defined as categorical, though in most cases a non-linear variable could be simplified into a two-level (binary) variable, or sometimes a 3-level variable was more appropriate. When entering a categorical variable in a model the lowest category was set to be the reference category. (For categorical variables it is preferable for the reference category to have an adequate n to ensure precision of

estimation of effects in the remaining categories.) All factors with more than 2 levels are linear unless indicated as being categorical.

Once the final model was obtained then the analysis was rerun offering only the variables determined as 'included' in the model, to maximise n by avoiding exclusion of cases due to missing data on variables that had been offered to the analysis but were not ultimately needed in the model. For key variables with large effects there was also checking for interaction effects.

'Goodness–of-fit' of the model was assessed by calculation of -2log likelihood, which tests the model obtained against a hypothetical perfect model, which would reproduce exactly the observed frequencies of the binary outcome variable. This can be compared to the χ^2 distribution for the degrees of freedom remaining after fitting the factors included in the model, to obtain a probability of obtaining the frequencies as predicted if the observed frequencies were the true situation (Tabachnick BG & Fidell 1996a). This means that a small probability (a 'significant' result) suggests that the model deviates from the hypothetical 'truth'. Therefore a non-significant result is aimed for, indicating an adequate model in respect of predicted frequencies. The predictive performance of the model is also reported: overall percent assigned to the correct outcome category, and percentages correct within each outcome category. In large analyses performance can be fairly good even when the model fails (statistically significantly) to reproduce the observed frequencies.

The odds ratios (ORs) summarising the association of the outcome variable with explanatory variables are those reflecting combined effects in the final model. The univariate ORs of association of single variables with dependent variables are not generally presented, for reasons of space. An OR reported for a multi-variable model represents the association for that (level of the) variable, *adjusted for* all other variables in that model. For a woman with a specific profile of explanatory variable values, her (combined) odds, relative to a woman with reference category values for the variables concerned, for the outcome that is the focus of the modelling, can be obtained by multiplying together the odds ratios corresponding to her values.

9.2.5 Recoding variables

Principal component scores estimated in **5.3.1.iv** were in general distributed in the range –2 to +2, although as can be seen in **Figures A5.2.1** and **A5.2.2** there were some individuals with more extreme scores. Component scores such as these have no intrinsic meaning. The information derived from the score is the position of that individual in the distribution of scores on that component for all individuals. Therefore, if these scores were entered as linear variables in logistic regression models the resulting ORs (per unit increase in component score) would be fairly uninterpretable, without access to the distribution of each component's scores. Furthermore, if the effect for a particular component score was not linear, recoding of the score would then be required, to achieve a categorical variable. It was decided that it would be helpful to reporting if each component was from the outset recoded into 5 categories of approximately equal size (20% sub-divisions of the distribution).

Such a recoded 5-level variable could still be entered as a linear variable, if the effect was linear, or if not it could be tested as a categorical variable. The quintiles were obtained for the distributions of the 5 components on dealing with periods and 5 on feelings about periods component scores. It was decided, for simplicity, to use uniform cut off values for all component recodings. Across the 10 components the first (bottom) quintile ranged from –0.99 for 'had enough of periods' to –0.71 for 'resource issues'. On the principle that the first category would be the reference category for logistic regression, and that estimation advantage derives if this n is adequate to generous, the value of -0.7 was chosen for the first cut off. This would ensure the n for that category was at least 20% of the sample for every component. The remaining cut-offs were chosen by reference to the corresponding quintiles, and were –0.3, 0.4 and 0.9. This is shown in the top half of **Table 9.1**. If such a 5-level variable did not have a linear effect for the logistic regression model, and if the categorical form of the variable entered in the model revealed that the effect showed a step-wise increase between some neighbouring categories and the remainder, then the variable could be further recoded as binary. An example of this is shown in the bottom two rows of **Table 9.1.** Sometimes recoding to a 3-level variable was more appropriate to the observed profile of effect.

Table 9.1 Recoding of principal component scores, from original scores to 'fifths' of the distribution, and an example binary recoding

	Values and distribution of component scores				
Cut off used	– 0.7	– 0.3	0.4	0.9	
Category scores	< – 0.7	≥ –0.7 to < –0.3	≥ – 0.3 to < 0.4	≥ 0.4 to < 0.9	≥ 0.9
Subsets of sample	Bottom 'fifth'	2nd 'fifth'	3rd 'fifth'	4th 'fifth'	Top 'fifth'
Example recoding			< 0.4	≥ 0.4	
Subdivision of sample			Bottom '3/5' (or '60%)	Top '2/5' (or '40%')	

Seven of the eight SF-36 scaled scores and the MEQ home and work facilities total scores also were recoded into 5-level variables, with sub-category n's as similar as possible (again, dividing the distributions into fifths). The very different distributions across SF-36 scaled scores meant that for each scale score the specific quintiles had to be used as cut-offs. Role Emotional had only 4 possible values, so already comprised a 4 level variable, and Health Transition was a five-level variable, The five categories for 'home facilities' were defined by scores of 0 to 1, 2, 3, 4 to 5 and ≥6, and the categories for 'work facilities' were defined by scores of 0 to 2, 3 to 4, 5 to 6, 7 to 9 and ≥10.

9.3 RESULTS

9.3.1 Reason for clinic attendance

9.3.1.i Concordance between patient's reason and GP reason for referral

The GPs were more likely than women to give suspected pathologies as reason for referral, for example 'fibroids' or 'low haemoglobin'. Both these reasons would be coded as 'other', whereas in both cases the GP may have menorrhagia in mind. The women were more likely to state 'symptom' reasons, such as 'irregular periods' which was coded as 'other', or terms like 'flooding', 'pain' or 'PMS' which could be coded directly as 'excessive bleeding', 'pain' or 'cycle' respectively.

Nevertheless, in terms of patient's self-stated reason for attendance at gynaecology clinic, the overall prevalences of cycle-related changes and 'other' reason are very similar to their prevalences as GP referral reasons, but bleeding was less often given as a patient reason (60% v 76%), and pain more often cited (30% v 23%). For each of the four reasons for clinic attendance, concordance between patient and her referring GP was examined by means of McNemar's test for paired proportions. Results for these analyses are presented in **Table 9.2**.

Table 9.2 Discordance between general practitioner referral reason and woman's stated reason for attendance at clinic.

Attendance Reason	Discordant cases *	GP:patient ratio of discordant citations #		McNemar	
	% of 952	Ratio	(95% CI)	χ^2	p value
Bleeding	27.4	4.01	(3.0-5.3)	93.2	<0.001
Pain	23.6	0.54	(0.4-0.7)	19.4	<0.001
Other	31.8	1.13		1.1	0.30
Cycle-related changes	4.9	1.04		0.0	0.99

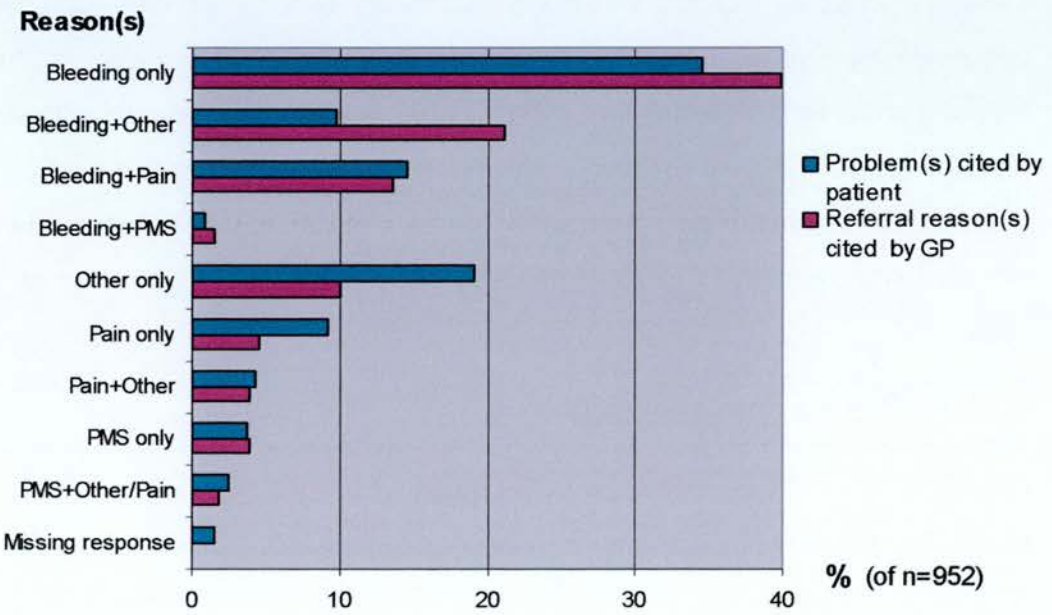
* *only one of doctor or woman cites this reason*

\# *ratio = frequency doctor only cites reason ÷ frequency woman only does so*

It was found that there was minimal discordance where cycle-related changes were the reason, but that in around a quarter of cases the referring doctor and patient disagreed whether bleeding was the reason. There was a similar level of disagreement for pain, while for 'other' there was discordance in a greater proportion, about a third of cases. For bleeding there was marked imbalance in the direction of discordance, with a ratio of 4:1 that it would be the doctor rather than the patient citing bleeding ($p<0.001$). In the case of pain as cited reason, discordance was in the opposite direction but not as marked, with general practitioners significantly *less* likely to mention pain ($p<0.001$). Despite the high level of discordance for 'other' reason there was no imbalance in the direction of discordance.

In **4.3.3.ix** the distribution of the various combinations of referral reasons was ascertained (as presented in **Figure 4.16**). The same summary was obtained for patients' self-stated reasons for clinic attendance. **Figure 9.1** shows the distribution of combinations of patients' self-stated reasons for attendance at the gynaecology outpatient clinic, compared against the distribution for combinations of referral reasons cited by GP.

Figure 9.1 Prevalence of the various (combinations of) reasons for clinic attendance, self-stated by patient and as cited by GP as reason for referral



By visual inspection it appears that participants were less likely than their referring GPs to cite bleeding only, or bleeding plus other, more likely to cite 'other' only, pain only and, marginally, bleeding with pain. This is generally consistent with the findings for the independent McNemar's tests reported in **Table 9.2**. The percentage and hence number of women with a combination of bleeding and pain as reason for clinic attendance was similar for both GP referral reasons and self-stated reasons (n=130 & 139). However, this was despite considerable discordance, since only 42 women were common to both subgroups i.e. were classified as 'bleeding with pain' for both GP referral reasons and self-stated reasons.

On the whole the associations of the patients' self-stated reasons for clinic attendance with the demographic variables (age, deprivation, parity, self-reported comparative health and extent of working) and sterilisation (either and female only) were very similar to those reported for GP referral reason in **4.3.3.ix**. The only notable differences were that for self-stated reason there were stronger associations of bleeding reason with age and parity, and of pain with lower parity, and that there was no detectable association with age of the combined reason 'bleeding and pain'.

9.3.1.ii Factors associated with discordance between self-stated and GP reasons

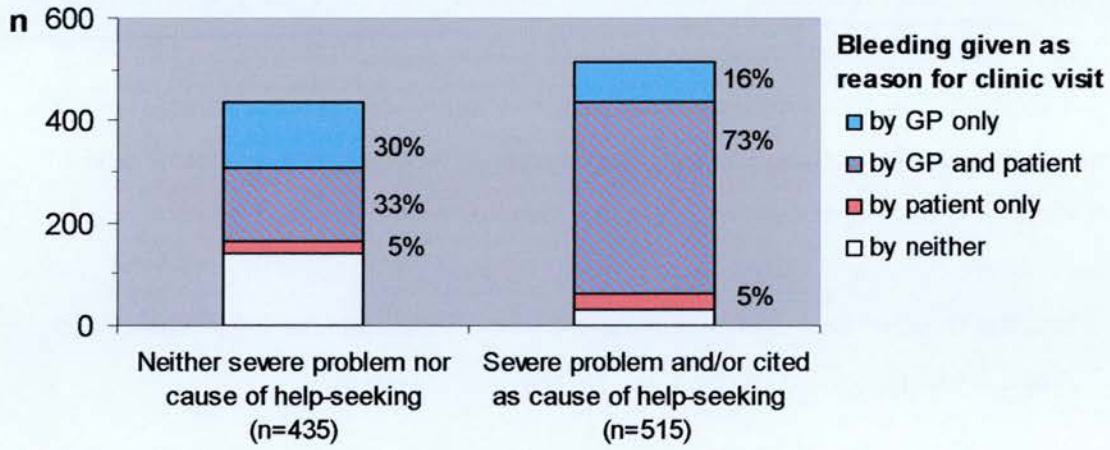
The discordance for bleeding was evident across age-bands, deprivation and parity categories and centres. It was more marked for women in deprivation areas 5 to 7, for nulliparous women, for women aged 35 to 39 years, and for women with self-reported health 'the same as others'. The discordance for pain was less evident in women from areas with least deprivation (codes 1 and 2), in Edinburgh, aged under 40 years, who were para 3 or more, and with self-reported health 'the same as others'.

9.3.1.iii Pathway to clinical care

Overall, of the 725 referred for excessive bleeding by their general practitioner, less than half (46%) had noted *volume* as 'cause' of help-seeking. Furthermore, this differed by subgroup: bleeding was identified as cause of help-seeking by 60% of the

311 reporting it as a severe problem, but by only 34% of the 414 who did not. **Figure 9.2** illustrates the healthcare pathway for menorrhagia (excessive bleeding), separately for those who do and do not identify volume of bleeding as a health problem in these ways. Among those who reported volume of bleeding as a health problem (right-hand bar), that is as a severe problem and /or as 'cause' of help-seeking, 89% were referred for bleeding, and the majority of these women also self-stated bleeding as the reason for clinic attendance. Of those who reported volume *neither* as a severe problem *nor* as 'cause' of help-seeking (left-hand bar), 63% were nevertheless referred for bleeding, and in just over half of these the woman stated that bleeding was a reason for the clinic referral. Therefore discordance was more prevalent in the latter subgroup (first column).

Figure 9.2 Frequency with which general practitioner (GP) and/or patient give 'excessive bleeding' as reason for clinic visit, separately for two subgroups



Diagnosis of dysfunctional uterine bleeding was made for over a third of women who neither reported periods as subjectively very heavy, *nor* reported excessive loss as severe problem, *nor* gave bleeding as reason for clinic visit (35% of 165). Considering the minority referred by their doctor for something *other than* excessive bleeding, diagnosis of dysfunctional uterine bleeding was nevertheless made for a third of them (30% of 150). Hysterectomy was more likely if there was diagnosis of fibroids (39% of 85 with fibroids). Among the remainder, without this pathology as

possible indication for surgery (n=545), hysterectomy was strongly associated with referral for bleeding (RR 4.9, 95%CI 1.6-15.6, Fisher exact test p=0.001), but was only marginally associated with reporting volume of loss a severe problem (RR 1.8, 1.02-3.2, p=0.051), and was *not* associated with excessive bleeding as patient's reason for attendance (p=0.21).

9.3.2 Measured menstrual loss

9.3.2.i Associations between measured menstrual blood loss and clinical factors

Referral by GP for bleeding was not indicative of significantly greater volume of loss (54mL v 43mL, n=196 v 30, ratio of means 1.35, 95% CI 0.91 to 2.00, p=0.14) *(see **6.2.3.ii** for explanation of ratio of the means)*. However, measured blood loss was greater for women who believed their clinic attendance to be for excessive bleeding, compared to the remainder (59mL v 39mL, n=160 v 66, ratio 1.54, 95% CI 1.15 to 2.06, p=0.004). The differences between centres in socio-demographic factors, and possibly in blood loss determinations, and very likely also in local referral 'practice', meant that checks of these comparisons separately within centre would be advisable. It was found that separately within centre there were not significant differences in mean blood volume between those referred by their GP for bleeding, and the remainder (ratio of back-transformed means for Edinburgh was 1.4 (95%CI 0.7 to 3.0) and for Glasgow 1.5 (95%CI 0.4 to 2.4).

With regard to self-stated reason for clinic attendance, there was no difference in Edinburgh (ratio of means 1.0, 95%CI 0.7 to 1.6), but there was in Glasgow (2.0, 95%CI 1.4 to 2.9).

Table 9.3 gives the associations of blood loss volume with key clinical menstrual variables, features that could be ascertained in the clinical history, and with demographic factors. Volume of menstrual blood loss was weakly associated with increasing age, and weakly negatively associated with deprivation, in that more deprived clinic referrals tend to have lower volumes. It is noteworthy that measured blood volume was not associated with female sterilisation in this sample.

At the group level the subjective judgement of heaviness of periods was supported, with the mean loss of 64 mL for those rating periods 'very heavy' compared to 40mL for the rest (predominantly 'heavy') (n=107 and 118, means back-transformed from logged data, $p<0.001$). The average ratio of volumes was 1.61 (95% CI 1.23 to 2.10), meaning losses that were 60% higher if periods were rated very heavy. However, it should be noted that there is nevertheless substantial overlap in the ranges of individual measured losses. For example, 25% of women who rated their periods 'very heavy' had volume of loss less than 35mL, and 25% of those rating their periods only as 'heavy' had loss exceeding 82mL.

Table 9.3 Association of blood loss volume with demographic/clinical factors

		Effective n	Correlation coeff. *rho* *	p
Demographics				
Age group	*(youngest to oldest)*	226	0.11	0.100
Deprivation	*(least to most)*	222	-0.11	0.095
Number of babies	*(0 to 6)*	226	0.11	0.109
Subjective heaviness of period				
Subjective rating of menstrual loss	*(moderate; heavy; very heavy)*	225	0.23	<0.001
Clots				
Size of clots	*(none; 20p; 50p; or bigger)* #	226	0.26	<0.001
Usual no. (per period) of clots > 50p#	*(0 to 28)*	214	0.26	<0.001
Iron status				
Ferritin	*('low'; normal)*	168	0.30	<0.001
Haemoglobin	*(<12g/dL; ≥12g/dL)*	182	0.23	0.002

* *Spearman rank order correlation*

\# *UK coins: size (diameter) of 50p is 1.1inches and of 20p is 0.85 inches*

CLOTS AND IRON STATUS

As can be seen in **Table 9.3**, the clinical features most strongly associated with blood volume were low ferritin result (rho = 0.30, 95% CI 0.15 to 0.45); the size and number of clots (for both rho = 0.26, 95% CI 0.12 to 0.40); and reported heaviness of periods (rho = 0.23, 95% CI 0.11 to 0.35). There was evidence that low iron status was associated with measured blood volume, for ferritin more strongly than for haemoglobin.

CONTAINMENT OF PERIOD

Other information that could be ascertained by the clinician would be about efforts required to contain the period. **Table 9.4** shows the containment factors (ascertained from MEQ and CQ) which were associated with blood volume.

Table 9.4 Association of blood loss volume with containment factors

CONTAINMENT OF PERIOD	Effective n	Correlation coeff. *rho* *	p
Quantity tampons/pads used in most recent period *(0 to 136)*	207	0.30	<0.001
Time until next change needed, during 'full flow' *(≥ 3 hours; 2 hours; about an hour; shorter)*	218	0.30	<0.001
How often periods...			
...require protection changed during the night *(seldom; some periods; most)*	226	0.26	<0.001
...leak through onto underclothes or bedding *(seldom; some periods; most)*	226	0.23	<0.001
Usual days per period double protection required *(0 to 12)*	221	0.25	<0.001
Number per period of leakage onto underclothes *(0 to 10)*	223	0.16	0.015

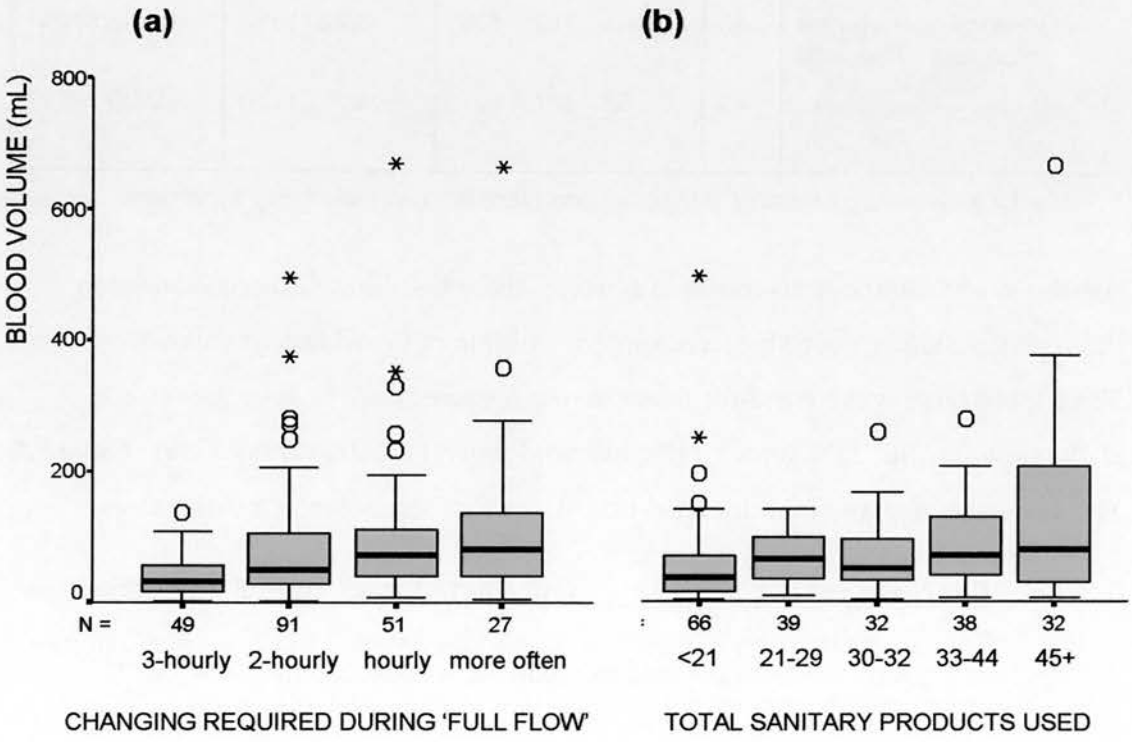
* *Spearman rank order correlation*

The most strongly associated factors were: the shortness of the time interval before another change of sanitary protection was needed, during full flow; the total number of pads/ tampons used in the most recent period; and the need for changes of

protection during the night (rho = 0.30, 0.30, 0.26; 95% CI 0.16 to 0.44). **Figure 9.3** presents box-plots of measured volumes against the first two of these MEQ variables, and shows the extent of overlap in ranges of volumes between the subgroups.

As detailed in **Chapters 5** and **6** there were concerns about differences in blood loss determinations between the two centres, so this is of concern when calculating Spearman correlation coefficients overall (ignoring centre). Therefore the associations presented in **Tables 9.3** and **9.4** were checked separately within centre, as far as was possible given the smaller n's for the strata (particular problem for ferritin results in Edinburgh). It was found that the associations for age and deprivation were stronger within strata than they appeared overall, possibly due to confounding by centre suppressing the effect when ascertained 'overall'. Conversely, the association with subjective heaviness was weaker within centres, suggesting that confounding had inflated this effect. There was also some suggestion of effect modification, since the effects for parity, low ferritin and leakage all showed considerably weaker effects within Edinburgh compared to Glasgow.

Figure 9.3 Associations with measured blood volume: a) Changing rate during 'full flow'; b) Total number of products used per period



Considering the study group as a whole there was very little difference in volume of loss between those proceeding or not to hysterectomy (median 59mL and inter-quartile range 21-140mL *versus* 53mL, 27 to 97mL). **Table 9.5** shows that amongst those diagnosed with fibroids (20/176, 11%), there were as expected slightly heavier losses, and higher rates of poor iron status.

Table 9.5 Blood loss volume and iron status by diagnosis, and hysterectomy as outcome

	n	Median blood volume mL (IQR)	'Low' ferritin (%)	Hb<12g/dL (%)
Diagnosis of fibroids				
Yes	20	85 (38 -168)	7/17 (41%)	5/18 (28%)
No - but hysterectomy performed	25	53 (20 -129)	5/16 (31%)	7/24 (29%)
and no hysterectomy	131	52 (27 - 93)	10/95 (11%)	17/100 (17%)
Total	176			
Other diagnoses				
Dysfunctional uterine bleeding - *regular*	64	63 (27 -111)	6/46 (13%)	14/52 (27%)
Dysfunctional uterine bleeding - *irregular*	43	41 (19 - 83)	5/28 (18%)	8/33 (24%)
Other *	49	52 (27 - 92)	4/37 (11%)	2/39 (5%)
Total	156			

* *Mainly anovulatory bleeding, polyps, endometriosis, polycystic ovary syndrome.*

Among women without diagnosis of fibroids, there was little difference between those proceeding or not to hysterectomy, in volume of blood loss (median 53 *versus* 52mL), but there was a trend for those having hysterectomy to have poorer iron status (low ferritin: 31% *versus* 11%; haemoglobin <12: 29% *versus* 17%). **Table 9.5** also gives the median blood loss and iron status for these women, by diagnosis.

9.3.2.ii Can blood volume over 80mL be predicted from clinical features?

A logistic regression model was fitted to predict losses exceeding 80mL, with potential predictors the clinical and demographic variables described above (but not

the chart data, which would not be available to the clinician unless charting was undertaken, and even if so not until some weeks later). Structural variables entered in the model were centre (Edinburgh or Glasgow), age group (under 40 years, or 40 plus). Additional variables required in the model to predict loss over 80mL were: clots greater than 50p size; 'low' ferritin result; and the interval possible between changes of sanitary protection during full flow. The model was rerun restricted to the variables established as *required* in the model, which minimised exclusion of women due to missing data on any one of the variables being *offered* to the model. This increased the number of useable cases to 161, producing the model in **Table 9.6**.

Table 9.6. Factors included in the logistic regression model predicting blood loss > 80mL

	n for subgroup *	OR	95% CI	p
Factors entered in the model				
Centre -Edinburgh	50	0.61	0.2 to1.5	0.287
Age - less than 40 years	82	0.97	0.6 to 1.5	0.873
Factors selected into model				
Clots - > 50p size	32	4.80	1.9 to 12.2	0.001
Ferritin result - 'low'	25	5.71	1.9 to 17.4	0.002
Maximum time before change of protection needed, during full flow:				0.006
3 hours or more	38	ref.		
1 to 2 hours	104	1.10	0.6 to 1.9	
Less than an hour	19	3.08	1.4 to 6.8	
Total n for model = 161				

* *For each of the 4 binary variables the n for the subgroup not shown can be obtained by subtraction from 161. For the categorical factor (time between changes) all three subgroups, including the reference category, are shown.*

The prediction success of this model was 76% overall, correctly predicting 60% of the 60 with measured losses exceeding 80mL, and 86% of the 101 with losses under 80mL. The coefficients and performance changed minimally from the initial model based on 151 cases. Since relatively few women had ferritin tests, only 151 women could be utilised to derive a model involving ferritin result (161 women once the

impact of missing data was minimised by re-running the model specifying only the variables needed in the model, as explained above). Nevertheless, the model including ferritin performed better than one not including iron status test data, and hence based on all collectors with complete data for the other model variables (performance 71%, n=202, model was otherwise little changed).

This model was derived using variables ascertainable at the initial clinic appointment. An alternative would be to request charting of the next period and use the chart data provided to estimate of blood volume itself, rather than merely the prediction of blood loss more or less than 80mL. This has been reported in **6.3.3**.

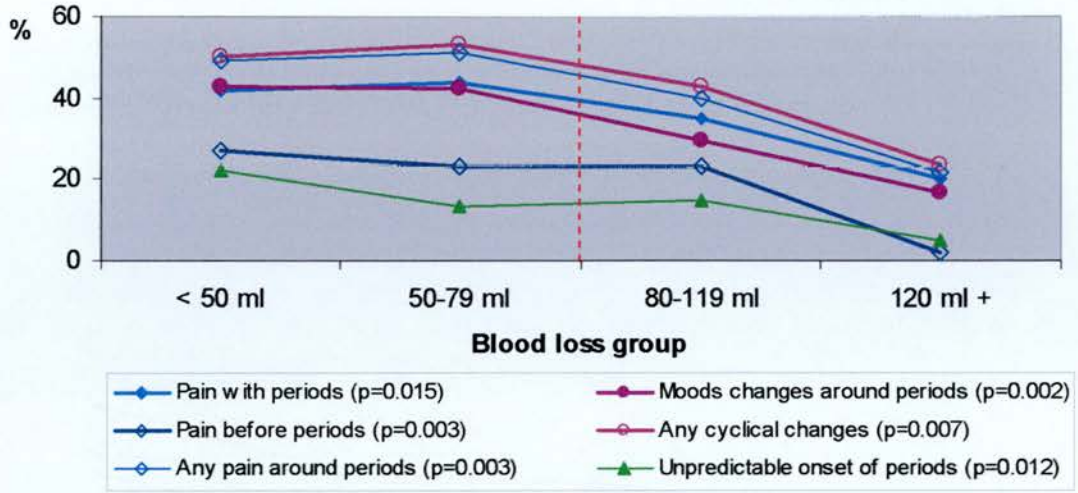
9.3.2.iii Is the 80-mL criterion useful in management of menorrhagia?

The distribution of measured blood losses have been reported in **6.3.1.i**; 46% of women had losses less than 50ml, 20% 50 to 79 ml, 15% 60 to 119 ml and 19% losses of 120ml or more (n=104, 45, 35 and 42). **Figure 9.4** shows the prevalence of reporting of problems with pain before or with periods, mood or general cyclical changes, and unpredictability of onset of periods. All are significantly associated with volume, but inversely, with problems greatest in those with lowest loss, in this clinic group.

Figure 9.5a and **9.5b** show two more sets of associations with blood loss group. Apart from the aspects shown in **Figure 9.4**, the only problems with periods significantly associated with blood loss were aspects of containment of flow, as shown in **Figure 9.5a**. The major differences were between the lightest and heaviest loss groups, with those on either side of the 80 ml criterion virtually indistinguishable. **Figure 9.5b** shows some other aspects of menstruation that might have been expected to be related to menorrhagia complaint. None increases significantly with volume. The pattern for worry was u-shaped, most prevalent in those with lightest and heaviest loss. Again there was little difference in prevalences for groups either side of 80mL.

Figure 9.4 Severe problems with periods inversely related to volume of loss: prevalences (%) by blood loss group for pain, cycle changes and unpredictable onset.

(All show a significant $\chi 2$ for trend –p values (1df) given in legend.)



With regard to potential physiological and treatment consequences of heavy periods, **Figure 9.6** shows that the proportions with 'low' ferritin levels and haemoglobin (below 120g/L) increases significantly across loss groups, but again no marked increase from less than 80mL to more.

The pattern was very similar in **Figure 9.7**, which shows proportions diagnosed with some pathology, or with fibroids specifically, and proportions recommended tranexamic acid as treatment, or with decision to have hysterectomy. However for these outcomes the trend is not statistically significant.

In all these blood group analyses checks were made for confounding by centre by repeating the analyses within centre. This was necessary because of the difference in blood loss volume determinations between the two centres.

Figure 9.5 **Prevalences (%) by blood loss group of severe problems with periods, for:**
(a) containment, extra washing and impact on daily life.
(All show significant $\chi 2$ for trend – p values (1df) given in legend.)
(b) volume of bleeding, feeling unwell/tired, and worry something is wrong.
(None shows a significant association, nor trend with volume.)

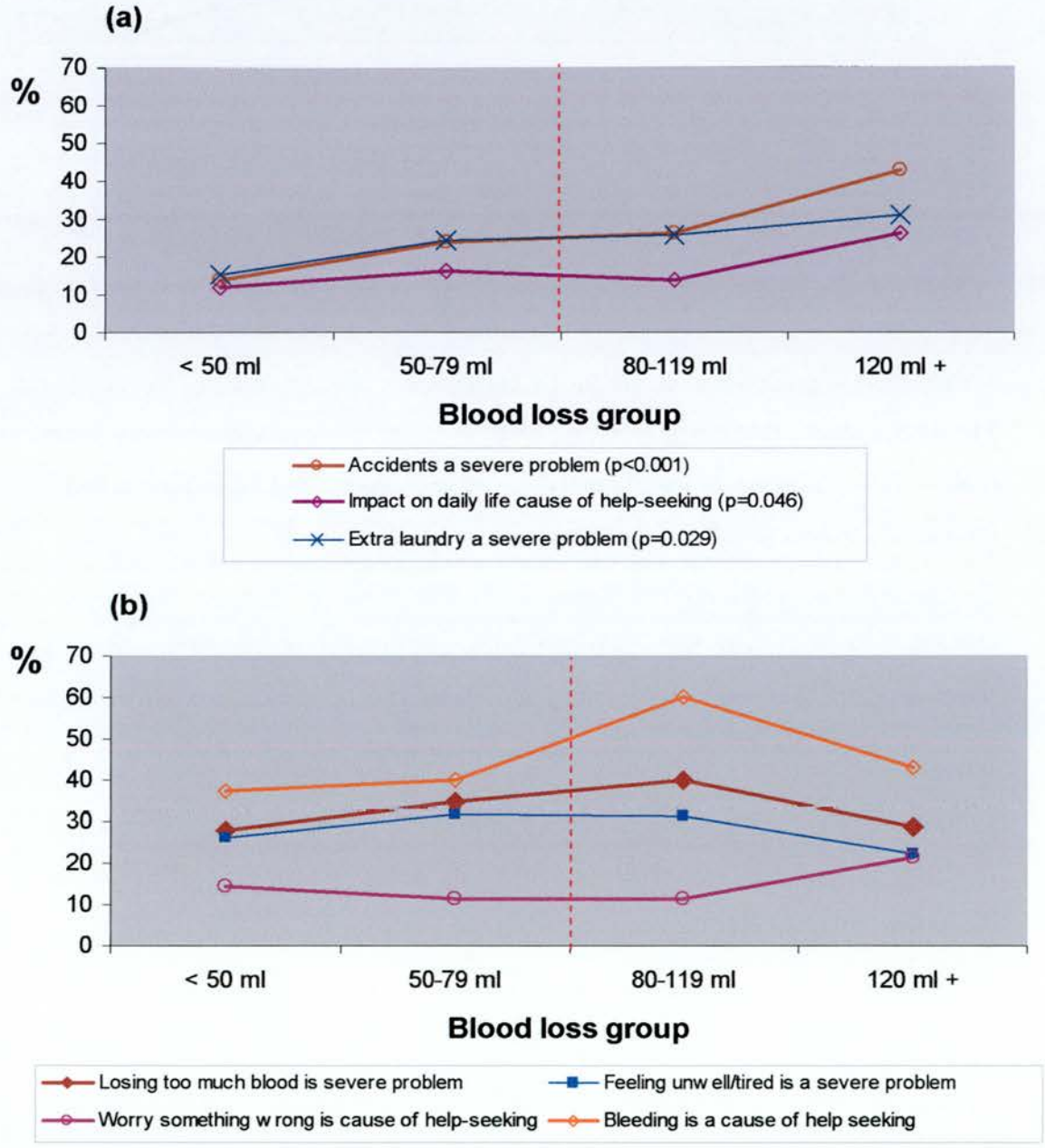


Figure 9.6 **Prevalences (%) by blood loss group of poor iron status: low ferritin and haemoglobin < 12 g/dL.**

(Both show a significant $\chi 2$ for trend –p values (1df) given in legend.)

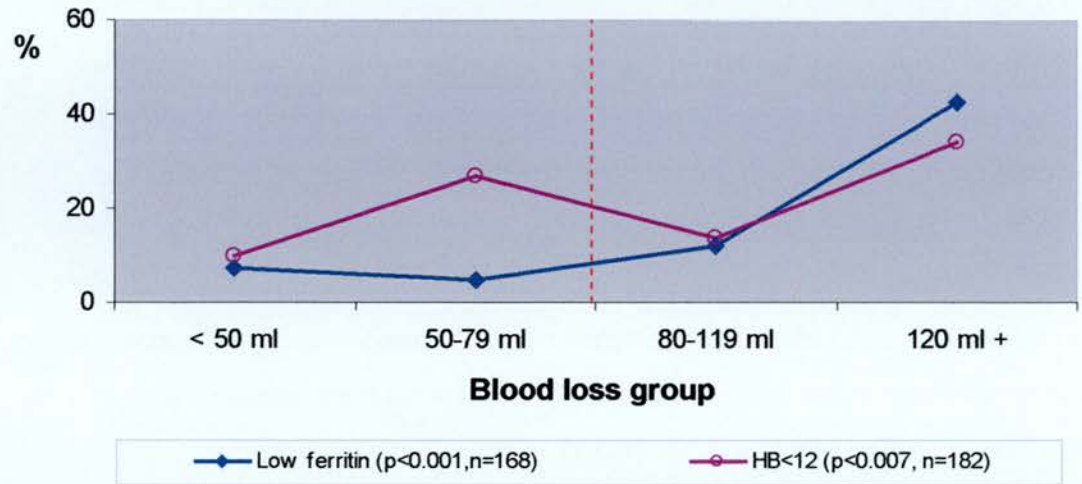
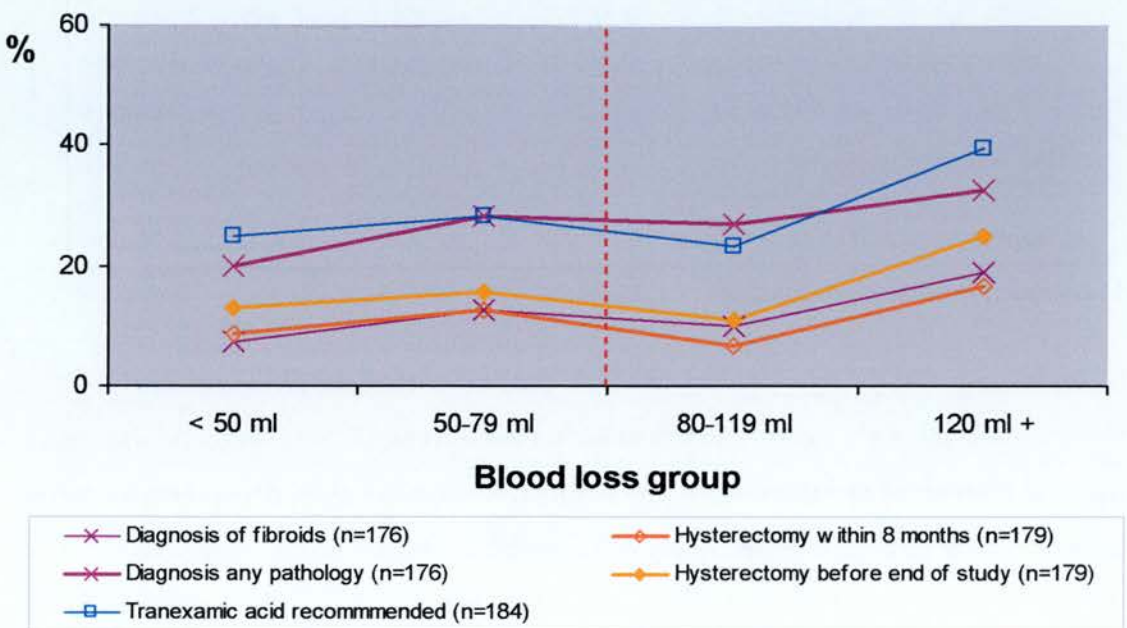


Figure 9.7 **Clinic outcome by blood loss group: diagnosis of fibroids or any pathology, tranexamic acid as treatment and performance of hysterectomy** *(None shows a significant association, nor trend, with volume.)*



9.3.2.iv Associations between measured menstrual loss and prospectively recorded menstrual chart variables

ASSOCIATIONS WITH DURATION, PRODUCT USE, ACCIDENTS AND CLOTS

The product usage variable used in **Figure 9.3** was the patient's recall of number products used for the most recent period, whereas for women who completed a menstrual chart, the exact number of products used for the period collected was recorded on the chart. Similarly the containment factors reported in **Table 9.4** were as recalled for recent periods, whereas more relevant and probably also accurate information was obtained on the Menstrual Chart. **Table 9.7** present the associations of measured blood volume and measured total menstrual fluid volume with prospectively charted features of the period.

Table 9.7 Associations of measured menstrual volumes with menstrual data prospectively recorded on the Menstrual Chart

	Measured Blood (n=206)		Total Fluid Volume (n=205)	
Chart data for period collected	**rho***	**p**	**rho***	**p**
Total products used	0.541	<0.001	0.565	<0.001
Total number of changes	0.462	<0.001	0.472	<0.001
Days duration of period	0.310	<0.001	0.376	<0.001
Number of clots ≥50p size	0.325	<0.001	0.311	<0.001
Number of leaks onto outer clothes or bedding	0.199	0.004	0.254	<0.001
Number of activities cancelled	0.154	0.057	0.192	0.006

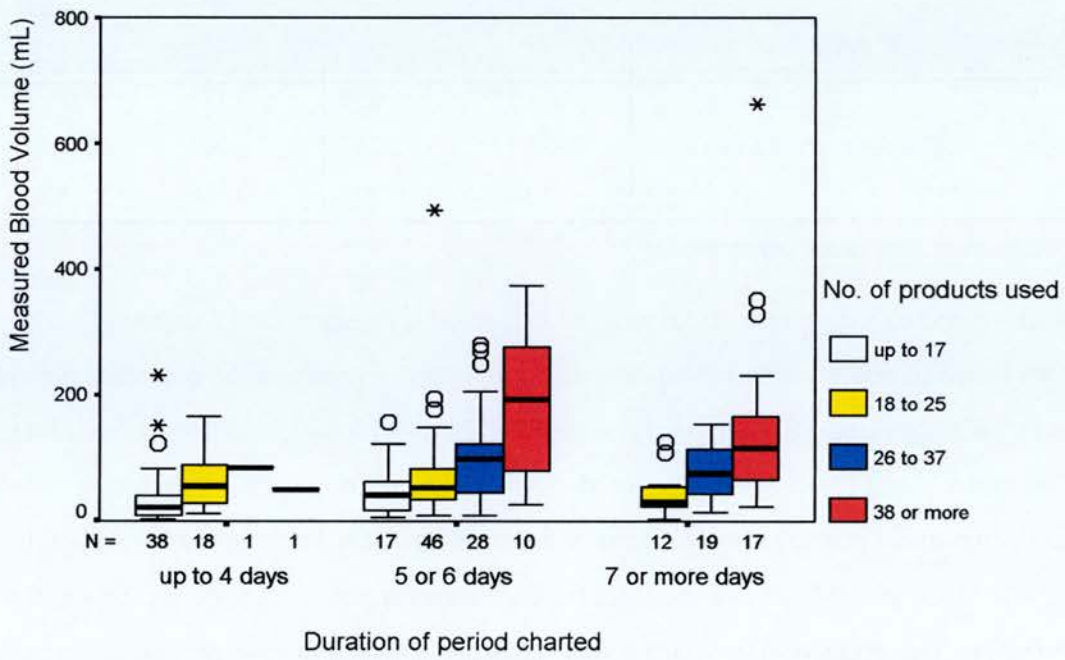
** Spearman rank order correlation.*

It can be seen that the associations of blood volume with these prospectively recorded variables are far stronger than for recalled 'typical' data, in particular with the total number of products used. The number of products must depend partly on the duration of the period, independently of the volume of loss. For women who completed a menstrual chart, the association between measured blood volume of that period could be examined in relation to both the total duration of the period and the number of products used in that time. This is shown in **Figure 9.8**. It can be seen that

compared to **Figure 9.3** (recall data), **Figure 9.8** (recorded usage) showed a steeper rise in volume across the levels of quantity of products used. (For recorded usage, the distribution of number of products has been recoded into quarters, approximately.) Therefore, the use of more than 25 products was indicative of heavy blood loss, but not so strongly indicative if the use of many products occurred in the context of a period lasting more than 6 days.

From **Table 9.7** it can also be seen that the correlations were much stronger with duration of period and number of products/changes required to contain the period than with individual rates of cancelled activities. It is also noticeable that for all variables other than clots the associations were stronger with total fluid volume than with measured blood volume.

Figure 9.8 Box-plots of measured volume by duration of period and number of products used (menstrual chart data)



MENSTRUAL VOLUMES BY JUDGEMENT OF COLLECTED PERIOD COMPARED TO 'USUAL'

On CQ and MEQ most items addressing periods asked for responses to reflect periods in the last 6 months. Each woman who undertook menstrual collection was asked at the end of it to indicate on the Menstrual Chart how the period collected compared to her periods in the last 6 months. She was asked to make this judgement

with respect to five features: the amount of loss, prevention of usual activities, leakage of period onto clothes, severity of period pain and tiredness. There was no association between measured volumes and judgements about tiredness and leakages relative to usual. **Table 9.8** presents the associations of measured volumes with judgements about how representative the other features were of usual periods. Measured blood volumes tended to be higher if loss was judged to be more than usual and if there had been more interference with activities. There were similar but stronger associations for total fluid volume. In contrast, if severity of pain was judged to be more than usual then blood volume tended to be lower.

Table 9.8 Associations of measured menstrual volumes with Menstrual Chart judgements of features of the collected period being *more* rather than less than usual

	Measured Blood (n=206)		Total Fluid Volume (n=205)	
Feature judged more than usual	**rho***	**p**	**rho***	**p**
Amount of loss	0.131	0.066	0.174	0.014
Prevention of activities	0.137	0.057	0.201	0.005
Pain	– 0.163	0.027	– 0.098	NS

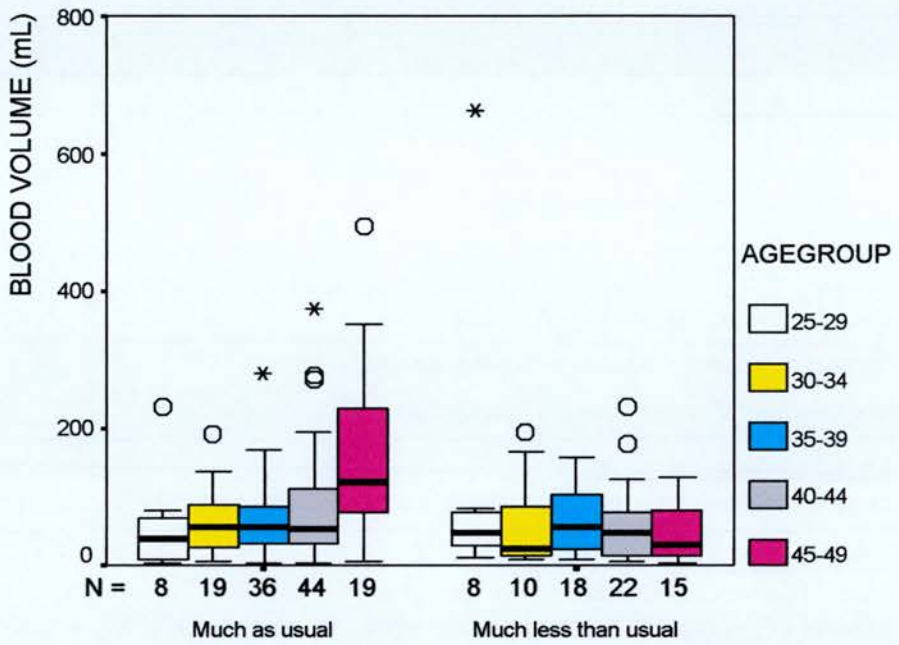
** Spearman rank order correlation.*

With regard to judgement about amount of period, disregarding 17 women (7.6%) who failed to complete this item, 5% of the remainder reported the collected period as more in amount, 16% as about the same, 42% as a bit less, and 36% as much less. The mean blood loss volumes differed significantly between those answering 'much less' than usual and the rest (40.3 mL v 54.9 mL, n=73 v 126, ratio 0.74, 95% CI 0.54 to 0.99, p=0.04), as did the total fluid volumes (ratio 0.70, 95% CI 0.53 to 0.93, p=0.02). This reduction in volume was more pronounced among certain subgroups: the oldest women, those who had had most babies, and the least deprived (relatively affluent). This is illustrated for blood volume by age group in **Figure 9.9**.

If the non-parametric associations of blood volume with these demographic variables were re-calculated excluding women whose collected period was 'much less than usual', the correlations obtained were, despite the smaller n, stronger than reported in

Table 9.3 for the entire group. That is, for age group rho=0.25, p<0.004; for number of babies rho=0.24, p<0.007; and for deprivation rho = -0.19, p<0.037 (n=126 for all three). There was however no improvement in the association between volume and referral for bleeding.

Figure 9.9 Box-plots of measured volume by 'representativeness' of collected period



9.3.3 Subjective menstrual complaint

9.3.3.i What are 'very heavy' periods?

A high proportion of study participants rated their periods as heavy (81%), but only 36% rated their periods as 'very heavy'. It is of interest to model the factors associated with such a judgement. Logistic regression models were developed by allowing the statistics program to select variables to be included in the model, as explained in **9.2.4**. **Table 9.9** lists the variables 'offered' to the model, grouped into broad categories.

Table 9.10 shows the model obtained for 'very heavy' periods, based on 540 women who had non-missing data for all the variables included in the model (out of a

potential n ostensibly 'completing' CQ and MEQ of 714. The model was adequate, showing insignificant deviation from the hypothetical perfect model (-2log likelihood=441, df=526, p>0.50). The predictive performance of the model was 81%, better at prediction of the 342 with periods less than very heavy (89% correct) than the 198 with very heavy periods (69%).

Table 9.9 Variables offered to the model for rating periods 'very heavy'

Source *	Variables
	Volume of loss
CQ	severe problems with aspects 'lose too much blood', 'difficulty preventing accidents', 'periods go on too long'; frequency of leakages and of having to get up at night to change; size of clots.
MEQ	recall of total number of sanitary products used for most recent period; usual number of days full flow; how frequently have to change during full flow; frequency of use of double protection
PCd	'impact of volume', 'resource consequences'
PCf	'containment distress', 'resent resources used'
	Change in amount of loss
CQ	severe problems with aspect 'amount is more than it used to be, normally'
	Other menstrual
CQ	created variable indicating the number of severe problems reported for 3 aspects of period-type pain (with/ before periods, and 'all the time'); similarly for 3 aspects addressing cyclic mood/physical symptoms and feeling 'generally unwell/tired because of periods'
MEQ	regular (troublesome) symptoms /feelings around periods
PCd	'variable flow', 'unpredictable onset', 'unwell/irritable during period'
PCf	'worry', 'feel periods a burden', 'had enough of periods'.
	Socio-demographic
CQ	age, centre, deprivation category, self-rated comparative health
MEQ	home facilities (for dealing with periods) deficit score

* *CQ = Clinic Questionnaire; MEQ = Menstrual Evaluation Questionnaire; PCd = principal components addressing 'dealing with periods' and PCf = components addressing 'feelings about periods' (PCs derived from MEQ data - see **5.3.1.iv**)*

Table 9.10 presents the factors in the model, grouped into variables relating to absolute volume, change in volume, other menstrual aspects, and socio-demographic factors. Within 'absolute volume' the variables can be further sub-divided into those addressing volume itself, and those addressing the containment implications of

volume. It can be seen that judgement of periods as 'very heavy' was more strongly associated with the containment implications (first 5 variables listed), than absolute volume itself (next 3 variables). In terms of effect size and subgroup n's, need to change during the night was a key variable. The 225 women who had to get up at night most periods had over 4 times the odds (relative to those who seldom had to do so) of rating their periods very heavy. The 282 women (52%) with highest scores on the component reflecting expressed distress regarding containment strain had double the odds of rating their periods very heavy. So did the 100 women (19%) with most extreme scores on the component 'impact of volume', reflecting the steps that have to be taken to deal with flow.

With regard to volume *per se*, **Table 9.10** shows that women 'losing too much blood' had 2.5 times the odds of judging their periods very heavy, but there were only 124 in this category. Rating periods as 'very heavy' was also associated with finding *increase* in period a severe problem (doubled odds). However, a high home facilities score (socio-demographic section), indicating deficit, was associated with, if anything, a *reduction* in odds of reporting periods very heavy (a halving of odds for those with the worst facilities, that is scores >5), but with a wide confidence interval, so that the null odds ratio of 1 is plausible. This nevertheless suggests that women's judgement of periods as very heavy is *not* a consequence of inadequate home facilities for dealing with periods.

With regard to other menstrual factors, finding a severe problem with periods going on too long (n=142) was inversely associated, in that the odds of rating periods 'very heavy' heavy was halved. The component reflecting symptoms of irritability and 'being unwell' during periods was related to 'very heavy', with doubled odds for the 199 (37%) with most extreme scores. Finally, there was a strong association with the component indicating that the woman had 'had enough of periods', with trebled odds of a 'very heavy' rating among the 199 (21%) with most extreme scores.

For a woman reporting severe problems with accidents and with losing too much blood, and that she has to get up at night to change most periods, her odds of rating her periods very heavy, relative to a woman with reference category values for all variables in the model, is 37.

Table 9.10 Model predicting subjective report of menstrual loss as 'very heavy' (n=540)

Variables in model	p	Levels	n	OR	(95% CI)
Absolute volume					
Difficulty preventing menstrual ACCIDENTS?	<0.001	not severe problem severe problem	453 87	 3.40	 (1.65, 7.00)
Have to get up to CHANGE AT NIGHT	<0.001	seldom some periods most periods	109 206 225	 2.08 4.33	 (1.41, 3.07) (2.25, 9.44)
PCf: Distress around CONTAINMENT **	0.010	lower 2/5 top 3/5	258 282	 2.05	 (1.19, 3.54)
PCd: IMPACT OF VOLUME on daily life (incl. containment) * #	0.082	bottom fifth second fifth ~~ top fifth	141 124 ~~ 100	 1.19 ~~~ 2.01	 (0.98, 1.43) (0.94, 4.28)
CHANGING INTERVAL when full flow	0.027	≥ 2 hours ≤1 hour	371 169	 1.75	 (1.05 2.93)
Lose TOO MUCH BLOOD?	0.004	not severe problem severe problem	416 124	 2.53	 (1.36, 4.69)
CLOTS	0.023	none/ ≤50p size > 50p size	456 84	 2.11	 (1.11, 4.03)
SANITARY PROTECTION used for most recent period	0.004	≤ 32 products ≥ 33 products	321 219	 2.06	 (1.27, 3.36)
Increase in volume					
Period AMOUNT IS MORE than it was?	0.011	not severe problem severe problem	398 142	 2.14	 (1.20, 3.54)
Other Menstrual					
Periods last TOO LONG?	0.093	not severe problem severe problem	427 113	 0.50	 (0.22, 1.12)
PCf: HAD ENOUGH of periods ***	0.003	bottom fifth middle 3/5 top fifth	159 72 112	 1.75 3.06	 (1.22, 2.50) (1.49, 6.27)
PCd: IRRITABLE / UNWELL during period **	0.037	bottom 3/5 top 2/5	371 199	 1.75	 (1.03, 2.92)
Socio-demographic					
AGE	0.007	< 40 years ≥ 40 years	276 264	 1.42	 (1.10, 1.82)
HOME FACILITIES score *(high⇒poor facilities)* #	0.092	0 or 1 2 ~~ 6 to 15	109 124 ~~ 109	 0.86 ~~~ 0.55	 (0.71, 1.03) (0.26, 1.15)

/ **/ * PCd= principal component about management of periods (**Appendix 5.2**), PCf = PC addressing feelings about periods (**Appendix 5.2**). The distributions were divided into approximately 'fifths' at – 0.7, – 0.3, 0.4, 0.9, as explained in **Table 9.1**.*

Footnotes to Table continued on next page.

Footnotes to Table 9.10 continued

** *Effect not linear but if recoded as binary, as shown, was a useful addition to the model.*

*** *Effect was not linear but if recoded as a 3-level variable, as shown, was a useful addition to the model as a* linear *variable.*

\# *For brevity results for these 5-level linear variables have been presented only for the bottom fifth (OR not shown but taken as 1), the next fifth up, and the top fifth. For each variable the ORs for the levels not shown can be obtained by squaring/cubing the first OR reported. The levels not reported make the total n up to 540.*

The modelling was also tried with the inclusion of the SF-36 quality-of-life scaled scores and Health Transition score offered to the model. (The scaled scores were first recoded into approximately fifths of the distribution, as for principal component scores (9.1.1).) This inevitably resulted in a greater loss of cases to missing data. The SF-36 scales included in the model were Physical Functioning, Vitality and Mental Health, with good physical status and vitality, or poor mental health, making rating of periods as very heavy more likely. Poor comparative health, and the component addressing worry about changes, were also included in that model for rating periods very heavy. Home facilities deficit score, containment distress and severe problem with losing too much blood were no longer included in the model.

9.3.3.ii What kind of periods are associated with citing volume of period as cause of help-seeking?

As was noted in the Introduction (**9.1**), citing one or more of the volume of loss aspects of periods as the 'cause' of help-seeking is probably the closest we have to an indicator of menorrhagia complaint. The three aspects considered as indicators of volume issues, and hence as potential volume causes (if cited at the end of question 5 of CQ), were 'lose too much blood', 'difficulty preventing accidents' and 'periods go on too long'.

For the binary 'volume as cause' variable a similar modelling process was undertaken as for 'very heavy' periods. The variables offered to the model were as already listed (**Table 9.9**), with the addition of the CQ variable 'heaviness of loss' (which could not be in the 'very heavy' model as a binary form of it was the

dependent variable for those analyses). **Table 9.11** presents the model for 'volume as cause of help-seeking', calculated on 524 cases.

Table 9.11 Model predicting citation of volume aspects of period as cause of clinic attendance (n=524)

Variable	p	Levels	n	OR	(95% CI)
Absolute volume					
HEAVINESS of period	0.003	light/moderate	95		
		heavy	237	1.65	(1.20, 2.26)
		very heavy	192	2.72	(1.44, 5.12)
LOSE TOO MUCH BLOOD during period?	<0.001	not sev. problem	406		
		severe problem	118	3.25	(1.92, 5.52)
'FULL FLOW' days of period	0.002	≤5 days	435		
		≥ 6 days	85	2.40	(1.41, 4.08)
How often use DOUBLE PROTECTION	0.002	some or no periods	307		
		most periods	219	1.39	(1.13, 1.70)
Other Menstrual					
Other CYCLIC symptoms/ feelings around periods?	0.032	not v. troublesome	389		
		very troublesome	135	0.58	(0.35, 0.95)
PCd: IRRITABLE / UNWELL during period *	0.066	bottom fifth	133		
		top 4/5	391	0.65	(0.41, 1.03)
PCf: Feel periods a BURDEN (on life/family) *	0.016	bottom 4/5	422		
		top fifth	102	0.47	(0.26, 0.87)

* *PCd= principal component about management of periods (**Appendix 5.2**), PCf about feelings about periods. The distributions were divided into approximately 'fifths' as explained in **Table 9.1**. The effect was not linear but if recoded as binary variable, as indicated, was a useful addition to the model.*

The model shows significant deviation from the hypothetical perfect model (-2log likelihood=588, df=516, p<0.02). The predictive performance of the model overall was 72%, but better at prediction of the 327 who did not cite volume as cause (88% correct) than the 197 who did (44%). The previous test informs that the frequencies reproduced differ from those observed; it can be seen that the model was better at exclusion of volume citation (88%), than predicting those who did cite volume (44%).

It can be seen that citation of volume as cause of help-seeking was strongly associated with volume factors. Heaviness was in the model, with rating of periods as

heavy, and even more so very heavy, increasing the odds of citation of volumes as cause of help-seeking (OR 1.65 and 2.72 respectively). As has been shown in the preceding section, rating of periods as very heavy is associated with a range of factors, mainly encompassing containment consequences of volume, but also volume itself, 'losing too much blood'. Despite the inclusion of heaviness in this cause model, 'losing too much blood' is also required, in the sense that it provides information additional to 'heaviness' needed by the model. The 118 women finding volume of loss a severe problem have trebled odds of citing volume as cause. Duration of the full flow phase of the period, and need for double protection, are also associated (OR 2.4 and 1.4 respectively). Apart from these variables there are no other variables positively associated with citation of cause as volume. Some other menstrual variables are protective, in that high scores on these variables are associated with lowered odds of citing volume as cause (troublesome cyclic symptoms, being irritable/unwell during period, feeling periods a burden, any of which approximately halves the odds).

For a woman reporting very heavy periods, severe problem with losing too much blood, and 'full flow' lasting more than 5 days, her odds of citing volume as cause of help-seeking, relative to a woman with reference category values for all variables in the model, is 21. However, if she is also unwell and irritable during her period, then her odds ratio would be only 14.

The modelling was also tried with the inclusion of the SF-36 variables offered to the model but none was included in the model.

It is of interest to compare the model for 'volume as cause of help-seeking' with that for rating periods as 'very heavy' (both as presented in the tables, without SF-36 quality-of-life factors being offered to the models). A schematic diagram of the models is presented in **Figure 9.10**. The factors in each model, and the degree of association, are represented by the bars, red for 'very heavy' and blue for 'volume as cause'. Bars to the right (OR>1) represent positive associations with outcome variable, the length of the bar being the size of the OR for the most extreme category/value in the relevant model (as reported in the corresponding table). Bars to the left (OR<1) represent negative or protective associations. The asymmetric nature

of the OR scale means that a negative (protective) association of OR=0.5 is of the same degree as a positive association of 2 (=1/0.5).

Figure 9.10 Comparison of factors associated with reporting periods as 'very heavy', and citing volume of loss as cause of help-seeking

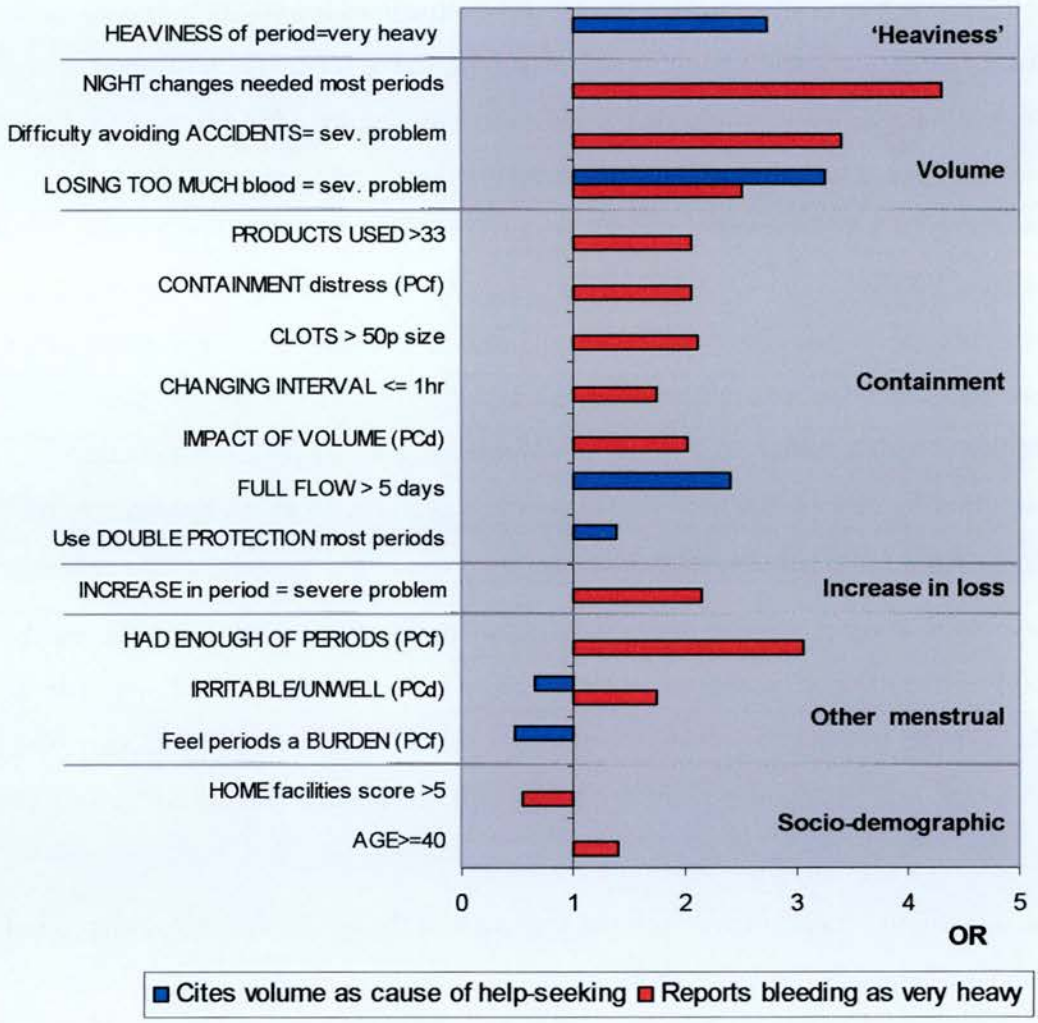


Figure 9.10 shows that the 'cause' model has fewer factors included, and that these are predominantly *volume/containment* variables. The variables offered to the two models were the same, with the exception of the additional offer to the 'cause' model of the 'heaviness' variable. As can be seen the model for very heavy (**Table 9.10**) was strongly and broadly associated with containment factors. Once heaviness was included in the 'cause' model there was apparently little need for further variables reflecting containment strain. The same appears to apply to the component 'had enough of periods' which was strongly associated only with 'very heavy'. Over and

above the extent to which the component (or factors associated with it such as intolerable periods) may be implicit in the rating of very heavy, it is not needed in the 'cause' model. However, in the case of 'losing too much blood', which was included in the 'very heavy model' there was nevertheless need to have the factor also in the 'cause' model, presumably because it provided additional predictive information about citation of volume as cause. In the context of other variables in the models, being unwell or irritable with the period was positively associated with rating periods very heavy, but protective against citing volume as cause.

9.3.3.iii What kind of periods are associated with referral to gynaecology clinic for bleeding?

REFERRAL BY GP FOR BLEEDING

GP reasons for referral (up to two reason per letter) were extracted from referral letters and coded into categories, one of which was excessive bleeding (**3.8.3.i**). For the binary variable 'referred by GP for excessive bleeding' a similar modelling process was undertaken as in the preceding sections. The variables offered to the model were as already listed (**Table 9.9**), with the addition of the CQ variable 'heaviness of loss' (as in **9.3.3.ii**), and the further addition of three variables indicating citations as cause of help-seeking. These were 'losing too much blood' cited (or not) as cause; increase in amount of period cited; and the variable indicating how many of the 3 volume causes had been cited. (These could not be offered to the 'cause' model of the preceding section given the dependent variable for that model.)

Table 9.12 presents the model for 'referral by GP for excessive bleeding', calculated on 666 cases with non-missing data for the relevant variables. The model was adequate, showing insignificant deviation form the hypothetical perfect model (-2log likelihood=571, df=653, p>0.50). The predictive performance of the model overall was 81%, but much better at prediction of the 511 who were referred for bleeding (94% correct) than the 155 who were not (39%).

Table 9.12 Model predicting GP reason for referral as excessive bleeding (n=666)

Variable	p	Levels	n	OR (95% CI)
Absolute volume				
No. of VOLUME 'CAUSES' cited for clinic visit	<0.001	none	412	
		1 to 3	254	3.03 (1.78, 5.15)
HEAVINESS of period *(categorical, overall p =0.004)*		light/mod	122	
	0.005	heavy	303	2.11 (1.25, 3.55)
	0.002	very heavy	241	3.00 (1.52, 5.91)
SANITARY PROTECTION used for most recent period	0.059	≤ 32 products	396	
		≥ 33 products	270	1.64 (1.02, 2.65)
PCd: IMPACT OF VOLUME on daily life **	0.005	bottom 2/5	330	
		top 3/5	336	1.93 (1.23, 3.02)
Increase in volume				
INCREASE IN PERIOD is CAUSE of help-seeking?	0.055	not cause	497	
		cited as a cause	169	1.74 (0.99, 3.05)
Other Menstrual				
No. of SEVERE PROBLEMS with CYCLIC WELL-BEING	0.003	none	377	
		1 to 3	289	0.50 (0.32, 0.79)
Periods last TOO LONG?	0.099	not sev. problem	520	
		severe problem	126	1.76 (0.90, 3.45)
PCd: VARIABLE FLOW *#	0.155	bottom fifth	176	
		second fifth	129	1.17 (0.98, 1.39)
		~~	~~	~~~
		top fifth	141	1.87 (0.93, 3.76)
PCd: ONSET of period is UNPREDICTABLE *#	0.085	bottom fifth	147	
		second fifth	143	0.87 (0.75, 1.02)
		~~	~~	~~~
		top fifth	112	0.57 (0.31, 1.05)
Socio-demographic				
CENTRE	0.025	Glasgow	275	
		Edinburgh	391	1.62 (1.06, 2.46)
AGE	0.028	< 40 years	330	
		≥ 40 years	326	1.27 (1.03, 1.57)

/ ** PCd= principal component about management of periods (Appendix 5.2**). The distributions were divided into approximately 'fifths' as explained in **Table 9.1**.*

*** Effect was not linear but if recoded as binary, as shown, was a useful addition to the model.*

 # For brevity results for these 5-level linear variables have been presented only for the bottom fifth (OR not shown but taken as 1), the next fifth up, and the top fifth. For each variable the ORs for the levels not shown can be obtained by squaring/cubing the first OR reported. The levels not reported would make the total n up to 666.

Referral by GP for excessive bleeding was strongly associated with both heaviness and 'volume' being cited as cause of help-seeking. The odds for referral for bleeding were doubled if 'heavy' periods, trebled if 'very heavy', and the odds would be further trebled if volume was also cited as a cause (resulting OR = 6.4 and 9.1 respectively). For the 336 women (just over half) with highest scores for 'impact of volume on daily life' odds were doubled. Referral was also associated with periods 'going on too long' (OR 1.76), which was interesting as this feature is sometimes included in the menorrhagia definition, but this variable was in the model for 'very heavy periods' as a *protective* factor. That is, jointly with the other variables in that model a problem with 'duration' tended to mean that periods would *not* be judged as very heavy.

With regard to factors not clearly to do with menorrhagia or (absolute) volume of menstrual loss, referral was also associated with *increase* in amount of period being cited as cause of help-seeking (OR 1.74). Problem with increased amount of periods was in the model for 'very heavy', but not in that for *volume* as cause of help-seeking. Referral for bleeding was associated only weakly with the component 'variable flow', with near doubled odds for the 141 women (21%) with highest scores for this component (but wide confidence interval, including 1). Severe problems with cyclic symptoms were associated with reduced odds of being referred for bleeding (reduced by a half). 'Unpredictable onset' was also associated with reduced odds of referral, but much less clearly. Finally, considered jointly with all the other factors in the model, Edinburgh women were more likely to have been referred for bleeding, as were women aged 40 years or over.

The modelling was also tried with the inclusion of the SF-36 quality-of-life scaled scores and Health Transition score offered to the model. The SF-36 variables included in the model were General Health scaled score and Health Transition, with good general health, and more strongly, deterioration in health during the past year, associated with referral for bleeding. Problem with avoiding menstrual accidents, troublesome cyclic symptoms and 'had enough of periods', were also included in the model. Heaviness, centre, and the two components that reduced odds of referral for

bleeding, unpredictable onset and variable flow, were no longer included in the model.

THE PATIENT'S SELF-STATED REASON IS BLEEDING

The patient's self-stated reason for coming to the clinic was coded from the response to the first free-text item on CQ and coded as for GP referral reason into categories, one of which was excessive bleeding (up to two reasons coded per woman, **3.8.3.ii**). For the binary variable 'self-stated reason is excessive bleeding' a similar modelling process was undertaken as in the preceding sections. The variables offered to the model were identical to the model for bleeding as GP referral reason (as in **9.3.3.iii**). **Table 9.13** presents the model for 'referral by GP for excessive bleeding', calculated on 569 cases with non-missing data for the relevant variables.

The model was adequate, showing insignificant deviation from the hypothetical perfect model (-2log likelihood=469, df=551, p> 0.50). The predictive performance of the model overall was 81%, and prediction was almost equally good for the 349 who self-stated bleeding as reason for clinic attendance (87% correct) and the 220 who did not (73% correct).

The variables most strongly associated with the patient self-stating excessive bleeding as reason for clinic attendance were having cited one or more volume aspects as cause (increasing the odds nearly seven-fold), and heaviness (for periods rated heavy, trebling the odds, for 'very heavy' periods, quadrupling the odds). The effect of heaviness was not linear, so the variable was defined as categorical.

The other 'volume' variables included in the model were to do with containment. Need for changes during the night and use of more than 32 products in the most recent period were included in the model for 'very heavy'. The fact that they are required in this 'reason for attendance' model, in addition to heaviness, suggests that they provide extra information about reason for referral (self-stated). There was also a strong association (nearly trebling of odds) with increase in amount of period having been cited as the cause of help-seeking, reflecting a relative rather than absolute judgement about volume of period.

Table 9.13 Model for self-stating bleeding as reason for clinic attendance (n=569)

Variable	p	Levels	n	OR (95% CI)	
Absolute volume					
No. of VOLUME 'CAUSES' cited for clinic visit	<0.001	none	352		
		1 to 3	117	6.74	(3.95, 11.50)
HEAVINESS of period *(categorical, overall p =0.003)*		light/moderate	105		
	0.002	heavy	260	3.04	(1.51, 6.13)
	0.002	very heavy	204	4.08	(1.75, 9.48)
SANITARY PROTECTION used for most recent period	0.004	≤ 32 products	338		
		≥ 33 products	231	2.09	(1.28, 3.58)
Have to get up to CHANGE AT NIGHT	0.020	seldom	115		
		some periods	217	1.51	(1.07, 2.13)
		most periods	237	2.28	(1.15, 4.54)
PCf: Distress around CONTAINMENT *	0.004	bottom 2/5	274		
		top 3/5	295	2.14	(1.28, 3.58)
PCf: RESENT RESOURCES used *	0.016	bottom 4/5	477		
		top fifth	92	2.45	(1.18,5.08)
PCd: RESOURCE consequences of periods *	0.012	bottom 2/5	274		
		top 3/5	295	0.46	(0.26, 0.98)
Increase in volume					
INCREASE IN PERIOD is CAUSE of help-seeking?	<0.001	not cause	422		
		cited as cause	147	2.70	(1.54, 4.75)
Other Menstrual					
No. of SEVERE PROBLEMS with CYCLIC WELL-BEING	0.016	none	325		
		1 to 3	244	0.50	(0.29, 0.88)
PCd: Period ONSET UNPREDICTABLE *	<0.001	bottom 2/5	253		
		top 3/5	316	0.54	(0.34, 0.84)
PCf: HAD ENOUGH of periods *(categorical, p=0.002)* **		bottom fifth	164		
	0.012	middle 3/5	285	1.56	(0.89, 2.74)
	<0.001	top fifth	120	3.58	(1.78, 7.20)
PCf: Feel periods a BURDEN (on life/family) *	0.043	bottom 4/5	462		
		top fifth	107	0.50	(0.26, 0.98)
Socio-demographic					
HOME FACILITIES score (high⇒poor facilities)	0.010	≤ 5	456		
		6 to 15	113	2.30	(1.22, 4.32)
AGE	0.023	< 40 years	280		
		≥ 40 years	289	1.33	(1.04, 1.69)
CENTRE	0.096	Glasgow	238		
		Edinburgh	331	0.66	(0.41, 1.08)

/ ** PCd= principal component about management of periods (Appendix 5.2**), PCf about feelings about periods. The distributions were divided into approximately 'fifths' as explained in **Table 9.1**. The effects were non-linear. However, recoded as ** 3-level or * binary variables, as shown, made useful additions to the model.*

Also included in this 'reason' model were the components reflecting emotional reactions to containment and the resources involved, 'containment distress' (with more than doubling of odds for the 295 women (52%) with highest scores) and 'resentment of resources used' (with odds increasing by a factor of 2.45 for the 95 women (17%) with most extreme scores). This latter component reflects not just resentment of cost but also embarrassment about changing rate and quantities of supplies needed, and even a sense of persecution (see **Appendix 5.2 Table A5.2.2**). In contrast to this positive association with bleeding as reason, the component reflecting the resource consequences of heavy periods (as a fact of menstrual life rather than in terms of feelings about this) was also included in the model, but as a *protective* factor. Therefore, for a sub-group of women these effects will almost cancel each other out ($2.45 \times 0.46 = 1.1$). The women with reduced odds for stating bleeding as reason for clinic attendance are those who really can *not* 'resource' periods, but who are not expressing a strong reaction of resentment/embarrassment (OR 0.46). The women with *increased* odds for stating bleeding as reason for clinic attendance are those who *can* 'resource' periods but nevertheless feel strong embarrassment/ resentment about resources used (OR 2.45).

Table 9.13 shows that among non-volume-specific menstrual variables, cyclic problems with well-being, and unpredictable onset of periods were protective against self-stating bleeding as reason (odds halved). The same was true for the component 'feel periods a burden' considered jointly with all the other variables in the model. An interpretation could be that if the other bleeding volume factors do not apply, and all there is is a high score for 'burden', then it will not tend to be bleeding that is self-stated as referral reason. However, the non-specific component 'had enough of periods' was positively associated with self-stating bleeding as reason, very strongly so for high scores (OR=3.6 for the 120 (21%) with highest scores). This implies that over and above all the volume factors associated with bleeding as reason, an expressed feeling of having 'had enough of periods' provides important extra information about the likelihood of bleeding as self-stated reason for clinic attendance. Similarly, the 116 women (20%) with a high home facilities deficit score had more than double the odds of for self-stating bleeding as reason. Older women

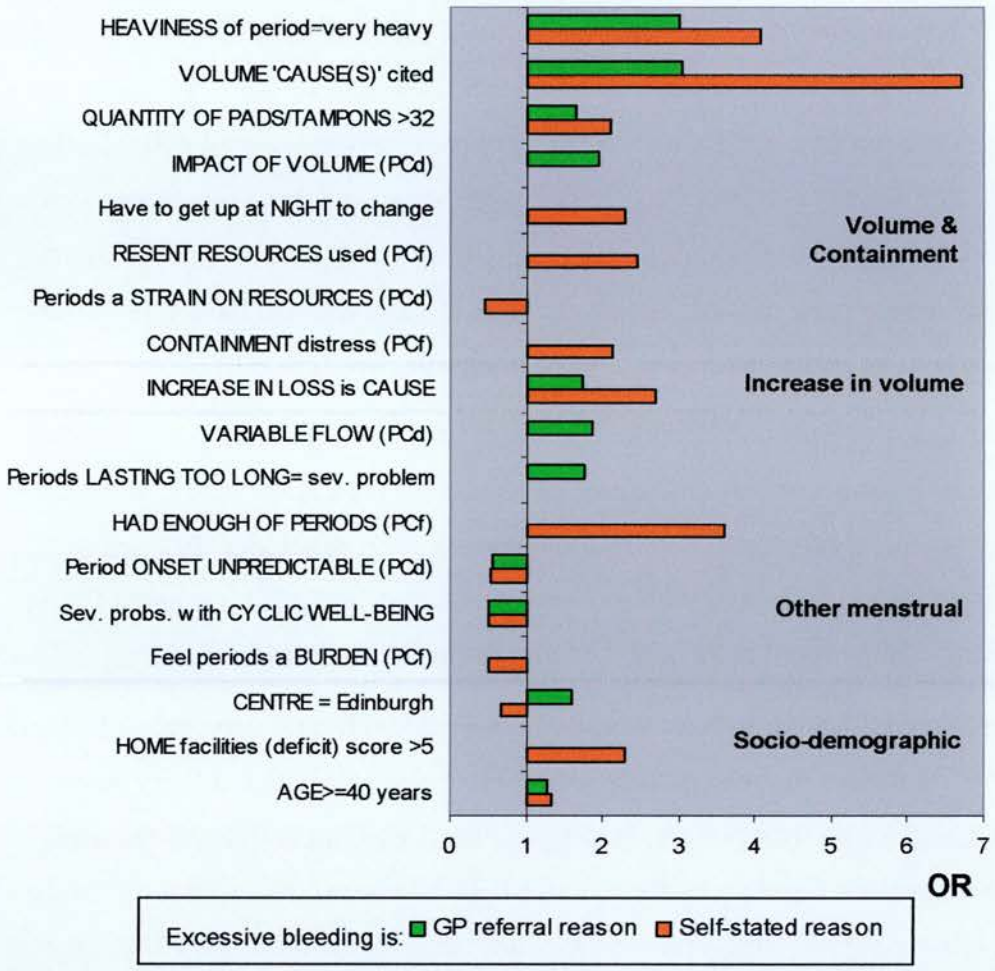
were more likely to give bleeding as their reason for clinic attendance, and Edinburgh women were less likely to do so, in the context of all the other factors in the model.

The modelling was also tried offering the SF-36 variables. The only SF-36 variable included was Role Physical (better scores were positively associated with bleeding as reason). 'Resource consequences', 'burden' and cyclic well-being problems were no longer needed (protective' factors), nor night changes and 'resent resources used' (positively associated). 'Impact of volume' was brought into the model, positively associated, and problems with period pain, as a protective factor.

It is of interest to compare the model for 'GP referral reason is excessive bleeding' with that for patient's self-stated reason (both as presented in the tables, without SF-36 quality-of-life factors being offered to the models). A schematic diagram comparing the models is presented in **Figure 9.11**, similar to that presented for the comparison of the 'very heavy' and 'volume as cause' models (**9.3.3.ii**).

The most striking feature is that the 'GP referral' model has no very strong factors. The strongest factors for both models are 'volume causes cited' and 'very heavy' periods. Considering these jointly, among women for whom both apply the odds ratio for referral for bleeding by the GP would be 9, whereas the odds ratio for the woman self-stating bleeding as reason for clinic attendance would be 27. For the 'self-stated bleeding reason' model there is stronger association with containment factors. Both models show an association with increase in periods cited as cause of help-seeking, but more strongly for excessive bleeding being the patient's self-stated reason. With regard to other menstrual factors, bleeding as the GP referral reason was associated with variable flow and periods going on too long, whereas for the 'self-stated bleeding reason' model there was a strong association with having 'had enough of periods'. In the context of all the other factors in the models, unpredictable onset and cyclic problems with well-being were negatively associated with both models ('protective') and if periods were felt to be a burden the woman was less likely to self-state bleeding as reason.

Figure 9.11 Comparison of factors associated with GP referral for excessive bleeding and self-stated reason as bleeding



With regard to socio-demographic factors, both outcomes were associated with age over 40 years, and Edinburgh GPs were more likely to refer for bleeding while Edinburgh patients were less likely to self state bleeding, all adjusted for other factors. Self-statement of bleeding as reason was strongly associated with a high deficit score for home facilities for dealing with heavy periods. This is contrary to the effect on rating periods very heavy, where home facilities deficit score was protective (negatively associated). Therefore, inadequate home facilities do not appear to influence judgements about excessive heaviness, but are associated with clinic attendance, and hence with self-stating bleeding as reason.

9.3.4 *Principal components of menstrual experience*

9.3.4.i What are the associations of component scores with menstrual symptoms, and other variables?

DEMOGRAPHIC AND MENSTRUAL VARIABLES

Tables 9.14a and **9.14b** show the non-parametric associations of components with menstrual and demographic variables. To save space, and for ease of perusal, only the strongest correlations have been shown ($|rho| \geq 0.1$ for demographic variables, $|rho| \geq 0.2$ for menstrual). All are statistically different from the null correlation of 0 ($p<0.007$). Correlations $|rho| \geq 0.4$ are highlighted in bold. The tables have been arranged so that components addressing resources, being unwell during period, and negative attitudes to periods ('burden' and 'had enough') are in **Tables 9.14a** and those addressing volume, containment, onset, flow and worry are in **Tables 9.14b**.

On the whole components in **Tables 9.14a** are not strongly related to volume. The only menstrual history variables with correlations $|rho| \geq 0.2$, and hence in the table, were heaviness and duration of problem. For 'volume' aspects of periods as well, and variables derived from them, there was scant association with these components.

Problems with accidents, laundry and cost were associated with affirmation of 'resource consequences' of periods, as were higher parity and greater deprivation, whereas only cost was associated with 'resentment of resources used'.

With regard to being unwell/irritable with periods and feeling them to be a burden, the longer the duration of problem (which, it should be remembered, may be something other than excessive bleeding), the higher the scores tended to be. These components were most strongly associated with period pain and, particularly, cyclic symptoms, and also with a general propensity to find many aspects of periods a marked or severe problem. They were also associated with younger age and greater deprivation.

Table 9.14a Association of principal component scores with menstrual and socio-demographic variables

	PCd * Resource Consequ. rho+	PCf * Resent Resource rho+	PCd * Unwell/ Irritable rho+	PCf * Periods a Burden rho+	PCf * Had Enough rho+
Age			– 0.28	– 0.22	0.10
Parity	0.17				
Deprivation	0.21		0.25	0.18	
Heaviness					0.25
Duration of problem			0.20	0.25	
Aspects of periods					
Lose too much				0.25	0.25
Go on too long					**0.40**
Accidents	0.25				
Count sev. 'volume'#	0.22			0.22	0.35
Pain with periods			**0.50**	**0.40**	
Pain before periods			**0.45**	0.37	
Pain all the time			**0.44**	0.34	
Count sev. pain #			**0.47**	0.39	
Cyclic mood			**0.63**	**0.53**	
Other cyclic			**0.46**	**0.44**	
Feel unwell/tired			**0.54**	**0.54**	0.22
Ct. sev. cyclic/unw. #			**0.58**	**0.51**	
Extra laundry	0.34				0.28
Cost	**0.43**	**0.43**			
Impact on daily life			0.29	**0.41**	
Loss increased					0.37
Worry ? wrong				0.26	**0.50**
Irregular			**0.43**		0.35
Bleeding between					0.23
Total ct. ≥ moderate ~	0.22		**0.42**	**0.46**	0.28

* *PCd = principal components 'dealing with periods' (n=712) and PCf = components 'feelings about periods' (n=687) (PCs derived from MEQ data - see **5.3.1.iv**)*

\+ *Spearman correlations /rho/ ≥ 0.1 shown for demographic variables (for all p<0.007), /rho/ ≥ 0.2 for remainder (for all p<0.001). For n's see * above (see **3.8.3**).*

\# *Counts of number of aspects rated 'severe problem' within groupings of aspects as specified (volume, pain and cyclic/unwell, each comprising 3 aspects, see **5.2.2.i** & **5.3.1.iii**).*

~ *Count of number out of all 16 aspects which are rated 'marked' or 'severe problem' (see **5.2.2.i**).*

Table 9.14b Association of principal component scores with menstrual and socio-demographic variables

	PCd* Impact of Volume rho+	PCf* Contain. Distress rho+	PCd* Variable Flow rho+	PCf* Worry re Changes rho+	PCd* Unpred. Onset rho+
Parity			0.19		
Deprivation				0.14	
Heaviness	0.38	**0.53**	0.35	0.20	
Duration problem	0.25	0.23		– 0.17	
Freq. periods leaks	0.33	**0.46**	0.28		
Night changes	0.36	**0.45**			
Usual duration period		0.24	**0.42**		
Days double protection	0.24	0.37	0.35		
Clots ≥50p size	0.34	**0.44**			
Days full flow		0.27	**0.44**	0.22	
Need freq. changes	0.34	**0.43**	0.28		
Total prods. used	0.23		0.32		
Know start next period					– 0.21
Aspects of periods					
Lose too much	0.35	**0.52**	**0.47**	0.29	
Go on too long		0.27	**0.65**	**0.40**	
Accidents	**0.40**	0.63	**0.44**		
Count sev. 'volume' #	0.22	**0.40**	**0.48**	0.35	
Extra laundry	0.39	**0.56**	**0.41**	0.28	
Cost		0.32	0.29		
Loss increased	0.30	**0.45**	**0.52**	0.37	
Worry something wrong			0.27	**0.50**	
Irregular				0.35	0.26
Bleeding between			0.30	0.23	
Pain with periods	0.29				
Impact on daily life	**0.58**	**0.51**			
Feel unwell/tired	0.32	0.24			
Count ≥ moderate ~	0.36	**0.44**	**0.44**	0.28	
Count sev. pain #	0.25	0.39			

* + # ~ *Please see footnotes to* ***Table 9.14a****.*

Of all the components in **Table 9.14a**, 'had enough of periods' was most strongly associated with volume, with higher scores related to heavier periods, degree of problem with losing too much blood and with number of severe problems with volume aspects. However this component was even more strongly associated with periods going on too long, increased loss, and worry about change in periods.

In contrast, **Tables 9.14b** shows the first three components related to many menstrual variables and aspects addressing volume. 'Unpredictable onset' was related to only two variables, with score on this component tending to be higher if the woman does not know by counting when her next period is due, and if she has a degree of problem with irregular periods. 'Worry re changes' was most strongly associated with increased loss, periods going on too long, and the aspect addressing irregularity and worry there may be something wrong. This component showed higher scores where there was greater deprivation and if the duration of problem was *shorter*.

Table 9.14b also shows that 'variable flow' is strongly associated with a number of volume variables, increased loss, periods 'going on too long', losing too much, duration of period, bleeding in between periods and number of products used, and with higher parity.

'Impact of volume' and 'containment distress' had very similar patterns of correlations to each other, and differed from 'variable flow' in being associated with duration of problem, clots, impact on daily life, pain and feeling unwell/tired because of periods. The differences between 'impact of volume' and 'containment distress' were that 'impact of volume' was also associated with number of products used for most recent period, while 'containment distress' was more strongly associated than 'impact' with leaks, need for night changes, heaviness, clots and duration of full flow, and with the extent of problem aspects: accidents, losing too much, increased loss, going on too long, extra laundry.

IRON STATUS

The principal component scores were examined in relation to iron status. There were significant differences by low haemoglobin status (<12g/dL) in scores on the 'impact of volume', 'unwell/irritable during period' and 'containment distress' components

(Mann Whitney z =2.6, – 2.4, 1.9 respectively, p= 0.007, 0.015, 0.05, n= 366, 366, 354). Therefore in this clinic population those with low haemoglobin tended to have higher scores for impact of volume and containment distress, but lower scores for 'unwell/irritable during period). For ferritin also those with low values tended to have lower scores on 'unwell/irritable' (Mann Whitney z = – 3.5, p<0.001, n= 230). There was no significant difference by ferritin status for any other components, but the n's were small (230 for dealing with periods components, 188 for feelings components).

QUALITY-OF-LIFE

The principal component scores were examined in relation to SF-36 quality-of-life scale scores. Associations |rho| ≥ 0.2 are shown in **Table 9.15**. Higher scores for 'impact of volume' and 'containment distress' were associated with poorer 'quality-of-life' for bodily pain, role physical and social functioning domains only. Higher scores for 'unwell/irritable' and 'feeling periods a burden' were associated with poorer 'quality-of-life' for all SF-36 scale scores other than 'Physical Functioning' (not shown) and other than the SF-36 Health Transition variable.

Table 9.15 Principal component scores associated with SF-36 Quality-of-life scaled scores (high Q-o-L score = good health status)

Q-o-L scale	PCd * Impact of Volume rho+	PCf * Containment Distress rho+	PCd * Unwell/ Irritable rho+	PCf * Periods a Burden rho+
Bodily Pain	– 0.33	– 0.30	– 0.40	– 0.41
General Health			– 0.31	– 0.32
Mental Health			– 0.38	– 0.36
Role Emotional			– 0.31	– 0.31
Role Physical	– 0.32	– 0.24	– 0.25	– 0.37
Social Functioning	– 0.35	– 0.33	– 0.35	– 0.49
Vitality			– 0.31	– 0.34

* *PCd = principal components 'dealing with periods' and PCf = components 'feelings about periods' (n=687) (PCs derived from MEQ data - see **5.3.1.iv**)*

\+ *Spearman correlations |rho| ≥ 0.2; for all p<0.001; (n ranges from 581 to 587 for PCd and from 561 to 567 for PCf).*

Principal component scores were examined in relation to current health and health history, including recalled number of previous attendances at hospital gynaecology clinic. **Table 9.16** presents all correlations |rho| ≥ 0.1, with correlations |rho| ≥ 0.3 high-lighted in bold. The components 'unwell/irritable during period' and 'feel periods a burden' were, among all components, most strongly associated with the 'health' variables. Of the five health variables, those most strongly associated with the two components were the number previous visits to the GP about periods and the number of minor physical symptoms experienced in the past 2 weeks (reported in MBQ). High scores on the 'variable flow' component were associated only with the number of past D&C's. Surprisingly, the strongest association with number of past D&C's was with the component 'unwell/irritable during period'.

Table 9.16 Association of PC scores with current health and health history

Health history variable *	PCd * Resource Consequ. rho+	PCf * Resent Resource rho+	PCd * Unwell/ Irritable rho+	PCf * Periods a Burden rho+	PCf * Had Enough rho+
Worse health	0.19	0.11	0.25	0.23	0.10
No. minor symptoms	0.22	0.12	**0.40**	**0.38**	0.15
No. visits to GP re periods	0.15		**0.30**	**0.35**	0.17
No. clinic visits	0.18		0.14	0.21	0.11
No. of past D&C's			0.14	0.12	0.13
	PCd * Impact of Volume rho+	**PCf * Contain. Distress rho+**	**PCd * Variable Flow rho+**	**PCf * Worry re Changes rho+**	**PCd * Unpred. Onset rho+**
No. minor symptoms	0.20	0.19		0.13	
No. visits to GP re periods		0.16		0.11	
No. clinic visits		0.13			0.11
No. of past D&C's			0.11		

* *PCd = principal components 'dealing with periods' and PCf = components 'feelings about periods' (PCs derived from MEQ data - see **5.3.1.iv**)*

\+ *Spearman correlations |rho| ≥ 0.1; for 'worse health' n= 682 for PCf, 714 for PCd, p<0.008 for all; for remainder n ranges 512 to 558, for all p<0.010.*

The principal component scores were also examined in relation to whether the woman had ever been treated for depression or anxiety (response on MBQ, n=198 had been so treated). Component scores tended to be *higher* if the woman had ever been treated for either of these conditions. There were significant associations for 'impact of volume', 'containment distress', 'irritable/unwell during period', 'resource consequences' and 'periods a burden' (Mann Whitney z = 4.0, 3.4, 3.4, 3.3, 2.6 respectively; p= <0.001, 0.001, 0.001, 0.001, 0.009; n= 578, 559, 578, 578, 559). Therefore in this clinic population the higher the component scores for 'impact of volume', particularly, and also for the other components listed, the more likely the patient is to have a past history of treatment for depressive or anxiety illness.

'COMPLAINT OF MENORRHAGIA'

There has been consideration of the relative merits of various variables as representing 'complaint of menorrhagia', and of the possibility that complaint of menorrhagia could be reflected by one or more of the component scores. It would therefore be of interest to examine the component scores in relation to the various menorrhagia complaint variables so far considered: referral reason (given by GP and self-stated by the woman), citation of volume aspect(s) of bleeding as cause of help-seeking, and subjective report of periods as 'very heavy'. Comparisons were made by Mann-Whitney, and the components which were most 'discriminating', in the sense of having most clear-cut differences between subgroups formed by the binary 'complaint' variables, are shown in **Table 9.17**.

All four 'complaint' variables' show greatest discrimination for containment distress scores, and next greatest for either impact of volume or variable flow. 'Very heavy' loss (or not) shows the strongest discrimination in 'containment distress' and 'impact of volume' scores. Self-stated bleeding shows next best discrimination of these component scores, but in addition is best at discriminating scores on 'variable flow' and 'had enough of periods'. GP referral for bleeding is least effective at discriminating 'had enough of periods' but best at discriminating 'worry'. Citing volume of bleeding as reason for help-seeking appears to be indicative of

'containment distress' and 'variable flow', with less discrimination for 'impact of volume', 'worry' and 'had enough of periods'.

Table 9.17 Comparison of component scores by 'complaint' or not, for four variables considered as 'complaint of menorrhagia'

	'Complaint of menorrhagia'							
	'Very heavy' loss		Bleeding as self-stated reason for clinic visit		Referral by GP for bleeding		Volume cited as cause of help-seeking	
Component *	z^+	p	z^+	p	z^+	p	z^+	p
Containment distress	12.0	<0.001	8.6	<0.001	6.6	<0.001	6.3	<0.001
Impact of volume	9.3	<0.001	6.8	<0.001	5.5	<0.001	3.3	0.001
Variable flow	6.7	<0.001	7.7	<0.001	6.4	<0.001	6.6	<0.001
Had enough of periods	5.0	<0.001	5.6	<0.001	2.7	0.008	2.7	0.006
Worry re change	3.8	0.001	2.6	0.009	4.5	<0.001	2.8	0.005

\+ *z score for Mann-Whitney non-parametric comparison of scores in the two subgroups*

* *n=687 except for 2nd and 3rd row components where n=721*

9.3.4.ii Is measured menstrual loss associated with component scores?

If menorrhagia complaint is about excessive menstrual loss then it would be expected that volume of menstrual loss would be associated with component scores most closely reflecting volume/'complaint'. Non-parametric correlations of measured volumes with component scores were calculated, and all those where $|rho| \geq 0.15$ are presented in **Table 9.18**.

None of the correlations is very strong, but the strongest are with the components 'impact of volume' and 'containment distress'. Volumes are inversely correlated with components 'unwell/irritable' and 'unpredictable onset', so the higher the scores on these components the less likely the woman is to have high menstrual volume. It is noteworthy that menstrual volumes were associated with only 5 out of the 10 components, and that 4 of the 5 are 'dealing with periods' rather than 'feelings about periods' components.

Table 9.18 Association of principal component scores with measured menstrual loss volumes

	PCd * Impact of Volume rho+	PCf * Contain. Distress rho+	PCd * Resource Consequ. rho+	PCd * Unwell/ Irritable rho+	PCd * Unpred. Onset rho+
Blood Volume (mL)	0.22	0.26	0.15	– 0.16	– 0.16
Total fluid vol. (mL)	0.21	0.23		– 0.15	– 0.18

* *PCd = principal components 'dealing with periods' and PCf = components 'feelings about periods' (PCs derived from MEQ data - see* ***5.3.1.iv)***

\+ *Spearman correlations |rho| ≥ 0.15; for PCd n= 189,190 for total fluid and blood volumes respectively, for PCf n=190, 191; p<0.04 for all.*

9.3.4.iii *Associations between the two sets of principal components*

The two sets of principal components, 'dealing with periods' and 'feelings about periods' were obtained by independent analyses of separate multi-part questions (MEQ questions 22 and 23 respectively). Within each set the method used to extract and rotate components means that the 5 components in that set are orthogonal (not correlated). However, there may be correlations between components in different sets. Data presented so far suggests considerable similarity between 'impact of volume' and 'containment distress', and also some similarity between the two components addressing resource use. Correlations were calculated between the two sets of components and all correlations |rho| ≥ 0.2 are presented in **Table 9.19**.

The strongest correlation was as anticipated between 'impact of volume' and 'containment distress' (0.65). The other strong associations between pairs of components have been highlighted in bold. ('Unpredictable onset' is not included in the table as it was not associated to this degree with any of the feelings components.)

Table 9.19 Associations between the two sets of principal components

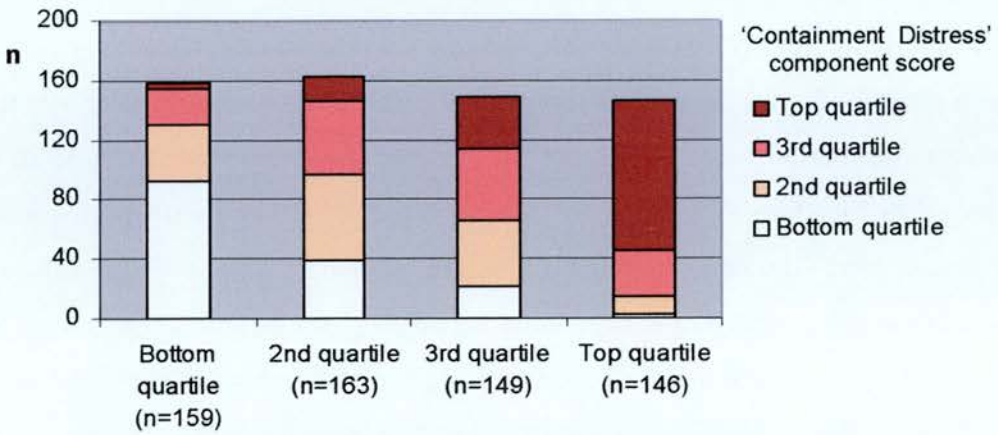
'Feelings about periods' components	'Dealing with periods' components			
	Impact of Volume rho+	Variable Flow rho+	Resource Consequences rho+	Unwell/ Irritable rho+
Containment distress	**0.65**	**0.31**	0.21	
Resent resources			**0.49**	
Worry re change		**0.52**		
Feel periods a burden	0.28			**0.62**
Had enough of periods		0.22		0.21

\+ *Spearman correlations /rho/ ≥ 0.2; n= 617; all p<0.001; 95% CI within 0.08 either side.*

Despite the strong association between 'impact' and 'containment distress' there were women with high scores on one component and low scores on the other, and vice versa. This is illustrated in **Figure 9.12**. Of those in the highest quartile for 'impact of volume', 10% (of 146) were nevertheless in the lower half of the distribution of containment *distress* scores (bottom two quartiles). This suggests that despite the extreme containment situation they were experiencing with their menstrual flow these women had not developed a strong emotional reaction to it. Similarly, of those in the third highest quartile for impact, 15% (of 149) nevertheless had containment distress scores in the lowest quartile.

Conversely, of those in the lowest quartile for 'impact' score, 18% (of 159) nevertheless expressed containment distress in the upper half of the distribution of scores for that component. This suggests that despite their flow not apparently posing a major containment challenge (relative to the study group), these women were expressing a strong emotional reaction to the containment imposition resulting from their periods. Similarly, of those in the second (lowest) quartile for impact, 10% (of 163) nevertheless had containment distress scores in the highest quartile.

Figure 9.12 Distribution of 'Containment Distress' scores within subgroups of 'Impact of Volume' component scores



9.4 DISCUSSION

9.4.1 Complaint and referral

There was striking discordance as to the rationale for referral to gynaecology clinics. In over a quarter of cases the patient and general practitioner disagreed as to whether excessive menstruation was a reason, with the doctor four times more likely to be the only one citing bleeding. Approximately equal proportions of women reported severe problem with pain, volume of loss or cycle-related changes (37% to 40%), with considerable overlap, and yet the predominant reason given for referral was bleeding problems (76%). Furthermore this tendency for general menstrual complaint to be re-framed as excessive bleeding appears to intensify within the clinic setting. Dysfunctional uterine bleeding is defined as '*excessive uterine bleeding* for which no pathology can be found' (Fraser & Inceboz 2000). Yet diagnosis of dysfunctional uterine bleeding was made for 35% of women who had *neither* cited excessive bleeding as a reason for attendance *nor* as a severe problem. Similarly, it was made for 30% of women whose doctors had *not* given bleeding problem as referral reason. Variation in menorrhagia referral rates has been taken to reflect 'clinical uncertainty about whether and how the problem should be treated' (Coulter 1995). Our data suggest clinical uncertainty about the very concept of menorrhagia.

9.4.2 Measured menstrual loss

9.4.2.i Associations with blood loss volume

It has been shown that the clinical features most strongly associated with blood loss volume are: required rate of changing sanitary protection during full flow, total number of products used, poor iron status, size of clots, and need to change protection during the night. Other studies have found associations with number of products (Fraser et al. 2001; Higham & Shaw 1999) and that with iron status is well known (Gao et al. 1981; Hallberg et al. 1966; Haynes et al. 1977; Higham & Shaw 1999; Hope 2000; Janssen et al. 1998). It is noteworthy that these features are not purely subjective, but either based on an objective test result (ferritin), or 'operational' (e.g. changing *rate* and clot *size*) and therefore less prone to

measurement 'error'. In addition, strong evidence was found that volume of loss was related to women's subjective judgement. Those rating their periods as 'very heavy' had mean blood loss that was 61% higher than for the remainder (95%CI 23% to 110% higher). This is all the more striking given the restricted range, among collectors, for subjective rating of periods - essentially just heavy or very heavy. Hallberg commented, based on inspection of a graph of measured volume against light/medium/heavy subjective ratings, that "The difficulties of evaluating the menstrual blood loss on the basis of patient's own judgement are well known. The results obtained in the present study emphasise this fact" (Hallberg et al. 1966). This study is now often cited in support of the belief that women are poor judges of their loss volumes, for example (Irvine & Cameron 1999). Two critiques could be made. One is that the judgements of loss were *elicited symptoms* in a community survey, and therefore these findings can not be extrapolated to the clinical situation. The second critique hinges on the fact that calculation of the correlation from that graphed data reveals very strong evidence *for* an association in that study between heaviness and volume (rho=0.34, n=474, p<0.0001) (Warner 1998), stronger even than in the study reported herein (rho=0.24).

Taken overall our findings suggest that women's success in judgement of loss is relative, and not calibrated to the clinical definition of menorrhagia. This is unsurprising, given that few think of their periods in volumetric terms. When required by a later questionnaire item to rate their usual period in terms of options formulated in volumes (teacup, mug, much more), the majority of women instead opted for the fourth response available, 'no idea' (55%). Still fewer women know of the clinical importance of the 80mL threshold for blood volume, nor that their menstrual blood loss is only about half by volume of the total menstrual loss, due to a non-blood component (Fraser et al. 2001).

Given the consensus view that measurement of blood loss is not practicable in routine clinical care, the question arises as to how feasible it is to judge menorrhagia from clinical/menstrual history. Our data suggest that management is minimally related to measured volume of blood loss. In the absence of any identifiable pathology, dysfunctional uterine bleeding is virtually a default diagnosis, and is

unrelated to actual loss. A similar picture is found for management of patients *without* fibroids, as judged by performance of hysterectomy or not. Blood loss measurements were not entered in patient notes, so either clinicians were unable to make a judgement of loss from the clinical history, or they could, but felt volume of loss had little bearing on management or diagnosis.

When menorrhagic blood loss (of 80mL or more) was modelled statistically, 76% prediction success was achieved by a model including clots greater the 50p in size, 'low' ferritin result, and rate of change of sanitary protection. However, given that predictive performance is ascertained against the same data that were used to derive the model, this is likely to be an optimum figure of model performance. On the other hand, the model is making predictions based on clinical history, and for a substantial number of women (36%) the amount of loss for the period subsequently collected was stated to be much less than the 'usual' described in the questionnaires. This unusually low loss will not so clearly reflect the predictors reported (for the usual heavy periods), so this sets the predictive model an almost impossible task, and a statistical 'false positive' in this analysis may in fact be a clinical true positive, for the woman's other periods. This was confirmed by the much stronger associations found for measured volumes with prospectively recorded details of product usage, duration or period, clots and adaptations to activities. It was also noticeable that the correlations with prospective data were much stronger for duration of period and product usage (likely to be more directly the physical manifestation of a specific flow) than with cancelled activities and leakages (which must involve an element of individual coping with that flow, and which is likely to reflect context – home circumstances/lifestyle/employment).

9.4.2.ii Utility of the 80mL menorrhagia definition

The most striking finding is the clinical irrelevance of the established definition of menorrhagia, blood loss in excess of 80mL. While there is a significant trend for difficulties with containment of flow to become more prevalent with increasing blood loss volume, this effect is largely due to the heaviest and lightest loss groups, whereas the two groups with loss either side of 80mL are virtually indistinguishable.

A similar pattern is observed for iron status, for diagnoses and for management. Our data confirm that the 80mL cut-off point does not convey any especial prognostic information: the 35% of collectors with losses between 50 and 119mL are fairly homogeneous with respect to difficulties with containment of periods, compromised iron status, pathological findings and management. This finding concurs with qualitative research findings among women with complaint of menorrhagia (Marshall 1998; O'Flynn & Britten 2000).

9.4.2.iii Associations with total menstrual fluid volume

The associations of prospectively rated features of the period, and changes in impacts of period from usual, were stronger with total fluid volume than blood loss volume. This is similar to the impression gained with other variables in previous research (Fraser et al. 2001). Given the conceptual appeal of measuring the actual menstrual loss, rather than a variable sub-component of it, and the more reliable and very much simpler methodology involved, it is surprising that total fluid measurement has not been more widely adopted.

9.4.3 Subjective menorrhagia complaint

Clinical menorrhagia complaint is clearly defined. With regard to subjective menorrhagia complaint, judging by the confirmatory assessments that have been applied it appears to have been assumed it is the woman's judgement of excessive volume of loss. But is it? Subjective complaint may reflect adverse impact on daily life through difficulties containing flow, or concern about other symptoms attributed to periods, such as tiredness, and indeed this has been shown in qualitative research (Marshall 1998; O'Flynn & Britten 2000). The problem may be acute unmanageable flow in the first day or so rather than total volume over the entire period, as gushes within the context of a less than excessive volume can cause accidents and social disability. It could be that a *change* in periods has been noted (Marshall 1998; O'Flynn & Britten 2000; Rees 1997), and which is causing concern that something sinister is wrong, particularly if periods have become more or differently painful. In support of this it has been reported that increase in amount of period was a more prevalent problem than absolute volume of period. To explore the nature of

subjective menorrhagia complaint four variables that could be construed as reflecting the complaint have been modelled in terms of the menstrual data collected in this study.

9.4.3.i Are 'very heavy', 'volume cause of help-seeking', and/or referral for heavy bleeding stand-ins for menorrhagia complaint?

'VERY HEAVY' AND VOLUME AS 'CAUSE' OF HELP-SEEKING

'Heavy' is not unequivocally an adjective denoting volume, so women describing their periods thus may well be conveying something more or other than the volume of their periods. This was supported by modelling analyses, since 'very heavy' was more strongly associated with containment aspects of volume rather than volume per se. However, *increase* in volume was important to the judgement 'very heavy', and so were (feelings) component scores regarding containment distress and burden of periods, and being unwell with the period.

Citing volume aspects of periods as 'cause' of help-seeking was thought to be conceptually closest to the clinical definition of menorrhagia complaint, and this opinion was supported by the findings. This model showed strongest association with volume variables (but not increase in period) and 'very heavy', but no positive associations with feelings about periods. (Interestingly, even if quality-of-life variables were offered none were helpful to this model.) However, this was the least satisfactory of the models in terms of fit.

Together these models suggest that very heavy is a broad judgement which does not depend mainly on absolute volume and is tied in with feelings about periods as currently experienced. Citing volume as cause appeared to reflect the clinical menorrhagia definition better, and more 'purely', but the judgement could not be reliably characterised by the available variables.

EXCESSIVE BLEEDING AS REASON FOR REFERRAL

Both models (GP and self-stated) were adequate and performed well overall (81%). They were most strongly associated with volume variables, but also with *increase* in period (the latter a particularly strong association for self-stated bleeding reason). The model for self-stated bleeding reason performed better than that for GP reason, in the sense that the GP model found it difficult to predict those not referred by GP for bleeding (39% success). However, this was a small subgroup in this sample, so arguably it was not well-characterised by the data. The GP model showed no very strong associations and none with feeling about periods, whereas the self-stated model was strongly associated with citing volume cause of help-seeking, heaviness, having had enough of periods, increase in period and containment distress.

OVERVIEW OF 'STAND-IN' COMPLAINT VARAIBLES

The impression gained is that citing volume as cause of help-seeking ('volume complaint') is closest to the clinical definition of menorrhagia, being focused on absolute volume and free of association with impact and feelings. However, neither the clinical menorrhagia complaint nor this 'volume complaint' reflect qualitative research findings for menorrhagia (Marshall 1998; O'Flynn & Britten 2000) .

The next closest was GP referral for bleeding ('GP-judged complaint'), which was free of emotional overlay, but did reflect *increase* in period, containment, duration and variable flow, which are not necessarily features of absolute volume. The remaining two models were fairly similar, except of course one was addressing a judgement about loss (heaviness), and the other a reason for a health-care encounter (lay complaint). 'Very heavy' captures volume and increase mainly, and incorporates associated symptoms and emotional reactions to periods. Self-stated bleeding reason ('lay complaint') captures heaviness and volume/increase *causes* of help-seeking, mainly, plus emotional reactions to periods. In addition lay complaint reflects poor facilities at home for dealing with periods.

For all models except 'volume complaint' older age was included in the model. This suggests a reproductive-life-stage effect on heaviness, and GP-judged and lay

complaint of menorrhagia, but not for 'volume complaint'. Increase in flow was important to heaviness and lay complaint, while duration and variable flow were important to GP-judged complaint.

9.4.3.ii Do principal component scores 'describe' complaint?

OVERVIEW

An alternative conceptualisation of subjective menorrhagia complaint is in terms of the principal component scores derived from responses to MEQ questions 22 and 23. Such principal components are believed to reflect underlying processes that have given rise to the observed data. Thus the components represent structurally important dimensions of variability for experience of periods and clinic attendance. As such they, or a subset of them, may well encapsulate 'menorrhagia complaint' from the woman's point of view.

Firstly the component scores were examined univariately in relation to demographic, menstrual, quality-of-life and health history variables. Much of the pattern of correlations would have been anticipated from results already reported, but this exercise helped to elucidate the distinction between the components 'impact of volume' and 'variable flow' (both are accounts of menstrual experience rather than emotional reactions to it). 'Impact of volume' component was most strongly associated with the aspects 'impact on daily life' and 'difficulty avoiding accidents', and to a lesser extent with a range of volume and containment variables. In contrast the 'variable flow' component was more strongly associated with all three volume aspects, most particularly 'going on too long' (the strongest correlation at 0.65) and increased loss. Particular differences between the two were that 'impact' only was correlated with duration of problem, pain with periods and feel unwell/tired, whereas 'variable flow' only was correlated with going on too long (see above), days full flow, days duration of period, bleeding between periods and parity.

VOLUME VERSUS VARIABILITY

Judged against an absolute criterion, only 34% of collectors had menstrual blood losses exceeding 80mL. This may be partly explained by period-to-period variability,

which has been demonstrated before in studies where women collected for more than one period (Baldwin et al. 1961; Cole et al. 1971; Fraser et al. 2001; Haynes et al. 1977). Ours is the first study to ask if the period collected was representative of periods as reported (in the questionnaire). For 36% of women the period collected was 'much less than usual', and this was substantiated by a lower measured volume in this subgroup. Considering only collected periods deemed to be much as usual, the strong associations of greater volume with older age and increasing parity replicate findings of a clinical study (Higham & Shaw 1999) and population research some years ago (Cole et al. 1971). Both studies also found an association of greater losses with having delivered heavier babies, which may partly explain our finding of heavier losses in the more affluent women. The observation in the present study that older parous subgroups were prone to heavy losses and marked variability in volume suggests a distinct subtype of 'menorrhagia complaint'.

A 'normal' volume for the period collected, if due to variable loss, does not necessarily invalidate complaint. It has been found that where variable losses occur it is the heavier periods which are most representative of complaint (Fraser et al. 2001). Excessive periods every few months may be more worrying than consistent losses, and are almost as disabling, as every period has to be anticipated as if it might be one of the heavier ones. Was this notion supported by these data?

The impression gained above, of two subtypes of menorrhagia complaint, was reinforced by other differences found between the two components. Of the two, only *impact of volume* was associated with (any) quality-of-life scores, with the number of minor symptoms reported for the last two weeks, past treatment for depression, *and* with measured volumes. It was correlated with all four putative complaint variables, but most strongly with 'very heavy', and of the five feelings components it was most strongly correlated with 'containment distress'. In contrast, *variable flow* only was associated with number of past D&C's (and was not associated with minor symptoms, depression, quality-of-life *nor* measured volumes). It was equally correlated with all four putative complaint variables, but for 'volume complaint' it was the component most strongly associated. Of the five feelings components it was most strongly correlated with 'worry re change' (and indeed it was the only 'dealing

with periods' component correlated with the worry component). Further study to obtain a better understanding of the two subgroups with high scores on the two different components could be illuminating.

9.4.4 Overview

Our data suggest that it is not just the 80 mL criterion that should be challenged, but also the idea that *volume* of blood loss captures the essential nature of the prevailing complaint of heavy periods. While our data do not support the wide-spread clinical belief that women are poor judges of their volume of menstrual loss, they do raise doubts about the calibration to 80mL. Furthermore, the findings raise doubts about volume being key to complaint.

Various explorations of stand-in complaint models showed only 'volume' complaint seems to reflect clinical menorrhagia (focused purely on volume). However it does not reflect the complaint themes running through all the analyses (and previously published qualitative research) - increase in loss, containment issues, emotional reaction to the periods, disordered flow. Also, paradoxically, the 'volume' complaint is only modestly associated with measured blood volume (rho = 0.014, compared to 0.23 for 'very heavy'). Part explanation of this may be that 'volume complaint' was most strongly related to the variable flow component. Perhaps the poor showing in terms of volume is because a number of women in this complaint group had one of their non-heavy periods for the collected period. A similar picture emerges if the examination of complaint is through the principal component scores, with 'impact of volume' and 'variable flow' in place of 'very heavy' and 'volume complaint' respectively.

This presents something of a dilemma. The patients whose 'volume complaint' profile best matches clinical menorrhagia, have variable periods and so are relatively unlikely to confirm menorrhagia objectively on one measured period, or on the average of more than one. In contrast, those whose periods are most reliably of relatively large volume, those with 'very heavy' periods, are not so much concerned about the volume of their periods but about change in loss, containment issues, clots, associated symptoms and how they feel about their periods. Surely both complaints

are worthy of a gynaecology response. This sub-grouping of menorrhagia complaint would offer scope for aetiological hypothesis generation. This in turn may lead to the development of new interventions, possibly more holistic.

9.5 SUMMARY

9.5.1 Pathway to clinic

- There was discordance between GP and self stated reasons for referral to gynaecology clinic, where this occurred GPs were 4 times as likely to cite bleeding and half as likely to cite pain.
- Fewer than 46% of those referred for excessive bleeding had noted volume as a cause of help-seeking.
- Diagnosis of dysfunctional uterine bleeding was made for over a third of women who neither reported periods as subjectively very heavy, *nor* reported excessive loss as severe problem, *nor* gave bleeding as reason for clinic visit (35% of 165).
- Examination of diagnosis and hysterectomy data suggests that clinicians either find it difficult to judge volume from the clinical history, or do not consider volume as key to management. Among those without fibroids, hysterectomy was strongly associated with *referral* for bleeding, but was only marginally associated with reporting volume of loss a severe problem.

9.5.2 Measured menstrual loss

- Volume of blood loss was strongly associated with rating loss 'very heavy' (volume 60% higher), and weakly associated with age and inversely associated with parity.
- Volume of blood loss over 80mL could be predicted (76% success) by clots, low ferritin result and changing rate needed during full flow.
- The 80 ML criterion is of dubious clinical utility as it is neither sensitive nor specific for adverse impact of periods, compromised iron status, or for pathology. There were no marked differences in volume, accidents, impact and containment variables, iron status or clinic outcome for blood loss groups on either side of the 80mL threshold (50 to 79mL v 80 to 119mL).
- Volumes were more strongly correlated with prospectively recorded (Menstrual Chart) parameters, than with retrospective CQ and MEQ data, and total fluid volume was more strongly correlated than blood volume.
- Of those collecting, 78% stated that the period was less or much less than usual, and these women had lower blood volume than the remainder of collectors.

9.5.3 Menorrhagia complaint

- Modelling of 'citing volume as cause of help-seeking' (volume complaint) showed it to be associated almost solely with aspects of volume.
- Modelling 'very heavy' periods showed that this reflects containment aspects of volume more than volume per se, *increase* in period, symptoms and feelings about periods.
- Both models for reason for referral (GP-judged complaint and self-stated or 'lay complaint') were most strongly associated with volume variables, but also with *increase*.
- Increase in flow was important to heaviness and lay complaint, while duration and variable flow were to GP judged complaint.
- Examination of associations for the two sets of principal components (dealing with periods and feelings about periods) revealed two subtypes of 'menorrhagia complaint':
  - *impact of volume* was associated with rating periods very heavy, measured volumes, aspects 'impact on daily life' and 'difficulty avoiding accidents', quality-of-life scores, number of minor symptoms reported in past 2 weeks and past treatment for depression, and was strongly associated with feelings component 'containment distress'.
  - *variable flow* was *not* associated with measured volumes, 'impact on daily life' aspect, period pain, quality-of-life scores, number of minor symptoms in past 2 weeks, nor past treatment for depression, but was strongly associated with all three volume aspects (most particularly 'going on too long'), count of severe problems with volume aspects, *increased* period and 'volume cited as cause', and furthermore, this (variable flow) component *only* was associated with duration of period, number of days full flow, number of past D&C's, and with the feelings component 'worry re change'.

Chapter 10

DISCUSSION AND CONCLUSIONS

10.1 DISCUSSION

There has been discussion of findings and methods throughout the data chapters. The aim of this final chapter is not to reprise the earlier discussion, but rather to discuss key points drawing on and integrating the findings and discussion of the earlier chapters.

10.1.1 Methodological issues in menstrual research

The study design and methods will be discussed under 4 sub-headings: the design, the sample, the questionnaire measures used, and quantification of menstrual loss. Within each section limitations will be considered.

10.1.1.i Design

The embedding of the menstrual collection study within a cross-sectional survey provided comprehensive background data on all women with measured menstrual loss. This is relatively uncommon in menstrual research, but has proved illuminating. What has been revealed is a picture of poor health status among many women referred to gynaecology clinics, with wide-spread experience of multiple minor general health symptoms, a high rate of chronic health problems and overweight/obesity and, often, multiple menstrual morbidity, typically over many years.

The wider survey also made it possible to ascertain that those who agreed to collect were in terms of the main socio-demographic characteristics similar to those eligible to collect who declined. To have such an epidemiological context for clinical menstrual research is rare, despite the important part this should play in interpreting findings and comparing them with other studies. If we imagine the hypothetical but possible situation that the two centres within the present study had instead been two independent studies following very similar protocols, but neither ascertaining the extent of background information that the present study actually has, then it would be almost impossible to make sense of differences in the research reports that would have emerged from the two 'studies'.

The two-centre aspect of our study design has brought both pain and pleasure. The very disparate socio-demographic and health profiles of patients at the two centres, and even more so the differences that emerged in the blood loss determinations, have complicated analysis and reporting, and diminished power. However, they have led to new insights about associations and disassociations in the study material, and have also revealed some very important methodological issues. So what could have been construed as a weakness has proved to be a bonus, maybe even a strength, not just for the present study, but also in alerting to potential dangers for menstrual research generally.

The study design meant iron status data would have been gathered only for those patients where the clinician had some concern about iron status, or some suspicion that periods were not that heavy and so wished to rule out adverse impact on iron status. While this observational approach ensured usual clinical practice was unaffected, minimising bias in management and outcome data, it also resulted in sparse data. In fact clinical management and outcome data were not a key part of this study, so preservation of their integrity at the expense of iron testing coverage was not such an advantage. With hindsight it would have been better to ensure resources were available to test all participants, except where such imposition would be the reason for an individual patient to decline to participate. It is likely an ethical case could be made for this, given the clinical concern that heavy periods have adverse impact on iron status and hence health and well-being, and the high prevalence among participants of 'feeling tired', and because such tests have a potential use as a screening tests for physiological health concern, provided good evidence could be produced to elucidate this issue.

10.1.1.ii Study sample

It had been noted in earlier research (Warner 1995) that there was some discordance between referral reason and subjective report of periods. It was therefore felt that a survey of menorrhagia, in the sense of troubling heavy periods, should not be confined to patients referred with this complaint by general practitioners, otherwise covert menorrhagia problems may be missed. In the event it was found that in this

study there was substantial discordance between referral reasons given by GP and the patient's self-stated reason for clinic attendance, or her report of heaviness (Warner et al. 2001). It was thus a wise precaution to have included in the study all women with putatively heavy periods, and not to have depended solely on referral letter to identify the study sample.

The intention of confining study to women newly-referred to gynaecology clinics had a sound rationale. A third of women in the study had attended a gynaecology clinic before, three-quarters of them for the 'same problem'. Median time from previous attendance was 3 years. Many had a history of a range of period problems (75% reported a past severe problem with heavy periods, 58% with period pain). So, women with 'intractable' problems were not entirely avoided. Indeed the data suggest that recurrent and serial menstrual problem is something of a feature of the gynaecology clinic population. A very small proportion of women were recruited despite clearly failing the criterion of one year since last attendance (2% had less than 10 months since last visit). However they were retained in the study as it was felt that they were so few in number as to have small potential for biasing findings. However the exclusion criterion did on the whole avoid the surveying of repeat-visit existing patients with, for some reason, delay to discharge. By defining 'new referrals' as those who have not attended the clinic for the same problem in the past year it was ensured the study would better reflect the entire throughput of patients referred to gynaecology clinics with period problems, and an over-representation of atypical patients, needing multiple appointments over an extended period before they could be discharged, was avoided.

10.1.1.iii Study measures

Multiple questionnaires were included in the design to address the many and varied causal attributions that have been advanced in the literature for women's menstrual complaints, and because of the aim to develop an assessment of the impact of menstrual problems on daily life. There was also a need to be able to compare findings with research already published. However, not all women participating were

able to complete all the questionnaires, and there are therefore concerns about missing data.

Furthermore, for this thesis space has not allowed analysis and reporting of all study data. Intriguingly, there are a number of findings already identified that would probably benefit from further elaborative analyses taking personality data or psychological well-being data into account. For example, the discordance observed between scores on 'impact of volume' and 'containment distress' may be explained by personality. Women susceptible to negative affectivity are likely to predominate in the subgroup with modest scores for containment challenge (impact) but disproportionately high scores for containment *distress*, so perhaps a different management approach would be helpful in that subgroup (Watson & Pennebaker 1989).

Despite the perhaps over-ambitious use of questionnaire assessment, the study does enable multivariate analyses of psychosocial variables, subjective menstrual variables and objective measurements, and these will inform future 'leaner' but effective and pertinent research design.

10.1.1.iv Quantification of menstrual loss

MENSTRUAL BLOOD LOSS MEASUREMENT

The methodological fragility of menstrual blood loss measurement has been demonstrated. Small perturbations to technique can have profound effects on volumes ascertained. Even where the technique used is optimal and consistent, the nature of the exercise (taking a ratio of two haematin concentrations, which are themselves regression estimates from optical densities) means that imprecision for individual measurements will be substantial. This makes it frankly 'unsafe' to measure blood volume to compare against an absolute criterion value. The methodological concerns will be much less for within-patient studies where repeat measurements are made on the each patient to assess treatment response, prior to averaging responses for the group, since any systematic laboratory effect will be eliminated when the difference is taken between the before and after measurements, and the 'grouping' will generate precision in estimation of the *group* effect.

(However, with regard to a dilution strategy that tends to result in large errors in both directions, as was also the case in Glasgow, this would remain, and tend to inflate experimental error and reduce power to detect treatment effect.)

Incomplete collection of menstrual loss has been proposed as a possible contributory factor for failure to confirm menorrhagia(Wyatt & O'Brien 2000). There have recently been attempts to allow for this when measuring blood volume, by adjusting for blood lost to the collection, because of clots or blood leakage into the toilet, or onto clothes or bedding (Hurskainen et al. 1998). Among 154 women recruited into a menorrhagia treatment trial the average adjustment to volume judged necessary, based on diary recording of uncollected menstrual loss, was an increase of 20mL. For many women the adjustment made was a surprisingly high proportion of the blood successfully collected, 57% in one case. The validity of the adjustments made was not demonstrated, so reassurance is required as to the rigour of this approach (Hurskainen et al. 1998).

Two reservations need to be expressed about this development in objective measurement menstrual blood loss. Firstly, even if the adjustments made could be by chance *exactly equal* to blood missed from the collection, the rationale for such adjustments is flawed. The volume criterion for menorrhagia was originally derived in terms of statistical abnormality, as judged from a population distribution of *unadjusted* menstrual collections (Hallberg et al. 1966). It can thus be properly applied only to other unadjusted measured volumes.

Secondly, if over half the 'measured volume' can arise from adjustments based on *subjective* accounts of clot size and leakages, then the 'objective' label begins to look distinctly threadbare.

TOTAL MENSTRUAL FLUID VOLUME

In this study total fluid volume measurement was undertaken in a very pragmatic way, without weighing of individual products prior to use. It was anticipated that this would inflate random error, and this seemed to be confirmed by the lower R^2 for the regression model, than had been obtained in previous research (Fraser et al. 2001). (However, it should be remembered that diminished fit could arise equally, or partly,

if the blood loss measurements in this study were more error-prone than in the published study.) Nevertheless, in simple univariate analyses relating volumes to prospectively-recorded Menstrual Chart data about products used, leaks and cancelled activities, total fluid volume was marginally more strongly correlated with them, than blood volume (**Table 9.7**). Furthermore, the goodness-of-fit of models for predicting total fluid and blood volumes from Menstrual Chart product/soaking pictogram data were very similar (**6.3.3**), and the fact that no coefficient for centre was needed for total fluid prediction reassures that there was no systematic difference in measurements between the two centres. If menstrual loss measurement is required, total fluid measurement is the far more attractive proposition, conceptually, methodologically and also, it seems, in terms of utility.

MENSTRUAL CHARTING

Menstrual charts have been developed with the aim of establishing an alternative method of quantifying menstrual blood volume. This has been driven not by a wish to circumvent the methodological dangers of blood loss measurement, which have been largely unrecognised, but rather with the main aim of avoiding collection and handling of used sanitary products, which is disliked by patients and laboratory staff. Previously published charts have used a score per pictogram, summed over all products used, with the total score being either the PBAC score, where a score of 100 equates to 80mL blood loss (Higham et al. 1990; Janssen et al. 1995), or converting directly to millilitres of blood (Wyatt et al. 2001). In this study it was found that such a 'summation' model does not fit the data distributions. Both pictogram counts and volumes need to be log-transformed for best regression analysis, and this means that the model that fits the data is, once back-transformed, exponentiated. This finding may explain the observation that all three published charts have shown increasing bias error between menstrual chart estimates and actual measured volumes, with increasing volumes.

The modelling analyses presented in this thesis show that the menstrual chart provides a less good estimate of blood volume than total fluid volume. Therefore the menstrual chart is even less likely than objective measurement to provide a precise enough estimate of true volume for use in the management of the individual patient.

However, it has the potential to provide rich information about the menstrual experience, and this may prove very helpful for discussion between patient and clinician. Some women, particularly those in the more deprived areas, were unable to complete the menstrual chart. If the menstrual chart was freed from its aim to quantify menstrual blood loss, it could perhaps be made much easier to complete, and clinically more useful.

10.1.2 Reconsidering menorrhagia

10.1.2.i What is menorrhagia?

MENORRHAGIA DEFINITION

The origin of the clinical (objective) definition of menorrhagia has already been explained. The criterion of 80 mL delimits the 3%-4% of the 'healthy' population with greatest loss. It does not reflect impact on health or well-being. The clinical utility of a definition depends on how predictive it is of adverse effects or pathology, or how much it aids management.

Our data show that for the vast majority of women referred with 'heavy periods', the 81% with losses up to 119 mL, the precise volume of loss is immaterial. About 10% will have fibroids, compromised iron status, or problem with impact on daily life; around 20% will have some pathology; and about 40 to 70% problems with containing flow.

RATIONALE FOR QUANTIFICATION OF MENSTRUAL LOSS

The first issue to be determined is the *point* of measurement. Does the woman have to prove her malady, before she can be provided with health care? Or is it that her menstrual blood volume is crucial to the management of her complaint? Or does the measurement enhance understanding of the complaint, so promoting improved communication about the problem between doctor and patient?

The main driver for blood loss determination appears to be that it can provide an objective confirmation of menorrhagia complaint. However, validity in terms of measuring menstrual loss volume, either total fluid or blood, whatever is decided as

relevant, is not necessarily the same as validity in terms of 'measuring' menorrhagia *complaint*. Measurement of blood volume has been possible for only six decades whereas problems with 'heavy periods' have been documented going back nearly six millennia. It is unlikely menorrhagia has ever been solely or even mainly about volume of blood loss.

A further factor militating against prospective measurement of *menorrhagia complaint* is the delay this imposes on commencement of medication which may alter (indeed, is intended to) that which is to be measured. In the case of a woman who has waited many months for an appointment at a gynaecology clinic, it is hardly humane to delay intervention for a further 6 weeks to allow quantification for the complaint. Furthermore, for women with variable losses, the measured period may not be one of the troublesome ones. In this study 80% of women reported the collected period was less or much less than usual (so, presumably, no longer representative of the complaint).

Over and above this issue, if women's accounts of their complaint can not be trusted and must be confirmed objectively, then what value can be placed on their unconfirmed record of products/soaking, clots and leakages (as would be supplied in a menstrual chart, or in the case of the latter two eventualities, used to augment the measurement) (Hurskainen et al. 1998; Wyatt et al. 2001).

10.1.2.ii Healthcare for menstrual problems

Many women are deterred from consulting at all, by reticence about discussing menstrual problems, anxiety about investigations, or a lack of belief that medical help will be forthcoming (Scambler & Scambler 1985). Health needs that remain unvoiced within the consultation have been related to poor outcomes (Barry et al. 2000).

Referral for menstrual problem

It was found that there was substantial discordance between referral reasons given by GP and patient. The GP referral reason was more likely, than the patient perception of reason for clinic attendance, to be excessive bleeding and, conversely, less likely

to be pain. On the other hand there were women with periods self-rated as very heavy, or who cited excessive bleeding as cause of help-seeking, who were not referred for excessive bleeding. Of course some of these may have been specific cases where the GP was concordant with the patient in knowing the 'complaint' to be excessive bleeding, but because he/she suspected the cause of the bleeding to be fibroids, fibroids was given as the referral reason, which would have been coded as 'other'. However, in terms of the general trend, we should question why this is happening and whether it affects the quality of health care women receive? Perhaps the partitioning into distinct and specific menstrual problems does not reflect the way women experience their periods, nor how menstrual problems are perceived by them.

Where there is co-morbidity between menstrual complaints it may seem unimportant which is selected as referral 'reason'. However, the divergence between menstrual experience and reasons given for clinic attendance reflects a disproportionate focus on the biomedical symptom of excessive bleeding, a tendency which is echoed within the clinic setting. Is this re-framing partly a consequence of *women's* beliefs that abnormal uterine bleeding is most worthy of medical attention? Or is there an astute lay understanding of what will be regarded *by others* as a valid reason for clinic attendance? There is already some evidence to support this (Marshall 1998; O'Flynn & Britten 2000; O'Flynn & Britten 2003), but further research is required to understand the part played by the cultural beliefs of both women and clinicians.

Clinic outcome

It is of concern that pain around periods was so commonly found to be problematic yet it was so 'invisible' in the referral and diagnostic pathways, and that dysfunctional uterine bleeding was so commonly diagnosed, often in cases where the women had given no indication on her questionnaires that absolute volume of bleeding was a problem for her. Relatively deprived women were less likely to receive diagnosis of fibroids, more likely to receive diagnosis of dysfunctional uterine bleeding, and more likely to fail to return to the clinic.

Among women free of pathology (as possible indication for surgery) hysterectomy was associated with *referral* for bleeding but *not* with volume of period being

reported as a problem. Perhaps referral for menorrhagia is strategic, based on the knowledge that it is likely to lead to surgery (Coulter et al. 1991; Grant et al. 2000), and aiming to increase the likelihood of this for a particular patient. Nevertheless, this is an unsound process for healthcare resource allocation; it would be preferable to reach a more explicit consensus regarding indications for such treatments.

10.1.2.iii What is menorrhagia *complaint*?

WHAT ARE PROBLEM PERIODS?

Periods can cause significant distress and disability, in the absence of serious pathology or risk to physical health (O'Flynn & Britten 2000; Thomas & Ellertson 2000). In an opinion poll of 1069 women, 60% espoused the view that not enough attention is paid to problems with periods (Corrado 1990). Patients may hold definitions of health and health care need that differ from those of clinicians (Hutchison 1993), perhaps more so in the case of periods, an intensely private ritual beset with societal constraints. In the Introduction to this thesis it was noted that it is usual for 'menstrual problem' to be sub-classified as excessive periods (menorrhagia), period pain, or cycle-related changes in mood and/or physical health (premenstrual syndrome). Irregular periods and/or inter-menstrual vaginal bleeding tend also to be thought of by women as menstrual problems. The explanation for the original partitioning may lie in the separate physiological or psychosomatic pathways presumed to lead to the problematic symptoms. However, the data presented here suggest that this convention warrants critical review.

WHAT ARE HEAVY PERIODS?

A judgement that periods are heavy, or even very heavy, may *not* constitute a complaint of *excessive* volume, or of problem. 'Heavy' can be simply a straightforward value-free account of how the woman classifies the volume of her period, most probably in relation to her own previous experience, but possibly also from type and quantity of sanitary protection required to contain the period, or from discussions comparing experience with other women. The distinction between absolute (and possibly intolerable) or relative symptom (and possibly associated with

worry about change) is an important one for both clinical communication with the patient and for research.

It is nevertheless of interest to explore the basis on which that judgement is made, not least because it is a descriptor of menstrual loss that is in such universal use, both in lay communication (O'Flynn & Britten 2000; O'Flynn & Britten 2003) and in clinical encounters (O'Flynn & Britten 2003). Even in specialist guidelines for management of menorrhagia there is recourse to the term 'heavy periods' as one criterion for deciding management of menorrhagia complaint (Royal College of Obstetrics & Gynaecologists 1998).

The fairly strong association between heaviness and measured volume reported in this study, does not necessarily reassure that women are complaining about volume itself - the association may be coincidental, because increase in volume is associated in some way with the factors leading to complaint, such as worry about change, accidents, containment burden. Rating loss 'very heavy' was modelled mainly on variables reflecting containment challenge, and failure (accidents), and to a lesser extent on problems with volume of period and increase in period.

Given that the definition of menorrhagia is volume-based, the readiness with which heavy periods are interpreted as 'menorrhagia' should raise concerns. Instead the interpretation of 'I have come about my periods, they are very heavy..' should perhaps be 'Doctor, I am having awful trouble trying to contain my periods and avoid accidents and I am totally fed up.'

WHAT IS THE MENORRHAGIA REFERRAL COMPLAINT?

Referral reason is often thought to be synonymous with complaint. This is not necessarily the case, as exemplified by a recently published clinical scenario, '10 minute consultation for menorrhagia' (Hope 2000). In fact the pathway to the GP surgery, in the case described, arose due to a chance finding of anaemia when donating blood, which led to a presumption of menorrhagia by the GP and a clinical encounter (and journal article) driven by that presumption (Hope 2000). One wonders what the referral letter would have said if the GP had referred the woman to the gynaecology clinic? A further doubt as to whether GP referral reason is

synonymous with complaint arises because general practitioners may feel daunted by the need to cite a reason for referral of the patient, and what they cite may be influenced by beliefs about what menstrual indications hospital gynaecologists will deem professionally acceptable as referral reasons.

It has been proposed that citing of volume of period as 'cause' of help-seeking, is the closest variable we have to menorrhagia complaint (complaint of excessive bleeding). For maximum 'equivalence' it needs to be assumed that those with complaint of menorrhagia would have no reticence in citing volume of period as 'cause', that they would feel it is a valid reason to cite for help-seeking. There is furthermore a reverse qualification to this definition. It assumes also that among those who do cite volume of bleeding as 'cause' of help-seeking, it truly is menorrhagia complaint that is their main health concern. That there is not some other aspect of periods (say, pain, cyclic symptoms) that is their true and troubling complaint, but which they feel would be unacceptable or inappropriate to be declared 'cause'.

WHAT DOES MENORRHAGIA COMPLAINT ENCOMPASS?

The co-morbidity of menstrual complaints reported here suggests that the conventional partitioned thinking about, and labelling of, menstrual problems will be unhelpful in the vast majority of cases. Contemporary menorrhagia complaint warrants reconsideration in terms of conceptualisation and assessment.

Models for referral by GP for bleeding, self-stating bleeding as reason for clinic attendance, and citing one or more volume aspects of periods as cause of help-seeking have been examined. The model for citing volume as cause was most clearly related to volume with severe problem with 'losing too much blood' having the strongest association. Both the models for referral to clinic are most strongly associated with rating periods very heavy, and with citing volume aspects as cause of help-seeking, but also with increased period a problem and being over 40 years of age. The self-stating model was also associated with having 'had enough' of periods, and containment variables. The impression is of an internal logic for these models, with home facilities deficit score for example having no part in the model for 'very

heavy' rating of periods, but being positively associated with self-stating bleeding as reason for clinic visit - a judgement that periods are not excessively heavy, but too heavy given the home circumstances.

10.1.2.iv Assessment of menorrhagia complaint

Guidelines for the management of menorrhagia make recommendations based on trials where menorrhagia has been confirmed by traditional measurement of blood loss (American College of Obstetricians and Gynecologists 2000; Coulter 1995; Prentice 1999b; Royal College of Obstetrics & Gynaecologists 1998), sometimes more stringently enforced by being applied to the average over a number of consecutive periods (Bonnar & Sheppard 1996). Strictly speaking, such trials, if deemed to be of adequate quality, provide 'grade A' evidence only for similarly selected patients. This is not how the medication is being prescribed, since measurement of menstrual blood volume is rarely undertaken in routine clinical practice.

Two important points need to be made. Firstly, if a reliable method became available that was suitable for routine clinical use and could identify patients with true menorrhagia (loss over 80 mL), there would remain an urgent need for trials of treatment strategies for the remainder, the substantial majority of patients with complaint of menorrhagia, but who have blood loss less than 80mL. Secondly, such a method would help clinical management of referrals for excessive periods only if volume of blood loss, and more specifically volume exceeding 80 mL, is the predominant issue in menorrhagia complaint, and is critically important to optimum care of patients.

The data show that volume of loss is only one among many concerns of women referred with putatively heavy periods, and not the main one, overall. This replicates findings in qualitative research (Coulter 1997; Geller et al. 1999; Marshall 1998; O'Flynn & Britten 2000). Two forms of assessment used in this study have proved to be very useful. The aspects of periods items were originally devised as a brief way of ascertaining, via the minimal level participation questionnaire CQ, the extent of problems for a broad scope of aspects of periods, without partitioning. Responses on

these items turned out to be very illuminating. It has the further advantage that it is formulated in terms of both occurrence and problem, so that items avoid the misunderstanding that occurs, for example, with the classic loss question 'How heavy are your periods?'. The other assessment that showed great promise was the MEQ, part of which was converted into principal components, one set about 'dealing with periods' and the other capturing 'feelings about periods'. Together these would appear to encompass menorrhagia complaint, and also hint at intriguing subgroups of patients. Impact (of volume) and containment distress components appear to be key to rating periods very heavy, variable flow plus containment distress to self-stating bleeding as reason, with having had enough of periods being fairly strongly associated with both judgements. GP referral for bleeding was the judgement most strongly associated with the worry component. Measured volumes were most strongly associated with impact (of volume) and containment distress, and were not associated with variable flow. So there appear to be two subtypes of menorrhagia complaint, one with heavy losses and the other not, or perhaps only intermittently so.

10.2 CONCLUSIONS

The themes for the menstrual data collection have been 'severity' of symptoms, change in symptoms, associated worry, impact on daily life and well-being. These appear to be more important dimensions for the women, than partitioning into excessive volume of menstrual blood loss, period pain, and premenstrual syndrome. This study can not give conclusive answers, but the wealth of data amassed allows informative descriptive analyses and detailed modelling.

The study objectives have been achieved, and work has progressed on the aims. This will continue, as there are further analyses to be undertaken utilising the personality and psychological well-being data.

There was no evidence to support the notion that volume of blood loss is key to complaint, or helpful to management, although there may be important clinical reasons to measure blood loss in specific cases. If measurement is needed then total fluid volume should be seriously considered, for conceptual, methodological and resource reasons. If total fluid measurement is to be pursued, further research would be valuable, with the aim of making measurement more reliable and the method easier for women involved.

The principal component scores show great promise as an assessment, so the next step would be to be refine the components, and reduce the number of items to be answered. Given the prevalence of reports of pain and cyclic symptoms, consideration should be given to including more items addressing aspects other than volume and containment. Validation in the context of a prospective clinical study would be the next step. The underlying complaint reflected by the component 'variable flow' warrants further attention. Qualitative interviews with women scoring high on this component would enhance understanding of the nature of the problem.

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APPENDICES

Appendix to Chapter 3: Methods

EXAMPLES OF STUDY MATERIALS

In pocket inside back cover

Appendix 3.1 MEQ – Menstrual Evaluation Questionnaire (yellow)

Appendix 3.2 CQ – Clinic Questionnaire (apricot)

Appendix 3.3 MBQ – Menstrual Background Questionnaire (green)

Appendix 3.4 SF-36 – 'developmental' version of questionnaire (white)

Appendix 3.5 Menstrual Chart (blue A5)

Appendix 3.6 Follow-up data extraction form (mauve)

The following pages

RECRUITMENT CRITERIA

I propose the following recruitment strategy, as a clarification of the study design outlined in the proposal.

TERMS

Referral condition - what is on the referral letter

Presenting complaint - what patient says, on CQ, is her 'main reason' for coming to clinic

Subjectively heavy periods - if she rates her loss at least as 'heavy' on CQ

Subjective menorrhagia - if she rates her loss as 'very heavy' on CQ

POTENTIAL RECRUITS

Level 1 - CQ + MEQ

Any woman aged 25 to 45 years, not a known drug addict nor satisfying any of the exclusion criteria listed in the protocol, who has **referral condition**:

menorrhagia, ?metrorrhagia, dysmenorrhea, premenstrual syndrome or unspecified 'menstrual problem'

Level 2 - detailed Q's

Any Level 1 woman with:

referral condition = menorrhagia, ?metrorrhagia, or heavy periods

or **presenting complaint** = menorrhagia, heavy periods, periods too long/?often

or **subjectively heavy periods** or **subjective menorrhagia**

Level 3 / 4 - prospective

Any Level 2 woman prepared to participate to these levels.

This means that any women referred for **menorrhagia**, **?metrorrhagia** , or **heavy/ excessive periods** will be potential recruits for ALL levels, regardless of what they report on CQ.

On the other hand, women with referral condition of **dysmenorrhea**, **premenstrual syndrome** or **unspecified 'menstrual problem'**, though eligible for Level 1 of the study, will only be taken past Level 1 if they have a CQ presenting complaint of menorrhagia or heavy periods, or in CQ rate their periods as heavy or very heavy.

Women with **other menstrual referral conditions** will not be recruited at all e.g. irregular periods, oligomenorrhea, amenorrhea, dyspareunia, inter-menstrual bleeding.

Please see Figure overleaf.

Updated Recruitment Plan - 10 Sep 96

CHARACTERTISTICS OF PATIENT: Aged 25-49, **not** 'excluded', and.....				POTENTIAL RECRUIT FOR...?			
REFERRAL CONDITION *Doctor's letter*	PRESENTING COMPLAINT *CQ qu.1*	RATING OF LOSS *CQ qu. 4*	LIKELY CYCLE LENGTH *MEQ qu 13*	**LEVEL 1** CQ MEQ	**LEVEL 2** MBQ, GHQ, EPI, SF-36	**LEVEL 3** Prospective - diaries + MC	**LEVEL 4** Menstrual collection
Menorrhagia M **Heavy periods H**	*any*	*any*	*usual cycle* ≤ *54 days*	✓	✓	✓	✓
Periods too long L **? Metrorrhagia**			*> 54 days*	✓	✓	no	
Dysmenorrhea Irregular periods	***M / H / L***	*any*	*usual cycle* ≤ *54 days*	✓	✓	✓	✓
Period Pain			*> 54 days*	✓	✓	no	
PMS	*Other i.e.*	***(v.) heavy***					
Unspecified Period problem(s)	***not** M/H/L*	***not** heavy*	*irrelevant*	✓	no		
Amenorrhea *Dyspareunia* *?Pelvic pain* *Other*	*CQ*	***not***	***done***	no			

Instructions for Menstrual Collection

We are extremely grateful to you for agreeing to collect your used products. This will be of great value to our research, and is likely to benefit other women with the same problem as yourself.

Here is a reminder of what we would like you to do:

1. Please use the products supplied - Bodyform Ultra Super Pads and Super and Regular Tampons.
2. Every time you change your sanitary protection please:
   i) put the used product(s) immediately into one of the storage bags supplied
   ii) tie the neck of the bag in a knot so it is airtight
   iii) as soon as possible afterwards, put the bagged product into the green courier bag provided for your collection, inside the yellow plastic bag liner.
3. If you use tampons, and you want to have a bath, or swim, please remove and 'collect' the tampon you are wearing just before you get into the water. *(If you want to wear another tampon while in the water that is fine, but it should just be discarded after you have got out of the water.)* Once you have got out of the water you can apply a new tampon, which you will later 'collect' in the usual way.
4. As well as collecting your used products, please also complete the menstrual chart throughout your period, to note the timing of product changes, the amount of soaking, any clots, 'accidents' etc.
5. When you are sure your period has finished, please telephone the clinic nurse, on xxx xxxx, to arrange the hand-over of your collection. Remember, you only need to hand in your filled-in diaries and menstrual chart, and the green courier bag with all the used products. You may keep any unused products.

Thank you, again.

What if I have to go out?

This is very likely, and should not be a problem. Please just take spare products and storage bags with you. Then if you need to change you can bag and tie your used product, to take home with you later, for placing in the collection.

What if I need to change and I have not any bags with me?

In an emergency any plastic bag will do, but please try to make it airtight.

What if I have not got any of the research-supplied pads/ tampons with me?

In an emergency use any product that you can get hold of, but please:

i) remember to 'collect' the product you arechanging, in the usual way

ii) notify us that you have had to use a different product, and exactly what it is.

If you have any difficulties, or second thoughts about the study

PLEASE DON'T WORRY about it

just telephone your research nurse xxxxxx on xxx xxxx

ASSESSMENT OF PERIOD PROBLEMS

Women referred to this clinic for period problems may be bothered by their periods in a number of ways e.g. period pain, tiredness or irritability, heavy periods. Depending on their circumstances, employment etc., their period problems may affect their lives in different ways. This research study is intended to **develop a standard questionnaire for assessing period problems,** and their effect on the women who have them.

We would be very grateful if you helped our research by completing some questionnaires. The new assessment, the **Menstrual Evaluation Questionnaire,** covers how your periods have been in recent months. The remaining questionnaires are important so we can check on the value and reliability of the new questionnaire. They cover background information about your circumstances, contraception, health and well-being, your way of dealing with day-to-day life, your attitudes to illness, any pregnancies you have had, and any period problems in the past. *In addition we would be grateful if you would give a blood sample, which will be used only to test for iron levels (haemoglobin and ferritin), which can be an indicator of the health impact of heavy periods.*

It would be preferable if you could complete our new Menstrual Evaluation Questionnaire, before seeing the doctor. This will take only about 10 mins. The remaining questionnaires may be completed in the clinic, or, if you prefer, may be taken away for completion at home, and returned in the Freepost envelope which will be provided.

Our Research Sister, ***XXXXX,*** will explain the questionnaires to you and will be able to deal with any queries you may have, either in person or by telephone.

All information given in the questionnaires will remain completely confidential. If at any point you decide to withdraw, i.e. that you do not to want to answer the questions, it will not affect your treatment in any way.

XXXXXX Dr Hilary Critchley Pamela Warner

If you have any queries, concerns or difficulties do please contact us.

XXXXXXX Phone no.:xxxxx

WEEKLY MONITORING OF WELL-BEING & CHARTING OF PERIOD

You have been good enough to agree to completing the questionnaire part of our research study into assessment of period problems, and we thank you for that.

A further very important part of checking of our new assessment questionnaire is to be able to compare it to how a real-life period is for the woman, and to her general health and well-being over a number of weeks.

Therefore, we are very keen that as many women as possible also **monitor their next period and their well-being** over a time-span of 6 weeks. This would involve filling in, once a week, a very brief questionnaire covering well-being and health in the week just past. In addition, we ask that when their next period starts they chart the heaviness of flow, sanitary protection used, and any 'accidents' or other relevant symptoms. Freepost envelopes would be provided so these questionnaires/charts can be mailed back as soon as completed.

This monitoring is not difficult to do, can be quite interesting in terms of learning about yourself, and would be very valuable to our research. Please do at least discuss the possibility with our Research Sister, ***XXXXXr***. She will explain the monitoring to you, show you the questionnaires, and deal with any queries you may have.

All information obtained from this monitoring will remain completely confidential. If at any point you decide to withdraw, i.e. that you do not to want to fill in the diaries and chart, it will not affect your treatment in any way.

XXXXXX Dr Hilary Critchley Pamela Warner

If you have any queries, concerns or difficulties do please contact us.

XXXXXX Phone no.: xxxxx

COLLECTION OF SANITARY PROTECTION

You have very generously agreed to completing the questionnaire part of our research study into assessment of period problems, and to monitoring your next period and your health and well being over the next 6 weeks. While we very much appreciate all this, there is one further way in which you could help our research project.....

The final but really most important part of checking our new assessment questionnaire is to be able to compare the information it gives to the woman's actual menstrual loss. For example, what patterns of menstrual loss are common in which women, and with what profiles of symptoms, etc...? As it happens menstrual loss can be measured, if all sanitary protection used is kept for laboratory evaluation.

Therefore we are also very keen that as many women as possible agree to keep for us all the sanitary protection they use during their next period. This may sound like an unusual request, but please do consider helping in this way, as it is a crucial part of this project. We have made every effort to ensure that the collection process would be as easy and discreet as possible for you, and we would provide air-tight sealable bags, and all the packaging required. At the end we would arrange collection, or re-imburse your travel costs if you deliver the collection to the clinic.

Please do at least discuss the possibilty of sanitary products collection with our Research Sister, ***Elaine Kacser.*** She will explain the process to you, show you the plastic bags and packaging, and deal with any queries you may have. You may be interested to know that this evaluation provides important information to help in treating heavy periods, and in many cases, especially for some treatments, it can be a requirement, before treatment is decided.

All information obtained from this collection will remain completely confidential. If at any point you decide to withdraw, i.e. that you do not to want to do the collection, it will not affect your treatment in any way.

XXXXXX Dr Hilary Critchley Pamela Warner

If you have any queries, concerns or difficulties do please contact us.

XXXXXX Phone no.: xxxxx

ASSESSMENT OF PERIOD PROBLEMS

- I have read the description of this study (InfoSheet 1) and I have had the opportunity to ask questions about it.
- I understand that I am under no obligation to take part in this study and that refusal to participate will not alter the treatment that I would normally receive.
- I agree that notice be sent to my General Practitioner about my participation in this study.
- I understand that I can withdraw at any stage or refuse to answer questions if I wish.

I agree to participate in the questionnaire stage of this study.

Signature of Subject: .....

Name of Subject:

Date: .....

Signature of Research Nurse: .....

Four copies to be made:
Top copy to be retained by Investigator
Second copy to be retained by subject
Third copy to be sent to subject's General Practitioner
An additional copy to be filed in hospital case notes

MONITORING OF WELL-BEING AND CHARTING OF PERIOD

- I have read the description of this stage of the study (InfoSheet 2) and I have had the opportunity to ask questions about it.
- I understand that I am under no obligation to take part in this and that refusal to participate will not alter the treatment that I would normally receive.
- I agree that notice be sent to my General Practitioner about my participation in this stage of the study.
- I understand that I can withdraw at any time or refuse to answer questions if I wish.

I agree to participate in the monitoring stage of this study.

Signature of Subject: .....

Name of Subject:

Date: .....

Signature of Research Nurse: .....

Four copies to be made:
Top copy to be retained by Investigator
Second copy to be retained by subject
Third copy to be sent to subject's General Practitioner
An additional copy to be filed in hospital case notes

COLLECTION OF SANITARY PROTECTION

- I have read the description of this stage of the study (InfoSheet 3) and I have had the opportunity to ask questions about it.
- I understand that I am under no obligation to take part in this and that refusal to participate will not alter the treatment that I would normally receive.
- I agree that notice be sent to my General Practitioner about my participation in this stage of the study.
- I understand that I can withdraw at any time.

I agree to participate in the collection stage of this study.

Signature of Subject: .....

Name of Subject:

Date: .....

Signature of Research Nurse: .....

Four copies to be made:
Top copy to be retained by Investigator
Second copy to be retained by subject
Third copy to be sent to subject's General Practitioner
An additional copy to be filed in hospital case notes

Appendix to Chapter 4: Study sample

4.1 RELIABILITY OF DATA ON CURRENT HEALTH, BETWEEN QUESTIONNAIRES AND CASE NOTES

Out of the 517 women who completed MBQ and had case-note review there were 9 with either a self-reported or notes-recorded history of cancer, but in only 5 cases was there concordance.

Current medication could be compared for the 517 women who completed MBQ and who had case-note review. However, it should be noted that the data were not directly comparable as in the case note review up to three medications were coded, whereas on MBQ only one medication was coded, or if more than one was reported then a special code for 'multiple medication' was assigned. Data for two medication groups will be considered, gastro-intestinal and cardiovascular.

Ten women reported taking gastro-intestinal medications and of these only 4 had gastro-intestinal medication recorded in their notes, so 6 out of 10 were missed in the notes. This may be partly because some of the self-report was of over-the-counter remedies rather than prescriptions. Viewed from the perspective of the notes, 12 women were found to have gastro-intestinal medication recorded, and of these 4 self-reported such medication (as noted above) and a further 5 reported multiple medication which may well have included gastro-intestinal medication. Therefore in only 3 out of 12 cases was there clear failure to self-report a medication recorded in the notes.

For cardiovascular medication 22 women self-reported this and in only 14 of these cases was it recorded in the notes, so 8 out of 22 were missed in the notes. Viewed from the perspective of the notes, 26 women were found to have cardio-vascular medication recorded, 14 of these self-reported such medication (as noted above) and a further 9 reported multiple medication which may well have included cardio-vascular medication. Therefore in only 3 out of 26 cases was there clear failure to self-report a cardio-vascular medication recorded in the notes.

4.2 MEASUREMENT ISSUES IN CONTRACEPTIVE METHOD 'USED' AND DURATION OF USE

4.2.1 Explorations of contraceptive method currently being 'used', as reported on CQ

The perforce succinct wording on the questionnaire CQ meant that there was a risk of misunderstanding by respondents to the item asking 'Do you *use* contraception currently?'. By reference to responses on the 'importance of possibility of future fertility' item on CQ (item 12), where one possible response was 'not applicable – already sterilised', it was clear that a number of sterilised respondents (n=6) had answered the CQ enquiry 'Do you use contraception currently? If so what method?' by ticking 'None'. This would be an understandable mistake since no contraception is actively *used.* These responses were therefore corrected to 'sterilised'.

Furthermore, for the 700 who had also completed MBQ, comparison was possible of the CQ responses with those for the MBQ item on contraception, which offered more detailed options and more examples. It was clear that some CQ respondents had mistakenly understood 'Other e.g. condom, cap', as inferring that the examples given were the *only* types of contraception comprising this category. Those who on CQ had responded 'None' but on MBQ responded 'rhythm method' or 'Other' (unspecified, but possibly withdrawal or spermicide) were therefore re-coded as 'Other' on the CQ variable (n=6).

Finally, some who responded 'Partner vasectomy' on MBQ were found to have responded 'None' or 'Other' for the CQ item, rather than 'Sterilisation – male or female'. They may not have known vasectomy as 'sterilisation', or may not have noticed the qualification 'male or female'. These (n=24) were therefore recoded as sterilisation for the CQ variable. Clearly these latter two checks (and where necessary corrections) were not possible for the 252 who completed only the CQ.

Therefore the proportions responding 'Sterilisation' and 'Other' on CQ may be an under-estimate of the true figure (by 8 and 2 women respectively), and the proportion answering 'None' may be an over-estimate (by about 10 women).

4.2.2 Categorisation as having 'ever used oral contraception'

This was calculated by accumulating as 'ever-pill-users' all respondents to items addressing current or past oral contraceptive use on CQ or MBQ. However participants who were *not* current pill users and did not go on to complete MBQ could only be identified as past pill users if they completed the 'years since stopping the pill' item on CQ. Of the 190 women who were not current pill-users and who did *not* answer the 'years since stopping item' on CQ, 135 went on to complete MBQ while the remaining 55 women did not. Of those who did complete MBQ, 53 (39%) gave answers indicative of past pill use. Therefore it is estimated that of the 55 who did not go on to complete MBQ, a further 21 (39%) are likely also to have been past pill users.

4.2.3 Missing responses for 'duration of use' of current method of contraception

The large amount of missing responses (17%) for duration of current contraception was predominantly women who had answered 'none' for current contraception, and who presumably, and understandably, did not realise the duration item was applicable to them (94 patients). There was also a tendency to non-response among patients who had answered 'sterilisation', who possibly did not realise this could be interpreted as a method being 'used', and as such required a response for duration of use. For 6 of the 10 where it was the woman herself rather than her partner who had been sterilised, it was possible to impute the duration of 'use' from responses regarding the time since (female) sterilisation item on CQ (second to last row of table). This left 9 male sterilisations and 4 female with missing responses for time 'using' this method. In addition to the cumulative total of 107 non-responses in these two categories, there were scattered across the other methods a further 4 who did not record duration of use, and 6 who 'completed' MBQ but had not answered any aspect of contraception.

4.3 MEASUREMENT ISSUES IN PREGNANCY DATA

4.3.1 Excess responses regarding time since last pregnancy ended

There were *more* than expected responses regarding time since last pregnancy ended. For this the potential n was calculated from information about births of *babies*, and there may have been women who were nulliparous (in the sense of babies born) who answered this item because they had experienced pregnancies, albeit not resulting in births.

Pregnancy outcome

If she had had any pregnancy at all the woman was also asked to record the outcome of the pregnancies, by providing counts for number of pregnancies resulting in each of miscarriage, abortion, still birth and live birth. It was possible that for this item there could have been mistakes in completion in the case of multiple pregnancies, if the counts requested, for *pregnancies*, were substituted with numbers of still-born and live born *babies*. That is, *one* twin pregnancy resulting in live births could have been recorded instead as *two* live births, or if miscarrying as *two* miscarriages. Such an error was almost inevitable if a twin pregnancy resulted in, say, one live birth and one still birth. The occurrence of such errors could be checked by comparing the overall number of pregnancies reported, as shown in **Figure 4.14**, against the total of the requested counts of the possible outcomes for the pregnancies (still birth, miscarriage etc.). In 8 cases the total of the requested counts was one more than the number of pregnancies, suggesting this error due to multiple pregnancy. Therefore, for presentation and analysis of the data for abortion and miscarriage/stillbirth, the variables have been re-coded into binary form, signifying for each respondent the occurrence or not of at least one pregnancy with such an outcome. Although the precise number of failed pregnancies per respondent, miscarriage say, may in some cases be biased upwards, as explained above, the fact of at least one failed pregnancy of that type, as conveyed by the binary variable, should be correct.

It should also be noted that it was possible, if there were multiple pregnancies, for the number of babies to exceed the number of pregnancies, which it did in 7 cases, but not by more than one. Furthermore, a multiple pregnancy may have occurred even if the number of babies equalled the number of pregnancies, if one pregnancy failed. By cross-referencing these variables 23 women were identified as having had multiple pregnancies (4% of 569).

4.4 RELIABILITY OF CONTRACEPTIVE AND OBSTETRIC HISTORY DATA BETWEEN QUESTIONNAIRES AND CASE NOTES

Some of the discrepancy between the succinct question on contraception in CQ and the more detailed question in MBQ has already been addressed (**Appendix 4.2**). Of 17 participants with current IUD use recorded in their notes, 3 did not confirm this by their responses to the contraception items in CQ or MBQ. Of 172 participants with sterilisation recorded in their notes, 8 did not confirm this by their responses to the contraception items in CQ or MBQ. Of the 145 women for whom years since sterilisation operation was recorded on CQ and extracted from the case note review, the two durations agreed to within two years of each other in 86% of participants, and there were quite substantial discrepancies in a few cases.

The data on outcome of pregnancies was ascertained on MBQ, and as already been noted (**Appendix 4.3**), there was the possibility that women entered for pregnancies resulting in 'live births' not the number of pregnancies but the number of infants. When the MBQ variable was cross-referenced to the corresponding parity data from the case note review it was found that the MBQ live birth count matched the case note version for 403 out of 416 who had both items completed. (There were 417 women who had ever been pregnant who had completed MBQ and had case-note review.) For 11 women the MBQ live birth count exceeded the corresponding case note count by one, and for 2 was one less. The data were less complete for the other parity variables, and less concordant. Of 369 women who had both miscarriage variables completed, 15 women self-reported one less miscarriage than was recorded in the case notes, and 24 reported miscarriages when the notes stated zero miscarriages. Of 369 women who had both abortion variables completed, 8 women self-reported no abortions when the case notes reported one, and 11 reported one or two abortions when the notes stated zero abortions. Of 368 women who had both still

birth variables completed, 1 woman self-reported no still birth when the case notes reported one, and 7 reported a still birth when the notes stated none.

Appendix to Chapter 5: Menstrual Problem

5.1 ADDITIONAL TABULAR DATA ON SUBJECTIVE REPORT OF MENSTRUAL LOSS, PAIN AND CYCLIC CHANGES

Table A5.1.1 Description of menstrual bleeding, ascertained from CQ & MEQ

	n	%
CQ data		
Heaviness of periods, in last 6 months (n= 945, missing = 7)		
Light loss	30	3
Moderate loss	152	16
Heavy loss	420	45
Very heavy loss	343	36
Does period include clots? (n=948, missing=4)		
No	96	10
Yes- about 20p size	435	46
Yes – about 50p size	272	29
Yes – bigger than 50p size	145	15
MEQ data		
How much do you think your whole period would measure? (n=817)		
No idea	448	55
Up to a teacupful	88	11
Full mug (half a pint)	122	15
Much more than a mug	159	19
Bleeding in between periods (n=821)		
No	425	52
Some cycles	250	30
Nearly all cycles	146	18
Spotting in between periods (n=813)		
No	440	54
Some cycles	256	32
Nearly all cycles	117	14

Table A5.1.2 Durations/counts of aspects of menstrual loss

	n	Median	Inter-quartile range	Maximum
CQ data				
Usual duration of period (days)	906	6	5 to 7	70
If varies, (a) *longest* period	737	9	7 to 14	90
(b) *shortest* period	743	5	3 to 6	49
(c) difference between longest and shortest	732	4	2 to 8	86
MEQ data				
Usual duration of period (days)	802	6	5 to 7	31
Usual number of days 'full flow'	811	3	2 to 4	50
Number of clots per period:				
– up to 20p size	762	4	0 to 8	50
– about 50p size	770	0	0 to 4	50
– bigger than 50p	793	0	0 to 0	30
– all three sizes totalled	725	6	3 to 12	65
Bleeding between periods (days)	307	3	2 to 6	30
Spotting between periods (days)	272	3	2 to 4	30

All responses apply to periods in last 6 months

Table A5.1.3 Anticipation of bleeding and planning for period, ascertained from MEQ

	n	%
Do you know by counting days when your period is going to start? (n= 822)		
Hardly ever	286	35
Yes, half the time	188	23
Yes most times	348	42
Do you have other signs that tell you your period is due in a few days? (n=820)		
Yes	741	90
How does your period start? (n=818)		
Spotting/streaks of blood	242	30
Very light bleeding	364	44
In a gush	212	26

Table A5.1.4 Containment of menstrual loss, ascertained from CQ and MEQ

	n	%
CQ data		
Sanitary protection used (n=946, missing=6)		
Tampons only (all absorbencies)	114	12
Pads only ('mostly regular/super')	207	22
Pads only ('mostly super plus')	245	26
Tampons & Pads (*both* 'mostly regular/super')	167	18
Tampons & Pads (*one or other* 'mostly super plus')	115	12
Tampons & Pads (*both* 'mostly super plus')	98	10
Have to get up at night to change pads/tampons? (n= 952)		
Very seldom	196	21
Some periods	353	37
Most periods	403	42
Periods leak through onto underclothes/bedding? (n= 952)		
Very seldom	132	14
Some periods	378	40
Most periods	442	46
Have to use more than one pad/tampon at the same time? (n=949, missing=3)		
Yes	568	60
MEQ data		
Do you ever use 'double' protection? e.g. two pads, or tampon & pad together (n= 824)		
No	251	31
Some periods	225	27
Most periods	348	42
How often do you have to change you tampon/pad when your period is 'full flow'? (n= 819)		
At least every 3 hours	246	30
Every 2 hours	303	37
Every hour	177	22
More often	73	11

Table A5.1.5 Durations/counts regarding containment of menstrual loss

	n	Median	Inter-quartile range	Maximum
CQ data				
Days using double protection	927	2	0 to 4	30
MEQ data				
Number of pads/tampons used in most recent period:				
– tampons (any)	794	2	0 to 22	100
(super to plus)	795	0	0 to 0	96
– pads (any)	779	18	9 to 30	164
(super to plus)	781	0	0 to 18	90
– total products (any)	772	30	20 to 40	164
(super-plus)	775	10	0 to 24	164
Number of leakages per period onto:				
– underclothes	781	3	2 to 5	50
– outer clothes	796	0	0 to 2	21
– bedding	785	1	0 to 2	21

 # in last 6 months, unless otherwise stated

Table A5.1.6 Description of pain around periods, ascertained from MEQ

	n	%
Do you have period-type pain around your periods? (n=827)		
Very seldom	98	12
Some periods	137	17
Most periods	592	72
Do you use pain-killers for pain around your periods? (n=829)		
Very seldom	186	22
Yes, some periods	152	18
Yes, most periods	491	59
If so: (a) what type of painkiller? (n=710)		
NSAID (paracetomol, profen etc.)	697	98
Codeine etc.	8	1
Others	5	1
(b) does your painkiller work i.e. control the pain? (n=740)		
Not usually	95	13
About half the time	296	40
Yes most times	349	47
(Any) pain: usual total days ('before' + 'with' periods) (n=799)		
None	98	12
1-2 days	111	14
3-4 days	172	22
5-6 days	155	19
7-10 days	158	20
≥ 11 days	105	13
***Severe* pain: usual total days ('before' + 'with' periods) (n=806)**		
None	218	27
1-2 days	206	26
3-4 days	178	22
5-6 days	90	11
≥7 days	114	14
***Severe* pain: usual number of days with periods only (n=811)**		
None	229	28
1-2 days	317	39
3-4 days	186	23
5-6 days	49	6
≥7 days	30	3

Table A5.1.7 Description of cycle-related symptoms, ascertained from MEQ

	n	%
Do you have other symptoms/feelings regularly around your periods, much more than at other times? (n=797)		
Very seldom	109	14
Yes, some periods	120	15
Yes, most periods	568	71
If yes, (a) are any of the symptoms troublesome to you? (n=741)		
No, not really	179	24
Yes	378	51
Yes, very troublesome	184	25
(b) when are the symptoms most troublesome? (n=720)		
Before period	217	30
Both equally	331	46
During period	172	24
(c) what are the worst symptoms for you:		
(i) before your period starts? (n=652 $^{\phi}$)		
Bloating/weight gain/breast tenderness	226	35
Back ache/pain	209	32
Irritable/angry	140	21
Tiredness	109	17
Mood swings	106	16
Headache/migraine	86	13
Miserable/depressed/sad	65	10
(ii) during your period? (n=627$^{\#}$)		
Backache/pain	329	53
Tiredness	197	31
Bloating/weight gain/breast tenderness	83	13
Headache/migraine	70	11
Irritable/angry	61	10

$^{\phi}$ *Percentages were calculated independently for each symptom by dividing the number of times a symptom was mentioned by the number of individuals answering the item (652). Since 367 of the 652 respondents reported two symptoms, the total of all percentages will be 156% (Note: only percentages of 10% or more are reported in the table).*

$^{\#}$ *As above, but using 627 as denominator. Since 315 of the 627 respondents reported two symptoms, the total of all percentages will be 150%.*

5.2 PRINCIPAL COMPONENT ANALYSIS OF ITEMS ABOUT PERIODS

5.2.1 Overview of principal components analysis

The goals of principal components analysis are to:

- Ascertain the minimum number of factors (axes) needed to position the variables.
- Discover the nature of the factors (underlying processes) that result in the observed values for the variables (Tabachnick BG & Fidell 1996b).

The first goal requires a decision about the number of factors to be retained in the solution. The second requires a decision about which if any rotation method to use.

5.2.2 Methods used

5.2.2.i Choice of extraction method

In factor analysis only is there a need to invert the covariance matrix, making collinearity between variables a serious problem for that method, but not for principal components analysis. The main difference between factor analysis and principal component analysis is in respect of the variance being analysed. In principal component analysis all the variance is analysed, whereas in factor analysis only the shared variance is analysed (after the unique variance and error variance have been estimated and eliminated). For these reasons it was decided that principal components analysis would be used.

5.2.2.ii Steps in principal components analysis

EXTRACTION OF COMPONENTS

The principal components method works on the correlation matrix for the p variables being analysed. From this, a set of p factors (components) is obtained which together can reproduce all the variance in the correlation matrix. The components are orthogonal to each other, that is, they comprise independent dimensions of variability. The matrix calculations ensure that as much as possible of the variance in

the variables is explained by the first component. Proportionately less variance is accounted for by each successive component. The statistical software also provides a factor loading matrix. This gives the correlations between the p factors and the p variables. If a variable has a strong (negative or positive) correlation with a factor then it is described as having a high (negative or positive) 'loading' on that factor. The interpretation of each factor is made in terms of the variables that are most highly correlated with it, and the directions of these correlations. Clearly this is easiest in the case of a factor for which few variables have substantial loadings.

DECIDING NUMBER OF COMPONENTS

Next, a decision is made as to how many components are to be retained in the solution. This is one of the most important decisions to be made in a factor (principal component) analysis. Parsimony will not have been achieved unless the number of factors in the final solution is less than the original number of variables. However, if too few factors are retained then the solution may be a poor fit to the data. The number of factors is decided on the basis of one or more of the following issues:

- The purpose of the solution – the need to be succinct and simple *versus* the need to encapsulate more of the underlying processes in the data.
- The total proportion of the variance that it is felt should be reproduced by the components.
- The relative importance of an additional component that might be retained, judged in terms of the variance accounted for by that component. If the component accounts for less variance than one of the original variables then it is unlikely to be more useful than the variable itself. (This is ascertained by the size of the eigenvalue corresponding to the component. The eigenvalues represent variance and are calculated in one of the intermediary matrices produced in the course of the analysis. Since the standardised variance of a single variable is 1, a component with eigenvalue less than 1 accounts for less variance than a variable.) A scree plot, showing the sizes of successive eigenvalues, can be used to help decide, by selecting the point where the slope flattens out. (Tabachnick BG & Fidell 1996b)

Once the number of factors to be retained is decided, say m, then the factor loading matrix is recalculated, to give the correlations between the m factors and the p variables. The interpretation of each factor is as described above, in terms of the variables that are most highly correlated with it.

ROTATING THE SOLUTION

The factor solution can then be subjected to 'rotation'. This does not in any way improve the mathematical fit of the factor analysis. The aim of rotation is merely to simplify *interpretation*, by creating an alternative solution, accounting for the same total variance as the m factors retained from the original extraction, but where the variables have mainly very high or negligible loadings on factors. Rotation can be orthogonal or oblique. In the case of *orthogonal* rotation, this is equivalent to moving (rotating) the multidimensional axes, while keeping them all fixed (at 90°) in relation to each other, until as many cases as possible are located along the various axes. Therefore after rotation the factors remain orthogonal (uncorrelated). However, sometimes the structure of a data set means that orthogonal rotation can not achieve a 'good' solution (with cases located along the axes). In such circumstances oblique rotation may be used, which allows the angles between the axes to change. If this method is used the resulting factors will no longer be orthogonal to (uncorrelated with) each other, which can complicate the interpretation of subsequent analyses of the factor scores. If a satisfactory solution can be obtained by orthogonal rotation then this is the preferred method. After rotation a new 'rotated' factor loading matrix is obtained, reflecting the polarised loadings. These factors are interpreted as before.

A number of methods of orthogonal and oblique rotation are available. The most commonly used method of orthogonal rotation is 'varimax', which seeks to minimise the complexity of components, and maximise the interpretability, by ensuring as few variables as possible load on each component. Varimax rotation also tends to even out the amount of variance accounted for across the m components in the solution, resulting in equally 'important' components. The most commonly used method of oblique rotation is 'oblimin' which seeks to simplify components by minimising the cross products of loadings.

Once the final factor loading matrix is available, factor scores can be estimated for each case. The factor scores are conceptualised as reflecting the underlying processes, whereas the variable values are held to be the observed manifestation of those processes. Therefore each variable is regarded as a weighted combination of the subject's underlying factors.

5.2.2.iii Checks with regard to solution

Application of the principal components method requires a series of analyses iterating to a solution. The solution ultimately interpreted should: be as consistent as possible across variations in number of retained factors and rotation method used; be interpretable; and should give scientifically useful results.

Variables should be checked for outliers – that is, variables that have low squared multiple correlations with all other variables and with other factors. These may be deleted from the analysis.

If any cases have extremely low or high factor scores they are termed case outliers. The interpretation is that for these cases the factor solution is inadequate. Examination of such cases may reveal a consistent pattern, and hence allow description of the characteristics of cases for whom the current factor solution is unsatisfactory.

5.2.3 Results

For both analyses undertaken in this chapter components with eigenvalues greater than 1.1 were retained.

5.2.3.i MBQ question 22 items - 'Dealing with periods'

The results for this principal component analysis and rotation are presented in **Table A5.2.1**, which presents only the 'substantial' factor loadings, those > 0.4. Since each loading is the correlation between the corresponding MBQ item, and the underlying component of variability in the data, the 'factor', the highest loadings give the best sense of what 'process' each component reflects. Other variables (items) also load on

the factors, but only minimally or negligibly. Labels have been assigned to each component, but it should be remembered that this is a subjective judgement, and usually has to be a succinct simplification of the observed pattern of loadings. For example, the first component has been labelled 'impact of volume' but items *a*, *j*, *k* and *s* could equally well be coping strategies for very severe period pain.

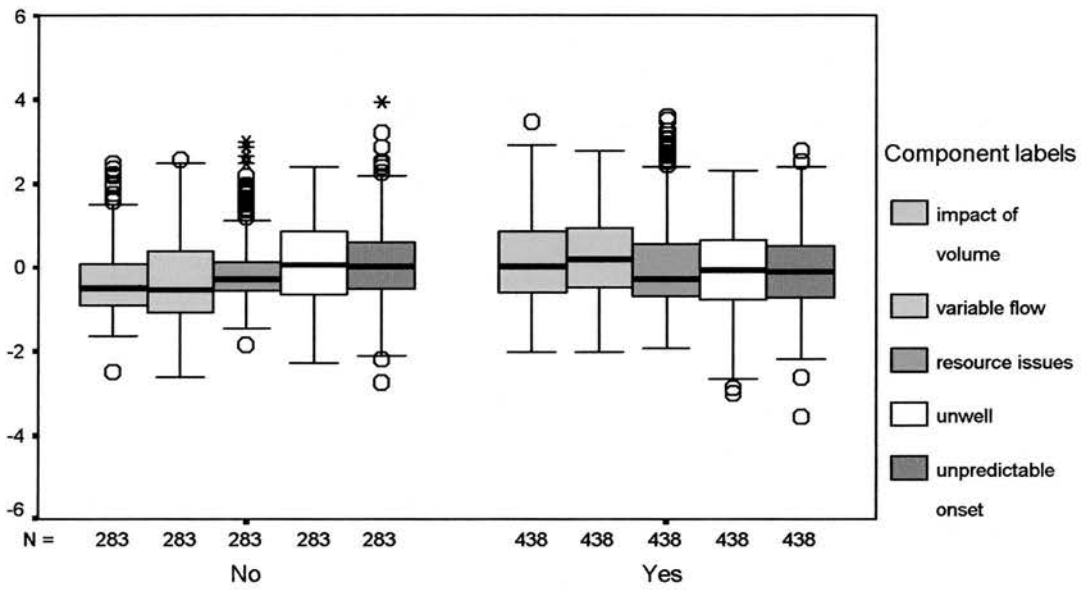
Loadings < 0.4 are excluded from the table, for ease of perusal, but remain in the formula estimating component scores for each respondent. A box-plot of estimated component scores is given in **Figure A5.2.1**. These scores will be further analysed in Chapter 9.

Table A5.2.1 Loadings* for estimating component (factor) scores for 'dealing with periods' – items from MBQ question 22 (n=721)

	COMPONENTS (FACTORS)					
						5: Unpredictable onset
					4: Loss of well-being	
				3: Resource issues		
			2: Variable flow			
Item	1: Impact of volume					
k	During period I limit where I go	.833				
a	Plan life to avoid outing when period	.827				
d	I limit what I do to avoid accidents	.773				
j	Cancel activities if unexpected period	.709				
s	Have to rest during full flow	.647				
b	Just can't prevent accidents	.567				
m	Wear different clothes during period	.560				
r	Spend a lot on pads etc. and washing			.542		
p	Can not afford money spent on periods			.809		
q	If run out difficult to get extra supplies			.797		
t	Leakage causes problems laundering			.671		
c	Feel unwell during period				.760	
e	Irritable while period is happening				.804	
g	Pattern of flow is unpredictable		.767			
n	Heaviness varies period to period		.723			
f	Period goes on too long		.721			
u	Never sure when period is finished		.672			
o	Periods have changed from normal		.666			
i	Never sure when full flow is starting		.465			.645
h	Wear protection before in case					.704
	% variance accounted for by component	21%	17%	13%	9%	6%

* *each loading is the correlation between the coresponding item and factor, and for simplicity only loadings greater than 0.4 are shown*

Figure A5.2.1 Distribution of estimated component scores for 'dealing with periods', separately by self-statement or not of bleeding as reason for clinic attendance
(low score = favourable, high score = adverse)



Bleeding is self-stated reason for clinic attendance?

Perusal of the box-plots show a number of outlier or extreme component scores, plotted as circles or stars respectively. The suggested interpretation is that for these cases the factor model is inadequate (Tabachnick BG & Fidell 1996b). Examination of the individual data may yield insights as to why the cases (factor scores) are outliers. In the meantime, for the analyses of Chapter 9, the scores have been subjected to non-parametric statistical methods, or recoded into quintiles, so avoiding undue influence by outlier scores.

5.2.3.ii MBQ question 23 items - 'Feelings about periods'

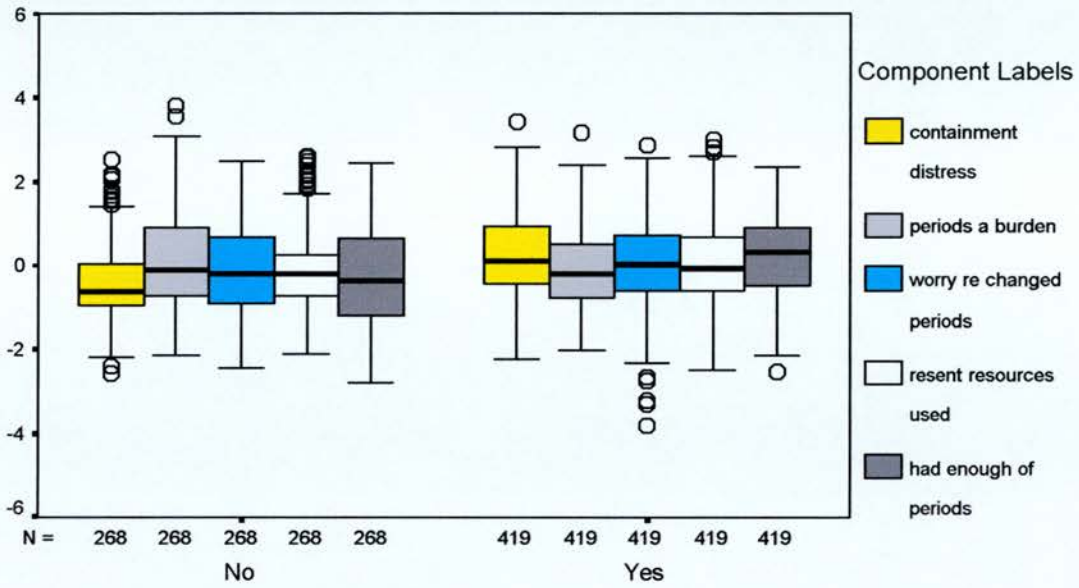
Similarly, the results for the principal component analysis for MBQ question 23 data, addressing emotional reaction to menstrual experience, are presented in **Table A5.2.2**. A box-plot of estimated component scores is given in **Figure A5.2.2**.

Table A5.2.2 Loadings* for estimating component (factor) scores for 'feelings about periods' – items from MBQ question 23 (n=687)

Item	COMPONENTS (FACTORS) 1: Containment distress		2: Periods a burden	3: Worry about change in periods	4: Resent resources used	5: Had enough of periods
a	Upsets me no way to avoid accidents	.748				
c	Worry all the time I need to change	.698				
y	Blood leakage on clothes is embarrassing	.689				
r	Worry if I will be able to avoid accidents	.676				
b	Annoyed I have to wear different clothes	.660				
nn	Dread difficulty of containing flow	.660				
w	I find flow overwhelming	.623				
k	Leakage onto bedding is embarrassing	.607				
dd	Blood stains are a nuisance to deal with	.599				
aa	Worrying about accidents is worse	.565				
u	Embarrassing to have to keep changing	.642			.416	
p	Feel abnormal buying such a lot of pads	.502			.598	
x	Feel embarrassed buying such a lot	.469			.643	
bb	Spend whole life thinking of changing	.446	.400			
m	Feel abnormal with such heavy periods	.486	.407			
n	Embarrassing cancelling arrangements	.683	.469			
i	Upsets me if have to cancel unexpectedly	.628	.495			
d	Annoyed at having to limit what I do	.682	.523			
s	My periods are intolerable	.407	.578			
e	I get upset by my period	.471	.591			
ii	Worry ahead of period because of impact	.411	.593			
ll	Feel bad family/friends are affected		.764			
ff	My periods put a burden on family/friends		.742			
t	My periods make me low/depressed		.644			
mm	My periods have taken over my life		.618			
j	Wish for someone to talk to re periods		.547			
l	My periods make me less healthy		.542			
q	My periods make me tired		.516			.412
pp	My periods feel like a punishment		.419		.493	
ee	Worries me my periods have changed			.787		
v	Wish my periods could be how they were			.691		
kk	Worry change means something serious			.670		
hh	Difficult as never sure when full flow			.534		
cc	Bothers me never sure when finished			.513		
jj	Sanitary protection is a waste of money				.759	
g	Resent all the money spent on pads etc.				.694	
oo	No more periods would be a great relief					.834
z	I just wish an end to periods					.824
	% variance accounted for by component	23%	17%	10%	10%	7%

** each loading is the correlation between item and factor, and for simplicity only loadings greater than 0.4 are shown*

Figure A5.2.2 Distribution of estimated component scores for 'feelings about periods', separately by self-statement or not of bleeding as reason for clinic attendance
(low score = favourable, high score = adverse)



These scores also show some evidence of outliers, but rather less than in the factor model for 'dealing with periods'. In Chapter 9 the same analytic approach has been taken for these components scores as for those presented in **Figure A5.2.2**.

5.3 RELIABILITY OF QUESTIONNAIRE DATA ABOUT PERIODS

5.3.1 Overview

In this Appendix some issues of data reliability are considered.

5.3.2 Concordance of data from different questionnaires

The same question about duration of period was asked in CQ and MEQ and, as can be seen from **Appendix Table A5.1.2**, the distribution of durations of usual period was very similar to that reported by the entire study group completing the CQ item.

There was also replication on MEQ (not reported) of the pattern for shortest and longest periods shown on CQ and presented in **Appendix Table A5.1.2**.

Although the subset of 821 women completing MEQ were very similar to the entire study sample in terms of their prevalence of use of double protection as reported on CQ, 62% compared to 60%, their prevalence of use of double protection as reported on the MEQ item addressing this issue differed slightly from the CQ report (69% v 62%, n=819). This difference may be due to the different wording. The CQ item posed a binary 'yes/no' question, whereas the MEQ item allowed some sense of the *frequency of use* of double protection to be indicated. For this item format 42% reported using double protection 'most periods', with another 27% reporting use 'some periods', and the remainder responded 'no'. A further difference was that the MEQ item asked a matter-of-fact question, whereas the CQ item was worded as an imposition 'Do you have to use..?'. Therefore responses on these two items would be expected to differ.

5.3.3 Reliability of data about menstrual experience

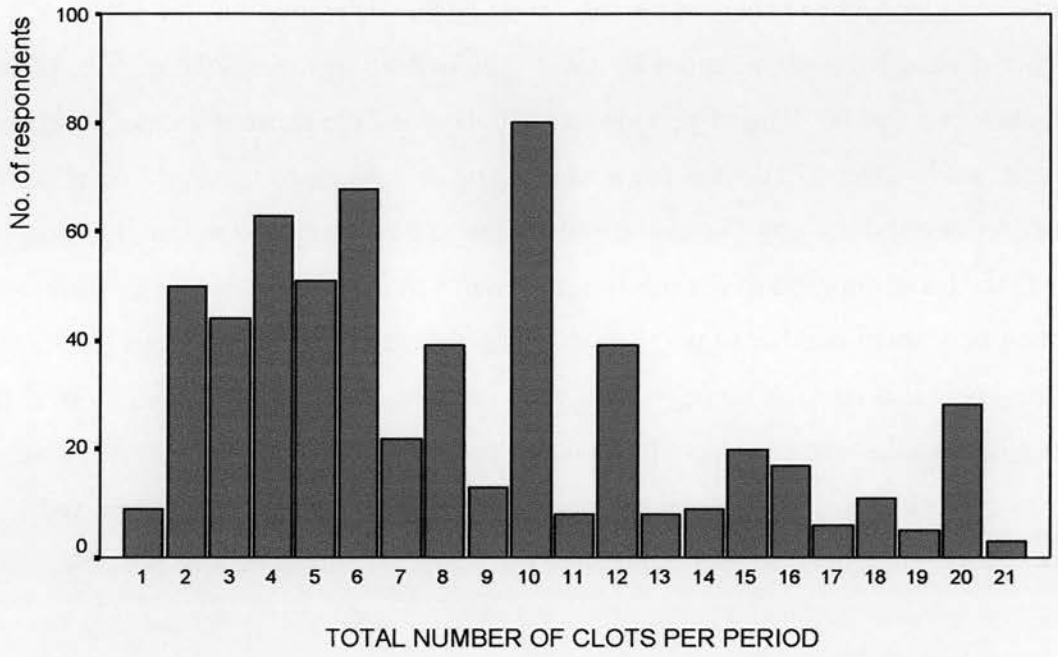
There are concerns about some of the high values, for days bleeding, days use of double protection, and for number of clots, all data intended to describe the usual count, per period, over the last 6 months. Given the variable nature of periods for most women, these data may be subject to recall error. In addition, it is possible that some women may have misunderstood the purpose of the specification of a time frame of the last 6 months, and thought a *total* count over this time was required,

rather than 'usual *per period*' over that time.. The positive skew of most of these variables, and anecdotal reports of extreme values – such as 'bleeding continuously for 6 weeks', makes it difficult to establish clear outliers by examination of the distributions. Some internal checks are possible, but even where the conditions tested are satisfied, this may merely indicate consistent reporting for a total of 6 months across a number of the questionnaire items. However, for those women who proceeded to menstrual collection, it will be possible to compare their prospective recording of duration of bleeding, sanitary protection use and clots against the accumulated counts provided in the retrospective questionnaires.

As was seen in **Appendix Table A5.1.2**, from the maximum count for each clot size (50, 50 and 30 respectively), some women reported very high numbers of clots. It is possible that some of the high values arise because the question was misunderstood, and reporting was for numbers of clots for the 6 months *in total*, not as requested, 'per period'. However, these counts were not stark outliers. Although occurrence of clots has been recorded in past research, for the purposes of calculating menstrual blood loss, or for making adjustments to such calculations, these data have not been reported. Therefore it is not possible to compare the counts for clots reported in this study with past research.

For reported counts, especially where varying in occurrence and vaguely recalled, there would be expected to be evidence of digit preference at multiples of 10 and to a lesser extent 5. If women have totalled up counts for the 6 months it may be expected that the values reported would be more likely to be multiples of 6 (provided that respondents are familiar with the 6 times table). The histogram presented in **Figure A5.3.1** shows clear peaks at 10 and 20, but also some evidence of peaking at 6 and 12.

Figure A5.3.1 Histogram of total number of clots per period - selected data, all women completing MEQ, with between 1 and 21 clots in total (n=673 of 725 completing item)



For the 546 women who used double protection, the distribution of days' use reported showed that relatively few used this strategy for just 1 day (5%), the majority for 2 to 5 days (82%), and a further 12% for 6 to 15 days. The highest values, such as the maximum of 30 days, and the next smaller value, 25 days, may indicate a misunderstanding of the question, or errors in the data. The duration of use of double protection was compared against the usual duration of bleeding. The woman reporting 30 days double protection did not report her usual duration of bleeding but did report 30 days of bleeding *between* periods (requiring sanitary protection), and the woman reporting 25 days double protection reported her usual duration of period as 30 days. Although these two values for double protection use are therefore plausible, there were also 6 women for whom the days of double protection reported exceeded the usual days of bleeding reported. Two of these also completed MEQ, and recorded days of break-through bleeding requiring sanitary

protection, so it is possible that containment of this unpredictable loss accounted for some of the discrepancy, for them and for others who did not complete MEQ.

For those whose periods varied in duration, from cycle to cycle, and who recorded duration of longest and shortest periods (n=732), the difference was for 50% of them between 2 and 8 days (maximum 86 days). The woman reporting 70 days bleeding did elaborate that her longest periods were 70 days and her shortest 2 days, so in this case it would appear 70 days is *not* a totalling up of days bleeding over 6 months, but an experienced duration of what she understood to be a 'period'. On both CQ and MEQ the usual duration of periods reported was 5 to 7 days (IQR), though there were a very small number of women who reported extremely long periods (31 days or 70 days). It is possible some women were totalling up all days of bleeding over the last 6 months, instead of reporting usual duration, in the last 6 months, of bleeding *per period.* However, there were certainly some women who elsewhere reported bleeding continuously, so such excessive 'durations' of period may be possible.

Appendix to Chapter 6: Quantification of loss

6.1 DETAILS OF OUTLIERS AND EXCLUDED CASES

Table A6.1.1 Further details of outliers and excluded cases in Chapter 6 regression analyses estimating menstrual volumes

Code	Blood Vol. (mL)	Total Fluid (mL)	Other features (Centre: G=Glasgow,E=Edinburgh)	Analysis where found	Action
A	57	509	Used all non-study pads, heavy ones. (G)	Table 6.2 analysis 2 Table 6.6 analysis 1	Excl. Excl.
B	65	306	Used standard pads. (G)	Table 6.2 analysis 3 Table 6.2 analysis 5	Retain Retain
C	58	267	Used large number of products, a third of these non-study. (G)	Table 6.2 analysis 5	Retain
D*	18	<1	Fluid measurement unreliable at low volumes, and residual extreme. (G)	Table 6.6 analysis 1 Table 6.7 incl. fluid	Excl. Excl.
E*	8	4	Fluid measurement unreliable as for D, but residual not extreme. (G)	Table 6.6 analysis 1 Table 6.6 analysis 2	Retain Retain
F*	9	18	Relatively large number of products (17) for loss contained. (E)	Table 6.6 analysis 2	Retain
G	493	593	Relatively very small number (24) of products for huge menstrual loss. (G)	Table 6.6 analysis 2 Table 6.7 chart data	Retain Retain
H*	2	47	Very low blood volume for fluid. Possible optical density error. (E)	Table 6.7 incl. fluid	Excl.
K*	107	57	Very high blood volume for fluid and possible optical density error. However, non-extreme residual. (E)	Table 6.7 incl. fluid	Retain

* *These collections would have been excluded from Table 6.2 analyses 2 to 5 since those analyses were restricted to cases with total fluid volume ≥ 80mL.*

Appendix to Chapter 7: Measurement issues

7.1 QUALITY CHECK 1: MEASUREMENT OF MENSTRUAL VOLUMES

7.1.1 Aim

To check process of measurement of blood and total fluid volumes of menstrual collections.

7.1.2 Method

A unit of fresh whole blood bank 'blood' was obtained and used to simulate three menstrual collections, two each with blood volumes 25mL, 65mL and 110ml. In addition six venous blood samples were 'created'. For each 'collection', phosphorylated saline was mixed with the blood to make the total menstrual loss up to likely total menstrual fluid losses (60mL, 125mL and 210mL respectively). Each menstrual loss was poured onto a set of sanitary pads, the number of pads used being roughly in proportion to the loss volume. Each 'collection' created was then placed in a polythene bag, without recourse to nappy sacks to seal individual products, and after about 10 minutes, sealed. The collections were then left to stand for two days. Each nurse was provided with one collection of each volume, and asked to follow the study procedure to ascertain the total collection weight and volume of blood loss. Both nurses were blind to the volumes of blood and total fluid that had been simulated.

7.1.3 Results

For this first quality check results for the total fluid measurement were excellent. The total fluid volumes simulated were 60mL, 125mL and 210mL. Total fluid estimates were within 0.6mL (1%) for the lightest loss (estimated volumes of 60.6mL and 59.5mL for Edinburgh and Glasgow respectively), within 2.3mL (1.8%) for the mid-loss (volumes 127.3 mL and 124.5mL), and within 4.4mL (2%) for the heaviest loss (volumes 214.4mL and 212.2mL).

The blood loss measurements however deviated disturbingly from the simulated blood losses, with marked underestimates at both centres for the lower losses, and

over-estimate for the heaviest. For the first two collections (25mL and 65mL blood loss volumes), the blood volumes estimated were under by 14ml (56%) or more for the lighter loss (estimated blood loss volumes at Edinburgh and Glasgow of 3mL and 11mL respectively), and under by 24mL (37%) or more for the moderate loss (volumes of 41mL and 26mL respectively). For the highest blood loss collection, 110mL, the last collection to be created, the estimate in Edinburgh was under by 9mL (8%) but the estimate in Glasgow over by 60mL (55%) (estimated volumes of 101mL and 170mL respectively).

7.1.4 Conclusions

Reflection on and discussion of these surprising blood extraction results led to the realisation that the simulated losses which had been underestimated were those which had been created first, the 25mL and 65mL losses, and the closer/over-estimates were for the last collections to be created. A possible mechanism was that in the 'blood' obtained from the blood bank there had been settling of the red blood cells in the blood pack, resulting in a lower proportion of red blood cells per volume in the earliest collections to be created. The order of creation of two collections of the same blood loss volume was not recorded, so it was not possible to check this potential explanation within 'equal' collections, but it was felt this may explain the one slightly under-estimate, and one grossly over-estimate in the two heaviest collections, the last to be created. It was decided the quality check needed to be re-run.

7.2 EXPERIMENT 1: TUBES, DILUTIONS AND SOAKING TIME

7.2.1 Aim

To evaluate the effects of venous sample tube and dilution, and soaking time.

7.2.2 Method

This factorial design required the measurement by each research nurse in her usual laboratory setting of the optical density for two different venous blood samples, both provided in each of two different tubes (purple cap or orange cap), but not labelled so as to be able to be paired. Each nurse was to measure each of her 4 assigned samples mixed with NaOH at two different dilutions (1 in 100 and 1 in 200). Spectro-photometric measurement was to be undertaken at each of three time points after mixing (48 hours, 4 weeks and 9 weeks). Therefore the design comprised 5 factors (nurse/centre, blood sample, tube, dilution of blood sample, delay to measurement) and resulted in a total of 48 data values.

7.2.3 Results

Analysis of variance showed, as would be expected, that the optical densities differed by dilution, but they also differed by centre ($F=25$, $df=1,38$, $p<0.001$), by delay to spectro-photometry ($F=6.3$, $df=2,38$, $p=0.004$), and there was an interaction between these last two factors ($F=6.6$, $df=2,38$, $p=0.003$). There was no effect of tube type, and as it happened the haemaglobin levels of the two bloods used were fairly similar. Interpreted, these findings were that Edinburgh optical densities were generally higher, optical densities declined with time to 4 weeks, and if measurement was delayed to 9 weeks after setting up then this pattern of decline in optical density continued for Glasgow but was reversed at Edinburgh.

The average optical densities, respectively for the two bloods used, were at 48hrs delay to measurement and 100ml dilution, 0.615 and 0.549 in Edinburgh and 0.539 and 0.562 in Glasgow, and at 200mL dilution 0.280 and 0.273 in Edinburgh and 0.272 and 0.272 in Glasgow.

However, since blood loss determinations use the relative optical densities of two solutions (menstrual and venous) measured within the *same* centre and after the same time delay, the between centre and by time differences may not matter, as long as the ratio of the optical densities for the two dilutions remains constant. Analysis was undertaken of the *ratios* of the optical densities for the corresponding 100mL and 200mL dilutions of the same sample. Given ideal proportionality of the relationship between optical density and concentration this ratio would be expected to be 2, whereas the overall mean for the data from this experiment was 1.96. Non-proportionality will be considered in **Appendix 7.6**. However, with regard to the factors under consideration in this experiment, there were no significant differences by centre, tube type, standing time or blood sample, nor any significant interactions with centre. **Table A7.2.1** shows the mean optical density ratios by centre and standing time, and it can be seen that the ratios reduce slightly with time.

Table A7.2.1 Ratio of optical densities (1 in 100 diluted blood : 1 in 200) by centre and standing time

Centre	Standing time	Optical Density Mean Ratio (100mL dilution:200mL)	95% Confidence Interval Lower	Upper
Edinburgh	48 hours	2.11	1.88	2.34
	4 weeks	1.91	1.68	2.14
	9 weeks	1.83	1.60	2.06
Glasgow	48 hours	2.03	1.80	2.26
	4 weeks	1.97	1.74	2.20
	9 weeks	1.89	1.66	2.12

It should be noted that both blood samples used for the experiment had good haemoglobin levels, and so these data apply to ratios of optical densities at the corresponding points on the haematin concentration axis. For different concentrations of similar blood (even if one sample is twice the dilution of the other,

say 1 in 200 and 1 in 400), or for blood samples with different levels of haemoglobin, the results might be very different. The confidence intervals reported for the ratios in **Table A7.2.1** are fairly narrow, but it should be remembered that these are confidence intervals for the *mean* ratio, not for individual determinations.

The similarity of the patterns in Edinburgh and Glasgow, for ratios of 100:200mL diluted optical densities, is in contrast to the disparity observed above with respect to absolute optical densities, where Glasgow readings continued to decline between 4 weeks and 9 weeks but Edinburgh readings increased by 9 weeks. The differing time patterns for absolute optical density readings and ratios, by centre and delay time, suggests that some technical artefact may have disturbed the 9 week optical density readings in Edinburgh. Fortunately it would appear, judged by the ratio of the readings for the two dilutions, that the reading ratios were comparable with the ratio for the same delay time in Glasgow, so the machine (or measuring process) appears to have remained internally consistent.

A measurement task that would correspond to this simulated exercise would be that of a collection with 80mL blood loss from a patient with normal haemoglobin levels, soaked in 8L NaOH, being measured against a 1mL blood sample diluted to 200mL. Depending on the delay to spectro-photometry the ratios in **Table A7.2.1** would predict a trend in blood loss estimations with time delay, from 81 to 75mL in Glasgow and from 84 to 73mL in Edinburgh.

The overall *mean* ratio at 48 hours (ignoring centre) was 2.07 (95% CI 1.9 to 2.2), but for an individual blood loss determination, the 95% prediction interval for the individual collection optical density ratio at the same time point (48 hours) is 1.62 to 2.46. For the measurement task described the previous paragraph this corresponds to a blood loss determination, for 95% of such 80mL true blood volume collections, ranging between 65 and 98mL.

7.2.4 Conclusions

Tube type had no bearing on optical densities. Optical densities did differ markedly by centre and time to measurement, but when the within-sample optical density *ratios* (1in 100 dilution to 1in 200) were considered there was no detectable effect

between centres nor across time. There was a trend for decline in optical density ratio with time, albeit not statistically significant in the small experiment undertaken. Optical density ratios varied quite markedly between individual readings, such that an 80mL blood loss collection requiring spectro-photometric assessment of two dilutions of blood (1 in 100 and 1 in 200) would in 95% of such determinations estimate the blood volume as between 65mL and 98mL. These results do not inform as to the situation at concentrations outside the range of 1:100 to 1:200 dilution of blood of normal haemaglobin content, nor in situations where very similar concentrations for venous blood and soaking solution are compared spectro-photometrically (say 1:150 to 1:150).

7.3 EXPERIMENT 2: VOLUME OF NAOH FOR SOAKING, AND FILTRATION/ DILUTION OF SUPERNATANT

7.3.1 Aim

To evaluate the impact of actual menstrual blood loss volume, volume of NaOH used for soaking, filtration method, and subsequent dilution of filtrate on *determination* of menstrual blood volume.

7.3.2 Methods

This simulation addressed the processes applied to the supernatant, with no sanitary products involved. The relevant volume of venous blood was simply mixed with the relevant volume of NaOH. In fact, to reduce the volumes of blood and NaOH needed for the experiment, the mixing was done in proportion, to produce about 500mL of each of the four differing 'supernatant solutions'.

The factorial design required the measurement by each research nurse in her usual laboratory setting of the optical density for two simulated menstrual loss collections (80mL and 120mL blood loss volume) soaked in differing volumes of NaOH (2L and 4L). Each of these 4 samples of 'supernatant' was to be filtered in two ways (through double regular filter paper and through single stiffened filter paper). Spectro-photometric measurement was then to be undertaken at 2 dilutions of the filtrate (undiluted and diluted 1 in 5 – that is, 20 mL filtrate made up to 100mL with NaOH). Therefore the design comprised 5 factors (nurse/centre, volume of blood loss in collection, volume of NaOH for soaking, filtering method, dilution or not of supernatant prior to optical density measurement) and resulted in a total of 32 data values. Two blood sources were used, one being used for the 120mL in 2L and 80ml in 4L supernatants, the other for the 80mL in 2L and 120ml in 4L supernatants, so blood source needs to be taken account of in the analysis. The nurses were blind to the 'collection' volumes of blood and non-blood fluid that were simulated.

7.3.3 Results

Some high optical density readings were indicated by the spectrophotometer as 'unreliable', those for the samples with highest blood concentration (the samples with 2L NaOH for 'soaking' and no secondary dilution). In addition, the readings for 120mL blood in 4L NaOH, undiluted, exceeded 1,which is beyond the range of the optical density scale where reliable measurement is expected. Therefore it was felt it would be advisable to restrict analysis to only the diluted supernatants, and the undiluted supernatant with lowest concentration (and hence optical density readings less than 1), that with 80mL blood in 4L NaOH. This left 20 readings in all for analysis and prevented examination of the preservation of proportionality when diluting the supernatant by a factor of 5. (However, we have already seen in Experiment 1 (**Appendix 7.2**) that the observed ODs suggested lack of proportionality for pairs of readings where one of the pair of solutions was twice the concentration of the other.)

To reduce the number of variables, the proportion of blood volume to total volume of 'supernatant', *Blood Concentration*, was calculated as

$$\frac{\textbf{Volume blood}}{\textbf{[(Volume NaOH + Volume Blood) } \times \textbf{ Dilution factor]}}$$

Regression analysis was undertaken of optical density by centre, blood source, filter and blood concentration. The overall regression analysis gave $F>4000$, df 4,19, $p<0.001$, and revealed that as expected optical density was very strongly linearly related to blood concentration [$\mathbf{b}_{\text{blood conc.}} = 48.0$ (95% CI= 47.2 to 48.8)]. It also showed that the optical density was slightly reduced if double standard filter paper was used [$\mathbf{b}_{\text{double filter paper}} = -0.014$ (95% CI= –0.022 to –0.006)]. That is, in terms of average optical densities, the optical density was lower by 0.014 if double filter paper had been used.

7.3.4 Discussion

The effect of filter paper type on optical density must be a result of excess absorption of heme chromogens in the double filter paper. Since in the formula for calculation

of blood volume, the optical density (for the menstrual solution) is multiplied by the effective volume of NaOH, the impact of the discrepancy in the OD due to filtration method will depend on that volume. For measurement of a collection effectively diluted in 4L of NaOH, say a blood loss of 80 mL, use of double filter paper (rather than stiffened) would result in the volume being under-estimated by 1.04mL. For a collection with a soaking volume of NaOH of 20L, say losses of 80 or120mL, the under-estimation of the volume would be by 5.19mL.

7.3.5 Conclusions

It was found the double filter paper used in Edinburgh resulted in slight underestimation of the blood volume. Since this affected only the collection optical density, the extent of underestimation is multiplied up if greater effective volumes of NaOH are used, from 1mL underestimation to 5.2mL if the volume of NaOH is increased by a factor of 5. This study highlighted the importance of NaOH volumes that ensure low enough concentrations of haematin for reliable readings. The upper limit of acceptable blood concentration is 80mL blood in 4L NaOH.

7.4 QUALITY CHECK 2: MEASUREMENT OF MENSTRUAL VOLUMES

7.4.1 Aim

To check process of measurement of blood and total fluid volumes of menstrual collections, in particular to check measurements when loss volumes were relatively high.

7.4.2 Method

This was a re-run of quality check 1, but taking care to stir the blood thoroughly prior to creating each simulated loss. In addition 2 packs of whole blood were used, to allow simulation of heavier collections. Three menstrual collections were created, two each with blood volumes 70mL, 120mL and 190ml. For each 'collection', phosphorylated saline was mixed with the blood to simulate the likely total menstrual fluid losses (160mL, 260mL and 420mL respectively). In addition a 'venous blood sample' was created for each collection. Each menstrual loss was poured onto a set of sanitary pads, the number of pads used being roughly in proportion to the loss volume, and each 'collection' created was then placed in a polythene bag, without recourse to nappy sacks to seal individual products, and after about 10 minutes, sealed. The whole blood was also used to provide simulated venous blood samples in purple tubes. The collections were left to stand for two days and then each nurse was provided with one collection of each volume, and asked to follow her usual study procedure to ascertain the total collection weight and volume of blood loss. Both nurses were blind to the volumes of blood and total fluid that had been simulated.

7.4.3 Results

For this second quality check, results for the total fluid measurement were not as accurate as for the first. The total fluid volumes simulated were 160mL, 260mL and 420mL. Total fluid estimates for the 420mL collection were within 4% of actual (under by 18mL in Edinburgh and 10mL in Glasgow), and for the 260mL collection within 3% of actual (exceeding the true value by 6mL and 3mL respectively). The

estimates for the smallest collection (160mL) were over by 7mL (4%) in Edinburgh and by 36mL (22%) in Glasgow.

The blood losses in the collections were 70, 120 and 190 mL, but as this was a full simulation, using pads, it would be expected that there would not be complete extraction of all the blood loss into the soaking NaOH. [Hallberg reported an extraction rate, per pad to which 10mL of blood had been added, equivalent to a mean underestimate of 3.7% (95% CI 2.7% to 4.7%) (Hallberg & Nilsson 1964).] The blood loss measurements in Edinburgh on the whole showed more extreme underestimation (-13%, -5% and -16% for the three simulated collections in order of increasing blood volume). On the basis of Experiment 2 (described above) some additional underestimation would be expected in Edinburgh due to the double filter paper used, but no more extreme than 1 to 2 mL underestimate (a further 1%). The Glasgow results however were puzzling and disturbing, in that blood volume was over-estimated (+26%, +35% and +13% respectively, for the three collections in ascending order of blood volume simulated).

7.4.4 Discussion

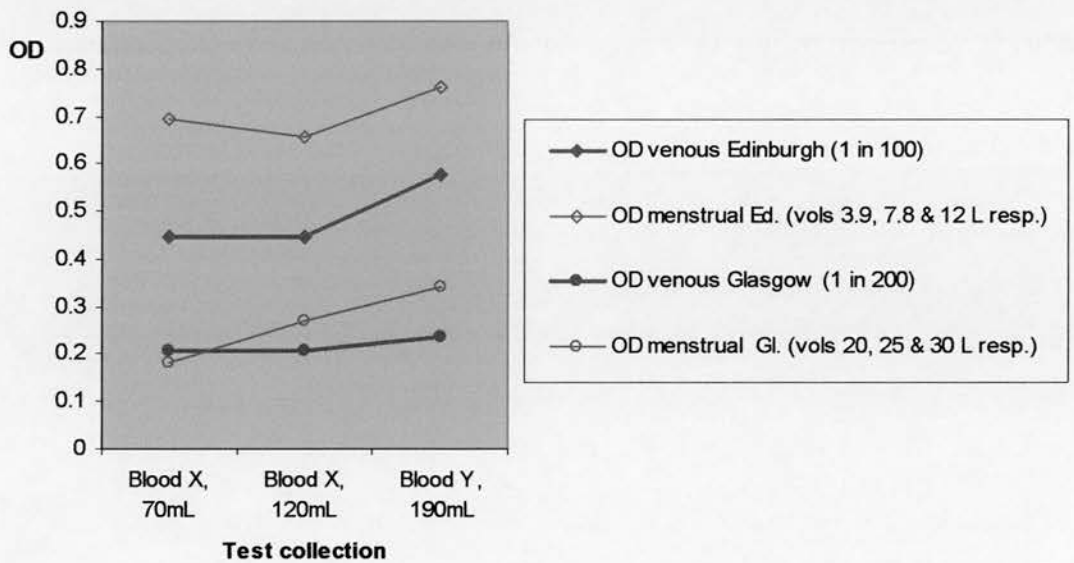
With regard to the total fluid volume measurement for the 160mL collection in Glasgow, by over 22%, it is possible that this was due to a transcription error in recording the total weight. If the 330.4 g total wet weight recorded was an erroneous transcription of a 303.4g weight reading, then the correct reading would have provided an estimate over by 9mL (6%).

With regard to blood volumes, some of the difference between Edinburgh and Glasgow estimated volumes may be due to differences in physical extraction rates of blood from the products into the soaking solution. With regard to the rest of the measurement process, slight differences may be due to the filter paper used in Edinburgh, as it has been shown in Experiment 1 (**Appendix 7.2**) that the double filter paper causes underestimation of blood volume by about 1 to 3 mL.

A further contributing factor may be the range of the optical density scale 'used' for calculations. The Edinburgh tests were undertaken at 100mL dilutions of the venous blood, and so optical densities for venous blood were in the range 0.44 to 0.58. The

soaking volumes of NaOH (3.9 to 6L), with subsequent dilution (1 in 2) of supernatant in two collections, giving effective soaking volumes of 3.9 to 12L), meant that the collection optical densities were in the range 0.654 to 0.762. In contrast, in Glasgow optical densities were lower, for venous blood (diluted 1 in 200) in the range 0.201 to 0.237. The soaking volumes of NaOH (2 to 3L), with subsequent dilution (1 in 10) of supernatant in all cases, giving effective soaking volumes of 20 to 30L), meant that the collection optical densities were in the range 0.181 to 0.339. This is illustrated in **Figure A7.4.1** where it can be seen that the Edinburgh spectro-photometric tests were typically at a higher point on the scale, and in addition that in Edinburgh there was greater separation between the *collection* optical densities and the corresponding *venous* optical densities.

Figure A7.4.1 Optical densities obtained in Edinburgh and Glasgow for quality check 2



Accurate estimation depends on optical density being proportional to haematin concentration, that is, that the relationship is a line through the origin. While for ranges of the concentration the relationship may well be linear, it may nevertheless be the case that the intercept is not zero. Furthermore, over the range of haematin concentrations the precise nature of the linear relationship may vary, in terms of

either or both of slope and intercept. This issue is further considered in **7.2.2.v** and **7.3.1.v**.

7.4.5 Conclusions

The total fluid measurements using standard pads and average weights were on the whole satisfactory (within 4% of actual fluid volume). There was one aberrant estimation, which was possibly due to a transcription error, the sort of error that could occur for fluid or blood loss volume measurements. The blood loss measurements were underestimated in Edinburgh (by 5 to 16%) and overestimated in Glasgow (by 13 to 35%). Some under-estimation may have been due to failure to extract all blood into the soaking solution, so consideration is required of the extent to which this may have differed between Edinburgh and Glasgow. Mechanisms for consistent overestimation are less easy to imagine. Further exploration is required of the extent to which under-estimation and over-estimation may arise as a result of failures in the proportionality between haematin concentration and optical density.

7.5 BLOOD LOSS ESTIMATION AND ADJUSTMENT FOR MENSTRUAL VOLUME

The formula for estimating blood volume in menstrual collection is based on the fact that optical density (absorbance) if proportional to haematin concentration.

If all haemoglobin in the blood is converted to alkali haematin in the presence of NaOH, then the concentration of heme chromogens in the alkali solution, corrected for volume of alkali used, is a direct indicator of the volume of haemoglobin in the blood contained in the solution. For an individual woman the concentration of haemoglobin in her menstrual blood loss is assumed to be the same as that in the venous blood. Using the following notation:

M = volume of menstrual blood loss to be estimated

h = concentration of haemoglobin in the woman's blood (per mL)
= amount of haematin in alkali solution, per 1 mL of blood added

V_v = volume to which 1mL of venous blood is diluted with NaOH

V_m = *initial* volume (mL) of NaOH used to soak menstrual collection

s = secondary dilution factor, such that 1mL of supernatant is diluted to s mL with NaOH, with s=1 if there is no secondary dilution

OD_m = optical density (absorbance) of supernatant for menstrual collection, after secondary dilution, if applied

OD_v = optical density (absorbance) of venous blood diluted as per V_v

The standard formula used to estimate volume of menstrual blood, and attributed to Hallberg (Hallberg & Nilsson 1964) is

$$\mathbf{M} = \frac{(OD_m \times V_m \times s)}{(OD_v \times V_v)} \quad \text{.. (i)}$$

Given that 1 mL venous blood produces **h** units of haematin (since concentration is h per mL), and V_v dilution of it still contains only 1 mL venous blood, then the diluted venous blood solution contains **h** units of haematin.

Therefore concentration of haematin in V_v dilution is $\mathbf{h / V_v}$.

Since optical density is proportional to concentration ($OD_v \propto h / V_v$),

$OD_v = \mathbf{k \times h / V_v}$ where k is a constant specific to a particular spectrophotometer.

So by manipulation,

$\mathbf{kh = OD_v \times V_v}$ ..... (ii)

Considering now the solution of the collection, the amount of haematin due to the menstrual blood loss will be $\mathbf{M \times h}$.

To establish the concentration of haematin in the supernatant we need to know the total liquid volume. This is the volume of NaOH added, plus the volume of blood in the collection i.e. '**M**' + $\mathbf{V_m}$. (Assuming the menstrual loss is blood only, and so has volume 'M'.) Therefore the concentration of haematin in the supernatant is ($\mathbf{M \times h}$)/('**M**' + $\mathbf{V_m}$), and

$OD_m = \mathbf{k \times (M \times h)/('M' + V_m)}$ where k is the same constant (same machine)...(iii)

If secondary dilution is used, say 1 mL of supernatant diluted up to **s** mL with further NaOH (with s=1 if there is no secondary dilution), then the formula (iii) becomes,

$$OD_m = \frac{\mathbf{k \times (M \times h)}}{\mathbf{s \times ('M' + V_m)}}$$ where k is the same constant (same machine)...(iv)

Re-arranging (and assuming that 'M' = M) gives

$\mathbf{M = (OD_m \times V_m \times s)/(k\,h - s \times OD_m)}$

And substituting for **kh** from (ii) this gives

$$\mathbf{M}_{\text{adjusted for blood volume}} = \frac{(OD_m \times V_m \times s)}{[(OD_v \times V_v) - (\mathbf{OD_m \times s})]}$$ .....(v)

This differs from the formula generally used, by the extra term '$-\mathbf{OD_m \times s}$' in the denominator. Using this derived correction would make the denominator smaller and hence **M**, the estimate of menstrual blood loss volume, bigger. So if the correction is not used the blood volume will be *under*-estimated.

This correction does not take into account the total volume of menstrual fluid loss, which as has been shown by Fraser is generally double the volume of the blood component (Fraser et al. 2001). If it was wished to correct for this, then if it is taken that the

total menstrual fluid volume = **2M**

and 2M is used instead of 'M' in equation (iii),

by the same sequence of re-arranging and substitution, a new formula is obtained:

$$\mathbf{M}_{\text{adjusted for TOTAL volume}} = \frac{(OD_m \times V_m \times s)}{[(OD_v \times V_v) - \mathbf{2OD_m \times s}]} \quad \text{.....(vi)}$$

This further diminishes the denominator, so the estimate for blood loss volume becomes even higher. The extent of underestimation by the standard formula (i) can be evaluated by taking the ratio of the standard formula to the adjusted formula (vi):

$$\textbf{Estimation (\%)} = [(M_{\text{regular formula}}) / M_{\text{adjusted for TOTAL volume}}] \times 100$$

$$= \frac{(OD_m \times V_m \times s)}{(OD_v \times V_v)} \Big/ \frac{(OD_m \times V_m \times s)}{[(OD_v \times V_v) - 2sOD_m]} \times 100$$

$$= \frac{[(OD_v \times V_v) - 2sOD_m]}{(OD_v \times V_v)} \times 100$$

$$= 100[1 - 2 \times s \times OD_m/(OD_v \times V_v)]$$

$$= 100[1 - 2 \times M/(2M + V_m)] \quad \textit{after substituting for the ODs} \text{ ..(vii)}$$

Therefore by subtracting from 100%, it can be derived that the percentage underestimation due to ignoring the addition to the supernatant of the menstrual blood volume and the roughly equal volume of non-blood in the menstrual loss:

$$\textbf{Underestimation (\%)} = \frac{\mathbf{2M}}{\mathbf{(2M + V_m)}} \times \mathbf{100\%} \quad \textit{using 2 x blood loss vol.} \quad \text{...(viii)}$$

Or, if we do not wish to assume that the Total Menstrual Fluid volume (TMF mL) is double the menstrual blood loss volume, and can measure TMF, then

$$\textbf{Underestimation (\%)} = \frac{\textbf{TMF}}{\textbf{(TMF + } V_m\textbf{)}} \times \textbf{100\%} \quad \textit{using } \textbf{\textit{total}} \textit{ menstrual volume} \quad ..(ix)$$

If, despite air-tight storage, there has been some evaporation of fluid from the used products, which is likely, then the underestimation will not be as much as indicated by the formulae above. However, evaporation is likely to be proportionately less in the heaviest periods, due to lower surface area of 'wetness'.

It should be noted that although it is the 'effective' volume of menstrual-NaOH solution, $\mathbf{V_m \times s}$, that is used for the purposes of calculation of menstrual blood loss volume (formula (i)), the volume of NaOH that applies when calculating the extent of underestimation due to menstrual fluid volume added to solution is $\mathbf{V_m}$, the *initial* soaking volume. This is because the key issue is the relative proportion of the menstrual loss volume in the initial NaOH soaking, and the bias this introduces to measurement. Subsequent secondary dilution will simply factor up the bias pro rata, and so retain it. This is made clear in formulae for the estimation and underestimation percentages (vii, viii and ix), which do not include any terms involving **s**, the secondary dilution factor.

7.6 BLOOD LOSS ESTIMATION AND FAILURE OF PROPORTIONALITY

In **Appendix 7.5** a necessary assumption for the estimation method was that optical density is proportional to concentration of haematin (OD $\propto$ h / V). For example, for the venous blood dilution **h** = haematin in 1 mL of blood and **V** = volume of blood and NaOH dilution/solution, then $\mathbf{OD_v = k \times h / V}$.

If the relationship is linear but not proportional, then

$\mathbf{OD_v = a + b \times h / V}$ where **a** is a constant (the intercept) and **b** is the slope.

Assuming the model applies across the range of concentrations to be used, from the equation for venous blood we get

$\mathbf{bh = (OD_v - a) \times V_v}$ ..... (i)

From the equation for menstrual solution, if (as in **Appendix 7.5**) **M**=menstrual blood volume, $\mathbf{V_m}$= initial soaking volume of NaOH, and **s** = secondary dilution factor:

$\mathbf{OD_m = a + b \times Mh / (s \times V_m)}$

We have for the moment ignored the addition to the total menstrual solution volume made by the liquid volume of the total menstrual loss (as considered in **Appendix 7.5**). Re-arranging the formula for $\mathbf{OD_m}$ gives

$\mathbf{M = (OD_m - a) \times s \times V_m / bh}$

And substituting for **bh** from (i) this gives

$$\mathbf{M}_{\text{allowing for non-proportionality}} = \frac{(OD_m - a)}{(OD_v - a)} \times \frac{sV_m}{V_v} \quad \text{..... (ii)}$$

Therefore, when proportionality does not in fact hold, application of the standard formula would lead to an error in estimation of

$$\textbf{Estimation Error}_{\text{standard -allowing for non-proportionality}}(\textbf{mL}) = \frac{OD_m \times sV_m}{OD_v \times V_v} - \frac{(OD_m - a) \times sV_m}{(OD_v - a) \quad V_v}$$

$$= \frac{a \times (OD_v - OD_m) \times sV_m}{OD_v (OD_v - a) \quad V_v} \ldots\ldots\ldots \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{(iii)}$$

If the ratio of the optical densities for the menstrual: venous solutions is written as $p = OD_m / OD_v$, then substituting for p we get an alternative formula:

$$\textbf{Estimation Error}_{\text{std. -adj. for non-proportionality}}(\textbf{mL}) = -a \times \frac{(p-1)}{(OD_v - a)} \times \frac{sV_m}{V_v} \ldots\ldots \text{(iv)}$$

If in formula (iii) we substitute for the optical densities, in terms of **b**, **h** and **M**, we get a further alternative formula that is easier to interpret:

$$\textbf{Estimation Error}_{\text{std. -adj. for non-proportionality}}(\textbf{mL}) = \frac{a}{OD_v} \times [\, sV_m / V_v - M] \ldots\ldots\ldots \text{(v)}$$

There are only three terms in the formula: **a**, OD_v and the term in brackets. Clearly estimation error will be zero if **a** is zero (proportionality applies). If not, then the error is greater in absolute terms for larger **a** (in absolute terms) and for smaller OD_v. With regard to the term in brackets, it is obtained by subtracting from the ratio of the effective menstrual soaking solution volume sV_m to the venous solution volume V_v, the menstrual blood volume **M**. V_v contains 1mL of the woman's blood and the menstrual solution sV_m contains **M**mL of blood, so if the sV_m volume could be chosen so that that solution had exactly the same blood concentration as the venous solution, then the ratio of the solution volumes would have to be **M**. In that case the difference would be zero, and hence the estimation error would be zero, even if non-proportionality applied. In the more usual circumstance that the ratio is not exactly equal to **M**, then estimation error will be greater for greater absolute difference between **M** and the ratio of solution volumes.

With regard to the direction of the estimation error, either or both of **a** and the term in brackets can be negative or positive. If only one or other is negative then the estimation error will be negative, meaning that the standard formula is *under*-estimating the blood volume. In the case that **a** is positive, then if the ratio of volumes of menstrual to venous solutions is less than **M**, as was typically the case in Edinburgh blood loss determinations, then the term in brackets is negative. Therefore, the estimation error is negative, meaning that there is *under*-estimation. If **a** is negative then the situation is reversed, and there will be *over*-estimation.

If both **a** and the term in brackets are positive or both are negative, the estimation error will be positive, meaning that the standard formula is *over*-estimating the blood volume. In the case that **a** is positive, then if the ratio of volumes of menstrual to venous solutions is *greater* than **M**, as was typically the case in Glasgow blood loss determinations, then the term in brackets is positive. Therefore, the estimation error is positive, meaning that there is *over*-estimation. If **a** is negative then the situation is reversed, and there will be *under*-estimation.

Formula (v) is the easiest to interpret, since its three terms are on the whole independent of each other. That is, **a** is a feature of the spectro-photometer, and possibly also of the range of the optical densities that are being measured; $\mathbf{OD_v}$ is a reflection of the laboratory practice in terms of dilution, and to a much lesser extent also of the woman's haemaglobin concentration; and the term in brackets is a reflection of the ratio of the menstrual:venous dilution volumes, and how this compares to the actual menstrual blood volume being estimated, **M**. However, since formula (v) is expressed in terms of **M** it is not so helpful in the situation that typically pertains, that the true value of **M** is unknown. In that case it may be easier to interpret formula (iii). The value for **a**, if non-zero, is almost certain to be close to zero, certainly less than the $\mathbf{OD_v}$'s that are likely to be obtained at even a 1 in 200 dilution. Therefore the bracketed term in the denominator, $(\mathbf{OD_v} - \mathbf{a})$ will almost always be positive. As before (formula (v)), one or both of **a**, and the numerator term in brackets in formula (iii), can be negative. Therefore, when the intercept **a** is greater than zero, then if $\mathbf{OD_m}$ is *greater* than $\mathbf{OD_v}$ there is a negative Estimation Error (comparing the standard formula assuming proportionality to the adjusted form

that should be used when there is non-proportionality, formula (ii)). This means that the standard estimate will be an *under*-estimate. However, when $\mathbf{OD_m}$ is *less* than $\mathbf{OD_v}$, then the numerator term in brackets will positive, as will the estimation error. So in this situation the standard estimate will be an *over*-estimate. Conversely, when **a** is less than zero, the pattern of under- and over-estimation is reversed, as found before with formula (v).

The absolute extent of deviation from the true value is less easy to judge by examination of formula (iii), because the optical densities are dependent on the choices of volumes for $\mathbf{sV_m}$ and $\mathbf{V_v}$. However, considered univariately, the absolute size of the estimation error *increases* directly with the absolute size of **a**, with the menstrual dilution volume $\mathbf{sV_m}$, and with the absolute size of the difference between $\mathbf{OD_v}$ and $\mathbf{OD_m}$. At the same time the absolute size of the estimation error *decreases* directly with increases in the absolute size of $\mathbf{OD_v}$, in the venous dilution volume $\mathbf{V_v}$, and in the size of the difference between $\mathbf{OD_v}$ and **a**. (Although probably only a theoretical possibility, it is worth noting that if $\mathbf{OD_v}$ 'approaches' **a** then the estimation error would become 'infinite'.)

$\mathbf{OD_v}$ is partly a reflection of the woman's haemoglobin level, but is also determined by the dilution factor for venous sample. All three formulae show that absolute estimation error increases with decreasing $\mathbf{OD_v}$. Since Glasgow typically used a dilution factor for venous samples twice that in Edinburgh, this gave OD's approximately *half* what they would be in Edinburgh (and hence also closer to **a**). So, all else being equal, greater absolute estimation error would be expected in Glasgow.

We have already seen that the size of the intercept **a** will influence the size of the error, but it should also be remembered that if the intercept is negative the whole pattern of error will be reversed, from under- to over-estimation.

The formulae (iii) to (v) were derived disregarding the addition to the menstrual solution volume due to the total liquid volume of the menstrual loss. The formula for the degree and direction of estimation error due to non-proportionality, also taking into account menstrual volume, corresponding to formula (v), would be:

Estimation Error$_{\text{std. –adj. for non-proportionality \& menstrual volume}}$ **(mL)** =

$$= \frac{a}{OD_v} \times [\, sV_m / V_v - M] - [M \times TMF/(TMF + V_m)] \ldots\ldots \text{(vi)}$$

This comprises essentially two separate components, the error due to non-proportionality, exactly as before, which may be positive or negative, and an additional component in this formula (relative to formula (v)), due to the impact of the menstrual volume added to the solution. This extra component is always negative error (or zero if the collection has been allowed to evaporate completely), and hence leads to a relative under-estimation.

7.7 FURTHER REFLECTIONS ON SPECTRO-PHOTOMETRY

In this Appendix further reflections are made on the issues of spectro-photometry and proportionality, in respect of **Figure 7.5**.

7.7.1 Extrapolation of simulation beyond the range of measured data

It should be noted that some of the Glasgow data have had to be extrapolated. The lowest concentration measured for the original data (shown in **Figure 7.1**) corresponded to a concentration of 1mL blood in 200mL NaOH, and gave an OD of 0.261. In practice ODs less than this were common in Glasgow, with 84% and 91% of menstrual and venous ODs there less than 0.261, in comparison to 27% and 2% respectively in Edinburgh (see also **Figure 7.3**). For the purposes of this exploration, of factors influencing errors in estimation, the same model used to fit the OD values between concentrations 0.02 and 0.005, was *extrapolated* to calculate OD values also for concentrations down to 0.0025. For the blood loss estimates made using the Glasgow process (green line), the data points marked with a solid diamond used fitted ODs corresponding closely to the *measured* data. The Glasgow data points marked with open circles correspond to blood volume estimates derived from the ODs *extrapolated* beyond the experimental data, albeit following the same linear relationship.

7.7.2 Possibility of range effects

One of the observations with respect to the measured data (**Figure 7.1**) was that the slope and intercept were not constant across the full range of the concentration values. Yet for this exploration of measurement error the OD values for concentrations lower than 0.005 have been obtained by extrapolation of the same line. It would thus be salutary to reflect on the impact if the OD values did not maintain the same line below concentration 0.005. Hence a second possible set of ODs was imputed for these concentrations, using a model with a higher intercept and flatter slope (a=0.06, b=38.5). Blood loss estimates calculated using these ODs are plotted as red stars. It can be seen that, all else being equal (that is, dilution volumes

and venous OD), if the intercept is higher then the estimation error is even more extreme.

These reflections show that where proportionality fails quite marked estimation errors can result, and that this is exacerbated for lower venous OD (as in Glasgow) and as the absolute size of the intercept **a** increases. In particular, if **a** is positive there will be over-estimation if the ratio of effective NaOH solution volumes $\mathbf{sV_m}$ /$\mathbf{V_v}$ is greater than the menstrual blood volume **M** (or equivalently, if venous OD exceeds menstrual OD). This latter condition was more often the case in Glasgow.

7.7.3 Possibility of a spectro-photometer effect.

It should be noted that the measured ODs (and underlying regression line) used as the basis for **Figure 7.5** were obtained using the *Glasgow* spectrophotometer, and so may not apply to the Edinburgh spectrophotometer. However, the graph does show what the impact of the differing measurement practices would be if both employed the Glasgow spectrophotometer operating in the way indicated by the observed data presented in **Figure 7.1**.

Since the measured ODs used as the basis for this exercise were obtained using the Glasgow spectrophotometer the observed linear relationship may not apply to the Edinburgh spectrophotometer. If the intercept in Edinburgh were to be negative then the estimation error would have been reversed, in terms of over- and under-estimation. While it is very likely that the model that best fits readings differs between spectrophotometer machines, it is also possible that it can vary within machine, from occasion to occasion. Experiment 1 (**Appendix 7.2**) showed that the 100 to 200 dilution OD ratios switched from over two to under two with standing time of the solution prior to measurement. Regression analysis confirmed that for the later data the intercept was negative. The best protection against measurement error due to non-proportionality would be to have the two samples to be tested as near as possible to each other in terms of concentration, and to have the venous blood *not* overly dilute.

7.8 EXPERIMENT 3: EVALUATION OF IMPACT ON BLOOD VOLUME ESTIMATE OF SQUEEZING/WRINGING OF PRODUCTS PRIOR TO SAMPLING FROM SUPERNATANT

7.8.1 Aim

To ascertain the extent of failure to extract entire blood loss if only soaking and 'prodding-stirring' are used.

7.8.2 Methods

The Edinburgh nurse was to undertake her next 5 collection measurements in her usual way. However, after having sampled from the supernatant, for filtering and spectro-photometric measurement, she was to don rubber gloves and squeeze/ agitate the products to ensure all blood extracted. She was then to repeat the sampling, filtering and measuring process, and re-calculate blood volume. (There would of course be a very small biasing upwards of the concentration at the second measuring, because some of the total volume of NaOH solution would have been removed. However this would be minimal, as only about 20 to 30mL need be removed for the testing.)

7.8.3 Results

The five collections when measured in the usual (Edinburgh) way gave estimated blood volumes of: 38.2, 46.1, 64.2, 69.9 and 111.1mL. On squeezing of products and re-measurement, the blood volumes estimated were 45.1, 49.2, 57.0, 77.3, and 177.5mL respectively. Therefore compared to thorough squeezing the Edinburgh process had estimated blood volume that differed from the squeezed estimate by –29%, –6.4%, +11%, –10% and –37%, the absolute differences in blood volume estimates being –7 mL, –3 mL, +7 mL, –7 mL and –66mL.

7.8.4 Discussion

Four out of five blood volume measurements were lower using the Edinburgh (non-wringing) method. For blood volumes in the range 40 to 77mL the differences were

within 7mL. However for the loss of over 100 mL difference was marked, 66mL (35% of the 'squeezed' estimate). The failure to mash or squeeze the products did lead to underestimation of blood volume in Edinburgh, and it is possible this is exacerbated for very heavy losses. In this case the heaviest loss comprised 14 tampons, as well as pads, and it is possible haematin does not extract as readily from tampons by soaking. Furthermore, the OD for the 'unsqueezed' supernatant was at the limit of acceptability, being 0.945. For the 'squeezed' supernatant the blood concentration was higher so the optical density exceeded 1. Therefore the supernatant was diluted by half and the OD re-measured, and then doubled to compensate. In fact this made little difference to the 'squeezed' blood volume determination (in this case lowered it by 1%). Perhaps the measurement issue is not just that there is greater non-proportionality for high optical densities but also that there is greater unreliability in readings, and that this applies even at the top end of the OD<1 range. Then the apparently extreme difference due to squeezing for the heaviest of these test determinations may have been accentuated by a biasing down of the 'unsqueezed' estimate due to an optical density reading that was by chance lower than it should have been.

7.8.5 Conclusion

The failure to mash or squeeze the products did lead to underestimation of blood volume in Edinburgh, and it is possible this is exacerbated for very heavy losses.

Appendix: Published papers

----- Original Message -----

From: Tony Delamothe

To: Pamela Warner

Sent: Wednesday, June 09, 2004 3:52 PM

Subject: Re: bmj.com webmailer: Permission to bind BMJ paper into thesis

Dear Pamela

You have our permission. (Thanks for asking.)

Tony Delamothe deputy editor, BMJ

"Pamela Warner" <p.warner@ed.ac.uk>
09/06/2004 14:59

To tdelamothe@bmj.com

cc

Subject bmj.com webmailer: Permission to bind BMJ paper into thesis

--- this message has been sent to you via bmj.com webmailer ---

I am shortly to be submitting a PhD thesis. A previously published paper of mine, published by BMJ [Warner et al, 2001, 323 (7 July) 24-28], reported some of the early (part)findings from the thesis study.

Our University requires that papers already published from the thesis project be bound in with the thesis. If reprints are used they need to be handstitched in. Alternatively, 'xeroxes' can be used, but then proof must be provided that the relevant Journal has given permission for this.

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Thank you in anticipation for your help.

Pamela Warner

Public Health Sciences
University of Edinburgh Medical School
Teviot Place
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December 1, 2004

Our ref: WarnerUEdinburghML12-04

Ms. Pamela Warner
University of Edinburgh
Fax: +44 131 650 6909

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Referral for menstrual problems: cross sectional survey of symptoms, reasons for referral, and management

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BMJ 2001;323:24–8

Abstract

Objectives To describe the menstrual experience of women referred for menstrual problems, in particular menorrhagia (excessive menstrual loss), and to assess associations with reasons for referral given by their general practitioners, the women's understanding of the reasons for their attendance at the hospital clinics, and clinic outcome.

Design Questionnaire survey, with partial review of case notes after 8 months.

Setting Three hospital gynaecology clinics in Glasgow and Edinburgh.

Participants 952 women completed the questionnaire, and the first 665 were reviewed.

Outcome measures Reason for referral, women's reported menstrual problems and reason for clinic attendance, diagnosis, and treatment.

Results Only 38% (95% confidence interval 34% to 41%) of women reported excessive menstrual loss as a severe problem. However 60% (57-63%) gave it as reason for attending a clinic, and 76% (73-79%) of general practitioners gave it as reason for referral. Reason for referral was significantly biased towards bleeding (McNemar odds ratio 4.01, 3.0 to 5.3, $P<0.001$) and against pain (0.54, 0.4 to 0.7, $P<0.001$). Dysfunctional uterine bleeding was diagnosed in 37% (31-42%) of the 259 women who gave as reason for attendance something other than bleeding. Women who were economically disadvantaged differed in prevalence of the main diagnoses and were more likely to fail to reattend. Hysterectomy was associated with referral for bleeding (relative risk 4.9, 1.6 to 15.6, $P<0.001$) but not with the patient stating bleeding as the reason for clinic attendance.

Conclusions Intolerance of the volume of their bleeding is not a key feature among women attending clinics for bleeding problems. Broad menstrual complaint tends to be reframed as excessive bleeding at referral and during management. This may result in women receiving inappropriate care. Conceptualisation and assessment of menorrhagia requires reconsideration.

Introduction

Menstrual problems account for much of the morbidity that occurs in women of reproductive age, being one of the four most common reasons for consulting a general practitioner.[1] Specifically, menorrhagia (excessive menstrual loss) is one of the most common reasons for referral to gynaecology clinics.[2] Organic disease is relatively uncommon with menorrhagia, but treatment typically involves powerful drugs or invasive surgery.[3,4] The formal clinical definition of menorrhagia is blood loss exceeding 80 ml per period, but objective measurement is rarely undertaken in routine clinical practice, despite reports that women are unreliable judges of their menstrual loss.[4] Unease has been expressed that management of menorrhagia is so dependent on "the personal history of the patient."[4]

Menstrual complaints typically present a complex clinical picture. A population survey among women of reproductive age found that 24% reported a recent painful period and 20% a heavy period, with about half experiencing both.[5] Mood changes around the time of a period were reported by 56% of those with heavy periods and 44% of those with pain.[5] The overlap of symptoms was similar in women referred to clinics with menstrual problems.[6] Such comorbidity among the three main menstrual complaints is likely to complicate healthcare seeking and management. Indeed, substantial variation in referral rates for menorrhagia has been reported, both nationally and internationally, and discordance has been found between symptoms and reasons for referral.[6,7] This is of concern because referral for menorrhagia is associated with a 60% probability of hysterectomy in the ensuing 5 years.[8] The pathway to the care for menorrhagia warrants careful study.

We undertook a cross sectional survey of women referred for menstrual complaints to hospital gynaecology clinics to assess the relation between symptoms, referral, and early management of menstrual problems. We aimed to ascertain whether patients and their general practitioners are concordant as to the reason for referral and whether subjectively reported excessive volume of menstrual loss is the basis for referral for menorrhagia.

Participants and methods

Study design

From 1996 to 1999 we undertook a cross sectional questionnaire survey of women aged 25 to 49 newly

referred for menstrual complaints to gynaecology clinics at Edinburgh and Glasgow Royal Infirmaries and Glasgow Western Infirmary. Exclusion criteria were attendance at the clinic for a menstrual problem in the previous year and a history of drug misuse or known to have HIV, or both. The ability to read simple English was a requirement for completion of the questionnaire.

We followed up and reviewed the case notes of the subset of women recruited early enough for eight months to have elapsed between initial appointment and the end of data collection. Our study was given ethical approval, and participants received written information about the study and provided informed consent.

Methods

The questionnaire assessed menstrual experience in several ways, including a subjective evaluation of blood loss. Women were also asked to report how problematic they considered various aspects of menstruation and the main reason for seeking help. We derived four summary variables from these responses, indicating whether there was a "severe problem" with volume of bleeding, pain, or cycle related changes and whether volume of bleeding had been noted as the reason for seeking help.

Reasons for referral were ascertained from the referral letters received from the general practitioners: as just over half (55%, 521 of 952) cited more than one reason, the research nurses recorded and coded the first two reasons. These codes were converted into four variables, indicating referral or not for excessive bleeding, pain, cycle related changes, or other reasons (for example, fibroids, endometriosis, irregular periods). In the same way the patient's understanding of the reason for attendance at the clinic was converted into four indicators.

We derived a Carstairs deprivation score (1 to 7) for each patient from their postcode sector.[9] Deprivation subgroups were combined as necessary to obtain fewer but larger strata (1 with 2 (most affluent), 3 with 4, and 6 with 7 (most deprived)). We reviewed the patients' case notes to ascertain management up to eight months after referral.

Statistical analysis

We tested for association in 2×2 tables by χ^2 with correction for continuity, by Fisher's exact test, or by McNemar's test if data were paired, and in tables with one binary and one ordinal variable by the χ^2 test for trend (χ^2_{trend}, df = 1). We used SPSS version 9.0. Data for duration are reported as medians and interquartile ranges. A small proportion (<4%) of information was missing; we report the effective (non-missing) sample size if different from the total sample size.

Results

Recruitment

We identified 1506 potential participants from the referral letters (fig 1). Only 4% of those invited to participate refused, but of those consenting 28% (368 of 1320) took the questionnaire home and failed to complete it, despite being reminded by telephone or letter. The 952 participants comprised 63% of eligible patients. Table 1 summarises the personal characteristics of the patients. The participants were similar to the 554 referrals who did not participate for age, deprivation score, and main reasons for referral. We reviewed the case notes of 665 (89%) of the 748 women recruited early enough for eight months to have elapsed before the completion of data collection.

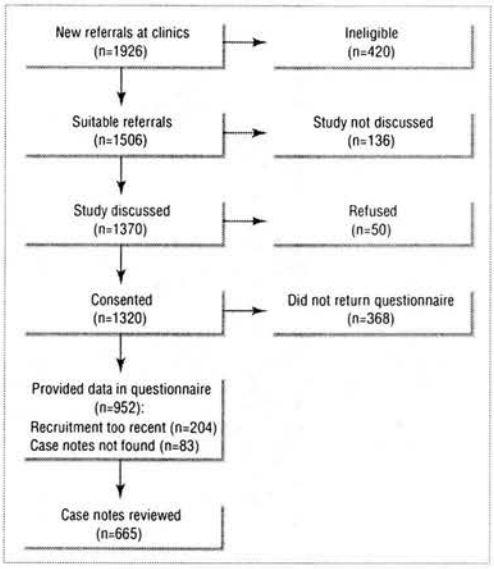

Fig 1 Study profile

Table 1 Personal characteristics of participants and non-participants

	No (%) of participants	No (%) of non-participants*
Age group (years)	(n=952)	(n=554)
25-29	90 (9)	58 (10)
30-34	164 (17)	93 (17)
35-39	224 (24)	124 (22)
40-44	257 (27)	152 (28)
45-49	217 (23)	127 (23)
Carstairs deprivation score	(n=934)	(n=544)
1 and 2 (least deprived)	179 (19)	91 (16)
3 and 4	327 (35)	179 (33)
5	183 (20)	135 (25)
6 and 7 (most deprived)	245 (26)	141 (26)
Parity	(n=950)	
No births	210 (22)	
1-6 births	742 (78)	
Reported heaviness of periods	(n=945)	
Light	30 (3)	
Moderate	152 (16)	
Heavy	420 (44)	
Very heavy	343 (36)	

*Eligible but not asked, refused, or defaulted.

Menstrual experience

A minority (36%; n = 343) of participants rated their periods as "very heavy" (table 1). The median duration of the current problem was two years (interquartile range 10 months to six years). Roughly equal proportions of women reported a severe problem with excessive bleeding, pain, or cycle related changes (fig 2), with considerable overlap between these. Overall, 587 of 948 (62%) reported at least one of these problems, 353 (37%) more than one, and 150 (16%) all three. A third of the women (32%, 301 of 940) had previously attended clinics for period problems, most of these (75%, 222 of 285) for the "same problem" as now.

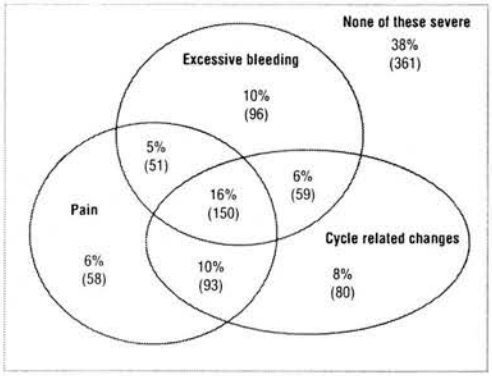

Fig 2 Percentages (numbers) of women experiencing as a "severe problem" one or more of excessive bleeding, pain around periods, or cycle related changes (n=948)

Table 2 Discordance between reason for referral by general practitioner and woman's stated reason for attendance

Reason for attendance	No (%) of discordant cases* (n=952)	Ratio (95% CI) of discordant reasons†
Bleeding	261 (27.4)	4.01‡ (3.0 to 5.3)
Pain	225 (23.6)	0.54‡ (0.4 to 0.7)
Cycle related changes	47 (4.9)	1.04 (0.6 to 1.9)

*Either doctor or woman cites reason but not both.
†Doctor only divided by woman only (McNemar odds ratio).
‡P<0.001 by McNemar's test.

Reasons for clinic attendance and referral by general practitioner

Each participant reported her belief as to the reason for attendance at the clinic: 568 of 952 (60%) stated bleeding problem, 283 (30%) period pains, and 67 (7%) cycle related changes, with 163 (17%) overall mentioning two. Referral letters cited excessive bleeding problems in 725 cases (76%), pain in 216 (23%), and cycle related changes in 68 (7%). In 27% of cases the referring doctor and the patient disagreed as to whether bleeding was the reason, and there was significant imbalance in the direction of discordance, with a ratio of 4:1 that it would be the doctor rather than the patient citing bleeding (table 2). There was a similar level of discordance about pain, but in the opposite direction, so that in discordant cases general practitioners were significantly less likely to mention pain.

Figure 3 illustrates the pathway to referral for menorrhagia. Among those who reported bleeding neither as a severe problem nor as a reason for seeking help, 63% were nevertheless referred for bleeding. Overall, of the 725 women referred for excessive bleeding, less than half (46%, n=330) had noted it as reason for seeking help, and this percentage breaks down as 60% (187 of 311) of those who reported bleeding as a severe problem compared with 34% (143 of 414) of those who did not.

Clinic outcome

Eight months after initial attendance at the clinic, no cancers had been detected in the participants, 53% (n=353) had been discharged, and 15% (n=98) failed to return for a further appointment. Table 3 shows that failure to return was strongly related to deprivation score, being more likely in disadvantaged groups, whereas there was an opposite gradient for diagnosis of fibroids, an association that persisted after controlling for age. Dysfunctional uterine bleeding (a diagnosis of exclusion, that no disease, such as fibroids, had been found that could account for reported abnormal bleeding) was the most common diagnosis (51%, 331 of 647; 175 with a "regular cycle" and 146 with an "irregular cycle"). After failure to return for further appointments, the most common final outcome was hysterectomy (12%, 79 of 661), with dysfunctional uterine bleeding or fibroids the most common indication.

Clinic outcome

Dysfunctional uterine bleeding was diagnosed for 34% (60 of 174) of the women who neither reported periods as very heavy nor reported excessive bleeding as a severe problem nor gave bleeding as reason for attending the clinic. In those referred by their doctor for something other than excessive bleeding, dysfunctional uterine bleeding was nevertheless diagnosed for 29% (46 of 158). Hysterectomy was likely if fibroids were diagnosed (39%, 33 of the 85 patients with fibroids). Among the remainder without fibroids as a possible indication for surgery (n=545), hysterectomy was strongly associated with referral for bleeding (relative risk 4.9, 95% confidence interval 1.6 to 15.6, Fisher's exact test

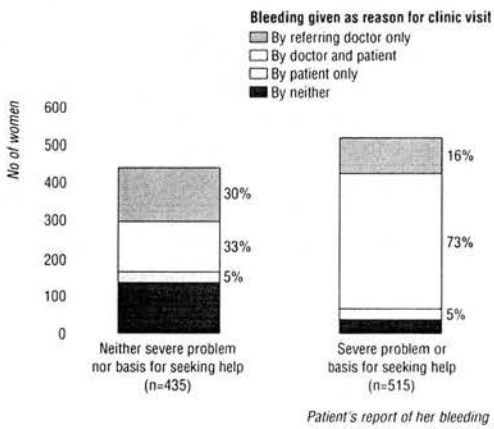

Fig 3 Frequency with which doctor, or patient, or both give "excessive bleeding" as reason for clinic visit, separately for two subgroups

Table 3 Failure to return for appointments and diagnosis of fibroids at eight months' follow up by deprivation subgroup

	Did not return for appointment			Fibroids diagnosed		
Deprivation subgroup	No in subgroup	No	% (95% CI)	No in subgroup	No	% (95% CI)
1 and 2 (affluent)	133	11	8.3 (4 to 13)	125	28	22.4 (15 to 29)
3 and 4	228	27	11.8 (8 to 16)	215	27	12.6 (8 to 17)
5	127	21	16.5 (10 to 23)	125	19	15.2 (9 to 21)
6 and 7 (deprived)	158	41	25.9 (19 to 33)	155	9	5.8 (2 to 9)
Overall	646	100	15.5 (13 to 18)	620	83	13.4 (11 to 16)
			χ^2 trend df=1, 18.1, P<0.0005			χ^2 trend df=1, 14.9, P<0.0005

P<0.001) but was only marginally associated with reporting volume of loss a severe problem (1.8, 1.02 to 3.2, P=0.051), and was not associated with excessive bleeding as the patient's reason for attendance.

Discussion

We found discordance as to the rationale for referral of women to gynaecology clinics. In over a quarter of cases the patient and general practitioner disagreed as to whether excessive menstruation was a reason, with the doctor four times more likely to be the only one citing bleeding. The proportions of women who reported severe problems with pain, volume of bleeding, or cycle related changes were similar (37% to 40%), with considerable overlap, and yet the predominant reason given for referral was bleeding problems (76%). Furthermore, this tendency for general menstrual complaint to be reframed as excessive bleeding seems to intensify within the clinic setting. Dysfunctional uterine bleeding is defined as "excessive bleeding for which no pathology can be found,"[10] yet dysfunctional uterine bleeding was diagnosed in 35% of women who had cited excessive bleeding neither as a reason for attendance nor as a severe problem. It was also diagnosed in 30% of women whose doctors had not given problematic bleeding as the reason for referral. Variation in referral rates for menorrhagia has been taken to reflect "clinical uncertainty about whether and how the problem should be treated."[3] Our data suggest more fundamental uncertainty about the concept of menorrhagia.

While acknowledging that objective measurement of volume of bleeding is rarely undertaken in routine clinical practice, guidelines on the management of menorrhagia do not offer alternative strategies for assessment of the complaint.[3 11 12] Rather, the requirement for a "convincing clinical history" is presumed to be uniformly understood and implemented. Yet we found that more than half (57%) of those referred for bleeding do not even judge their periods as very heavy. Perhaps this partly explains the "normal" measured blood losses commonly reported in women referred with menorrhagia.[13–15]

Strengths and weaknesses

Reasons for referral were extracted from general practitioners' letters, ensuring naturalistic data. The recording of two reasons when given, and the general brevity of the letters, minimised the need for subjective judgment. Participants were also asked their reason for attendance at the clinic, because earlier research found divergence between menstrual problems and presentation at a clinic.[5] That questionnaires were not returned by 28% of those recruited raises concerns, but participants were similar to non-participants for age, deprivation score, and reason for referral. Questionnaire surveys can deter those with poor literacy, but the questionnaire was brief and support was provided by a research nurse, ensuring broad participation. Deprivation scores have been utilised as a proxy for individual socioeconomic status, because the detail required for determination of social class can not be gleaned from a brief questionnaire. Although time constraints meant follow up was confined to the first 79% recruited, these women were similar to the entire study group for all key variables.

What is already known on this topic

Excessive menstrual loss (menorrhagia) is one of the commonest reasons for secondary referral of women, but there is no formalised clinical assessment in routine use

Management typically involves potent drugs or invasive surgery, with 60% of women having hysterectomy within 5 years

Many women referred for menorrhagia have menstrual blood loss that is not excessive

What this study adds

Discordance exists between symptoms and both referral and diagnostic pathways, arising from a disproportionate focus on menstrual bleeding

Among women referred for menorrhagia, volume of bleeding is not a key symptom

This raises concerns about conceptualisation and assessment of menstrual complaint and the appropriateness of healthcare provision

Explanation of findings

Although there may be no underlying serious disease or risk to physical health, periods can cause major distress and disability.[16 17] Many women are deterred from consulting by reticence about discussing menstrual problems, anxiety about investigations, or a lack of belief that medical help will be forthcoming.[18] In an opinion poll of 1069 women, 60% espoused the view that not enough attention is paid to problems with periods.[5] Patients may hold definitions of health and healthcare needs that differ from those of clinicians,[19] perhaps more so with periods, an intensely private event beset with societal constraints. Health needs that remain unvoiced within the consultation have been related to poor outcomes.[20] We found that pain around periods is commonly reported as problematic yet relatively "invisible" in the referral and diagnostic pathways, and also that the more deprived women were less likely to be diagnosed with fibroids, more likely to be diagnosed with dysfunctional uterine bleeding, and more likely to fail to return to the clinic (table 3).

Where there is comorbidity between menstrual complaints which one the doctor selects to give as the reason for referral may seem unimportant. We found, however, that among women free of disease (as a possible indication for surgery) hysterectomy was associated with referral for bleeding but not with volume of bleeding being reported as problematic. Perhaps referral for menorrhagia is strategic, based on the knowledge that it is likely to lead to surgery and aiming to increase the likelihood of this for a particular patient.[8 21] Nevertheless, this is an unsound process for the allocation of healthcare resource; a more explicit consensus regarding indications for such treatments would be preferable.

The divergence between menstrual experience and reasons given for referral to and attendance at a clinic reflects a disproportionate focus on excessive bleeding, a tendency that is echoed within the clinic setting. Is this reframing partly a consequence of women's beliefs that abnormal uterine bleeding is most worthy of medical attention? Or is there an astute lay understanding of what will be regarded by others as a

valid reason for attendance at a clinic? Assessment of menstrual complaints needs to be improved, and further research is required to understand the part played by the cultural beliefs of both women and clinicians. The comorbidity of menstrual complaints shows that the conventional partitioned thinking about menstrual problems will be unhelpful in most cases.

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Primary care groups
Progress in partnerships

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This is the fourth in a series of five articles

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BMJ 2001;323:28–31

Partnership—between organisations, services, and frontline staff—is widely promoted as an alternative to large scale structural reorganisation of the relation between the NHS and local government. However, there is still relatively little evidence on the effectiveness and outcomes of such partnerships. One of the difficulties in establishing an evidence base is the wide variety of relationships that can be described as partnerships. A second difficulty is the risk that working in partnership may be regarded as an end in itself rather than as the means to an end. The Audit Commission identified four potential areas of focus for groups working in partnership in public services (box).[1] However, implementing these activities and measuring progress is far from easy.

The Health Act 1999 imposed a duty on all NHS organisations to work in partnership. Nowhere has working in partnership been given more backing than in the relations between the NHS and local authorities, where collaboration is required to tackle "wicked issues"[1]—that is, complex problems like health improvement, community safety, and community care. Primary care groups and trusts are required to give priority to forming partnerships with local authorities' social services departments, especially in developing services for older people. In its plan for the NHS in England, the government announced that additional financial

Summary points

Primary care groups and trusts are expected to develop partnerships with local authorities, particularly for commissioning services and developing services for older people

Nearly half of the groups and trusts surveyed do not routinely consult with social services when commissioning community health services, and even fewer consult with social services about commissioning acute care

Relationships between frontline social services staff and community based and practice based health professionals are improving

The development of robust partnerships may be threatened by disruption to established relations as primary care groups merge or become trusts

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Menorrhagia I: Measured blood loss, clinical features, and outcome in women with heavy periods: A survey with follow-up data

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KEY WORDS
Menorrhagia
Subjective judgment
Measurement

Objective: Menorrhagia is defined as blood loss of >80 mL, but in routine clinical practice measurement is seldom undertaken. Our aim was to identify the features of the clinical history that best predict menorrhagic blood loss.

Study design: A questionnaire survey of 952 menstrual complaint referrals at 3 hospital gynecology clinics in Glasgow and Edinburgh included 226 women with putatively heavy periods who also had consented to the measurement of their blood loss.

Results: Only 34% (95% CI, 28%-40%) of women had blood loss volume of >80 mL, but the volume was associated with subjective heaviness of period. Logistic regression with ferritin status, clots, and changing rate during full flow correctly predicts a loss of >80 mL for 76% of women (n = 161 patients; sensitivity, 60%; specificity, 86%). Diagnosis and treatment of patients seem unrelated to the volume of blood loss.

Conclusion: The subjective judgment of the volume of blood loss is better than has been believed. Clinical features can be combined to predict losses of >80 mL.

The clinical definition of menorrhagia is blood loss of > 80 mL per period.[1-5] Treatment trials for menorrhagia usually involve laboratory measurement of blood loss so that trial participants are women with objectively confirmed menorrhagia, and changes in volume can be used as outcome measure.[6-9] However, in the course of screening patients for trials, it has been found that only a minority of women who have been referred for menorrhagia have loss of > 80 mL.[6,8,10,11] Concern has been expressed that powerful drugs are prescribed and that invasive surgery is undertaken on the basis of patients accounts' only.[12]

Guidelines for the management of menorrhagia make recommendations that are based on trials in which menorrhagia has been confirmed by measurement,[1,2,4,5,13] with the definition sometimes more stringently enforced by being applied to the average over a number of consecutive periods.[6] Such trials, if of adequate quality, provide top-grade therapeutic evidence only for similarly selected patients, not for all women presenting with

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menorrhagia. However, guidelines either acknowledge that the measurement of blood loss is impracticable for routine clinical use[1,2,4,13] or do not discuss the assessment of menstrual volume.[5] Instead, there is dependence on clinical/menstrual history, but without guidance on how to accumulate the clinical features to judge the likelihood of menorrhagia in a particular patient. The question therefore arises as to how feasible it is to judge menorrhagia from clinical history.

We collected comprehensive clinical data for women who had been referred with menstrual problems and undertook the measurement of menstrual blood loss in those women with putatively heavy periods. The aims of this report were to describe the associations between menstrual history, diagnosis, and measured volume of loss and to explore the feasibility of the assessment of the volume of loss by means of specific clinical features.

Methods

Study design

From 1996 to 1998, we surveyed 25- to 49-year-old women who were newly referred for menstrual complaint to Scottish gynecologic clinics, at Edinburgh and Glasgow Royal Infirmaries, and at Glasgow Western Infirmary.[14] The goal was to measure the volume of menstrual loss in women with "putatively" heavy periods (that is, women who were subjectively reporting heavy periods on the initial questionnaire or who were referred for or stated that they were attending the gynecology clinic for excessive periods). Measurement of loss requires the collection of used sanitary protection for 1 period; the women were told that this was specifically for research purposes and not part of their clinical care. Because menstrual collection is known to be unappealing to women, it was anticipated that the subset of women who would be providing such data would be relatively small. To be able to describe the characteristics of collectors compared with the wider study group, there was nested data collection to ensure that all eligible women provided at least minimum data. Collectors had to be eligible, in the sense of having putatively heavy periods, but also had to have completed the preceding questionnaire stages. Follow-up involved case note review 8 months after the initial appointment but, because of the time constraint on the study, only for the first 79% of the women who were recruited. The study was approved by the relevant local ethics committees; signed consent was obtained for all stages.

Methods

A brief clinic questionnaire that was completed by all women provided basic details of the menstrual complaint and patient background. A longer menstrual evaluation questionnaire (MEQ), which was evaluated as a potential tool for the clinical assessment of menorrhagia, ascertained more details of the menstrual complaint; 90% of women (782/865) who were eligible to collect completed the MEQ. Additional questionnaires that addressed psychiatric well-being, quality of life, and personality were also completed, but findings for these and all but 4 items of MEQ will be reported separately.

The reason for referral was ascertained from the referring physician's letter; terms for excessive bleeding were menorrhagia, excessive or heavy periods, periods going on too long, frequent periods, continuous bleeding, clots, and dysfunctional uterine bleeding.[14] On the clinic questionnaire, each woman reported, in her own words, her understanding of the reason for the clinic visit, which was categorized in a similar way. Over the study period, 4 different ferritin assays were used in the 3 hospitals; each ferritin value has been categorized as low or not, in accordance with the specifications of the relevant assay (details available from authors). Hemoglobin results are categorized as $<$ or ≥ 12 g/dL, in accordance with Milman et al.[15] Deprivation score (1 [most affluent] to 7 [most deprived]) was derived from the postcode sector.[16]

Collectors were provided with tampons (regular and super Tampax; Procter and Gamble, Brooklands, Survey, UK) and sanitary pads (Bodyform Ultra Super and Super plus sizes; Mölnycke Ltd, trading as Sancella, Aylesford, Kent, UK) as needed for use in the period of the collection. The women were advised about how to avoid the loss of menstrual blood when washing or using the toilet, and they completed a menstrual chart about the period during which the collection took place. To allow calculation of menstrual blood volume by the method of Hallberg and Nilsson[17] with the use of spectrophotometric comparison of a solution of the menstrual collection against venous blood, a venous blood sample was taken close to the time of the period.

Analysis

SPSS software (version 9.0; SPSS Inc, Chicago, Ill) was used. There was a small proportion of nonresponse for the questionnaires. The effective (not missing) number is reported if it is different from the total number. Skewed data are presented as median and interquartile range and are plotted as box plots. Blood loss volumes were log-transformed before parametric analysis (t-test for independent groups). Group means of these logged data are back-transformed for reporting as geometric means. To provide confidence intervals for comparisons between groups, each difference between groups in mean logged volume (with confidence interval) is back-transformed, which provided a ratio (of the geometric means) and confidence interval for the ratio. The association between measured blood volume and

Table I Description of women who undertook menstrual collection and of women who were not collectors

Sociodemographic factor	Collector (%)	Declined*/ defaulted (%)
Age group (n = 226 and 639 women, respectively)		
25-29 Y	8	9
30-34 Y	15	16
35-39 Y	27	23
40-44 Y	33	25
45-49 Y	17	26
Carstairs deprivation code (n = 222 and 630 women, respectively)		
Least deprived: 1 & 2	19	19
3 & 4	35	35
5	16	21
Most deprived: 6 & 7	31	25
Parity (n = 226 and 639 women, respectively)		
0	20	21
1-6	80	79
Employment status (n = 226 and 632 women respectively)		
No job	28	24
Part-time work	31	30
Full-time work	41	46
Factors used to determine invitation to collect (n = 226 and 639 women, respectively)		
Referral for excessive bleeding	87	83
Patient believes referral is for excessive bleeding	71	64
Subjective heaviness of periods (n = 225 and 634, respectively)		
Moderate	3	14
Heavy	49	49
Very heavy	48	37
Total "heavy"	97	86

* Declined to complete further questionnaires or completed questionnaires but then declined to undertake menstrual collection.

ordinal questionnaire variables is summarized by Spearman rank correlation. Although 25 such tests were undertaken, no adjustment for multiple testing has been made, partly because the main purpose was not hypothesis testing, but comparison of strength of association within the variable set, and partly for simplicity. Table II reports only those associations with a rho value of ≥ 0.11 (nominal $P \leq .109$). For succinctness, a cut-off point of 0.11 was chosen so that an important variable (referral by general practitioner for bleeding) would be reported.

Results

Recruitment and participation

Potential recruits were identified from referral letters; the 952 participants of the wider study are representative of the entire group of 1506 suitable referrals, in terms of age, deprivation code, and referral reason.[14] The 226 women who collected their used sanitary protection comprised 26% of the 865 women who were eligible for collection (that is, excluding the 87 women who were not categorized as having putatively heavy periods). Table I shows the sociodemographics of collectors and of those who were eligible but did not collect. It can be seen that the 2 subgroups are well-matched, except for slightly fewer collectors aged 45 to 49 years and collectors being slightly more likely to judge their periods **very** heavy. Although 97% of the collectors judged their periods to be heavy or very heavy, this does not necessarily denote a judgment of absolute volume. In the more detailed MEQ, women were asked to judge their usual periods in absolute volume. The following distribution of responses were made by 751 women who had completed this item of the MEQ (out of the 865 eligible women) up to a tea cup, 9%; about 1 mug (half-pint), 15%; and much more than a mug, 21%, whereas 55% of the women chose the response "no idea." There was a striking similarity in the distributions of responses to this item for the collecting and noncollecting subgroups (data not shown; n = 226 and 525 women, respectively). We set out to obtain iron status measures (hemoglobin and ferritin) for all patients for whom the treating clinician judged that such a blood test was required. The level of testing for iron status was generally lower in Edinburgh compared with Glasgow (among eligible women, 40% and 68%, respectively, underwent hemoglobin tests); the ferritin test was used relatively less often at the Edinburgh site than at the Glasgow site (13% and 59%, respectively, underwent ferritin tests). The proportion of low values was 16% for ferritin (n = 168 women), and 20% of the women had a hemoglobin level of <12 g/dL (n = 182 women).

Association of measured blood loss with clinical features, demographics, and iron status

The distribution of measured blood losses for the 226 collectors is shown in Figure 1; the median loss was 53 mL (interquartile range, 27-101 mL), and 34% of the women had losses of ≥ 80 ml. At the group level, the subjective judgment of heaviness of periods is supported, with a significantly greater mean loss for those women who rated periods "very heavy" compared with the rest (predominantly "heavy"; geometric mean volumes, 64 and 40 mL, respectively; $t = 3.56$; n = 107 and 118, respectively; $P < .001$). The back-transformed difference between means of logged data gives 1.61 as

the ratio of means (very heavy:heavy; 95% CI, 1.23-2.10). Measured blood loss was also greater for women who believed that their clinic attendance was for excessive bleeding, compared with the remainder (geometric mean, 59 vs 39 mL; $t = 2.94$; n = 160 vs 66 women; $P = .004$; ratio of means, 1.54; 95% CI, 1.15-2.06). However, referral for bleeding was not indicative of significantly greater volume of loss (geometric mean, 54 vs 43 mL; $t = 1.48$; n = 196 vs 30 women; $P = .14$; ratio of mean, 1.35; 95% CI, 0.91-2.00). Even where there is significant difference at the group level, there is substantial overlap in the ranges of individual measured losses. For example, 25% of women who rated their periods "very heavy" had volume of loss of <35 mL, and 25% of those who rated their periods as only "heavy" had loss of >82 mL.

Table II gives the associations of blood loss volume with clinical/menstrual history variables. The clinical features that were associated most strongly with blood volume were the required rate of change of sanitary protection during full flow and the total number of pads and tampons used (rho = 0.29 and 0.30, respectively; both $P < .001$). Figure 2 presents box-plots of measured volumes against these variables and shows the extent of overlap in ranges of volumes between the subgroups. Volume is also associated with the size of the clots with periods, the number of clots > 50-pence coin size (1.1-inch diameter) per period, and the need for changes of protection during the night (rho = 0.26, 0.26, 0.26, respectively; all $P < .001$). There is strong evidence that low iron status is associated with measured blood volume, for ferritin more than for hemoglobin (rho = 0.30 [$P < .001$] and rho = 0.23, [$P = .002$], respectively).

At the time of collection, each woman recorded how the amount of the period that was just collected compared with her periods in the last 6 months (the timeframe for responses in the questionnaires). Seventeen collectors (7.6%) failed to record this detail; however, of the remaining 209 collectors, 5% reported the collected period as more in amount; 16% reported about the same; 42% reported a bit less, and 36% reported much less. Mean loss volume for those answering "much less" differed significantly from that for the remainder (40.3 vs 54.9 mL; n = 73 vs 126 women; $P = .04$; ratio, 0.74; 95% CI, 0.54-0.99). This reduction in volume was more pronounced among older women, as shown in Figure 3. The nonparametric associations of Table II were recalculated after the women whose collected period was "much less than usual" were excluded. This yielded stronger associations of blood loss volume with age, parity, and deprivation (n = 126 women; for age group, rho = 0.25 [$P < .004$]; for number of babies, rho = 0.24 [$P < .007$]; and for deprivation, rho = −0.19 [$P < .037$]) than were found for the entire group (Table II). There was, however, no improvement in the association between volume and referral for bleeding.

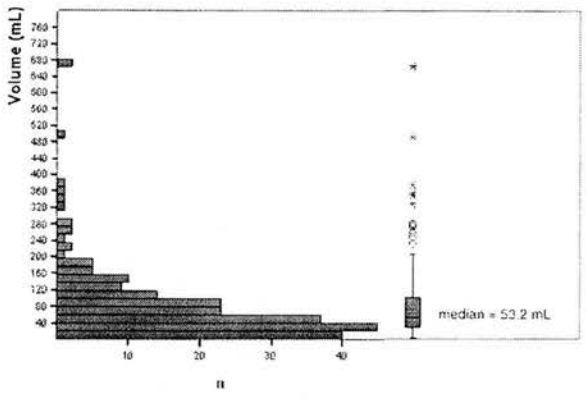

Figure 1 Histogram of measured blood loss, with superimposed box plot (n = 226 participants).

Association of measured blood loss with diagnosis and treatment

Overall, the volume of loss differed little between those proceeding or not to hysterectomy (median, 59 mL, and interquartile range, 21-140 mL, vs median, 53 mL, and interquartile range, 27-97 mL, respectively). Among those women who were diagnosed with fibroid tumors (20/176 women; 11%), there were slightly heavier losses and higher rates of poor iron status (Table III). Even among women with no diagnosis of fibroid tumors, there was little difference in volume of blood loss between those proceeding or not to hysterectomy (median, 53 vs 52 mL). However, there was a trend for those women who had undergone hysterectomy to have poorer iron status (low ferritin level, 31% vs 11%; hemoglobin level <12 g/dL, 29% vs 17%). Table III also gives the median blood loss and iron status for women with other diagnoses.

Using clinical history to predict blood loss of > 80 mL

A logistic regression model was fitted to predict losses that exceeded 80 mL, with the potential predictors of the clinical and demographic variables described earlier. Structural variables entered in the model were the center (Edinburgh or Glasgow) and the age group (<40 years old or ≥40 years old). Over and above these, the variables that were required in the model to predict a loss of > 80 mL were clots > 50-pence in size, low ferritin level, and frequency during full flow of needing to change sanitary protection. Although relatively few women underwent ferritin testing (only 161 women had complete data), the model that included ferritin performed better than the model without iron status test data, which was based on all collectors with complete data for the remaining model variables (performance, 71%; n = 202 women). There was otherwise little difference between the models. Table IV shows the model that includes ferritin level, which had a prediction success of

Table II Association of blood loss volume with demographic, clinical, and containment factors

	N	Spearman rank order correlation	*P* value
Demographic			
Age group (youngest-oldest)	226	0.11	.100
Deprivation (least-most)	222	−0.11	.095
No. of babies (0-6)	226	0.11	.109
Pathway to clinic			
Subjective heaviness of period (moderate; heavy; very heavy)	225	0.23	<.001
Patient believes clinic attendance is for bleeding (no; yes)	226	0.18	.006
Volume of loss cited as cause of seeking help (no; yes)	226	0.14	.034
General practitioner referred patient for bleeding (no; yes)	226	0.11	.109
Clots			
Size of clots with period (none; 20-pence; ≥50-pence)*	226	0.26	<.001
Usual no. of clots (per period) bigger than 50 pence* (0-28)	214	0.26	<.001
Iron status			
Ferritin level (low; normal)	168	0.30	<.001
Hemoglobin level (<12 g/dL; ≥12 g/dL)	182	0.23	.002
Containment of period			
Usual total no. of tampons/pads used per period (0-136)	207	0.30	<.001
Rate of change of protection necessary during full flow (every 3 hr or less often; every 2 hr; hourly; more often)	218	0.29	<.001
How often periods...			
Require protection changed during the night (seldom; some periods; most)	226	0.26	<.001
Leak through on to underclothes or bedding (seldom; some periods; most)	226	0.23	<.001
Usual no. of days (per period) double protection is required (0-12)	221	0.25	<.001
No. of times per period that there is leakage on to underclothes (0-10)	223	0.16	.015

* UK coins: size (diameter) of 50 pence is 1.1 inches and of 20 pence is 0.85 inches.

76% overall, correctly predicting 60% of the 60 women with measured losses of >80 mL and 86% of the 101 women with losses of <80 mL.

Comment

We have shown that the clinical features that are associated most strongly with blood loss volume are the required rate of changing sanitary protection during full flow, the total number of products used, poor iron status, the size of clots, and the need to change protection during the night (Table II). It is noteworthy that these features are not purely subjective, but either based on an objective test result (ferritin) or operational (eg, changing rate and clot size) and therefore less prone to measurement error. In addition, we found strong evidence that volume of loss is related to a woman's subjective judgment: those women who rated their periods as "very heavy" have a mean blood loss that is 61% (23%-110%) higher than the remainder of the women.

In absolute terms, only 34% of the collectors had menstrual blood losses of >80 mL. A partial explanation may be period-to-period variability.[18-21] Ours is the first study to ask whether the period that was collected was representative of periods as reported. For 36% of the women, the period collected was "much less than usual," which was substantiated by a lower measured volume. Excessive periods once every few months may be more worrying than consistent losses and are almost as disabling, because every period has to be anticipated as if it might be 1 of the heavier ones.

Among those women who reported the period collected as "much as usual," only 38% had measured a loss of >80 mL, which is lower than the prevalence that was found in other measurement studies.[7-10,22,23] This may be because our study is the first to measure blood loss in routine patients who were referred to a clinic with heavy periods rather than women who were selected for clinical trials. Alternatively, it may be because not all patients who were referred with menorrhagia considered their periods to be excessive. It has been reported that there is a tendency for broad menstrual complaint, or even pain specifically, to be reframed as "excessive bleeding" both at referral and at the gynecology clinic (that is, the referring physician is much more likely than the woman to cite excessive bleeding as the reason for clinic attendance).[14] This is supported by our finding that referral by the family physician for excessive bleeding was not prognostic for higher mean blood loss.

In contrast, a woman's subjective report of heaviness was related to measured loss; therefore, our data contradict the widespread clinical belief that women are poor

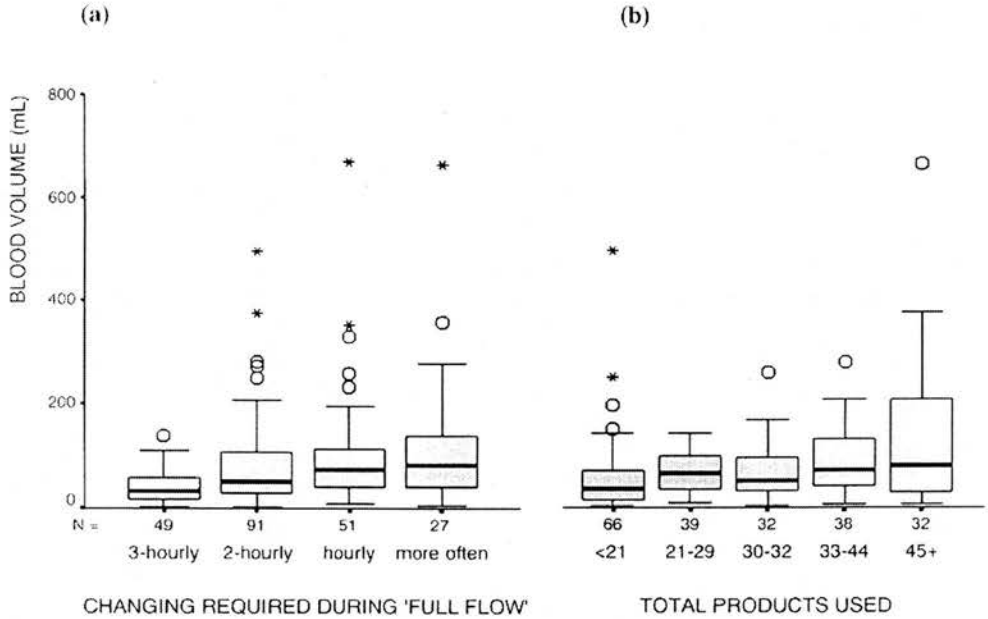

Figure 2 Box-plots of volume of blood loss by (**A**) changing rate of pads/tampons during full flow and (**B**) total number of products used per period. Note: The axis in **A** applies to both graphs.

judges of their volume of menstrual loss.[3,24] However, the relatively low proportion of women with measured loss of >80 mL does raise doubts about calibration to the clinical definition of menorrhagia. This discordance with the menorrhagia definition is unsurprising, given that very few women know of it and only a minority of women think of their periods in volumetric terms. When required to rate their usual period in terms of options that are formulated in volumes (teacup, mug, much more), most women instead opted for the fourth response available, "no idea" (55%).

Our data suggest that treatment is not related to measured volume of blood loss. In the absence of any identifiable disease, dysfunctional uterine bleeding is virtually a default diagnosis and is unrelated to actual loss. A similar picture is found for the treatment of patients without fibroid tumors and with hysterectomy outcome unrelated to volume of loss (Table III). Blood loss measurements were not entered in patient notes, so either clinicians are unable to make a judgment of loss from the clinical history or they feel that volume of loss has little bearing on treatment or diagnosis.

When menorrhagic blood loss was modeled ($\geq$80 mL versus <80 mL), 76% prediction success was achieved by a model that included clots >50 pence in size (1.1-inch diameter), low ferritin level, and rate of change of sanitary protection. On the 1 hand, the performance of 76% may be an optimum figure, given that model performance is ascertained against the same data that are used to derive the model. On the other hand, it may be an underestimate of performance, in that the model is making predictions on the basis of clinical history,

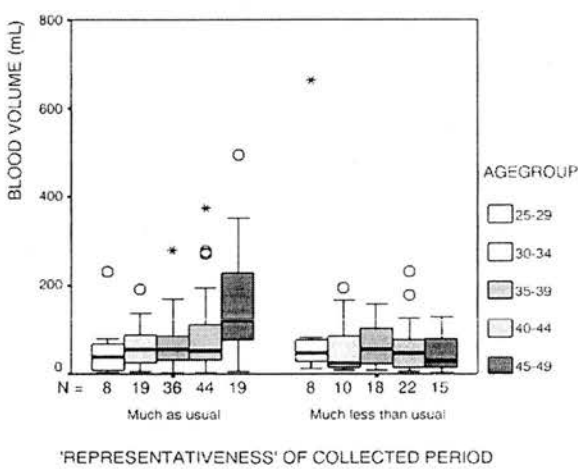

Figure 3 Box-plots of measured volume by age-group and representativeness of collected period.

an overview of recent months. For a substantial number of women (36%), the amount of loss for the single period that was collected subsequently was stated to be much less than the usual amount of loss that was described in the questionnaires. This unusually low loss rate will not reflect so clearly the predictors that were reported (for the usual heavy periods). Therefore, the predictive model is set an almost impossible task, and a statistical false-positive result in this analysis may be, in fact, a clinical true-positive result for the woman's other periods.

Two important points must be made. First, if a method became available that was suitable for routine

Table III Blood loss volume and iron status by diagnosis and with hysterectomy as outcome

	N	Median blood volume (mL)	Interquartile range	Low ferritin level (n/N)	Hemoglobin level <12 g/dL (n/N)
Diagnosis of fibroid tumors					
Yes	20	85	38-168	7/17 (41%)	5/18 (28%)
No, but hysterectomy performed	25	53	20-129	5/16 (31%)	7/24 (29%)
No, and no hysterectomy	131	52	27-93	10/95 (11%)	17/100 (17%)
Total	176				
Other diagnoses					
Dysfunctional uterine bleeding—regular	64	63	27-111	6/46 (13%)	14/52 (27%)
Dysfunctional uterine bleeding—irregular	43	41	19-83	5/28 (18%)	8/33 (24%)
Other (polycystic ovary syndrome, anovulatory bleeding, endometriosis, polyps)	49	52	27-92	4/37 (11%)	2/39 (5%)
Total	156				

Table IV Factors included in the logistic regression model that predicted blood loss of >80 mL

	N (for subgroup)	Odds ratio	95% CI	*P* value
Factor entered				
Center: Edinburgh	50	0.61	0.2-1.5	.287
Age <40 years	82	0.97	0.6-1.5	.873
Factors selected into model				
Clots > 50-pence diameter*	32	4.80	1.9-12.2	.001
Ferritin level: low	25	5.71	1.9-17.4	.002
Required frequency of changing protection				.006
≤3 Hr	38	Reference		
Every 1-2 hr	104	1.10	0.6-1.9	
More often than hourly	19	3.08	1.4-6.8	
Total	161			

* UK coin size: 1.1 inch in diameter.

clinical use and that could identify patients with true menorrhagia (loss of > 80 mL), there would remain an urgent need for trials of treatment strategies for the remainder of women, the substantial majority of patients who are referred with heavy periods but who have blood loss of < 80 mL. Second, such a method would help clinical management of referrals for excessive periods only if the volume of blood loss, and more specifically a volume of > 80 mL, is the key issue for patients and is critically important to optimum care. In a second article, we will consider the clinical usefulness of the 80-mL threshold.[25]

Past evaluation of a woman's ability to judge menstrual loss volume may have been clouded by misleading referral reasons or period-to-period variability in loss. The volume of blood loss is associated more closely than has been believed with subjective judgment of heaviness and is even more strongly associated with specific clinical features. A loss of >80 mL can be predicted moderately well by a model that includes poor ferritin level, clot size, and the changing rate of pads/tampons during full flow. An examination of clinical outcome data suggests that clinicians either find it difficult to judge volume from the clinical history or do not consider volume as key to management. This raises a concern about the implementation of current guidelines in unselected patients.

Acknowledgments

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Menorrhagia II: Is the 80-mL blood loss criterion useful in management of complaint of menorrhagia?

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KEY WORDS
Menorrhagia
Volume
Measurement
Cyclic mood change
Period pain

Objective: Menorrhagia is defined in terms of statistical"abnormality"as blood loss of >80 mL. We examined the usefulness of this definition in women who were referred to gynecology clinics with heavy periods.

Study design: A questionnaire survey of 952 menstrual complaint referrals at 3 hospital gynaecology clinics in Glasgow and Edinburgh included 226 women with heavy periods who had also consented to the measurement of their blood loss.

Results: Women reported a range of problems with their periods, but absolute volume (31.2%) was less prevalent than period pain (37.5%), mood change (35.7%), and change in the amount (volume) of the period (33.8%). Although there were associations with volume, these associations were due to the heaviest and lightest of the loss groups, whereas the 2 groups with loss either side of 80 mL were virtually indistinguishable.

Conclusion: The 80-mL criterion for menorrhagia is of limited clinical usefulness because it is prognostic neither for problems nor iron status and apparently does not guide management.

Menorrhagia is defined as excessive menstrual loss and accounts for a substantial proportion of health care resources among women of reproductive age.[1-3] There are 2 biomedical reasons that excessive periods warrant clinical scrutiny: the risk to iron status and to health and vigor that may ensue and the fact that increased loss may be indicative of some serious disease that requires urgent intervention. However, even if neither of these situations are pertinent, help may be warranted because of the disability and handicap that the woman experiences as a consequence of her menstrual periods.[4-6]

The formal definition of *menorrhagia* is blood loss in excess of 80 mL per menstrual period.[1,2,7] In research studies in which blood loss has been measured in women who were referred with menorrhagia, it has been found that fewer than half of women experience a loss of >80 mL.[8-11] In our companion paper,[12] we raised concerns at the dearth of evidence to inform treatment of the routine menorrhagia referral, because recommendations

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in menorrhagia guidelines[1,13,14] are derived from trials that involved women with generally much heavier menstrual loss (>80 mL, averaged over ≥2 periods). For example, in a recent drug trial only 20% of referrals for menorrhagia satisfied the volumetric criterion for trial entry that was applied.[8]

The fact that laboratory measurement of blood loss is impracticable in routine clinical care raises the question as to whether a volumetric definition that can so seldom be implemented is a useful way of thinking about the prevailing complaint of "heavy periods." More fundamentally, some reflection is warranted as to whether the contemporary menorrhagia complaint hinges on the volume of blood loss or whether it is precipitated by a broader adverse impact of menstruation. The clinical definition was formulated following a Swedish study that measured blood loss in a population sample of 476 women.[15] It found a significantly greater prevalence of impaired iron status among women with losses of >60 mL. Using estimates of daily dietary intake for Swedish women then (1966) and of likely daily and menstrual excretion of iron, calculations showed that menstrual blood loss of ≥63 mL endangered iron status. After excluding women with abnormal iron status or who considered themselves unhealthy or to have abnormal menstruation, the 95th percentile of blood loss for the 183 healthy women was 76 mL. The authors concluded that the upper limit of normal menstrual blood loss lay between 60 and 80 mL,[15] but subsequently the most extreme endpoint of this range (80 mL) was adopted as the clinical threshold for menorrhagia.

To be of value in clinical care, the menorrhagia definition should reflect the underlying complaint and be prognostic for disease, for compromised iron status or for adverse impact on quality of life, or it should lead to more appropriate and effective clinical treatment. The aims of this paper were to examine the performance of the 80-mL definition for menorrhagia in respect of prognosis and treatment and, more fundamentally, to examine the nature of the problems that are experienced by women who are referred for excessive periods, and to ascertain whether absolute volume is the key issue.

Methods

Study design and methods

The basic study design and methods, including coding of referral reason and patient reasons for clinic attendance, were described elsewhere[16]; blood loss collection and measurement are described in a companion article.[12] The self-completed clinic questionnaire asked each woman to respond to 16 statements about menstrual experience and to report for each experience whether it occurs in her case and, if so, how much of a problem it poses (no/slight/marked/severe problem) and to note which of these problems (≤3) led her to seek help. Responses were analyzed as binary variables (severe problem vs the rest); binary variables were derived for each aspect that indicated whether it had been cited as a cause of seeking help.

Analysis

Association in 2 × 2 tables was tested by chi-squared test, with correction for continuity. For tables with 1 variable binary and 1 ordinal, the chi-squared test for trend was applied. SPSS software (version 9.0; SPSS Inc, Chicago, Ill) was used. There was a small proportion of nonresponse; therefore, the effective (nonmissing) number is reported if it is different from the total number (except in Table, to be succinct). In Table, the percentage of the missing responses, for all eligible women, is <2% for most aspects and <3% for the remainder, except for "money spent," which has 4.6% missing values. For collectors, the corresponding percentages with missing responses are <1%, <2%, and 3.1%. Collectors were classified into 4 groups by measured blood loss: <50 mL, 50 to 79 mL, 80 to 119 mL, and ≥120 mL.

Results

Recruitment and participation

Recruitment for the wider study (952 participants) has been reported,[16] and the characteristics of the subset who collected their used sanitary protection have been described in the companion article.[12] The 226 women who collected their used sanitary protection comprised 26% of the 865 women who satisfied the criteria for collection, and 180 of these women were recruited early enough for an 8-month follow-up by case note review (80%).

Description of menstrual experience

The distribution of measured blood losses has been reported in the companion paper[12]; 46% of the women had losses of <50 mL; 20% of the women had losses of 50 to 79 mL; 15% of the women had losses of 60 to 119 mL, and 19% of the women had losses of ≥120 mL (n = 104, 45, 35, and 42, respectively). Table shows the prevalence of reporting the various aspects of menstruation as a severe problem for all women who were eligible to collect and for the subset of women who actually did the collecting. Pain with periods, mood changes, and increased amount of period were most problematic for all women who were eligible to collect and for the subset of women who did the collecting, and, although not shown, for all women in the study

Table Prevalence of severe problem with aspects of menstruation for all women with putatively heavy periods* and for the subset of women who collected

Aspects of periods (listed in order of prevalence among all women who were eligible to collect)	Rating aspect as severe problem: All eligible women (%)†‡	Rating aspect as severe problem: Collectors (%)§‖	Rank order among collectors
Period-type pain with periods	33.0	37.5	1
Mood changes around periods	32.8	35.7	2
Amount of period more than it used to be	29.1	33.8	3
Periods keep on for too many days	25.3	28.9	6
Lose too much blood	24.6	31.2	4
Interruption to daily life	24.2	30.0	5
Feel unwell/tired because of periods	23.4	27.4	8
Other changes around periods	22.6	27.8	7
Difficulty in preventing blood leakage	20.1	23.0	9
Worry that something may be wrong	18.6	20.6	12
Period pain before periods	17.5	21.2	11
Unpredictable onset of periods	17.0	16.1	14
Periods cause extra washing	16.9	21.7	10
Pain all the time	15.0	18.1	13
Money spent on pads/tampons	12.6	14.2	15
Bleeding between periods	8.8	5.8	16

There are small amounts of missing data for some aspects (see "Analysis" in the Methods section of the text).

* Referred for excessive periods/attending for excessive periods/reporting periods heavy or very heavy.

† N = 865 women.

‡ 95% CIs are 3 percentage points either side of the figure that is reported for prevalences of ≥20% and 2 percentage points either side for those of <20%.

§ N = 226 women.

‖ 95% CIs are 6 percentage points either side of the figure reported for prevalences of ≥24%, 5 percentage points either side of those from 23% to 14%, and 4 percentage points either side for those of <14%.

(n = 952) and for the subset of women who were referred for bleeding (n = 725). The prevalences of severe problems among the group of women who collected are slightly higher in general, but the relative ranking is very similar. It can be seen that absolute volume (lose too much blood) is only fifth in the order of prevalence overall and fourth among collectors. Among collectors, 50% of women reported a severe problem with some aspect of volume of bleeding (4th, 5th, or 9th aspects; Table), 43% of women reported pain around periods (1st, 11th, or 14th aspects; Table), and 45% of women reported cycle-related changes (2nd or 8th aspects; Table).

Prognostic value of the 80-mL cut-off for menorrhagia

Figure 1 shows the prevalence of the reporting of problems with pain before or with periods, mood or general cyclical changes, and the unpredictability of the onset of periods. All problems are associated significantly with volume, but inversely, the problems in this clinic group are greatest in those patients with lowest loss.

Apart from these aspects, the only problems with periods that are associated significantly with blood loss categorization are aspects of containment of blood flow (Figure 2, *A*). The major differences are between the lightest and heaviest loss groups, with those on either side of the 80-mL criterion virtually indistinguishable. Figure 2, *B*, shows some other aspects of menstruation that might have been expected to be related to menorrhagia complaint; lose too much blood; worry (that) something is wrong; feel unwell/tired because of periods; and volume of bleeding is the reason for seeking help (any of 4th, 5th, or 9th aspects as listed in Table). None of these problems or reasons increases significantly with volume. The pattern for worry is U-shaped, most prevalent in those women with the lightest and the heaviest loss. Again, there is little difference in prevalences for groups either side of 80 mL.

With regard to potential physiologic and treatment consequences of heavy periods, Figure 3 shows that the proportions with low ferritin levels and hemoglobin (below 12 g/dL) increase significantly across loss groups, but with no marked increase from <80 mL to >80 mL. The pattern is very similar in Figure 4, which shows the proportions of women who were diagnosed with some disease or with fibroid tumors, specifically, and the proportions for whom tranexamic acid was recommended as treatment or who made the decision to have hysterectomy. However, for these outcomes, the trend is not statistically significant.

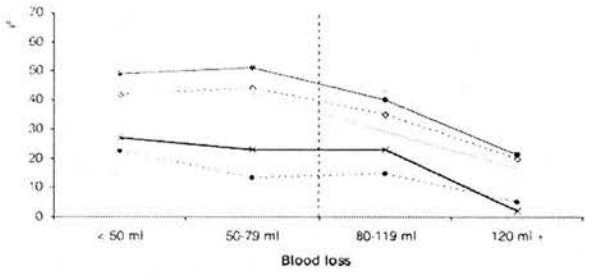

Figure 1 Severe problems with periods that are related inversely to volume of loss: prevalences (%) by blood loss variable of pain, cycle changes, and unpredictable onset. All data show significant chi-squared for trend. The *open diamonds* denote the "pain with periods" variable ($P = .015$); the *solid line with an* × denotes the "pain before periods" variable ($P = .003$); the *solid line with a closed circle* denotes the "any pain around periods" variable ($P = .003$); the *open squares* denote the "moods changes around periods" variable ($P = .002$); the *dashed line with the closed circle* denotes the "unpredictable onset of periods" variable ($P = .012$); and the *light gray line with an* × denotes the "any cyclic changes" variable ($P = .007$).

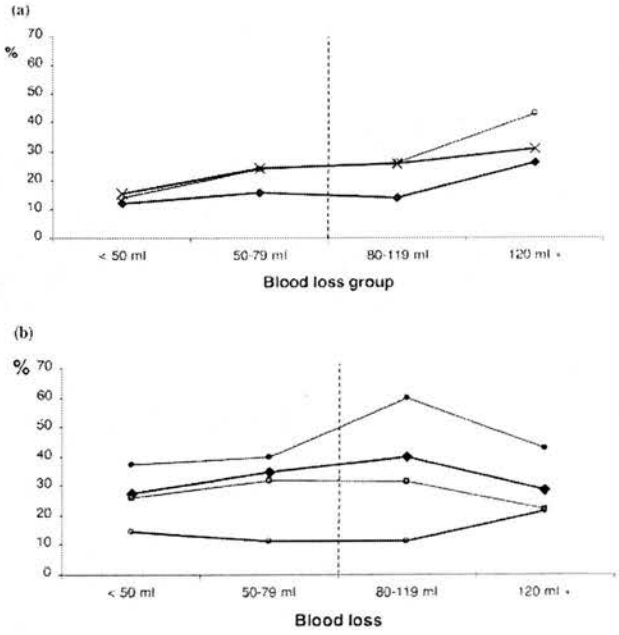

Figure 2 **A,** Prevalences (%) by blood loss variable of severe problems with periods for containment, extra washing, and impact on daily life. All data show significant chi-squared for trend. The *open circles* denote the "accidents are a severe problem" variable ($P < .001$); the *closed diamonds* denote the "impact on daily life cause of seeking help" variable ($P = .046$); and the × denotes the "extra laundry as a severe problem" variable ($P = .029$). **B,** Prevalences (%) by blood loss variable of severe problems with periods for volume of bleeding, feeling unwell/tired, and worry that something is wrong. None of the data show significant association nor trend with volume. The *closed diamonds* denote the "losing too much blood is a severe problem" variable; the *open circles* denote the "worry that something is wrong is the cause of seeking help" variable; the *closed squares* denote the "feeling unwell/tired is a severe problem" variable; and the **closed circles** denote the "bleeding is a cause of seeking help" variable.

Comment

The most striking finding is the clinical irrelevance of the established threshold definition of menorrhagia, blood loss in excess of 80 mL. Although there is a significant trend for difficulties with containment of blood flow to become more prevalent with increasing blood loss volume, this effect is largely due to the heaviest and lightest loss groups, whereas the 2 groups with loss either side of 80 mL are virtually indistinguishable. A similar pattern is observed for iron status, for diagnoses, and for treatment. Our data confirm that the 80-mL cut-off point does not convey any special prognostic information: the 35% of collectors with losses between 50 and 119 mL are fairly homogeneous with respect to difficulties with containment of periods, compromised iron status, pathologic findings, and treatment.

The menorrhagia definition simply identifies those women with blood loss in the upper 3% to 4% of a healthy Swedish population in 1966. The well-recognized problem with a statistical definition of this sort is that some women with abnormally heavy losses may find them manageable, nevertheless, and that symptoms (losses) that are less than this may be statistically fairly common, but for some women not tolerable.[17] Furthermore, the secular changes in reproductive patterns and diet since 1966 may mean the original iron risk calculations no longer apply, possibly never did in some non-Swedish communities. The clinical usefulness depends on how much the definition aids management or how predictive it is of adverse effects or disease. For the 81% of women in our study with losses of ≤119 mL, the precise volume of loss is immaterial: approximately 10% of the women have fibroid tumors, compromised iron status, or a problem with the impact on daily life; approximately 20% of the women have some disease, and approximately 40% to 70% of the women have problems with containing blood flow.

Furthermore, our data suggest that not only the 80-mL criterion should be challenged but also that the idea that volume captures the essential nature of the prevailing complaint of heavy periods. *Heavy* does not unequivocally describe volume, so the complaint may reflect adverse impact on daily life through difficulties with the containment of blood flow or associated symptoms.[6] The problem may be acute unmanageable blood flow in the first few days rather than total volume, or it could be that a change in periods has been noted, which leads to concern that something serious is wrong. In support of this, we have reported that pain, mood changes, and an increase in the amount of the period

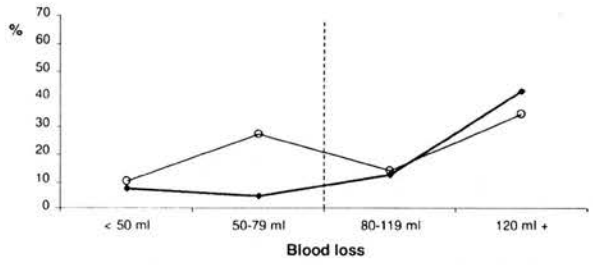

Figure 3 Prevalences (%) by blood loss variable of poor iron status: low ferritin level (*closed diamonds*; $P<.001$; n = 168 women) and hemoglobin level <12 g/dL (*open circles*; $P<.007$; n = 182 women). Both sets of data show significant chi-squared for trend.

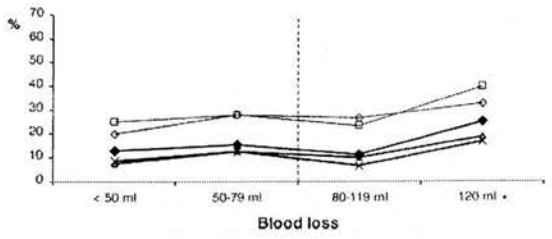

Figure 4 Clinic outcome by blood loss variable: prevalences (%) of diagnosis of fibroid tumors (*closed triangles*; n = 176 women) or any pathologic evidence (*open diamonds*; n = 176 women), tranexamic acid as treatment (*open squares*; n = 184 women), and hysterectomy (× denotes within 8 months [n = 179 women]; *closed diamonds* denote before the end of data collection [n = 179 women]). None of the data show a significant association nor a trend with volume.

were reported more commonly as severe problems than absolute volume and that pain around periods was more often a problem in cases in which measured losses were low. The association between heaviness and measured volume that was reported elsewhere[12] does not necessarily reassure that women are complaining about volume itself; the association may be coincidental, because greater volumes are associated in some way with the factors that lead to the complaint.

Stirrat[18] has highlighted a strong unease that, in the case of menorrhagia, drugs are prescribed or invasive surgery undertaken on the basis of the patient's account of her symptoms; the implication is that reported volume of loss will be misleading. On the contrary, the unease that should be felt is that the definition for menorrhagia takes so little account of a woman's experience of heavy periods, which is the menorrhagia complaint in its broader sense. Few clinicians request measurement of menstrual loss, and many clinicians take a holistic approach to the treatment of menorrhagia, perhaps in tacit acknowledgement of the shortcomings of the definition. It is, however, highly unsatisfactory that clinicians have to provide care for so many patients outside of the menorrhagia guidelines that address only 1 aspect of the problem and that are applicable only to a minority of patients (those women with blood losses of >80 mL over ≥2 periods). Our data confirm that the volume of loss is only 1 concern among many concerns of women who are referred with heavy periods, and not the main one concern overall. This replicates findings in qualitative research.[3,4,6,19] It would be better for the future care of women with menorrhagia if the definition was reformulated to reflect this. Only then can an appropriate research evidence base be built, to provide guidelines for pragmatic treatment and shared decision-making in women with heavy periods but without statistically abnormal volume of blood loss.

The 80-mL criterion is of dubious clinical usefulness because it is neither sensitive nor specific for adverse impact of periods, compromised iron status, or disease. Furthermore, the current focus on the volume of blood loss in the menorrhagia complaint is unhelpful to patients and clinicians, because it ignores the associated symptoms and social disability that play a key role in leading a woman to seek help. Appropriate research is required to derive recommendations for assessment and treatment of heavy periods, which should be conceptualized broadly.

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Appendix 3.1

Study Number ⌊_⌊_⌊_⌊_⌊_⌋

MEQ

MENSTRUAL EVALUATION QUESTIONNAIRE

This questionnaire asks **all about your periods and how they affect you**. Periods differ enormously from one woman to another. So too do general health, hobbies, and home and work circumstances. So when there is a period problem the main reason for complaint is likely to differ from one woman to another.

In the following pages you will find many questions about periods and how to deal with them, and about health, home, work and daily life. Some questions may seem to apply directly to you and your period problem, others may seem totally unneccessary. Nevertheless, it is **very important to this project that all questions are answered**.

So, please would you go through the questionnaire carefully, answering every question as accurately as you can. Thank you.

HOW TO FILL IN THIS QUESTIONNAIRE: There are 3 ways we ask for information -

○ ✓ tick the answer that applies to you

[2,3] write in a number answer, or 0 if none

.....very much.....write an answer in words

Today's Date *Please write in* ⌊_⌋ ⌊_⌋ ⌊_⌋

Date of Birth *Please write in* ⌊_⌋ ⌊_⌋ ⌊_⌋

Day Month Year

Unless otherwise requested, please answer about ***your periods in the last 6 months***

1. How would you describe the **AMOUNT** of your period? Very Heavy ○4 Heavy loss ○3 Moderate ○2 Light loss ○1

Please tick one

2. Have you had **BLEEDING** in between your periods?
i.e. bleeding that really needs sanitary protection,
but on days that are separate from your proper periods.

No ○3 Some cycles ○2 Nearly all cycles ○1 ⌊_⌋

No. of days bleeding that are not periods, but in between them

Please tick one, and write in the number, or 0

3. Have you had **SPOTTING** in between your periods?
i.e. very light blood streaks or spots that do not really need sanitary protection (except perhaps panty liners)

No ○3 Some cycles ○2 Nearly all cycles ○1 ⌊_⌋

Usual number of days spotting between periods

Please tick one, and write in the number, or 0

4. How many days does your actual **PERIOD** last?

Usual days of period ⌊_⌋ Longest period ⌊_⌋ Shortest period ⌊_⌋

Please write the usual number of days .

If your periods have varied, sometimes more days bleeding than others, please also write in the longest and shortest periods in the last 6 months.

5. How many of these days, usually, are **FULL FLOW**? *Please write the usual number of days 'full flow'.* ⌊_⌋ days full flow

Please answer about your periods **in the last 6 months**: ✓ ○ tick one answer ⌊4⌋ number ....anything.... words

6. How much do you think your whole period would **MEASURE**?
Please tick one

No idea ○ 4 | Up to a teacupful ○ 3 | Full mug (half a pint) ○ 2 | Much more than a mug ○ 1

7. How many **PADS AND/OR TAMPONS** did you use for your most recent period? *Please write the number, or 0, in each box.*

Total used **in one period** of <u>each type</u> of sanitary protection:

TAMPONS			PADS		
SuperPlus	Super	Regular	SuperPlus	Super	Regular
⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋

8. **HOW OFTEN** do you have to change your tampon/pad when your period is full flow?

Please tick one

At least every 3 hours ○ 4 | Every 2 hours ○ 3 | Every hour ○ 2 | More often ○ 1

9. Do you ever use "**DOUBLE** " **PROTECTION** i.e. more than one item at a time?
e.g. two pads, or tampon + pad, **together**

Please tick one

Most periods ○ 3 | Some periods ○ 2 | No ○ 1

10. Do you have "**ACCIDENTS**" even when you are using pads/tampons?
In each box please write the <u>usual</u> number of times this happens.

<u>Usual</u> Number of Times in one period that Blood soaks through onto:

Underclothes	Outer clothes	Bedding
⌊_⌋	⌊_⌋	⌊_⌋

11. Does your period include **CLOTS** ?
i.e. blackish-red jelly-like lumps that might come away with the period

In each box please write in <u>how many</u> clots of <u>that size</u>, usually, in one period.
Write 0 (zero) if <u>no</u> clots that size.

<u>Usual Number of Clots of each size in one period</u>

Up to about 20p size	About 50p size	Bigger than 50p
⌊_⌋	⌊_⌋	⌊_⌋

12. What **DATE** did your most recent period start? *Please write in* Day ___ Month ___ Year ___

13. In the last 6 months, what was the usual **CYCLE LENGTH**?
i.e. number of days from start of one period to start of the next

Usual cycle length (days)	Longest cycle	Shortest cycle
___	___	___

*Please write your usual cycle length, in the **last 6 months**.*
If your cycles have varied, with some cycles longer than others, please also write in the longest and shortest cycles in the last 6 months.

14. Do you know by counting days **WHEN** your period is going to start?
Please tick one Yes, most times ○ Yes, half the time ○ Hardly ever ○

15. Do you have **OTHER SIGNS** that tell you your period is due in a few days? *Please tick one* Yes ○ No ○

Please describe signs that tell you a period is soon to start .....

16. Do you have period-type **PAIN** around your periods? *Please tick one* Yes, most periods ○ 3 Some periods ○ 2 Very seldom ○ 1

If 'Yes' or 'Some periods', on **HOW MANY DAYS** do you have pain, and how many of these are **SEVERE**?
*Please answer separately for during(**with**) the period and before the period.*

In each box please write the usual number of days of pain, or 0 if no pain.

	USUAL Number of Days of Pain: **With** the period	**Before** the period starts
a) **HOW MANY DAYS** of pain?	___ days pain	___ days pain
b) For how many of these days is the pain **SEVERE**?	___ days severe	___ days severe

Please answer about your periods **in the last 6 months:** ○ ✓ tick one answer 46 number many words words

Please turn over

17. Do you use **PAIN-KILLERS** for pain around your periods? Yes, most periods ○ Yes, some periods ○ Very seldom ○

Please tick one

If you use painkillers: a) Do they **WORK** i.e. control the pain? Yes, most times ○ About half the time ○ Not usually ○

b) Please **NAME** the pain-killer you usually use: *Write in.* .....

18. Do you have any other **SYMPTOMS** or **FEELINGS** regularly around your periods, much more than at other times?

Please tick one Yes, most periods ○ Yes, some periods ○ Very seldom ○

If 'Yes':

a) Are any of the symptoms really **TROUBLESOME** to you? No, not really ○ Yes ○ Yes, very troublesome ○

b) **WHEN** are the symptoms **most** troublesome, before or during your period? During period ○ 3 Both equally ○ 2 Before period ○ 1

c) What are the **WORST** symptoms for you? *Please write in, separately for before and during the period.*

Worst symptoms with (during) the period: .....

Worst symptoms before the period starts: .....

19. How does your period **START**? Spotting or streaks of blood ○ 3 Very light bleeding ○ 2 In a gush ○ 1

Please tick one

20. How easy is it for you to manage your periods **AT HOME**?

a) How many people live in the house with you? b) How many toilets are there in your home? No. of people ⌊__⌋ No. of toilets ⌊__⌋

20. How easy is it for you to manage your periods **AT HOME**? *continued*

Is there a toilet separate from the bathroom?		Yes ○	No ○
Do you think others in your home realise when you are having a period?		Yes ○	No ○
Is there somewhere suitable to soak blood-stained clothes or bedding?		Yes ○	No ○
Do you have a washing machine?		Yes ○	No ○
Are you short of space to store supplies of pads/tampons?	No ○	A little ○	Very much so ○
Is it hard to keep supplies of pads/tampons private enough?	No ○	A little ○	Very much so ○
Is it difficult to dispose of soiled pads/tampons?	No ○	A little ○	Very much so ○
Is it hard for you to get enough privacy for changing pads/tampons?	No ○	A little ○	Very much so ○
Do your periods inconvenience others in your home?	No ○	A little ○	Very much so ○
Do others in your home complain about your periods?	No ○	A little ○	Very much so ○
	3	2	1

21. Do you **WORK** outside the home, either <u>paid or unpaid</u> (voluntary)? Yes ○ No ○

If 'No' please skip to Question 22.

If 'Yes' please answer the rest of this question:

How easy is it for you to manage your periods **AT WORK**?.

Does your job involve standing for a lot of the time?	Yes ○	No ○
Does your job involve lifting and carrying?	Yes ○	No ○
Does your job require you to wear a pale or white uniform?	Yes ○	No ○
Are there enough toilets available at work?	Yes ○	No ○
Are frequent trips to the toilets very noticeable?	Yes ○	No ○
Is it possible for you to go to the toilet whenever you need to?	Yes ○	No ○
Does someone have to take your place while you go to the toilet?	Yes ○	No ○
Is there somewhere for you to store supplies of pads/tampons?	Yes ○	No ○
Is the storage place private enough for you?	Yes ○	No ○
Is your job something that is impossible to do while full flow? e.g. swimming instructor	Yes ○	No ○

Please answer about your periods **in the last 6 months:** ✓ ○ <u>tick</u> one answer [18] <u>number</u> anything <u>words</u>

21. *continued* How easy is it for you to manage your periods **AT WORK**? *Please answer this if you do paid or unpaid (voluntary) work.*

Are frequent trips to the toilets disapproved of?	No	○	A little	○	Very much so	○
Is it difficult for you to get at your supplies of pads/tampons?	No	○	A little	○	Very much so	○
Is it difficult to dispose of soiled pads/tampons at work?	No	○	A little	○	Very much so	○
Is it hard for you to get away from your post to change pads/tampons?	No	○	A little	○	Very much so	○
Is absence from work because of periods disapproved of?	No	○	A little	○	Very much so	○
Can you always get access to a toilet if you urgently need to change	Yes	○	Most times	○	Not easily	○
		3		2		1

If you have to miss work because of heavy periods, how many days usually? No. of days per period off work for heavy periods ⌊__⌋

22. **GENERALLY**, how do you to manage your periods? *(i.e. apart from work)*

How well do the following statements describe your periods.... *Please tick once on each line.*

	Not at all	A little	Quite a bit	A lot	Very much
I plan my life to avoid outings when I have a period	○	○	○	○	○
I just can't prevent accidents when I have my period	○	○	○	○	○
I feel unwell during my period	○	○	○	○	○
During my period I limit what I do (e.g. standing, lifting, sport) to try and avoid accidents	○	○	○	○	○
I am irritable while my period is happening	○	○	○	○	○
My period goes on too long	○	○	○	○	○
The pattern of flow over the days of the period is unpredictable - when it is light, when flooding	○	○	○	○	○
I wear sanitary protection before my period begins just in case it starts unexpectedly	○	○	○	○	○
I am never sure when my period is really starting full flow	○	○	○	○	○
If my period comes unexpectedly I have to cancel outings	○	○	○	○	○
During my period I limit where I go, so that I will always be able to change pads etc. if I need to	○	○	○	○	○
My partner complains about interruption to our sex-life caused by my periods *(if not applicable, write n/a)*	○	○	○	○	○
	5	4	3	2	1

22. *continued* How do you manage your periods....

Please tick once on each line.

	Not at all	A little	Quite a bit	A lot	Very much
During my period I have to wear different clothes so the sanitary protection doesn't show	○	○	○	○	○
The heaviness of flow is unpredictable, some periods are heavier than others	○	○	○	○	○
My periods have changed from how they were normally	○	○	○	○	○
I can not afford all the money I spend on pads/tampons, laundry etc.	○	○	○	○	○
If I run out of pads etc. it is very difficult for me to get emergency supplies	○	○	○	○	○
I spend a lot of money on pads/tampons and washing bedding etc.	○	○	○	○	○
During full flow I can not do my usual tasks, as I need to keep still/rest	○	○	○	○	○
Leakage of blood onto the bedding causes problems in laundering	○	○	○	○	○
I am never sure when my period is finished	○	○	○	○	○

23. How true are the following of **HOW YOU <u>FEEL</u> ABOUT YOUR PERIODS** nowadays.....

Please tick once on each line.

	Not at all	A little	Moderately	A lot	Very much
It upsets me that there seems to be no way I can prevent accidents with my periods	○	○	○	○	○
I get annoyed that I have to wear different clothes during my period	○	○	○	○	○
During my period I worry all the time whether I need to change etc	○	○	○	○	○
I get annoyed that I have to limit what I do, where I go	○	○	○	○	○
I get upset by my period	○	○	○	○	○
I feel bad I have to miss work because of flooding (*if not applicable, write n/a*)	○	○	○	○	○
I resent all the money I spend on pads/tampons	○	○	○	○	○
It embarrasses me that I have to miss work because of flooding (*if not applicable, write n/a*)	○	○	○	○	○
	5	4	3	2	1

Please answer about your periods **in the last 6 months**: ○ ✓ <u>tick</u> one answer [63] <u>number</u> ...any words... <u>words</u>

Please turn over

23. *continued* How do you **feel** about your periods nowadays.....?

Please tick once on each line.

	Not at all	A little	Moderately	A lot	Very much
It upsets me that if my period comes unexpectedly I have to cancel outings	○	○	○	○	○
I wish there was someone I could talk to about my periods	○	○	○	○	○
Leakage of blood onto the bedding is embarrassing	○	○	○	○	○
I feel my periods make me less healthy	○	○	○	○	○
With periods as heavy as mine I feel abnormal	○	○	○	○	○
It is embarrassing to have to cancel arrangements because of periods	○	○	○	○	○
I resent the interruption to my sex-life caused by my periods (*if not applicable, write n/a*)	○	○	○	○	○
I feel abnormal buying such a lot of pads/tampons	○	○	○	○	○
I feel my periods make me tired	○	○	○	○	○
Before my period I worry whether I will be able to get through it without accidents	○	○	○	○	○
Altogether my periods are intolerable	○	○	○	○	○
I think my periods make me feel low/ depressed	○	○	○	○	○
It is embarrassing when you have to keep changing pads/tampons	○	○	○	○	○
I just wish I could have my periods back how they used to be	○	○	○	○	○
I find the flow of my periods quite overwhelming	○	○	○	○	○
I feel embarrassed because I have to buy such a lot of pads/tampons	○	○	○	○	○
Leakage of blood onto my clothes is embarrassing	○	○	○	○	○
I just wish an end to periods	○	○	○	○	○
Worrying about the possibility of accidents is almost worse than accidents happening	○	○	○	○	○
I seem to spend my whole life thinking about bleeding, sanitary protection etc.	○	○	○	○	○
	5	4	3	2	1

23. *continued* How do you **feel** about your periods nowadays.....?

Please tick once on each line.	Not at all	A little	Moderately	A lot	Very much
It bothers me that I am never sure when my period is finished	○	○	○	○	○
Blood-stained clothes or bedding are a nuisance to deal with	○	○	○	○	○
It worries me that my periods have changed from how they were normally	○	○	○	○	○
I feel my periods put a burden on my family/friends	○	○	○	○	○
The difficulty is that I am never sure when my period is really starting full flow	○	○	○	○	○
Before my period I worry when it is going to start, because of the effect on my life	○	○	○	○	○
Sanitary protection is a waste of money each month	○	○	○	○	○
I worry that the change in my periods might mean there is something serious going wrong	○	○	○	○	○
I feel bad about the way my family/friends are affected by my periods	○	○	○	○	○
I feel my periods have taken over my life	○	○	○	○	○
I dread my period starting because of the difficulty of trying to contain the flow	○	○	○	○	○
No more periods would be a great relief	○	○	○	○	○
My periods make me feel I am being punished	○	○	○	○	○
	5	4	3	2	1

24. Please add any **comments** you wish about heavy periods and their effect on you:

Study Number |_|_|_|_|_|_|

CLINIC QUESTIONNAIRE

We wish to survey all women attending this Clinic.

This will be so we can check on the types of problems needing treatment, and the numbers of women suffering these problems.

This will help us to plan our clinic service for the future, to ensure the best possible treatment for all.

Please would you answer the following questions about your attendance at this Clinic.

How to Fill in this Questionnaire:

☑ ○ — tick the answer that applies to you

2,9 — write in a number answer, or 0 if none

any words — write an answer in words

NOTE:

Your answers will be kept quite **confidential.**

This sheet will be unnamed, and it will not form part of your clinical notes.

We will simply combine the information from all women attending this clinic and then computer-analyse it to obtain summary totals of their various answers.

We would very much appreciate your help.

Today's Date *Please write in* ⌊__⌋ ⌊__⌋ ⌊__⌋
Day Month Year

1. What problem, mainly, has brought you to this Clinic?

Please say in your own words......

2. How long has this been bothering you? *Please write in* ⌊__⌋ years ⌊__⌋ months

3. Have you ever before **attended a clinic for period problems**? *Please tick one* Yes ○ 2 No ○ 1

If No, please go on to question 4.

If Yes: a) How long ago was your last attendance? ⌊__⌋ yrs ⌊__⌋ mths ago

b) Have you attended before for the same problem as now? Yes ○ No ○

4. Please would you **descibe your periods nowadays** (the last 6 months):

a) How **heavy** are your periods?

Please tick one Light loss ○ 4 Moderate ○ 3 Heavy loss ○ 2 Very Heavy loss ○ 1

b) How many days do your periods usually last?

*Please write the usual number of days your period has lasted (in the **last 6 months**).*

If your periods differ in length please also write in the longest and shortest periods in the last 6 months.

Usual number of days bleeding	Longest period	Shortest period
⌊__⌋	⌊__⌋	⌊__⌋

c) What **sanitary protection** do you use, mainly?

Pease tick one in each line.

	Don't use at all	Mostly Super plus	Mostly Super	Mostly Regular
Pads:	○	○	○	○
Tampons:	○ 4	○ 3	○ 2	○ 1

d) Do you have to use **more than one pad/tampon at the same time**? Yes ○ No ○

If Yes, **on how many days** of the period, usually, do you use double protection? ⌊__⌋ days

e) Does your period include **clots** (shiny dark red-black lumps)? *Please tick one*

No ○ 4 Yes - About 20p size ○ 3 Yes - About 50p size ○ 2 Yes - Bigger than 50p ○ 1

HOW TO COMPLETE: ○ ✓ tick one ⌊4 write a number anything say in words

f) Do you have to **get up at night to change** your pads/tampons? *Please tick one*

Very seldom ○ Some periods ○ Most periods ○

g) Does your period **leak through onto your underclothes or bedding?** *Please tick one*

Very seldom ○ 3 Some periods ○ 2 Most periods ○ 1

5. There are lots of different ways in which periods can be a **nuisance, or a real problem.** Please tell us what happens in your case, and how much it bothers you.

Please tick one answer on each line.	**Does not happen**	**Happens but no problem**	**___ Happens and is slight problem**	**marked problem**	**severe problem ___**
a. You feel generally unwell/tired because of your periods	○	○	○	○	○
b. The amount of your periods is more than it used to be, normally	○	○	○	○	○
c. Your periods cause interruption to your daily life..... e.g. work, sport, going out	○	○	○	○	○
d. You have bleeding in between periods.....	○	○	○	○	○
e. Your periods are irregular i.e. don't know when to expect them	○	○	○	○	○
f. You have period-type pain with your periods	○	○	○	○	○
g. You have other bodily changes before your periods ..... e.g. bloating, breast discomfort	○	○	○	○	○
h. The money you have to spend on sanitary pads &/or tampons		○	○	○	○
i. Your periods keep on for too many days	○	○	○	○	○
j. You have period pain **before** your periods	○	○	○	○	○
k. You worry that recent change in your periods , from before, could be a sign that something might be wrong	○	○	○	○	○
l. You have difficulty in preventing accidents (blood leakage)	○	○	○	○	○
m. Your periods cause extra washing, of bedding, clothes etc.	○	○	○	○	○
n. You have period-type pain **most** of the time	○	○	○	○	○
o. Mood changes around your periods e.g. irritability, depression	○	○	○	○	○
p. Your periods mean you lose too much blood	○ 5	○ 4	○ 3	○ 2	○ 1

Which of these has been the **main cause** of your coming to this clinic?

Please note in words, or by using the corresponding letter in the list above .....

You may note up to 3 reasons/ causes, but please put strongest reason first. .....

.....

Please turn over

HOW TO COMPLETE: ○ ✓ tick one [2,6] write a number .....words..... say in words

And finally, please would you give some background details about yourself.

6. What is your **date of birth** ? *Please write in* ⌊__⌋ ⌊__⌋ ⌊__⌋ Day Month Year

7. How long did you continue with your **education**? *Please tick one, the highest level reached*

Left school by age 16 years ○ Studied A-levels, Highers ○ Full-time student at College/ University ○

8. Are you currently **living with a partner or with your husband**? Yes ○ No ○

If No, are you.....? Separated/ divorced ○ Widowed ○ Single ○

9. Do you **work**? *Please tick one* Yes - full-time ○ 3 Yes - part-time ○ 2 No job ○ 1

What is your job, or what was your job when you last worked? .....

10. How would you rate your **general health**, compared to other women about your age?

Please tick one Worse than most ○ 3 About the same as others ○ 2 Better than most ○ 1

11. Children and babies:

How many babies have you had altogether? *Please write in how many, or 0 if none* ⌊__⌋ births

How many of these children do you still have living with you? ⌊__⌋ at home still

Do you have any other children living with you (adopted etc.)? ⌊__⌋ others

What **year did your most recent pregnancy end**? Last pregnancy ended in ⌊1 9__⌋

Please leave blank if no pregnancies

12. Is it important to have the possibility that you could, if you wanted, get **pregnant** in the future?

Not applicable - already sterilised ○ 4 Not important ○ 3 Fairly important ○ 2 Very important ○ 1

If you have already been sterilised, **how many years ago** was the operation? ⌊__⌋ years ago

13. Do you use **contraception** currently? If so, what method? *Please tick one*

Hormonal contraceptive e.g. *'the pill' or Norplant* ○ 5 Sterilisation *male or female* ○ 4 IUD ○ 3 Other e.g. *condom cap* ○ 2 None ○ 1

If you have used 'the pill' in the past, **how many years ago did you stop?** ⌊__⌋ years ago

14. Do you currently **smoke?** *Please write in how many cigarettes a day, usually* ⌊__⌋ cigs. per day

If you do not smoke please write 0

HOW TO COMPLETE: ✓ ○ tick one 18 write a number describe say in words

THANK YOU SO VERY MUCH FOR YOUR HELP.

Appendix 3.3

Study Number ⌊_⌊_⌊_⌊_⌊_⌊_⌋

MENSTRUAL HISTORY & BACKGROUND HEALTH QUESTIONNAIRE

This questionnaire asks how your periods have been, and about your health and past pregnancies.

Some questions may seem to apply directly to you and your period problem, others may seem totally unneccessary.

Nevertheless, it is important to this project that all questions are answered.

Please would you go through the questionnaire carefully,
answering every question as accurately as you can.

N.B.
Your answers will be kept quite confidential.

Today's Date *Please write in* ___ ___ ___

Date of Birth *Please write in* ___ ___ ___
Day Month Year

CURRENT WELL-BEING & HEALTH

1. **PHYSICAL SYMPTOMS.** Below you will find a list of common problems which affect us from time to time in our daily lives. During the past **TWO WEEKS** have you been bothered by any of them?. *Please tick one answer for each problem*

	Yes	No		Yes	No
Swelling of parts of your body	○	○	Shortness of breath	○	○
Lack of energy	○	○	Backaches	○	○
Diarrhoea/ constipation	○	○	Sore throat	○	○
Persistent cough	○	○	Trouble sleeping	○	○
Feeling sad or downhearted	○	○	Loss of appetite	○	○
Tingling/ 'pins & needles' in hands or feet	○	○	Dizzy spells	○	○
Upset stomach	○	○	Nervous tension	○	○
Headaches	○	○	Difficulty in concentrating	○	○
Migraine headaches	○	○	Cold sweats	○	○
Problems with control of your urine	○	○	Rapid heart beat	○	○
Aches...stiff joints	○	○	Hot flushes	○	○
Bladder infection problems	○	○	Craving for particular foods	○	○
	2	1		2	1

2. What is your **HEIGHT**, and what is your current **WEIGHT**?

Height:.....

Weight:. .....

3. Have you ever **SMOKED** regularly? *Please tick one* Never smoked ○ 3 Used to smoke ○ 2 Still smoke ○ 1

If you have ever smoked: For **HOW MANY YEARS** have you smoked, and how many cigarettes a day? ⌊__⌋ Years of smoking ⌊__⌋ Cigs. per day

If you 'Used to smoke': **HOW MANY YEARS AGO** did you give up smoking? Gave up smoking ⌊__⌋ years ago

4. How **OFTEN** do you drink **ALCOHOL**? *Please tick one* Most days ○ 4 3 to 4 days a week ○ 3 1 to 2 days per week ○ 2 1 or 2 days per month, or less ○ 1

If you drink alcohol: (a) **WHAT** do you drink, most often? *Please tick one* Beers ○ Wines ○ Spirits ○

(b) In total, **HOW MANY DRINKS** (glasses) have you had in the last week? ⌊__⌋ drinks/glasses

(c) Was last week's drinking **THE SAME AS USUAL**? About the same ○ 3 More ○ 2 Less ○ 1

5. **HEALTH.** Do you have any of the following long-term health problems? *Please tick one answer for each problem*

	Yes	No		Yes	No
Arthritis or Rheumatism	○	○	Diabetes	○	○
High blood pressure (Hypertension)	○	○	Asthma	○	○
Ulcers (stomach or bowel)	○	○	Heart disease	○	○
Allergies/ Ezcema	○	○	Migraine	○	○
Thyroid	○	○		2	1
Cancer	○	○	..... *If 'Yes', please specify*		
Other	○ 2	○ 1	..... *If 'Yes', please specify*		

PERIODS

6. How old were you **WHEN YOU HAD YOUR FIRST PERIOD**? ⌊__⌋ years old when started periods

7. If you have had any of these **PERIOD PROBLEMS,** ever, please say at what ages you first noticed them:

Please tick one answer in each line, and for each problem you have had please give ages requested.

	No, never had this problem	Yes, have had this problem		Age first started	Age most recently occurred again
Period Pain	○ 1	○ 2	*If yes,* →	⌊__⌋	⌊__⌋
Irregular Periods	○ 1	○ 2	*If yes,* →	⌊__⌋	⌊__⌋
Heavy Periods	○ 1	○ 2	*If yes,* →	⌊__⌋	⌊__⌋
Premenstrual symptoms	○ 1	○ 2	*If yes,* →	⌊__⌋	⌊__⌋

(leave blank if only one episode)

8. If any of these **PERIOD PROBLEMS** have been **SEVERE** (i.e. really troublesome), please say at what age this happened:

Please tick one answer in each line, and for each severe problem you have had please give ages requested.

	No, not been a severe problem	Yes, has been a severe problem		Age first became severe	& Age became severe again
Period Pain	○ 1	○ 2	*If yes,* →	⌊__⌋	⌊__⌋
Irregular Periods	○ 1	○ 2	*If yes,* →	⌊__⌋	⌊__⌋
Heavy Periods	○ 1	○ 2	*If yes,* →	⌊__⌋	⌊__⌋
Premenstrual symptoms	○ 1	○ 2	*If yes,* →	⌊__⌋	⌊__⌋

(leave blank if only one episode)

9. Has there been any **CHANGE IN YOUR PERIODS** recently? e.g. number of days, colour, flow

Change noticed	How long ago? *months*
.....	.....
.....	.....

MEDICAL HISTORY

10. Have you ever before **SEEN A GP OR HOSPITAL DOCTOR ABOUT PERIOD PROBLEMS,** *Please tick one* Yes ○ No ○
apart from the visit that has brought you to this clinic now?

If Yes, previously seen by a doctor ....

Number of previous visits to a doctor for period problems

(a) **HOW MANY TIMES** have you been to a doctor about period problems? to GP ⌊__⌋ to Hospital Doctor ⌊__⌋

(b) **WHAT PERIOD PROBLEMS** have you ever been seen for? *Please tick any that apply*

(i) By a GP:	Yes	No	(ii) By a Hospital Doctor:	Yes	No
Heavy periods	○	○	Heavy periods	○	○
Painful periods	○	○	Painful periods	○	○
Irregular periods	○	○	Irregular periods	○	○
Premenstrual symptoms	○ 2	○ 1	Premenstrual symptoms	○ 2	○ 1

	Your Age at visit	About what period problem(s)?
(c) **WHEN** were your visits to the GP? **First** visit ever	⌊__⌋	.....
Most recent visit before this current problem	⌊__⌋	.....
(d) **WHEN** were your visits to hospital? **First** visit ever	⌊__⌋	.....
Most recent visit before this one	⌊__⌋	.....

11. Have you ever had a **D & C** (dilation and curettage, womb scrape) for period problems? *Please say how many (0 if none)* ⌊_⌋ D&C's

12. Are you taking any regular **DRUGS, PILLS OR MEDICINES?** *Please tick one* Yes ○ No ○

If Yes, please specify:

What taken	Reason Taken
.....	.....
.....	.....
.....	.....

13. Have you ever been given medication by a doctor for **ANXIETY?** *Please tick one* Yes ○ No ○

If Yes, please state medications and for how long taken:

Medications	Longest course of treatment
.....	..... months
.....	
.....	

14. Have you ever been given medication by a doctor for **DEPRESSION?** *Please tick one* Yes ○ 2 No ○ 1

If Yes, please state medications and for how long taken:

Medications	Longest course of treatment
.....	..... months
.....	
.....	

CONTRACEPTION

15. What method of **contraception** are you using at the moment? *Please tick **one**, your main method*

You are sterilised ○ 14	Partner vasectomy ○ 13	Condom or sheath ○ 12	Coil or IUD ○ 11
Oral contraceptive - 'the pill' ○ 24	Cap or Diaphragm ○ 23	Rhythm method ○ 22	
Other hormonal e.g. depo injection, Norplant ○ 34	Other - *please specify* ○ 33		
None needed - no sexual relationship ○ 44	None - planning family ○ 43	None ○ 42	

16. How **LONG** have you been using this method of contraception?

Please write the number of years, or 0 if less than 6 months. This method used for ⌊__⌋ years

17. If <u>you are NOW USING or have EVER USED the pill</u>: *(If you have NEVER used the pill please skip to Question 18, next page.)*

(a) **HOW OLD** were you when you first started taking the pill? ⌊__⌋ years old when starting the pill

(b) Why did you **FIRST START** taking the pill? *Please tick one.*

Contraception only ○ 6	Painful periods ○ 5	Heavy periods ○ 4	Premenstrual symptoms ○ 3
	Irregular periods ○ 2	Other -please specify ..... ○ 1	

(c) **HOW LONG <u>ALTOGETHER</u>** have you taken the pill? ⌊__⌋ years altogether on pill

(d) While on the pill does it/did it have an **EFFECT ON YOUR PERIODS**?

Please tick one answer in each line.

	Not applicable/ Can't remember	Pill had NO effect	Made better	Made worse
Period pain	○	○	○	○
Regularity of periods	○	○	○	○
Heaviness of periods	○	○	○	○
Premenstrual symptoms	○	○	○	○
	4	3	2	1

(e) Have you been troubled by **SIDE-EFFECTS** while on the pill ? *Please specify what side-effects*

.....

PREGNANCIES

18. **HOW MANY PREGNANCIES** have you had, altogether? ⌊__⌋ pregnancies

Please write the total number of all pregnancies, including any miscarriages, still births or abortions.

If Never pregnant, write in 0 and then you have finished.

19. What was the **OUTCOME** of these pregnancies?

Please write in the number of each of the following, in your case.

If No live births, then you have finished.

Live births	Miscarriages	Abortions	Still births
⌊__⌋	⌊__⌋	⌊__⌋	⌊__⌋

20. Did you ever have '**BABY BLUES**'? (emotional, weepy for a day or two in first week after birth)'Baby blues' with ⌊__⌋ babies
Please write in <u>how many</u> births were followed by 'baby blues'. Put 0 if none.

21. Did you **BREASTFEED** any of your babies? Breastfed ⌊__⌋ babies
Please write in <u>how many</u> babies you breastfed for 6 weeks or more.

22. Some women feel **DEPRESSED FOR A WEEK OR MORE** during the first 6 months with a new baby....

(a) With **HOW MANY** of your babies were you depressed for a week or more in the first 6 months? ⌊__⌋ babies
Put 0 if did not happen and then you are finished.

(b) **HOW BAD** were any of the depressions you had after the birth of any of your babies? *Please tick one answer to describe the <u>worst</u>*

Not depressed with any baby ○5 <u>Brief</u> depression (<u>less than 2 weeks</u>) ○4 Depressed for <u>2 or more weeks</u>, but <u>only mildly</u> ○3

<u>Moderately</u> depressed for <u>2 or more weeks</u> ○2 <u>Severely</u> depressed for <u>2 or more weeks</u> ○1

(c) Did you ever **SEE YOUR DOCTOR** about depression with your babies (i.e. starting within 6 months of the birth) ? *Please tick one*

No, never ○4 Yes, but anti-depressants were not suggested ○3 Yes, & anti-depressants were suggested/ prescribed, but I never took them ○2 Yes, & at least once anti-depressants were prescribed and I took them ○1

23. *Here are some questions about you and your health. Please tick in **one** circle on **each** line to indicate your answer to the question.*

	No	Yes, a bit	Yes, very much
(a) Do you worry about your health?	○	○	○
(b) Do you think there is something seriously wrong with your body?	○	○	○
(c) Does your family have a history of illness?	○	○	○
(d) Do you think you are more liable to problems with your periods than other people?	○	○	○
(e) Do you find that you are aware of various things happening in your body?	○	○	○
(f) Do you ever think of your period problems as a punishment for something you have done wrong in the past?	○	○	○
(g) Are you bothered by aches and pains?	○	○	○
(h) Are you more sensitive to pain than other people?	○	○	○
(i) Can you express your personal feelings easily to other people?	○	○	○
(j) Do you think that you worry about your health more than most people?	○	○	○
(k) Except for your period problem, do you have any problems in your life?	○	○	○
(l) Do you care whether or not people realise you have period problems?	○	○	○
(m) Do you ever have silly thoughts about your health that you can't get out of your mind, no matter how you try?	○ 3	○ 2	○ 1

23. contd. *Please tick in **one** circle on **each** line to indicate your answer to the question.*

	No	Yes, a bit	Yes, very much
(n) Do you worry about the possibility that you have a serious illness?	○	○	○
(o) When you are angry, do you tend to bottle up your feelings?	○	○	○
(p) Do you get the feeling that people are not taking your period problems seriously enough?	○	○	○
(q) Are you upset by the appearance of your face or body?	○	○	○
(r) Do you find that you are bothered by many different symptoms?	○	○	○
(s) Do you worry or fuss over small details that seem unimportant to others?	○	○	○
(t) Are you a co-operative patient?	○	○	○
(u) Would all your troubles be over if your periods were normal?	○	○	○
(v) Do you think that your period problems may be caused by worry?	○	○	○
(w) Do you have personal worries which are not caused by your period problem?	○	○	○
(x) Is it hard for you to show people your personal feelings?	○	○	○
	3	2	1

Thank You Very Much for Completing this Questionnaire

ASPECTS OF YOUR HEALTH SF-36

Study Number |_|_|_|_|_|_|

The following questions ask for your views about your health and how you feel about life in general. If you are unsure about how to answer any question, try and think about your overall health and give the best answer you can. Do not spend too much time in answering as your immediate response is likely to be the most accurate.

1. In general would you say your health is?

Excellent	○ 5
Very good	○ 4
Good	○ 3
Fair	○ 2
Poor	○ 1

2. Compared to one year ago, how would you rate your health in general now?

Much better than one year ago	○ 5
Somewhat better now than one year ago	○ 4
About the same	○ 3
Somewhat worse now than one year ago	○ 2
Much worse now than one year ago	○ 1

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

		Yes limited a lot	Yes limited a little	No, not limited at all
i.	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	○	○	○
ii.	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf.	○	○	○
iii.	Lifting or carrying groceries.	○	○	○
iv.	Climbing several flights of stairs	○	○	○
v.	Climbing one flight of stairs	○	○	○
vi.	Bending kneeling or stooping	○	○	○
vii.	Walking more than one mile	○	○	○
viii.	Walking half a mile	○	○	○
ix.	Walking 100 yards	○	○	○
x.	Bathing and dressing yourself	○ 3	○ 2	○ 1

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		Yes	No
i.	Cut down on the amount of time you spent on work or other activities	○	○
ii.	Accomplished less than you would like	○	○
iii.	Were limited in the kind of work or other activities	○	○
iv.	Had difficulty performing the work or other activities (e.g. it took extra effort)	○	○

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		Yes	No
i.	Cut down on the amount of time you spent on work or other activities	○	○
ii.	Accomplished less than you would like	○	○
iii.	Didn't do work or other activities as carefully as usual	○ 2	○ 1

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Not at all	○ 5
Slightly	○ 4
Moderately	○ 3
Quite a bit	○ 2
Extremely	○ 1

7. How much bodily pain have you had in the past 4 weeks?

None	○ 6
Very mild	○ 5
Mild	○ 4
Moderate	○ 3
Severe	○ 2
Very severe	○ 1

8. During the past 4 weeks, how much did pain interfere with your normal work (including work both outside the home and housework)?

Not at all	◯ 5
A little bit	◯ 4
Moderately	◯ 3
Quite a bit	◯ 2
Extremely	◯ 1

9. These questions are about how you feel and how things have been with you during the past month. (for each question please indicate the one answer that comes closest to the way you have been feeling).

How much time during the past month.....	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
i. Did you feel full of life?	◯	◯	◯	◯	◯	◯
ii. Have you felt particularly nervous?	◯	◯	◯	◯	◯	◯
iii. Have you felt so down in the dumps that nothing could cheer you up?	◯	◯	◯	◯	◯	◯
iv. Have you felt calm and peaceful?	◯	◯	◯	◯	◯	◯
v. Did you have a lot of energy?	◯	◯	◯	◯	◯	◯
vi. Have you felt down-hearted and miserable?	◯	◯	◯	◯	◯	◯
vii. Did you feel worn out?	◯	◯	◯	◯	◯	◯
viii. Have you been happy?	◯	◯	◯	◯	◯	◯
ix. Did you feel tired?	◯	◯	◯	◯	◯	◯
x. Has your health limited your social activities (like visiting friends or close relatives)?	◯ 6	◯ 5	◯ 4	◯ 3	◯ 2	◯ 1

10. Please choose the answer that best describes how true or false each of the following statements is for you.

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
i. I seem to get ill more than other people	◯	◯	◯	◯	◯
ii. I am as healthy as anybody I know	◯	◯	◯	◯	◯
iii. I expect my health to get worse	◯	◯	◯	◯	◯
iv. My health is excellent	◯ 5	◯ 4	◯ 3	◯ 2	◯ 1

.....End of questionnaire.....

Appendix 3.5

MENSTRUAL CHART

Study Number ⌊⌊⌊⌊⌊⌊⌊

1. Please write in when, for **this period**, you **began** using sanitary protection: **Date** ⌊⌊ ⌊⌊ ⌊⌊ **Time:** ..... am/pm

2. Each page is labelled 'Day 1', 'Day 2', in order. Please start a new page each day when you get up, even though there may be space left.

3. Please fill in a line of the chart every time you change any of your sanitary protection.

   This gives us details of your loss and product usage - the time you change, what products you change, how much period there is on the products you change, whether you have had pain, whether you have seen any clots, whether there has been any leakage of your period onto your clothes.

   NOTE : The first line of each 'Day' is an **example**, to show you how a variety of things could be filled in.
   However, your own period is very likely to be different from these made-up examples - please tell us what **your** period is like.

4. At the end of each day, at your last change before you go to bed, please answer the questions at the bottom of the page, about the whole day.

5. When your period is finished please answer the questions here ⇩, and then put the chart somewhere safe to give/post to the research nurse.

How does this period that has just finished **compare with your periods in the last 6 months**?

Please tick one answer on each line.

		DURING THIS PERIOD				
		Much less	**A bit less**	**About the same**	**A bit more**	**Much more**
a.	Amount of loss	○	○	○	○	○
b.	Stopping you from doing your usual activities	○	○	○	○	○
c.	Leakage of period onto clothes etc.	○	○	○	○	○
d.	Severity of period pain	○	○	○	○	○
e.	Tiredness	○	○	○	○	○
		5	4	3	2	1

Any difficulties....?

If you have any difficulty with this study, or completing this chart, PLEASE telephone your research nurse -

Dorothy Lyons 0141-211 2911 or Elaine Kaeser 0131- 229 9702.

Thank you very much for your help.

DAY 1: **Mon Tues Wed Thurs Fri Sat Sun** ←*Please ring one*

Please fill in one line each time you change. At the end of the day, at your last change before going to bed, please answer the questions below the chart.

TIME of Changing *Only the hour and am / pm needed* *e.g. 10 am 6 pm*	**HOW MANY items changed now?** *Write in the number (P+T)* *e.g. 1 P + 1T =2 items*	**HOW MUCH PERIOD WAS THERE ON THE PAD(S) CHANGED NOW?** *Please tick once to describe each PAD changed now* 	**IF you also changed a TAMPON now:** **HOW MUCH PERIOD WAS SOAKED INTO THE TAMPON?** *Please tick one* 	**HAVE YOU HAD PAIN SINCE YOUR LAST CHANGE?** *Please tick one*	**DID YOU HAVE ANY CLOTS?** *Please write how many clots, by size*	**IF there has been any LEAKAGE of your period i.e. 'ACCIDENT":** *Please tick one to say how much*	**OPTIONAL** **ANY EXTRA COMMENTS** *In this space please write anything else you want to tell us about your period*
				none/ mild / moderate / severe	20p / 50p / much bigger	under clothes only / outer clothes too / bedding / furn. too	
2 pm		✓		✓			Example – one item changed
		5 4 3 2 1	5 4 3 2 1	3 2 1		4 3 2	

Before you go to bed, please answer the following about your period today:

a. Have you had to **cancel any activities/ tasks** today, because of your period? Yes ○ No ○

Please tell us what.....

b. If you have taken any **pain-killers** today, how many in total today? *Please write in* ⌊__⌋ pain-killers

c. Have you taken **any other medication** today, because of your period? Yes ○ No ○

If so, what? *Please write the name*.....

DAY 2: Mon Tues Wed Thurs Fri Sat Sun ←*Please ring one*

Please fill in one line each time you change. At the end of the day, at your last change before going to bed, please answer the questions below the chart.

TIME of Changing *Only the hour and am / pm needed* *e.g. 10 am 6 pm*	HOW MANY items changed now? *Write in the number (P+T)* *e.g. 1 P + 1T =2 items*	HOW MUCH PERIOD WAS THERE ON THE PAD(S) CHANGED NOW? *Please tick once to describe each PAD changed now*					IF you also changed a TAMPON now: HOW MUCH PERIOD WAS SOAKED INTO THE TAMPON? *Please tick one*					HAVE YOU HAD PAIN SINCE YOUR LAST CHANGE? *Please tick one*			DID YOU HAVE ANY CLOTS? *Please write how many clots, by size*			IF there has been any LEAKAGE of your period i.e. 'ACCIDENT': *Please tick one to say how much*			OPTIONAL ANY EXTRA COMMENTS *In this space please write anything else you want to tell us about your period*
												none/ mild	mod-erate	severe	20p	50p	much bigger	under clothes only	outer clothes too	bedding / furn. too	
7am	2	✓							✓				✓								Example – moderate pain & pad + tampon changed
		5	4	3	2	1	5	4	3	2	1	3	2	1				4	3	2	

Before you go to bed, please answer the following about your period today:

a. Have you had to **cancel any activities/ tasks** today, because of your period? Yes ○ No ○
Please tell us what.....

b. If you have taken any **pain-killers** today, how many in total today? *Please write in* ⌊_⌋ pain-killers

c. Have you taken **any other medication** today, because of your period? Yes ○ No ○
If so, what? *Please write the name*.....

DAY 3: **Mon Tues Wed Thurs Fri Sat Sun** ←*Please ring one*

Please fill in one line each time you change. At the end of the day, at your last change before going to bed, please answer the questions below the chart.

TIME of Changing *Only the hour and am / pm needed* *e.g. 10 am 6 pm*	HOW MANY items changed now? *Write in the number (P+T)* *e.g. 1 P + 1T =2 items*	HOW MUCH PERIOD WAS THERE ON THE PAD(S) CHANGED NOW? *Please tick once to describe each PAD changed now* 5 4 3 2 1	IF you also changed a TAMPON now: HOW MUCH PERIOD WAS SOAKED INTO THE TAMPON? *Please tick one* 5 4 3 2 1	HAVE YOU HAD PAIN SINCE YOUR LAST CHANGE? *Please tick one* none/ mild / moderate / severe 3 2 1	DID YOU HAVE ANY CLOTS? *Please write how many clots, by size* 20p / 50p / much bigger	IF there has been any LEAKAGE of your period i.e. 'ACCIDENT': *Please tick one to say how much* under clothes only / outer clothes too / bedding / furn. too 4 3 2	OPTIONAL ANY EXTRA COMMENTS *In this space please write anything else you want to tell us about your period*
5 am	2	✓ ✓		✓	3	✓	Example - 2 pads changed (+3 clots)

Before you go to bed, please answer the following about your period today:

a. Have you had to **cancel any activities/ tasks** today, because of your period? Yes ○ No ○

Please tell us what.....

b. If you have taken any **pain-killers** today, how many in total today? *Please write in* ⌊__⌋ pain-killers

c. Have you taken **any other medication** today, because of your period? Yes ○ No ○

If so, what? *Please write the name*.....

DAY 4: Mon Tues Wed Thurs Fri Sat Sun ←*Please ring one*

Please fill in one line each time you change. At the end of the day, at your last change before going to bed, please answer the questions below the chart.

TIME of Changing *Only the hour and am / pm needed* *e.g. 10 am 6 pm*	HOW MANY items changed now? *Write in the number (P+T)* *e.g. 1 P + 1T =2 items*	HOW MUCH PERIOD WAS THERE ON THE PAD(S) CHANGED NOW? *Please tick once to describe each PAD changed now* 					IF you also changed a TAMPON now: HOW MUCH PERIOD WAS SOAKED INTO THE TAMPON? *Please tick one* 					HAVE YOU HAD PAIN SINCE YOUR LAST CHANGE? *Please tick one*			DID YOU HAVE ANY CLOTS? *Please write how many clots, by size*			IF there has been any LEAKAGE of your period i.e. 'ACCIDENT': *Please tick one to say how much*			OPTIONAL ANY EXTRA COMMENTS *In this space please write anything else you want to tell us about your period*
												none/ mild	mod-erate	severe	20p	50p	much bigger	under clothes only	outer clothes too	bedding / furn. too	
12 noon	1									✓		✓			1						Example - 1 tampon (+1 clot)
		5	4	3	2	1	5	4	3	2	1	3	2	1				4	3	2	

Before you go to bed, please answer the following about your period today:

a. Have you had to **cancel any activities/ tasks** today, because of your period? Yes ○ No ○
Please tell us what.....

b. If you have taken any **pain-killers** today, how many in total today? *Please write in* ⌊_⌋ pain-killers

c. Have you taken **any other medication** today, because of your period? Yes ○ No ○
If so, what? *Please write the name*.....

DAY 5: Mon Tues Wed Thurs Fri Sat Sun ←*Please ring one*

Please fill in one line each time you change. At the end of the day, at your last change before going to bed, please answer the questions below the chart.

TIME of Changing *Only the hour and am / pm needed* e.g. 10 am 6 pm	HOW MANY items changed now? *Write in the number (P+T)* e.g. 1 P + 1T =2 items	HOW MUCH PERIOD WAS THERE ON THE PAD(S) CHANGED NOW? *Please tick once to describe each PAD changed now* 					IF you also changed a TAMPON now: HOW MUCH PERIOD WAS SOAKED INTO THE TAMPON? *Please tick one* 					HAVE YOU HAD PAIN SINCE YOUR LAST CHANGE? *Please tick one*			DID YOU HAVE ANY CLOTS? *Please write how many clots, by size*			IF there has been any LEAKAGE of your period i.e. 'ACCIDENT': *Please tick one to say how much*			OPTIONAL ANY EXTRA COMMENTS *In this space please write anything else you want to tell us about your period*
												none/ mild	mod-erate	severe	20p	50p	much bigger	under clothes only	outer clothes too	bedding / furn. too	
7pm	1		✓										✓		1		2				Example (+3 clots)
		5	4	3	2	1	5	4	3	2	1	3	2	1				4	3	2	

Before you go to bed, please answer the following about your period today:

a. Have you had to **cancel any activities/ tasks** today, because of your period? Yes ○ No ○
Please tell us what.....

b. If you have taken any **pain-killers** today, how many in total today? *Please write in* ⌊_⌋ pain-killers

c. Have you taken **any other medication** today, because of your period? Yes ○ No ○
If so, what? *Please write the name*.....

DAY 6: Mon Tues Wed Thurs Fri Sat Sun ←*Please ring one*

Please fill in one line each time you change. At the end of the day, at your last change before going to bed, please answer the questions below the chart.

TIME of Changing *Only the hour and am / pm needed* *e.g. 10 am 6 pm*	HOW MANY items changed now? *Write in the number (P+T)* *e.g. 1 P + 1T =2 items*	HOW MUCH PERIOD WAS THERE ON THE PAD(S) CHANGED NOW? *Please tick once to describe each PAD changed now*					IF you also changed a TAMPON now: HOW MUCH PERIOD WAS SOAKED INTO THE TAMPON? *Please tick one*					HAVE YOU HAD PAIN SINCE YOUR LAST CHANGE? *Please tick one*			DID YOU HAVE ANY CLOTS? *Please write how many clots, by size*			IF there has been any LEAKAGE of your period i.e. 'ACCIDENT': *Please tick one to say how much*			OPTIONAL ANY EXTRA COMMENTS *In this space please write anything else you want to tell us about your period*
												none/ mild	mod-erate	severe	20p	50p	much bigger	under clothes only	outer clothes too	bedding / furn. too	
4pm	2	✓									✓	✓							✓		Example - pad + tampon
		5	4	3	2	1	5	4	3	2	1	3	2	1				4	3	2	

Before you go to bed, please answer the following about your period today:

a. Have you had to **cancel any activities/ tasks** today, because of your period? Yes ○ No ○
Please tell us what.....

b. If you have taken any **pain-killers** today, how many in total today? *Please write in* ⌊_⌋ pain-killers

c. Have you taken **any other medication** today, because of your period? Yes ○ No ○
If so, what? *Please write the name*.....

DAY 7: Mon Tues Wed Thurs Fri Sat Sun ←*Please ring one*

Please fill in one line each time you change. At the end of the day, at your last change before going to bed, please answer the questions below the chart.

TIME of Changing *Only the hour and am / pm needed* *e.g. 10 am 6 pm*	HOW MANY items changed now? *Write in the number (P+T)* *e.g. 1 P + 1T =2 items*	HOW MUCH PERIOD WAS THERE ON THE PAD(S) CHANGED NOW? *Please tick once to describe each PAD changed now*					IF you also changed a TAMPON now: HOW MUCH PERIOD WAS SOAKED INTO THE TAMPON? *Please tick one*					HAVE YOU HAD PAIN SINCE YOUR LAST CHANGE? *Please tick one*			DID YOU HAVE ANY CLOTS? *Please write how many clots, by size*			IF there has been any LEAKAGE of your period i.e. 'ACCIDENT': *Please tick one to say how much*			OPTIONAL ANY EXTRA COMMENTS *In this space please write anything else you want to tell us about your period*
												none/ mild	mod-erate	severe	20p	50p	much bigger	under clothes only	outer clothes too	bedding / furn. too	
11 pm	1							✓				✓									Example
		5	4	3	2	1	5	4	3	2	1	3	2	1				4	3	2	

Before you go to bed, please answer the following about your period today:

a. Have you had to **cancel any activities/ tasks** today, because of your period? Yes ○ No ○
Please tell us what.....

b. If you have taken any **pain-killers** today, how many in total today? *Please write in* ⌊__⌋ pain-killers

c. Have you taken **any other medication** today, because of your period? Yes ○ No ○
If so, what? *Please write the name*.....

DAY 8: Mon Tues Wed Thurs Fri Sat Sun ←*Please ring one*

Please fill in one line each time you change. At the end of the day, at your last change before going to bed, please answer the questions below the chart.

TIME of Changing *Only the hour and am / pm needed* *e.g. 10 am 6 pm*	HOW MANY items changed now? *Write in the number (P+T)* *e.g. 1 P + 1T =2 items*	HOW MUCH PERIOD WAS THERE ON THE PAD(S) CHANGED NOW? *Please tick once to describe each PAD changed now* 					IF you also changed a TAMPON now: HOW MUCH PERIOD WAS SOAKED INTO THE TAMPON? *Please tick one* 					HAVE YOU HAD PAIN SINCE YOUR LAST CHANGE? *Please tick one*			DID YOU HAVE ANY CLOTS? *Please write how many clots, by size*			IF there has been any LEAKAGE of your period i.e. 'ACCIDENT': *Please tick one to say how much*			OPTIONAL ANY EXTRA COMMENTS *In this space please write anything else you want to tell us about your period*
												none/ mild	mod-erate	severe	20p	50p	much bigger	under clothes only	outer clothes too	bedding / furn. too	
8am	1		✓									✓									Example
		5	4	3	2	1	5	4	3	2	1	3	2	1				4	3	2	

Before you go to bed, please answer the following about your period today:

a. Have you had to **cancel any activities/ tasks** today, because of your period? Yes ○ No ○

Please tell us what.....

b. If you have taken any **pain-killers** today, how many in total today? *Please write in* ⌊__⌋ pain-killers

c. Have you taken **any other medication** today, because of your period? Yes ○ No ○

If so, what? *Please write the name*.....

DAY 9: Mon Tues Wed Thurs Fri Sat Sun ←*Please ring one*

Please fill in one line each time you change. At the end of the day, at your last change before going to bed, please answer the questions below the chart.

TIME of Changing *Only the hour and am / pm needed* *e.g. 10 am 6 pm*	HOW MANY items changed now? *Write in the number (P+T)* *e.g. 1 P + 1T =2 items*	HOW MUCH PERIOD WAS THERE ON THE PAD(S) CHANGED NOW? *Please tick once to describe each PAD changed now* 5 4 3 2 1	IF you also changed a TAMPON now: HOW MUCH PERIOD WAS SOAKED INTO THE TAMPON? *Please tick one* 5 4 3 2 1	HAVE YOU HAD PAIN SINCE YOUR LAST CHANGE? *Please tick one* none/ mild / moderate / severe 3 2 1	DID YOU HAVE ANY CLOTS? *Please write how many clots, by size* 20p / 50p / much bigger	IF there has been any LEAKAGE of your period i.e. 'ACCIDENT': *Please tick one to say how much* under clothes only / outer clothes too / bedding / furn. too 4 3 2	OPTIONAL ANY EXTRA COMMENTS *In this space please write anything else you want to tell us about your period*
9pm	1		✓	✓			Example – 1 tampon

Before you go to bed, please answer the following about your period today:

a. Have you had to **cancel any activities/ tasks** today, because of your period? Yes ○ No ○

Please tell us what.....

b. If you have taken any **pain-killers** today, how many in total today? *Please write in* ⌊__⌋ pain-killers

c. Have you taken **any other medication** today, because of your period? Yes ○ No ○

If so, what? *Please write the name*.....

HEALTH HISTORY, DIAGNOSES, TREATMENT & OUTCOME

Appendix 3.6

Study Number ⌊_⌊_⌊_⌊_⌊_⌋ Today's date __ / __ / __

1st clinic date __ / __ / __ Date most recent appointment __ / __ / __

Total no. of appointments with clinician during 8-mth period (including 1st clinic visit) ⌊_⌋

HISTORY (to be completed for **all** study recruits)

No. of :

livebirths ⌊_⌋ miscarriages ⌊_⌋ stillbirths ⌊_⌋ abortions ⌊_⌋

Any recorded history of :

	Yes	No	N/K		Yes	No	N/K	
abnormal smear	○	○	○	sterilisation	○	○	○	no. years ago _____
removal of ovary	○	○	○	use of IUD	○	○	○	previous / current
thyroid disease	○	○	○					(*circle which one*)
cancer	○	○	○ site _____					

Any chronic medical condition (as noted in case notes) _____

Medication at time of referral : _____
(*ie OC, NSAID's, tamoxifen etc*)
_____

Treatments tried by GP (*list all trts mentioned in referral letter or in case notes at 1st visit*): _____

_____

✸ Please enter Hb and ferritin results (if available) for **ALL** study recruits (see below).

INVESTIGATIONS

Enter how many of each investigation carried out during ***8 months*** since 1st clinic date :

Hysteroscopy (OP)	⌊_⌋	Thyroid function test	⌊_⌋	result.....
Hysteroscopy (theatre)	⌊_⌋	Clotting screen	⌊_⌋	result.....
D & C	⌊_⌋	✸ Hb	⌊_⌋	result.....
Suction curretage	⌊_⌋	✸ Ferritin	⌊_⌋	result.....
Laparoscopy	⌊_⌋	Ultrasound	⌊_⌋	
Colposcopy	⌊_⌋	Other, incl. interim referrals elsewhere	⌊_⌋	specify.....

.....Biopsy ⌊_⌋ .....path findings (*see guidelines*).....
enter endometrial/cervical etc .....

DIAGNOSIS

Enter code, from list below, and date of all interim/final diagnosis/es made, ***upto 8 months:***

⌊_⌋ __/__/__ ⌊_⌋ __/__/__ ⌊_⌋ __/__/__

1 dysfunctional uterine bleeding (DUB) (with regular cycle)
2 DUB - with irregular cycle
3 polycystic ovary syndrome
4 anovulatory bleeding without evidence of 3 (above)
5 hypothyroidism
6 endometriosis
7 PID
8 polyps
9 fibroids
10 carcinoma - endometrium
11 carcinoma - cervix
12 iatrogenic - IUCD
13 iatrogenic - anticoagulation trt
14 other, specify .....

TREATMENTS

Tick all treatments given during ***8 months*** since 1st clinic date, and date started or date of procedure/surgery:

		Name of drug	Date
1	prostaglandin synthetase inhibitors	.....	__/__/__
2	progestogens	.....	__/__/__
3	OC	.....	__/__/__
4	antifibrinolytic agents	.....	__/__/__
5	clomiphene	.....	__/__/__
6	~~clomiphene~~ ethamoylate	.....	__/__/__
7	danazol	.....	__/__/__
8	thyroid replacement treatment	.....	__/__/__
9	HRT	.....	__/__/__
10	LHRH analogue	.....	__/__/__
11	other drugs.....	.....	__/__/__
12	hysterectomy - abd/vag/LAVH (*circle which one*)		__/__/__
13	endometrial ablation		__/__/__
14	myomectomy (removal of fibroids)		__/__/__
15	D & C		__/__/__
16	hormone-releasing IUCD		__/__/__
17	removal of IUCD		__/__/__
18	adjust anti-coag dosage		__/__/__
19	cancer trt		__/__/__
20	other		__/__/__

OUTCOME (at 8 months)

This patient: still under care ○, discharged ○, referral elsewhere (final) ○
If discharged or referred elsewhere, enter date __/__/__
Did patient fail to return (rather than be formally discharged)? **Y / N**

Final diagnosis/es (if applicable): enter no. from above list ⌊_⌋ and date __/__/__

⌊_⌋ and date __/__/__

Most recent treatment, at 8 month cut-off date, (*enter no. from above list*) .....
Any subsequent treatment (after 8 months) .....