CONSERVATIVE MANAGEMENT OF SPONTANEOUS MISCARRIAGE

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ACKNOWLEDGEMENTS

DECLARATION OF ORIGINALITY

I hereby declare that this thesis was composed entirely by me and has not been submitted previously for a degree. I performed the initial literature search concerning the management of first trimester spontaneous miscarriage using computer Midline and Cochrane search. I was also involved in the design of all the studies presented in this thesis at different levels and in obtaining the ethical committee approvals, preparing the study packages and flyers required to conduct the work at Forth Park Maternity Hospital.

I counseled, recruited, consented and followed up all women involved in the different studies. I provided direct patients' care responsibilities especially when they represented with clinical problems out of the office-hours. I performed the pelvic ultrasound scanning for all the women who took part in the different studies presented in this thesis.

I designed the sheets required to capture the clinical data in relevance to the different clinical studies conducted during the research period. I also designed all the spread sheets and reports on the computer system used to store the data collected from the different studies. I performed the statistical analysis of all the data using the Graph Pad Instat Statistical Package.

All endocrine assays described in this thesis were performed by the technical staff of the Reproductive Endocrine Laboratory, Department of Obstetrics and Gynaecology, the Royal Infirmary, Edinburgh. I am familiar with laboratory techniques of the assays performed for studying the peripheral hormonal milieu.

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ABSTRACT

Surgical evacuation of retained products of conception has for many years remained the standard management of spontaneous miscarriage. It is estimated that 80 000 evacuations are performed each year in the United Kingdom for women with early miscarriages (missed abortion and incomplete miscarriages). During the past decade preliminary reports of alternative non-surgical options demonstrated the safety of these options in relation to surgical uterine evacuation. There is still, however, some reluctance among clinicians in offering these alternative options to women. The work in this thesis is mainly focused on the role of conservative management of women with retained products of conception following a spontaneous miscarriage in the first trimester in comparison to the 'gold standard' surgical evacuation of the uterine cavity under general anaesthesia.

An extensive review of the literature relevant to the management of these clinical conditions was carried out in the first chapter. It was very clear following the literature review that the lack of randomised trials of appropriate size, power and design has resulted in reluctance from the clinicians' side in adopting these options into routine daily practice.

The second chapter in this thesis presents the results of a large randomised trial comparing the safety and efficacy of an expectant approach against those of surgical intervention using suction evacuation under general anaesthetic. This chapter has

confirmed the safety and the relative effectiveness of conservative management when compared to surgical evacuation.

A self-administered questionnaire based study was conducted to investigate the impact of seeing and handling the products of conception on the incidence of psychological adverse reactions in women managed conservatively as compared to the control group (women managed by surgical uterine evacuation). Women managed conservatively seemed to recover psychologically quicker than women managed by surgical evacuation.

The impact of conservative management on the reproductive potential of women with retained products of conception was assessed in the fourth chapter. The first part of the fourth chapter studied the return of ovulation in a subgroup of women (n = 30) randomised to conservative management as compared to women (n = 30) randomised to surgical evacuation. The return of normal ovulation was examined by assessing the daily urinary excretion of luteinizing hormone (LH), pregnanediol (P_4) and total urinary oestrogen (E_2), follicular and endometrial development using transvaginal ultrasound. The second part of this chapter concentrated on following up women who desired to become pregnant from the two management groups. Conservative management had similar outcomes to surgical evacuation in relation to the reproductive performance.

Finally, a systematic assessment of the cost-effectiveness of conservative management was carried out in comparison with surgical evacuation in the last chapter of the thesis, which revealed a potential for substantial cost savings in NHS resources with the widespread use of conservative management.

ABBREVIATIONS

CSO	Chief Scientist Office
CRP	C-reactive protein
CI	95% Confidence Interval
CV	Co-efficient of variation
E2	Oestradiol
EPD questionnaire	Edinburgh postnatal depression questionnaire
EPL	Early Pregnancy Loss
FBC	Full Blood Count
hCG	Human chorionic gonadotrophin
iu / l	International units / litre
L	Longitudinal
LH	luteinizing hormone
LUF	Luteinized unruptured follicle
mm	millimetre
MSD	Mean sac diameter
NHS	National Health Service
nmol/l	Nanomole / litre
P_4	Progesterone
PAS	Patient administration system
PCV	Packed cell volume
PG	Prostaglandins

PID	Pelvic inflammatory disease
Pmol/l	Picomole / litre
POC	Products of conception
RR	Relative Risk
RCOG	Royal College of Obstetricians and Gynaecologists
RCR	Royal College of Radiologists
S	Sagittal
SEM	Standard error of the mean
T	Transverse
TVS	Transvaginal scan
UK	United Kingdom

CHAPTER I

REVIEW OF THE LITERATURE:

Clinical Management of First Trimester

Spontaneous Miscarriage

Introduction

Spontaneous miscarriage is the most common complication of pregnancy, and its incidence varies between 10 and 20% in clinically recognised pregnancies (Heritage et al. 1959; Jorgenson et al. 1980; Pandya et al. 1996). It is estimated that around 80, 000 uterine curettage procedures are carried out every year in the UK for women with spontaneous miscarriage (Jurkovic, 1998). It is also recognised as an adverse life event with negative impact on women's psychological welfare (Neugebauer et al., 1992). Therefore, the management of spontaneous miscarriage represents a substantial part of the emergency gynaecological workload for general practitioners and gynaecologists in the NHS.

Definitions and Terminology

Various authors have used different terminologies to describe early pregnancy problems. This needs to be standardised to allow clinicians to compare the outcomes following the use of available management options. The terminology used should provide a clear description of the actual clinical condition to guide further management and should also give a sensitive description of this emotionally upsetting clinical event as experienced by many women in their reproductive years.

In the past, *"threatened miscarriage"* was used to describe the clinical findings of any vaginal bleeding during the first half of the pregnancy in the presence of a closed uterine cervix (Donald, 1969). With the increasing use of ultrasound imaging it was realised that

similar clinical findings can be associated with any of the following conditions: on-going pregnancy, non-viable pregnancy (missed abortion), incomplete miscarriage, complete miscarriage and ectopic pregnancy. At present *"threatened miscarriage"* is confined to describe an on-going pregnancy with bleeding per-vaginam (Williams Obstetrics, 1993). However, it is still debatable whether an on-going pregnancy can be labelled as "threatened miscarriage" while the cause of bleeding is usually unknown and in the majority of these cases, the pregnancy would continue to the age of viability (Christiaens and Stoutenbeek 1984; Wilson et al., 1986; Cashner et al., 1987; Levi et al., 1990; Hill et al., 1991; Achrion et al., 1991; Merchiers et al., 1991; Frates et al., 1993; Benson et al., 1997).

The terminology *"missed abortion"* was first described by Matthews Duncan in 1874 as a clinical entity in which the fetus died before viability with no effort at its expulsion by the uterus (Litzenberg, 1921). Since this definition did not stipulate the duration of retention of the dead fetus in utero, it inevitably became a point of dispute among different investigators. In order to differentiate between missed abortion, threatened and/or incomplete abortion, various arbitrary limits were set; varying from periods of retention of products of conception of four weeks (Greenhill, 1960; Dodson, 1980) eight weeks (Brewer et al., 1974 and Lees et al., 1982) and up to two months, (Litzenberg, 1921). On the other hand, some clinical workers have designated "missed abortion" as fetal death in utero before the age of viability, regardless of the duration of the retention of the fetus, provided that there was no evidence of spontaneous abortion at the time of the diagnosis (Goldstein, 1990).

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The term *non-viable pregnancy*, diagnosed in the first trimester, is often referred to as a missed abortion (Pridjian et al., 1989). It is, however, very difficult to justify the classical definition of retention of retained products of conception for eight weeks or more when the diagnosis of a non-viable pregnancy is made during the first 12 weeks of pregnancy amenorrhoea (Grimes, 1985). Therefore alternative terms have been adopted to describe non-viability at different durations of amenorrhoea such as chemical pregnancy (Glatstein et al., 1995), blighted ovum (Donald et al. 1972), anembryonic gestation (Pridjian et al., 1989) impending abortion (Hurd et al., 1997) and first trimester intrauterine fetal demise (Pridjian et al., 1989).

With the availability of higher resolution ultrasound scanning distinction between *blighted ovum* and missed abortion has also been disputed. Goldstein (1990) suggested that most of these anembryonic pregnancies are not truly without embryos. They simply lose viability before our ability to image them. He also suggested that in many cases there is initially early embryonic development with subsequent loss of viability and then embryonic resorption. This then ultimately results in sonographic appearance of empty sac.

The use of the term spontaneous "abortion" rather than "miscarriage" has been considered to be inappropriate (Beard et al., 1985), as it may lead to negative self-perception in a group of women, who already have a sense of guilt and inadequacy because of their unfortunate miscarriage. Other inadequate terminologies, such as

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pregnancy failure, abnormal pregnancy, silent miscarriage and delayed miscarriage should be replaced by appropriate terminology, which could describe the exact diagnosis of the clinical condition. We suggest the use of the term "retained non-viable pregnancy" as an alternative to the term "missed abortion".

Prevalence

Biochemical Assessment of Early Embryonic Loss:

Early miscarriages can happen before the date of the next cyclical bleeding. The earliest studies of pregnancy loss reported their results based on life-table methods among clinically diagnosed pregnancies (French and Bierman, 1962; Shapiro et al., 1971). Subsequently published studies on early pregnancy loss (EPL) were based on measurements of hCG concentrations either in urine from fertile couples trying for natural conception (Miller et al., 1980; Edmonds et al., 1982; Ellish et al., 1986) or in blood samples from fertile (Whittaker et al., 1983) and infertile women (Braunstein et al., 1977; Charteir et al., 1979). These prospective studies reported EPL rates, which varied between 8% and 57%. This wide difference in EPL rates was most likely due to the type of the assay used, methodology employed and number of the women studied. Recently studies have used more sensitive assays (immunoradiometric assays) to measure hCG concentrations in urine (Wilcox et al., 1988; Ellish et al., 1986) and the reported rate of EPL in these studies was 22% (95% CI 16 - 28).

Clinically Recognised Miscarriages:

Three studies suggested a fetal loss rate of clinically recognised pregnancies between 12% and 15% (Miller et al., 1980; Edmond et al., 1982 and Whittaker et al., 1983). However, studies where ultrasound scanning was used as a routine have reported an early pregnancy failure ranging from 2% to 53% in the different populations studied (Table 1). Such a huge variation may be a consequence of the relatively small number of women studied in the majority of the reports, a wide range of gestational age at ultrasonic examination (5 - 16 weeks), differences in characteristics of the population studied (maternal age) and differences in the indications for the ultrasonic scans. It is of interest to note that the incidence of pregnancy failure at routine examination at the antenatal booking visit varied between 2% and 14%, compared to an incidence of early pregnancy failure between 25% and 52% for women presenting with history of vaginal bleeding.

Factors influencing early pregnancy failure

A number of factors have been studied with the aim of identifying prognostic predictors in relation to pregnancy loss in women; such as, gestational age, maternal age, indication for ultrasonic examination, history of previous miscarriage, parity and the documentation of normal ultrasound in the first trimester. There is an inverse relationship between the *gestational age* and the incidence of spontaneous miscarriage (Simpson 1984; Wilson et al., 1986; Levi et al., 1990; Barrett et al., 1991; Frates et al., 1993; Goldstein 1994; Pandya et al., 1996; Benson et al., 1997). There is further evidence to suggest that a pregnancy surviving the first 70 days from the last menstrual

period has a very high likelihood (between 96% and 100%) of progressing to term (Simpson 1984, Christiaens and Stoutenbeek 1984; Wilson et al., 1984; Barrett et al., 1991; Frates et al., 1993; Goldstein 1994, Benson et al., 1997).

Increasing *maternal age* was reported to be associated with a detrimental effect on pregnancy outcome in both fertile (Gilmore and McNay 1985; Wilson et al., 1986; Goldstein, 1994; Pandya et al., 1996) and infertile couples who failed to achieve a spontaneous conception within 12 month of unprotected intercourse (Smith et al., 1996). Although the incidence of chromosomal abnormalities increases and fertility declines with increased maternal age, there is an association between early pregnancy failure and maternal age even in chromosomally normal pregnancies (Pandya et al., 1996) (Table 2.1 -2.3).

The incidence of spontaneous miscarriage after documentation of *fetal cardiac activity* at first trimester ultrasound scanning varies between 2% and 24%. In addition, the presence of *bleeding per vaginam* has been reported to be associated with high incidence of spontaneous pregnancy loss in most of the studies as summarized in table (3) (Benson et al., 1997; Pandya et al., 1996; Frates et al., 1993; Hill et al., 1991; Levi et al., 1990; Cashner et al., 1987; Wilson et al., 1986). There is only one study, which reported similar incidence of early pregnancy loss between symptomatic and asymptomatic spontaneous pregnancies (Frates et al, 1993).

The effect of *previous pregnancy loss* on the occurrence of a subsequent miscarriage is controversial. Pandya et al. (1996) showed no significant difference between the prevalence of early pregnancy failure and a history of previous pregnancy loss. In contrast, Regan et al., (1989), in a study of 407 pregnancies reported that this was the most relevant predictive factor. The latter study reflected a selection bias as 70% of the women studied had a history of a previous recurrent miscarriage.

Diagnosis of Early Pregnancy Failure

Incomplete Miscarriage:

One of the difficult areas in the management of women with pregnancy failure is the establishment of the right diagnosis. Clinical history alone is not a useful guide to the diagnosis and clinical management of incomplete miscarriage. Therefore, investigators have described diverse ultrasound features for complete and incomplete miscarriage (Rulin et al. 1993, Haines et al.1994, Nielsen et al. 1995, Chipchase et al. 1997, Jurkovic et al. 1998 and Schwärzler et al. 1999, Sairam et al, 2001). These features are summarised in table (4). These criteria, however, show inconsistencies between the ultrasound findings suggestive of the presence or absence of retained products of conception. While there are subjective descriptions given by some authors for the diagnosis of complete and incomplete miscarriage other reports describe ultrasound measures for complete and incomplete miscarriage. Nevertheless, the different cut off measures for the diagnosis of complete miscarriage overlap with those for incomplete miscarriage in different reports. For these reasons, these diagnostic parameters have not

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been adopted universally in clinical practice. The clinicians usually use both clinical and ultrasound findings for further management of these cases (Siaram et al., 2001).

Diagnostic Uncertainties with Non-viable pregnancy:

The recognition of cases of non-viable pregnancy is not always a straightforward diagnosis. Misdiagnosis of a normal pregnancy believed to be miscarrying may occur (Hately et al. 1995).

Guidelines for Diagnosis of Non-viable Pregnancy:

In 1993, a number of cases were reported in Wales where fetal death was erroneously diagnosed by ultrasound examination. As a consequence, an independent inquiry was set up to investigate the circumstances of these cases and to make recommendations to prevent recurrence. The committee of the enquiry made the following recommendations for sonographic diagnosis of nonviable pregnancy:

- The presence of either an empty gestational sac of >20 mm is the mean sac diameter to be considered highly suggestive of the presence of non-viable pregnancy.

- The presence of an embryo of crown rump length > 6 mm with no evidence of fetal heartbeats are to be considered highly suggestive of missed miscarriage.

- It was recommended that when the gestational sac is less than 20 mm or the crown rump length is less than 6 mm, then a repeat examination should be performed at least one week later, to assess the growth of gestational sac and embryo and to

establish whether heart activity exists. If the gestational sac is smaller than expected for gestational age the possibility of incorrect dates should always be considered, especially in the absence of clinical features suggestive of a threatened miscarriage. With the latter findings a repeat scan should be arranged after a period of at least 7 days and be performed by an experienced personnel (Hately et al. 1995).

Hurd et al, (1997), also reported their guidelines for the diagnosis of a non-viable pregnancy by the use of ultrasound features alone or in combination with biochemical assays. According to their experience, a non-viable pregnancy was diagnosed without the aid of ultrasound in women of less than six weeks of gestation when βhCG levels were found to be decreasing before reaching 1,000 mIU/ml. Over six weeks of gestation the diagnosis of non-viable pregnancy was made if there was no growth in visible gestational sac over a one-week period and the βhCG level failed to increase normally (approximately doubling every 48-72 hours). In the presence of an increasing βhCG level "non-viable pregnancy" was also diagnosed when fetal cardiac activity could not be detected with either a gestational sac of > 17mm in diameter or with a βhCG level of > 30,000 mIU/mL (Hurd et al. 1997).

Management

Historical background. At the beginning of the last century Tassig F J (1936) reviewed twenty eight case series published on the management of women with spontaneous miscarriage from Europe, USA, Canada and Russia between 1918 and 1930. The

number of women studied in these series varied from 297 - 10,000. These 28 reports included cases of miscarriage up to 28 weeks of gestation and also cases with febrile complications (possibly septic abortion?) These reports showed that a large number of deaths were associated with septic miscarriages (1.2% - 27.3%), as compared to afebrile miscarriages (0% - 1%). Tassig (1936) also proposed that spontaneous uterine evacuation could be awaited in afebrile cases even if the entire products of conception or placenta had been retained in uterus.

Following this several case series were published between the periods of 1930 - 1950s (Dunn, 1937; Hertig et al. 1944; Russell, 1947; Hartman, 1953) recommending the use of surgical management because of the high incidence of maternal morbidity and mortality due to pelvic sepsis in women with retained products of conception. Since then surgical uterine evacuation has become the mainstay of management of all cases of spontaneous miscarriage in the first trimester of pregnancy. Although it is invariably accepted as a safe procedure, serious sequelae have been reported by some investigators (Farrell, 1982; Heisterberg, 1986), which stimulated clinicians to investigate the use of non-surgical options.

In the 80s and 90s preliminary work on the use of medical agents like RU486 and prostaglandin analogues for the management of women with spontaneous miscarriage demonstrated their efficacy (el-Raefy et al., 1992, Henshaw et al., 1993). A few years later reports on expectant management (Nielsen et al., 1995; Schwarzler et al., 1999) of women with spontaneous miscarriage also demonstrated the efficacy and safety of an

expectant approach for selected cases of spontaneous miscarriage in the first trimester when compared to the use of surgical uterine evacuation. These reports have generated new interest in exploring these alternative management options in terms of women's acceptability, safety in short and long terms, and the health-economic implications.

Surgical Management

Surgical uterine evacuation:

The two known surgical methods to evacuate intrauterine retained products of conception are (i) sharp curettage and (ii) suction evacuation. Up until the late 60s and early 70s sharp curettage using the curette and the ovum forceps was employed in evacuation of the gravid uterus (Peretz et al., 1967). It has now largely been replaced by suction evacuation of the uterus.

It has been suggested that with sharp curettage it is almost impossible to differentiate precisely between the basal and functional layers of the endometrium. Therefore, there is always a possibility of causing damage to the deeper basal layer of the endometrium and the myometrium, which could lead to complications such as intrauterine adhesions, oligomenorrhoea, amenorrhoea, infection and subfertility. Peretz et al. (1967) commented that at suction evacuation, smaller, delicate and blunt instruments are used with shorter operating time as compared to sharp curettage. Consequently, they anticipated a reduced blood loss and a reduction in the risk of infection. The other advantages of suction evacuation claimed by the same group of investigators were a reduction in the occurrence of uterine perforation, lower incidence of incomplete

evacuation of the retained products of conception requiring a repeat surgical evacuation, lower risk of haemorrhage, sepsis, or unexpected bleeding (Peretz et al., 1967). This group also pointed to the limitations of suction evacuation such as: (a) The inability of the suction tube, being not sufficiently delicate, to differentiate fine anatomical changes in the uterine cavity (b) The instrument can be blocked by the dense placental tissues during the process of suction in pregnancies more than 10 weeks of gestation (c) The retrieved tissues could lose their anatomical shape.

Success rate and incidence of complications following surgical management: There is, however, a generalised agreement about the safety of the surgical management of spontaneous miscarriages especially in the first trimester. Several small studies reported a success rate between 89% and 100% for surgical uterine evacuation of retained products of conception (Tan et al. 1969; Suter et al. 1969; Farrell et al. 1982; Kizza et al. 1990; Ben-Baruch et al. 1991; Verkuyl et al. 1993; de Jonge et al. 1995; Nielsen et al. 1995 and Chipchase et al. 1997). These studies have mainly compared between sharp curettage and suction evacuation of retained products of conception or between surgical management and other alternative management options.

There were no agreed criteria on the definition of a failed surgical management in these studies. The criteria used for "failed surgical management" were the re-evacuation rate of the uterus following surgical management, or the incidence of pelvic infection or any other complications.

The re-evacuation rate of the uterus following surgical management of incomplete miscarriage varied between 1.1% and 2.1% in different reports (Tan et al. 1969; Suter et al.; 1969; Beric et al. 1971; Verkuyl, 1993). There was no mention in these reports of the factors responsible for the failed surgical evacuation, but Kaunitz et al. (1985) in a large study for elective abortion reported that the risk of failed surgical abortion was found to be higher among women with one or more previous pregnancies (RR = 2.2) women having an abortion at less than six weeks' gestation (RR = 2.9), particularly when small suction cannulae were used (RR = 11.1), when the procedure was performed by inexperienced medical staff (RR = 2.2) and when they were performed on women with uterine anomalies (RR = 90.6).

The postoperative sepsis rate following surgical suction evacuation ranged between 1% and 2.3% (Filshie et al. 1973; Verkuyl et al. 1993) compared to higher rates of 4% for conventional sharp curettage (Verkuyl et al. 1993; Beric and Kupresanin 1971). Data from pregnancy termination, however, suggest that infective complications in these cases can be up to 10%. The presence of C. trachomitis, N. Gonorrhea (Westergaard et al. 1982, Qvigstad et al. 1983 and Morton et al. 1990) or bacterial vaginosis (Hamark et al. 1991 and Larsson et al. 1992) in the lower genital tract at the time of abortion is associated with an increased risk (Penney et al. 1998). A randomised trial of prophylactic single intravenous dose of doxycycline (100 mg) administered at curettage for incomplete miscarriage showed no obvious benefits of routine chemoprophylaxis. However, it has to be mentioned here that, this study was of insufficient power to detect a clinically meaningful change in infectious morbidity (Prieto et al. 1995).

Other recognised complications of surgical management reported by different investigators can be broadly classified into either anaesthetic complications or complications which resulted from traumatic injuries related to the surgical procedure.

Risk of surgical uterine perforation in first trimester elective abortion was reported by Hodgson (1975) to be less than 1%. But the rate of detection of uterine perforation reported in another two studies of pregnancy termination (Kaali et al. 1989 and Lindell et al. 1995) ranged from 0.09 - 19.8/1000 and was much higher (up to 2%) when direct visualisation using laparoscopy was carried out.

The prevalence of intrauterine adhesions following surgical uterine evacuation has been evaluated in a number of studies (Adoni et al. 1982; Schenker et al. 1982; Lancet et al. 1988; Martius 1989; Friedler et al. 1993; Romer, 1994). Investigators assessed women following surgical evacuation by performing hysterosalpingography (Adoni et al., 1982) or by hysteroscopic examination (Golan et al., 1992; Friedler et al., 1993). They reported an incidence of intrauterine adhesions between 16% (Golan et al., 1992) and 19% (Friedler et al, 1993) following hysteroscopic examination and between 15% (Adoni et al., 1982) and 22.7% (Martius, 1989) following hysterosalpingography.

There was no difference in the occurrence of adhesions among women managed surgically for either missed or incomplete miscarriage (Golan et al. 1992; Romer. 1994), in contrast to what was previously reported (Sugimoto, 1978; Vallae and Sciarra, 1988).

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From previous data reported it seems that with an increased number of curettage following miscarriage, the incidence of intrauterine adhesions also increased (Schenker et al. 1982) with an incidence ranged from 32% to 47% following two or more uterine curettage procedures (Freidler et al. 1993 and Romer, 1994).

Medical Management

Various therapeutic agents were used for medical management of women with spontaneous miscarriage, including: hypertonic fluids (Brosset, 1958; Wagner et al. 1962; Sciarra et al. 1964), rivanol (Olund, 1981), mifepristone, prostaglandins (natural and synthetic) and other oxytocics (Karim, 1970; Filshie, 1971; Naismith et al., 1974; Karim et al., 1982; Satho et al., 1982; Christensen et al., 1983).

Medical agents used for first trimester spontaneous miscarriage:

From among all these agents, investigators used hypertonic fluids, prostaglandins and mifepristone for the management of women with spontaneous miscarriage in the first trimester (Ekman et al., 1983; Thavarasah et al., 1986; Gulisano et al., 1987; Fruzzetti et al., 1991; Ragusa et al., 1994; Jaschevatzky et al., 1994).

Hypertonic fluids: Reports about the use of intra-amniotic injection of hypertonic fluids such as 50% glucose solution, 20% and 10% sodium chloride, were characterised by a high incidence of failures among women with less than 15 weeks of gestation, whom required surgical uterine evacuation.

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Prostaglandins: Karim et al. (1969) were the first to report on the successful use of prostaglandins in the management of cases of intrauterine fetal death. Following this, the use of prostaglandins in missed miscarriage and intrauterine fetal death has been researched in many trials, where different types of prostaglandin, natural and synthetic had been used for the management of early pregnancy failure. *Natural prostaglandins* ($PGF_2\alpha$ or PGE_2) stimulate the pregnant and non-pregnant uterus and have proved to be effective in inducing labour in cases of intrauterine fetal death and missed miscarriage (Mapa et al., 1982). The *prostaglandin analogues* (gemeprost and misoprostol) are more potent (Mapa et al., 1982), can be used at a lower dose and by different routes with fewer side effects (table 5 and 6) compared to the natural prototypes. The prostaglandin analogue (PGE1) **gemeprost** is relatively expensive and requires refrigeration, while **misoprostol** is rather stable at room temperature and also cheaper than gemeprost.

Prostaglandins administered intra-amniotically (Toppozada et al., 1971; Frumar et al., 1974) or extra-amniotically (Embrey et al., 1974; Calder et al., 1976) (although these routes are clearly inappropriate in cases of first trimester miscarriages) or systemically, either intravenously or intramuscularly (Mapa et al., 1982) had been shown to have frequent side effects when compared with local administration.

Combining prostaglandins with mifepristone: Subsequent to the successful use of a combination of prostaglandins and mifepristone in the management of women requesting therapeutic abortion (UK Multicentre trial, 1990; WHO study, 1989 and

1990; Norman et al. 1991; Thong et al. 1996; Urquhart et al. 1996), investigators combined them for the management of women with early pregnancy failure (el-Refaey et al. 1992; Nielsen et al. 1997 and 1999). It should, however, be recognised that these drugs remain unlicensed for their use to procure medical abortion or cases of early pregnancy failure.

Health hazards related to the use of medical agents:

Some of the medical agents used for the management of women with spontaneous miscarriage have been abandoned because of their health hazards (Wagatsuma, 1965; Anonymous, 1991). Warnings were issued based upon the experience of Japanese doctors, in which maternal deaths have occurred, as a complication of termination of the pregnancy by instillation of hypertonic solution in the amniotic sac (Wagatsuma, 1965). Two cases of maternal mortality were also reported following the use of PGE2 and sulprostone. As a result the manufacturer withdrew sulprostone from the market (Patterson et al., 1979; Anonymous, 1991). Cardiogenic shock was the cause of death in the sulprostone report, which quoted an incident related mortality rate of 1.3 (CI 0.025 - 5.8) per 100 000 abortions.

It is true that gastrointestinal symptoms and the need for analgesia are the most frequent side effects encountered with the use of different prostaglandins. However, serious complications following the use of different prostaglandins were also reported, for example, uterine rupture (Sandler et al., 1979; Schulman et al., 1979), chorioamnionitis

(Schulman et al., 1979) and excessive blood loss (Baily et al., 1975; Rutland et al., 1977).

Medical management of women with incomplete miscarriage:

Studies of medical management of cases with residual intrauterine tissues following spontaneous miscarriage in the first trimester of pregnancy, showed a wide range of success rates (table 5). Henshaw et al (1993) reported a 95.3 percent success rate using a single 0.5 mg dose of intra-muscular sulprostone or a 400 µg dose of oral misoprostol. Conversely de Jonge et al. (1995) in a randomised trial reported success rate of 13% after a single dose of oral misoprostol 400 µg. All other published studies failed to replicate the excellent results reported by Henshaw et al (1993). The largest series however was reported by Chung et al (1999), which involved 635 women with residual intrauterine tissues following spontaneous miscarriage, which was diagnosed by the use of transvaginal scanning. Women were randomised into either surgical uterine evacuation (n = 314) or were given medical treatment in form of misoprostol 400 µg orally every four hours for a total of 1,200 µg. Although, in their study women managed medically had fewer side effects compared to surgical management, the success rate of the medical management was only 50%.

Comparing the different studies, concerning the use of medical management for women with incomplete miscarriage, has been difficult because of the diversity of the data collected with regard to the population studied, regimen used and outcome measures

reported. The mean gestational age of the women recruited into the different studies varied between 9 and 12 weeks of gestation. Oral misoprostol has been the most commonly investigated prostaglandin. Different dose regimens of misoprostol has been used in different studies ranging from a single oral dose of 400 μg to a four hourly dose of 400 μg with a total of 1,200 μg per day for one or two successive days (Henshaw et al. 1993; Chung et al 1994; de Jonge et al. 1995; Chung et al, 1995; Chung et al 1997; Chung et al. 1999). Gemeprost given vaginally up to 5 mg in total and sulprostone intramuscularly were tried in two different studies. A study by Pang et al. (2001) demonstrated that vaginal misoprostol is as effective as oral misoprostol for the management of women with incomplete miscarriage with a reduction in the incidence of diarrhoea with the use of the vaginal route from 61% with the oral preparation down to 13% with the use of vaginal misoprostol.

Medical management of women with non-viable pregnancy:

Earlier reports of medical management of cases, where the pregnancy was considered to be non-viable in the first 12 weeks of gestation, have been incorporated with data for the second trimester missed abortion and third trimester intrauterine fetal death (Rutalnd et al., 1977; Ekman et al., 1980; Mapa et al., 1982; Garcea et al., 1987; Herabutya et al., 1997). Recently, several studies have concentrated on medical management of non-viable pregnancies in the first trimester (el-Refaey et al. 1992; Lelaidier et al. 1993; Egarter et al. 1995 and Nielsen et al. 1997).

El-Refaey et al. (1992) reported a success rate of 93% for women with missed miscarriage or anembryonic pregnancy in the first trimester treating them as inpatients with mifepristone 600 mg orally followed 36 hours later by either misoprostol or sulprostone to be repeated if necessary. The women in their series (n = 60) had an average gestational age of 71 (42-110) days and were either symptomatic or asymptomatic at recruitment, which could be the reason behind the high success rate, as symptomatic women with history of threatened miscarriage may have started already the process of spontaneous miscarriage. However, El-Refaey et al. (1992) did not report on their criteria of making a diagnosis of missed abortion or anembryonic pregnancy. They also defined success as the verification of the passage of products of conception or the resolution of the gestational sac on ultrasound scanning. But there was no mention how products of conception were verified and what was their further management if following the expulsion of the gestational sac there was evidence of incomplete miscarriage. Women in this series had experienced the following side effects: 8.4% needed anti-emetic, 11.8% had diarrhoea and 33.4% needed analgesia.

Lelaidier et al. (1993), in a small randomised, double blind placebo trial reported on the use of mifepristone alone in the management of first trimester non-developing intrauterine pregnancy in asymptomatic women with a mean gestational age of 11 (range 6.6 - 14) weeks. Women were given either mifepristone 600 mg (n = 23) or placebo (n = 21). Women were reviewed five days later with an ultrasound examination to confirm natural expulsion of the retained products of conception. Natural expulsion was achieved in 82% of women treated medically compared to 8% in the placebo group. Nine percent

of the medically treated group had an emergency curettage but it was not indicated whether any of these women required blood transfusion or iron supplementation.

Egarter et al. (1995) carried out a randomised trial to compare between medical treatment and surgical evacuation of the uterine cavity in the management of women with non-viable pregnancy. Women had a mean gestational age of 10.1 (range 8 – 12) weeks and were randomised to either medical (n = 43) or surgical management (n = 44). In this study initial diagnosis of non-viability was based on failure to show a progressive intrauterine pregnancy and/or if βhCG failed to increase by at least 200 mIU/ml per day. These given criteria of diagnosis of non-viability have not been validated by any previous work. All women in the medical group were treated as inpatients with 1 mg pessary of gemeprost (PGE1 analogue) to be repeated three hourly, with a maximum dose of 3 mg per day for two days. Success rate of the medical management was 76.7% and success was defined as the passage of products of conception with decline in βhCG level on repeated examinations. Histopathologic examination was carried out on all the tissues retrieved by surgical evacuation or passed by the women following their medical treatment. The results of the histopathologic examination, however, were not reported and no comment had been made on the correlation between ultrasonic findings and clinical diagnosis. Twenty-six women (60%) of the medically managed group required analgesia because of moderate or severe crampy abdominal pains, and 9.3% had severe bleeding, but it was not mentioned whether any of them required blood transfusion or iron supplementation.

Nielsen et al. (1997) reported on the use of a combination of mifepristone (400 mg oral dose) followed 36 hours later by a single dose of misoprostol 400 µg orally for the management of women with missed abortion in the first trimester. Women were asymptomatic and were treated on an outpatient basis (n = 31). The mean gestational age was 77 days in the successful group compared to a mean gestational age of 70 days in the unsuccessful group and the success rate was only 52%. They concluded that their results did not support the use of mifepristone and misoprostol for medical management of women with missed abortion.

Nielsen et al (1999) reported a second study comparing medical management (n = 60) with expectant management (n = 62) for women with non-viable pregnancy with symptoms of bleeding and/or pain. The average gestational age of the study population was 67 - 68 days. All women in the study were less than 13 weeks of gestation and were randomised to either treatment groups. Women in the former group were treated by 400 mg of mifepristone orally as outpatients followed by a single oral dose of 400 µg misoprostol 48 hours later. They achieved a success rate of 82% compared to a 76% success rate noticed among women managed expectantly.

Wagaarachchi et al. (2001) reported on the use of 200 mg of mifepristone followed 36 - 48h by vaginal misoprostol for the management of women with early fetal demise. The success rate was 84.1% based mainly on clinical verification of the passage of POC and the occasional use of ultrasound when required. They concluded that the mifepristone

dose of 200 mg was probably responsible for the lower results as compared with el-Refaey et al. (1992) who used 600 mg. They were also suggesting that the routine use of ultrasound to diagnose complete miscarriage following medical treatment would lead to increased intervention and lower success rates. However, they reported 2% incidence of PID that probably could have been avoided if ultrasound was used routinely and surgical evacuation was carried out if necessary.

Demetroulis et al. (2001) conducted a prospective randomised trial to assess the effectiveness of a single dose, 800 μg misoprostol administered vaginally compared with surgical evacuation for the treatment of early pregnancy failure, either incomplete or nonviable pregnancies. Eighty women were randomised to receive either medical treatment (n = 40) or surgical evacuation (n = 40). They achieved 82.5% success rate with medical management, 94% (1/14) in incomplete miscarriage and 77% (6/26) for women with non-viable pregnancy.

Wagaarachchi et al. (2002) were the first to report on the use of sublingual misoprostol for the medical management of early fetal demise (n = 56). Two thirds of their women were asymptomatic at presentation and the rest were symptomatic. The overall success rate was 83.9% and the median induction to miscarriage interval was 8.9 hours. Success rate was unexpectedly higher among asymptomatic group than symptomatic women. The reasons for these differences are not understood. They concluded that this route of administration is an alternative to vaginal or oral misoprostol for the management of this

condition. Their population suffered a high incidence of side effects; 50% suffered from diarrhoea and 82% required analgesia.

In summary, the success rate in various randomised trials where medical treatment has been compared with either placebo (Lelaider et al, 1993) or surgical evacuation (Egarter et al., 1995; Demetroulis et al., 2001) or conservative management (Nielsen et al., 1999) varied between (76.6% - 82.5%). A higher success rate was reported with medical management in non-randomised observational studies varying between 83.4% and 93%. The total *number of women* involved in randomised reports varied between 46 - 122, with a variable gestational age between 9 - 11 weeks of gestation. The number of women offered medical management in the non-randomised reports varied between 31 and 220 women. The duration following medical management till offering surgical evacuation for "failed" cases also varied in these reports between few hours and up to five days.

Medical agents used in these reports included mifepristone alone (600 mg orally) with a success rate of 82% (Nielsen et al., 1999), misoprostol (vaginally 800 µg) with a success rate of 82.5% (Demetroulis et al., 2001), gemeprost (vaginally 1mg/3h) with a maximum dose of 3 mg per day with a success rate of 76.7% (Egarter et al., 1995), and a combination of mifepristone (400 mg) with misoprostol (400 µg orally), which had a success rate of 82% (Nielsen et al., 1999). The *medical regimen*s used in the non-randomised reports were usually a combination of mifepristone (200 – 600 mg) and misoprostol. However the route and frequency of administration of misoprostol tablets

varied in these reports. Misoprostol was administered sublingually by Wagaarachchi et al (2002), who reported an overall success rate of 83.4% and this was accompanied by a high incidence of side effects. The same group of investigators reported a similar 84.1% success rate, but a lower incidence of side effects when the first dose of misoprostol was given vaginally and followed by subsequent doses given either vaginally or orally. Nielsen et al (1997) administered a single dose of vaginal misoprostol, with low incidence of side effects but with a high failure rate of 48%. El-Raefy et al (1992) used repeated doses of oral misoprostol for two days to achieve a 93% success rate but again reported a high incidence of side effects.

The *incidence of side effects* for women managed medically in randomised studies was comparable to the incidence of complications in the control groups. The incidence of different complications and side effects with medical management as given in randomised and non-randomised reports were as follows: the need for readmission (3.6 – 6%), pelvic infection (0.8 – 4%), heavy bleeding > 500 ml or requiring blood transfusion (1 – 26%), the need for analgesia (24.2 – 85%), the need for parenteral analgesia (2 – 32.1%), diarrhoea (4 – 65.3%), nausea and vomiting (1.4 – 30%), pyrexia (9%) and postural hypotension (1.4%). The variation in the incidence of these side effects were related to the route of administration of prostaglandins and the dose given to induce expulsion of the retained products.

Direct comparisons between the different medical agents are not available. Only one study (Creinin et al., 1997) with small numbers (n = 20), compared between misoprostol

given orally (400μg daily for 2 days) or vaginally (800 μg daily for 2 days) for the management of early pregnancy failure where the gestational age was eight weeks or less confirmed by ultrasound and pelvic examination. The success rate in the former group (oral route) was 25% compared to 88% in the latter group (vaginal route). There was also a higher incidence of gastrointestinal side effects when misoprostol was given orally.

Following reviewing the evidence reported in all these studies, it is obvious that the ideal medical regimen for the management of women with non-viable pregnancy is still to be determined. Medical regimen, which used combinations of mifepristone with multiple doses of prostaglandins, demonstrated higher success rates (82 – 93%) compared to the use of either of these agents alone (76.5 – 82%). Furthermore higher success rate(s) required repeated administration of misoprostol, which was also accompanied by higher incidence of side effects. In general, there is lack of randomised trials of optimal power and appropriate design to assess the effectiveness of medical treatment against the surgical management. This partially explains the reluctance on the part of medical fraternity of introducing medical management as an option for women with early pregnancy failure.

Conservative Management

Investigators have used either the terminology of "expectant" or "conservative" management, to describe "the watchful waiting of the occurrence of spontaneous miscarriage" instead of surgical intervention. On the other hand, Tassig F J, (1936), used

the term "expectant" to describe an observational period of care, which was usually followed by surgical evacuation of products of conception and he used the term "conservative" to describe any form of care provided to the woman, but surgical management. Chung et al (1999) also used the word "conservative" to describe a non-surgical approach when they treated their women with prostaglandin E1 analogue (misoprostol).

Conservative management of women with complete miscarriage:

Robinson (1972) reported the use of transabdominal ultrasonography in the management of a group of 53 women presented with a history of spontaneous miscarriage. In this prospective study, a complete spontaneous miscarriage was suggested in 25 (48%) women by observing an empty uterus on ultrasonographic examination. Five women in this group underwent curettage because of heavy bleeding and in only two of them chorionic villi were obtained. The negative predictive value for detection of chorionic villi was 92% but only 80% had complete abortion with no further management. In the remaining 28 women ultrasonographic examination showed significant echoes; at curettage 23 out of the 28 women had products of conception, with a positive predictive value of 82%. Therefore, Robinson (1972) concluded that it was possible to reduce the number of unnecessary evacuations and the duration of stay in hospital. Other clinicians did not adopt the observations described in this study at that time.

Mansur, (1992), reported a series of forty-three women with spontaneous miscarriage who were managed conservatively after they stopped bleeding and their ultrasonic

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examination demonstrated the presence of an empty uterus. Women in their series encountered no complications during their follow-up period. The predictive value of ultrasound examination in diagnosing complete abortion was 97.6%, suggesting that ultrasound may be useful in avoiding unnecessary curettage. This study has several problems, (a) the diagnostic ultrasonic criteria for complete miscarriage were subjective, (b) no data were provided on the amount or duration of blood loss following the conservative management, (c) the length of the follow up period was not discussed and (d) no attempt was made to carry out quantitative assessment of the intrauterine residual tissues seen in the other group.

Rulin et al. (1993) managed a group of 49 women conservatively when the ultrasonic examination showed an endometrial thickness ≤ 10 mm. This cut off figure was derived from Fleischer et al. (1986) report. Of these 49 women only one woman experienced pain and bleeding and a small amount of tissues was removed at surgical evacuation. The predictive value of ultrasonic examination was 98%. On the other hand sixty-nine percent of women with thickened endometrium more than 10 mm on ultrasonic examination had chorionic villi obtained at curettage. The data on the follow-up of the study population were incomplete.

Haines et al. (1994) attempted to select cases suitable for conservative management by using transvaginal scanning in a group of 50 women. Out of the fifty women reviewed, thirty-two women were selected for non-operative management as the sagittal and the

transverse area of the endometrial lining were below 6 cm^2 and 5 cm^2 respectively. These measurements were less than the calculated value of the mean plus two standard deviations (SD) of the endometrial thickness, which was previously recorded as being representative of an empty uterine cavity following surgical evacuation of the uterus (Haines et al. 1991). Sixty-four percent of women were selected for conservative management and no complications were noted during the follow-up period. The negative predictive value of transvaginal scanning for detection of the absence of chorionic villi was 100%. However, Haines et al. (1994) did not describe an upper cut off limit on ultrasonic measurements where conservative management may not be offered.

Conservative management of women with retained products of conception: *The first randomised study* comparing expectant management versus surgical management of women with residual intrauterine tissues following spontaneous miscarriage was reported by Nielsen et al. (1995). One hundred and three women with incomplete and inevitable miscarriage were randomised to expectant management compared to fifty-two women managed by surgical uterine evacuation. The women managed expectantly had a complete miscarriage rate of 79% within three days of observation. Women with asymptomatic non-viable pregnancy were excluded but it was not clear whether women with pain and bleeding and a closed cervical os were recruited into the study or not. There were three cases (3%) of pelvic infection among women randomised to expectant management compared to five (10%) among women managed surgically. Nielsen et al (1995) study although of considerable interest it had several methodological problems (Ankum et al. 1995). There may have been a sampling bias as not all the women

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presenting with spontaneous miscarriage in their unit were considered for the study. Given the arbitrary measurement of the antero-posterior diameter of more than 15 mm, it also seemed likely that, women with blood clots, decidua or residual villi in the uterine cavity could have been included in their study cohort. Ankum et al (1995) also pointed out that Nielsen's report did not include any findings from histopathology of retained products or human gonadotrophin hormone monitoring, which were important diagnostic parameters for managing women with early pregnancy failure. Furthermore, Nielsen et al. (1995) did not justify their choice of the short three-day follow-up period for the conservative management. Despite these reservations it must be acknowledged that their prospective study did create a lot of interest among gynaecologists as regards non-surgical management of incomplete miscarriage.

Chipchase et al. (1997) reported a small study of 35 women with residual intrauterine tissues, of whom 19 women were randomised to expectant management and 16 women had surgical uterine evacuation. There were no differences in the main outcome measures between the two groups in terms of duration of pain in days, bleeding, sick leave and return to normal periods. However in this study they did not provide an accurate description of ultrasound criteria employed for selecting women suitable for the study. Given the mean diameter of 11 mm of the retained products of conception suggests that women with complete miscarriage were recruited into the study (Ankum et al., 1995). The results of the histopathological examination of the retained products of conception in their surgical group were not described. They also did not describe their criteria to diagnose pelvic infection. Although it was reported that women were satisfied

with their expectant management, no information was provided of how satisfaction was assessed.

Hurd et al. (1997) reported a historic cohort study of conservative management versus surgical management and concluded that women with impending miscarriages could be safely managed expectantly if there was minimal amount of intrauterine tissue (gestational sac $\leq$ 10 mm). For women with significant intrauterine tissues (gestational sac >10 mm), the risk of complications might be decreased by elective curettage compared with expectant management. This was an observational study with an inherent potential of bias. Allocation of every woman to a particular management was based on women and physician preferences. The amount of residual intrauterine tissues was not assessed ultrasonically in all women and their report did not provide enough information about the group of women with significant intrauterine tissues.

Jurkovic et al. (1998) reported a non-randomised prospective study of 221 women managed either expectantly (n = 85) or by surgical evacuation of the uterine cavity (n = 136). It was not clear whether their women were symptomatic (experiencing bleeding $\pm$ pain) or the diagnosis of non-viable pregnancy was made at routine clinical examination. Also the state of the cervix uteri at recruitment was not reported. Twenty-four percent of the conservatively managed group had complete miscarriage and only 20% within two weeks; 16.5% had incomplete miscarriage necessitating surgery, and 58.8% requested surgery when spontaneous miscarriage did not happen after a long waiting time or when

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the symptoms of the miscarriage started. In addition, one woman required blood transfusion in the expectantly managed group because of heavy vaginal bleeding. No pelvic infection was reported in either group. Three women in the surgical group required re-evacuation of the uterus. Jurkovic et al. (1998) concluded that the low success rate of expectant management of non-viable pregnancy did not justify its use in routine clinical practice.

Schwarzler et al (1999) recruited 108 women with a diagnosis of missed/an-embryonic miscarriage for a non-randomised study and women were given the choice of expectant (n = 85) or surgical (n = 23) management. The success rate in the conservatively managed group was 84% at the end of the fourth week. This report did not provide information about the short/medium term complications, the fall in haemoglobin (Hb) or Haematocrit (Hct) levels prior to and after management especially among expectantly managed group, the severity of pain experienced and the use of analgesia. The psychological impact of this rather long expectant management of four weeks was not also discussed in their report.

Sairam et al. (2001) reported on the use of ultrasound in the expectant management of women with early loss, 221 with incomplete miscarriage and 84 with missed miscarriages. They reported 86% success rate and the success rate was higher among women with incomplete miscarriage (96%) than women with nonviable pregnancy (62%). The allocation to the two treatment options was based on patient's choice of the type of management. They did not specify in their report whether they used

transabdominal or transvaginal ultrasound or both. Their definition of incomplete miscarriage was endometrial thickness > 5mm in diameter, which according to the definition given by Nielsen's et al (1995) means that they have included cases of complete miscarriage in their study. Moreover, they have not reported the details of the scan findings for the studied groups.

Luise et al. (2002) reported in a prospective observational study a 70% success rate following conservative management of women with retained products of conception (n = 478). This was achieved within two weeks from diagnosis. The success rate was 81% when the expectancy period was prolonged to four weeks. Not all the patients were followed up but a selected few for unsatisfactory developments. The uptake of conservative management by all women with RPOC referred to their unit was 70%.

In Summary, of all the studies of conservative management of women with retained products of conception reported so far, only two were randomised (Nielsen et al., 1995; Chipchase et al., 1997) and the rest were either observational (Jurkovic et al., 1998; Schwarzler et al., 1999; Sairam et al., 2001; Luise et al., 2002) or were retrospective reports (Hurd et al., 1997). The number of women managed conservatively in these two randomised trials was 19 in Chipchase et al (1997) and 103 in Nielsen's et al (1995) whereas in the non-randomised trials the total numbers varied between 84 and 478. The number of women with non-viable pregnancies included in the non-randomised reports varied between 85 and 230. The length of the expectancy period, ranged from three days (Nielsen et al., 1995) to 49 days (Jurkovic e al., 1998).

The success rate reported in the two randomised trials (Nielsen et al., 1995; Chipchase et al., 1997) for women with incomplete and inevitable miscarriage who were managed conservatively varied between 79% and 100%. The success rate reported in the non-randomised reports varied between 25% and 100%. The success rate for women with incomplete miscarriage varied between 79% and 100% and for women with non-viable pregnancy ranged between 25% and 84%.

Similar incidence of *complications* was reported in the individual studies following randomisation to either conservative management or surgical evacuation of women with residual intrauterine tissues. The incidence of different complications for women managed conservatively varied between 1 – 8% compared to 2 - 13% reported for women managed by surgical uterine evacuation. The overall incidence of emergency curettage for haemostatic uterine evacuation, suspected genital tract infection or any other complications for women managed conservatively varied between 0.2% - 5.8%. The reported incidence of *pelvic infection* was higher among women managed surgically (0 – 10%) than women managed conservatively (0 – 3%).

Meta-analysis comparing conservative management and surgical uterine evacuation (Figure 1): A meta-analysis of all the studies comparing conservative management versus surgical uterine evacuation for the incidence of complications did not show any difference between the two management strategies [P = 0.27, OR 1.4 (0.8 - 2.4)]. However, a meta-analysis comparing the two management options showed a

trend towards a lower incidence of pelvic infection in women managed conservatively as compared to women managed by surgical evacuation [P = 0.07, OR 0.36 (0.12-1.1)].

All published studies on three management options describing success rates have been described in table (8). The cumulative success rate was 87% for women managed expectantly; 68% for those managed medically and 90% for those who underwent uterine evacuation.

Predictors of success in expectantly managed women: *Colour Doppler* imaging of the intervillus space and the uterine artery blood flow has been used to predict the occurrence of successful outcome following conservative management of women with non-viable pregnancy. The blood flow in the former was found to be more useful than the latter in this respect (Schwarzler et al., 1999). It was also suggested that the use of serum βhCG levels might help in selecting women with retained products of conception who will benefit from surgical evacuation (Nielsen et al., 1996).

Future fertility following expectant management (Table 9). The effect of conservative management on future fertility was studied by **Ben-Baruch et al. (1991)**, who studied the probability of conception, outcome of subsequent pregnancies and rate of subsequent miscarriages among 87 women with an early spontaneous miscarriage, who were allocated to either surgical (n = 52) or expectant management (n = 35) and desired to become pregnant. The median follow-up period after miscarriage was 28 months (range

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12 - 68) in the surgically managed group and 26 (range 12 - 72) in the conservatively managed group. Infertility (failure to conceive for more than 12 months after miscarriages or after stopping contraception) was observed in 13 women (25%) in the surgical group and eight (23%) in the conservatively treated group (non-significant difference). The rate of history of infertility was relatively high in the two groups 36.5% in the surgically treated group and 34.3% in the conservatively treated group. During the follow up period 39 women (75%) in the surgically treated group and 27 (77%) in the conservatively treated group conceived. There was no difference with regard to the rate of normal deliveries and rate of recurrence of miscarriage. The authors concluded that the main factor that significantly influenced the probability of post-abortion infertility was a past history of infertility prior to their miscarriage. There was only one ectopic pregnancy in the conservatively managed group (3.7%) compared to none in the surgically managed group.

Kaplan et al. (1996) followed up 172 women with spontaneous complete miscarriage of less than eight weeks of gestation with regard to their future fertility following a successful conservative approach, which had a success rate of 97.6%. The conception rate was 73.3% among the 161 women who desired to become pregnant within 18 months. These figures were comparable to those reported for a normal fertile population (Speroff et al. 1994). Of the 118 pregnancies, 35 (29.7%) ended in miscarriage. Six (5.1%) of the 118 pregnancies ended in complete miscarriage and two women (1.7%) had an ectopic pregnancy. Kaplan et al. (1996) concluded that future fertility was not impaired by employing a conservative approach in selected cases of early pregnancy

loss. The above two studies (Ben-Baruch et al. 1991; and Kaplan et al. 1996) although non-randomised in design provide interesting data on the impact of conservative management on future fertility.

Chipchase et al. (1997) and Blohm et al. (1997) have reported on future fertility following randomisation to either surgical or conservative management. Chipchase et al. (1997) reported that nine of 12 women from expectant group and six out of nine women from surgical group who were trying to conceive did so by six months. The number of women in their study was small. Blohm et al. (1997) reported no difference in cumulative conception rates (88% for women managed by surgical evacuation versus 93% for women managed expectantly) or in pregnancy outcome between the two groups of women previously randomised by Nielsen et al. (1995) who desired to become pregnant (37 women managed surgically and 76 managed expectantly). The original study (Nielsen et al. 1995) was, however, criticised for its poor design and these data should be interpreted carefully (Ankum et al., 1995).

Women's Satisfaction following Management of Early Pregnancy Loss

The psychological impact of management of early pregnancy losses has in the past been ignored or underestimated in clinical trials (Sharma JB, 1993). Medical termination of pregnancy with misoprostol and mifepristone is generally well tolerated (UK Multicentre Trial, 1990), but this treatment may not be so well tolerated by women with miscarriage. The pain and bleeding of a miscarriage can be severe and some women might prefer an operative treatment (Jurkovic et al., 1998). Women's acceptability and

quality of life as a reflection of their acceptance to their management should be considered in future trials investigating alternative forms of management of spontaneous miscarriages in comparison to the standard surgical management.

Health Economic Aspects of the Management of Early Pregnancy loss

Assessment of effectiveness alone is unlikely to determine whether a new treatment makes best use of available resources. Economic evaluation as part of randomised clinical trials on alternative clinical management is still a rarity, accounting for less than 1% of studies published between 1966 and 1988 (Adams et al. 1992). Reports on the health-economic implications of medical management of induced abortion suggest that no extra resources are required to provide medical abortion service (Henshaw et al. 1994). It was also reported that it might be possible to generate savings by introducing medical methods in the management of spontaneous early miscarriages, provided that the costs associated with theatre use can be correctly estimated (Hughes et al. 1996). In case of conservative management, there are potential cost savings with reduction in inpatient care episodes and consequently reductions in acute bed occupancy, as well as potential benefits to the women with natural methods of management. More research is required in this area.

Conclusion

Among the three options available for the management of women with spontaneous miscarriage, **surgical evacuation** of the uterine cavity is currently accepted as the standard management, particularly in the presence of retained products of conception.

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Between the two known methods of evacuation of the uterus, suction evacuation seems to be the preferred method. It is accompanied by lower incidence of complications and requires less operative time compared to sharp curettage. There is a scarcity of data available on the effect of sharp curettage versus suction evacuation on duration of postoperative pain, the postoperative analgesia required and the pathogens, which can complicate either method.

Although surgical evacuation has a low incidence of immediate complications; 2.1% incomplete evacuation, 2.3% sepsis rate and less than 1% perforation rate. However, the reported incidence of intrauterine adhesions varied between 15% and 47%. The incidence of adhesions seems to increase with increasing frequency of pregnancy related curettage. Little is known about the effect of these adhesions on either short or long-term complications, such as: the occurrence of pelvic pain, menstrual abnormalities and future reproductive performance, especially in women with two or more pregnancy-related curettages.

As regards **medical management** of women with spontaneous miscarriage, prostaglandins analogues gemeprost and misoprostol currently represent the most commonly used agents in the medical management of spontaneous miscarriages as they are accompanied by lower incidence of side effects than their prototypes. The optimal regimen for the management of women with incomplete and non-viable pregnancy needs to be defined, taking account of its efficacy, frequency of side effects, acceptability and cost effectiveness. It should also be judged in comparison to the

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alternative options, i.e. surgical evacuation of uterine cavity and conservative management. The current evidence comparing medical management with expectant management of women with non-viable pregnancy reports no difference in success rate between the two managements. Moreover, available data suggest that conservative approach for women with incomplete miscarriage is more feasible than medical treatment as it is cheaper, more acceptable and free from side effects.

Studies have demonstrated that routine surgical evacuation of the uterus in women with complete miscarriage could not be justified and a **conservative approach** is rather more appropriate. The evidence on the role of conservative approach, however, in the management of women with spontaneous miscarriage complicated by the presence of residual intrauterine tissues, especially when residual tissues represent the intact gestational sac, was controversial. In this respect success rates varied between 25% and 100% according to the groups of women recruited and selection criteria used. Randomised studies of appropriate design and power are required to assess the role of conservative approach in the management of women with retained products of conception either incomplete miscarriage or non-viable pregnancy. The uptake of conservative approach and women's satisfaction with this approach needs to be examined. The impact of a conservative approach on future reproductive performance also needs to be assessed in these randomised studies. Identification of various prognostic factors, which are easily reproducible and which can help in selection of women suitable for conservative management, is also required. There are potential cost savings with conservative management and this also needs to be systematically assessed.

CHAPTER II

A Randomised Trial Comparing Conservative Management versus Surgical Uterine Evacuation for First Trimester Miscarriage with Retained Products of Conception

Introduction

Over the past 50 years, surgical evacuation of retained products of conception under general anaesthesia has remained the conventional method of management, especially in the first trimester of pregnancy as retained products of conception were considered to increase the risk of sepsis and haemorrhage (Tassig et al., 1936; Dunn et al., 1937; Russell, 1947; Hartman et al., 1953; Heritage et al., 1959).

Although surgical evacuation of the uterine cavity is accepted as a safe and an effective procedure, it can sometimes have serious, even, fatal complications (Farrell et al., 1982; Heisterberg et al., 1986) and also data from medically treated pregnancy terminations suggest that retained products of conception do not result in an increased risk of endometritis and routine surgical evacuation of the uterine cavity may not necessarily prevent post-abortal sepsis (Ullmann et al., 1992).

During the last decade, two preliminary reports, by Nielsen et al. (1995) and Schwarzler et al. (1999) suggested that expectant management is safe and has a similar outcome compared with surgical evacuation of the uterus for retained products of conception. The length of the expectancy period for conservative management in these reports varied between three days and four weeks. These were small studies and did not demonstrate the optimum protocol for conservative management of women with significant residual intrauterine tissues following spontaneous miscarriage. The aim of this prospective randomised trial was to study the safety and efficacy of conservative management

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compared to surgical evacuation of the uterine contents, in women with residual intrauterine tissues following spontaneous pregnancy failure at less than 13 weeks of gestation.

Methods

All women with a history of vaginal bleeding and/or lower abdominal pain less than 13 weeks of gestation referred to the Early Pregnancy Clinic or the gynaecological ward at Forth Park Hospital, Kirkcaldy, Scotland were assessed clinically and underwent a transvaginal ultrasonic examination *(Toshiba TOSBEE with 6 MHZ vaginal probe)* to establish the diagnosis and to measure the maximum antero-posterior (AP) diameter of products of conception in the sagittal plane prior to their recruitment into the study.

The Inclusion Criteria.

The inclusion criteria for the study were:

(a) Evidence of retained products of conception with an AP diameter greater than 15mm measured in the sagittal plane.

(b) A diagnosis of either incomplete miscarriage or non-viable pregnancy following spontaneous pregnancy failure (less than 13 weeks of gestation).

(c) A history of vaginal bleeding and /or lower abdominal pain within one week prior to recruitment.

(d) Haemodynamically stable with haemoglobin (Hb) level > 10 g/dl.

(e) No clinical evidence of sepsis.

(f) More than 16 years of age

(g) Able to understand the protocol.

Women with incomplete miscarriage, with retained products of conception measuring more than 15mm in the AP diameter assessed in the sagittal plane, were selected to join the study only if their scans showed evidence of thick irregular echoes in the uterine cavity (Stabile et al., 1987). Women with non-viable pregnancy were also selected in accordance with the RCR/RCOG recommendations of diagnosing spontaneous miscarriage (Hately et al., 1995). In all subjects each of the three diameters [sagittal (S), longitudinal (L) and transverse (T)] of the area with retained products of conception were required to measure more than 15 mm for eligible entry into the study. Similarly the three diameters of the gestational sac (S, L and T) were measured with and without the choriodecidual reaction around the sac. These measurements were used to calculate the volume of the gestational sac, mean sac diameter and volume (Rumack et al., 1998) of the products of conception (gestational sac plus the choriodecidual reaction around it).

Sample size: The sample size of the randomised groups was calculated using the "negative trial design" which assumes that two treatments are equally effective (Pocock, 1985). A preliminary Swedish study (Nielsen et al., 1995) reported that conservative management for three days had a 79% success rate. If we assume that there would be a 15% difference in the clinical effectiveness between the two management groups, then for $\alpha = 0.1$ and a power of 95%, the number of women required for the study would be

302. Taking into account a 5% withdrawal rate from the study or protocol violation, the planned sample size was a minimum of 320. The research team prepared three hundred and fifty envelopes. At the end of two years, an open interim analysis was prepared and submitted by the grant holders to the Chief Scientist Office (CSO) Committee members. The CSO Committee agreed to provide funding for another 12 months and an orderly termination of the study. Two hundred and eighty three women were randomised by the time the study was terminated.

Randomisation: The process of randomisation was carried out as complete randomisation (without blocking) using randomisation tables described by Kirkwood (1988) where a block of 350 of odd and even numbers were used to randomise women to either surgical evacuation (odd numbers) or conservative management (even numbers). Each number was written on a small piece of paper with the relevant type of treatment allocation and was sealed in a brown opaque envelop by the research team. These envelopes were serially numbered from outside from 1 to 350 and were kept in a drawer in the locked research office, which was 50 meters from Forth Park Hospital. Access to the research office was restricted to the research team employed in this CSO grant.

Recruitment Process: All women who attended the Early Pregnancy Clinic and fulfilled the study criteria were given the standard patient's information sheet of the randomised study by the Research Nurse. Women who agreed to be randomised (n = 283) were asked to sign the consent form. Following this the Research Nurse telephoned

the Research Secretary to register them giving them the same serial number on the study envelop which was due to be opened. Once this process was completed the brown opaque envelope, which belonged to the newly registered woman, was opened and the allocated randomised management was registered into the computer database and the woman was informed about her treatment allocation. Women who refused to be randomised (n = 85) who had a particular preference to either management were allowed to undergo their chosen management (54 chose surgical evacuation and 31 chose conservative management). Their data were kept in a separate database for the non-randomised groups.

Women from both randomised and non-randomised groups were managed and followed up using the same protocol (Figure 2), which had been previously approved by the ethics committee of the Fife Health Board, Scotland. A brief history, general and pelvic examination with bacteriological screening for chlamydia, gonorrhoea and other relevant microbes was carried out at recruitment. Blood samples were also taken to estimate full blood count (FBC), C-reactive protein (CRP) and serum human chorionic gonadotrophin (HCG) levels.

Blood Loss Assessment. Women from both groups were given pictorial blood loss measurement charts adopted from a previously published study of women with menstrual loss (Higham et al., 1990). Women were instructed to record their blood loss on sanitary towels with reference to the printed shapes of used towels given on the charts. They were advised to record the number of the blood clots passed and refer them

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to coinage sizes (5, 10 and 50 pence) or to estimate the size of the blood clots in inches or centimeters when clots of blood were bigger than coinage sizes. The amount of blood loss was assessed using a modified scoring system, as women with miscarriage were more likely to experience heavier blood loss than the group of women in Higham's study (Higham et al., 1990). The **scores** assigned **for the blood loss** charts were as follows: **1** for each lightly stained towel; **5** for moderately soiled and **20** if it was completely saturated with blood. Small and large blood clots scored 1 and 5 respectively. For women who experienced bleeding coming through the sanitary towel(s) and staining their clothing (flooded with their bleeding) accompanied by the passage of blood clots or gushes of blood, an extra score of **100** was given in that particular day to be added to the total score on the chart.

Assessment of Pain: A subgroup of 88 consecutive women from the randomised group (44 in each treatment arm) and 31 from the non-randomised group (15 conservative and 16 ERPC) were given numerical pain assessment charts (McCaffrey et al., 1994) (Appendix 1), where the severity of pain experienced every day was measured according to a **scale of 1 - 10** (1 = no pain, 2 – 4 = mild pain, 5 – 7 = moderate pain, 8 – 9 = severe pain and 10 = excruciating pain). Of the 88 women randomised to the treatment options, 75 (85%) completed their forms (38 of 44 women managed surgically and 37 of 44 women managed conservatively). Of the 31 women from the non-randomised group 27 (87%) completed their forms (13 of 15 women managed conservatively and 14 of 16 women managed surgically).

Conduct of the study. All women in this study were given emergency contact telephone numbers for the hospital. Women in both groups were scheduled for their follow-up visits after one and two weeks. Women managed conservatively were allowed home following recruitment. Women who underwent surgical evacuation were admitted to the hospital as day cases within 24 hours of recruitment. Evacuation of retained products of conception was carried out under general anaesthesia by suction curettage. Rhesus negative women in both treatment groups were given an intramuscular dose of 250 IU of anti-D immunoglobulin following surgical procedure or within 72 hours from the occurrence of spontaneous miscarriage.

Follow-up Measurements. At the follow up visits, a record was made of symptoms and clinical signs suggestive of pelvic sepsis (PID). For the purpose of this study, the diagnosis of pelvic inflammatory disease was defined by three or more of the following criteria: purulent vaginal discharge, temperature $\geq 38°$ C for more than 24 hours, uterine or adnexal tenderness on pelvic examination, "positive" bacteriological swabs, ultrasound features of adnexal mass with or without fluid in the Pouch of Douglas and/or increase in c-reactive protein (CRP). Bacteriological swabs and blood samples similar to those taken at recruitment were obtained at each follow up visit. Women with raised serum CRP were contacted and clinical assessment was made for symptoms or signs of pelvic inflammatory disease before the prescription of antibiotics was issued. Women were also prescribed antibiotics if they had positive swabs for chlamydia, gonorrhoea and/or bacterial vaginosis. Iron supplements were given if the haemoglobin dropped below 10 g/dl, after recruitment into the study.

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A transvaginal ultrasonic examination for retained products of conception was performed at the follow-up visits in both treatment groups. Women were considered to have complete miscarriage if there was no evidence of retained products of conception (Rulin et al., 1993), and the vaginal bleeding had stopped. At the second follow-up visit, women who did not expel the non-viable gestational sac or had retained products of miscarriage (incomplete miscarriage) were advised to have surgical uterine evacuation. Those who did not wish to have surgery were followed up at weekly intervals until complete miscarriage was achieved. Blood loss and pain assessment charts were collected at each follow-up visit. Women were also asked to fill in a questionnaire regarding acceptability of conservative or surgical management at the last follow-up visit.

Statistical tests:

Comparisons between groups for any statistical differences were carried out using either a two-tailed t-test ($\pm$ 95% CI) or Mann-Whitney (U) test with Range ($\pm$ 95% CI) where relevant. Measures with a discrete distribution were expressed as counts and percentages and analysed by X^2 or Fisher's exact test as appropriate using the Graph Pad Instat Statistical Package. A P value of <0.05 was considered significant (Brown et al., 1990).

Results

A total of 368 women were invited into this study. Of these 283 women consented to be randomised. The presenting diagnosis in the randomised group was either incomplete

miscarriage (n = 52, 18%) or nonviable pregnancy (n =231, 82%). Of these 283 women 122 (43.1%) were randomised to surgical management and 161 (56.9%) were randomised to conservative management. The unequal numbers has resulted from the use of complete randomization rather than blocked randomization as will be explained in the discussion section. Eighty-five women did not agree to enter the study and decided their own management (54 chose surgical uterine evacuation and 31 chose conservative management) and they were followed up by the same protocol used for the randomised group (this group will be referred to as the non-randomised group). However, only the data for the randomised groups were used to compare conservative management with surgical uterine evacuation.

Of the 368 women recruited only seven from the randomised group requested to change their management. Of these six women with nonviable pregnancies, initially randomised to conservative management requested surgical evacuation of retained products of conception following discussion with their partners. The seventh woman with a diagnosis of incomplete miscarriage, who was randomised to be managed surgically did not turn up for her operation and achieved a spontaneous complete miscarriage. These seven were followed up by telephone calls to their general practitioners. None of these women had complications and their data were analysed in their original randomised groups based on intention to treat.

Women randomised to the two treatment groups were similar in age, parity, duration of amenorrhoea, AP diameter and volume of products of conception, volume of gestational

sac, haemoglobin (Hb), haematocrit (Hct) values and serum βhCG blood levels (Table 10) The characteristics of women in the randomised and non-randomised groups were also similar (Table 11).

Complete miscarriage rate at the follow-up visits:

Of the 122 women managed surgically 118 (96.7%) achieved complete miscarriage. Four [3.3%, 95% CI (1–8%)] of the 122 women randomised to surgical evacuation group (n = 122) had transvaginal ultrasound findings suggestive of retained products of conception following receiving their management. Two of them requested re-evacuation of the uterine cavity when they presented as emergencies with persistent heavy bleeding. The remaining two women requested no further surgical intervention and were followed up expectantly and they achieved complete miscarriage.

At the end of 14 days from recruitment women randomised to conservative management (n = 161) achieved a complete miscarriage rate of (132/161) 82% (95% CI 75-87.6%) following spontaneous expulsion of the retained products of conception as confirmed by transvaginal ultrasonic examination. Three women required surgical evacuation during this period, one for haemorrhagic expulsion of the retained products of conception and two for clinical suspicion of pelvic sepsis, although, the investigations carried out for both of them did not confirm the presence of pelvic infection. Of the 26 women who did not expel the products of conception two requested to have surgical evacuation because spontaneous miscarriage did not take place and the remaining 24 women requested to continue with expectant management. After a further 5 weeks, a total of seven weeks

from recruitment, eighteen achieved spontaneous expulsion of the retained products and six had surgical evacuation. Four requested surgical evacuation as they felt that they waited longer than what they had expected. The waiting period before they requested surgical evacuation varied between 3 – 7 weeks from recruitment.

The total incidence of complete miscarriage was 93.2% (95%CI 88-96%) after 49 days of expectant management. The total incidence of complete miscarriage for women initially recruited with a diagnosis of incomplete miscarriage was 100% and for those recruited with non-viable pregnancy was 91% (95% CI 85-95%). The cumulative complete miscarriage rate in relation to the length of the expectancy period is shown in Figure (3) and Table (12).

Screening for infection:

Routine screening for pathogens, which may complicate the two management options, did not show any difference in the proportion of women who had chlamydia or bacteriological findings suggestive of bacterial vaginosis (Table 13). There was no significant difference in the total number of women who were prescribed antibiotics (15.5% versus 16.4% in the conservative and surgical evacuation groups respectively; P = 1.0).

Three women [2.5%, 95% CI (1% - 7%)] from the surgical evacuation group, compared to none from the conservative group, suffered from lower abdominal pain, pyrexia > 38°C, pelvic tenderness, cervical excitation with positive bacteriological swabs. They

were diagnosed to have pelvic infection and were successfully treated with oral antibiotics.

Women with clinically significant blood loss:

All women in the randomised groups stopped bleeding within two weeks, but 5 (3.1%) women from the conservative group bled irregularly for more than 14 days [Median 20 days (15 – 27)]. Seven women (4.3%) randomised to the conservative group had a haemoglobin drop of more than 2 g/dl (Range 3 – 7 g/dl) following the spontaneous expulsion of the retained products as compared to one woman (1%) from the surgical group who suffered a Hb drop of 4.9 g/dl following her operation (P = 0.1).

Six women (3.7%) randomised to conservative management as compared to three women (2.4%) from the surgical evacuation group required iron supplementation (P = 0.7). Only one [0.5%, 95% CI, (0.0 – 0.04)] woman who was managed conservatively in the randomised group was given a blood transfusion (2 units of packed cells). Her Hb was 9.0 g/dl at the beginning of the transfusion. The comparative assessment of the clinically significant outcomes as regard to the amount and duration of the blood loss is given in table (13).

Women reviewed as emergencies: Significantly, more women [n = 20; 12.4%, 95%CI (7.7 – 18.5%)] randomised to conservative management requested to be reviewed as emergencies for assessment compared with surgical management [n = 2; 1.7%, 95%CI

(0.2 – 5.8%)] (P < 0.001). The main reasons were prolonged/heavy bleeding, abdominal pain or for emotional support (Table 14).

Assessment of pain: There was no significant difference in the duration of pain experienced by women randomised to conservative management, a mean of 6.7 days (SEM 6.4) as compared to women randomised to surgical management 6.4 days (SEM 5.2) [t test = 0.38; P = 0.7]. The difference in the highest score given by the former group, a mean of 6.7 (SEM 0.35) was insignificant when compared to the score given by women in the later group, a mean of 5.9 (SEM 0.33) [t = 1.7; p = 0.08).

The incidence of complications among women in the two management groups:
There was no significant difference in the frequency of complications between the two treatment groups. Details of complications encountered in each management group are summarised in table (15). Two women from the surgical group experienced excruciating lower abdominal pain following their discharge from the hospital. They were seen as emergencies and their scans were suggestive of possible uterine perforation observed as a thick line originating in the uterine cavity and extending through the myometrium to the peritoneal cavity (Lajinian et al., 1994). Both were managed conservatively with antibiotic cover.

Assessment of patients' satisfaction with their management:
Of the 161 women managed conservatively, four (2.4%) considered the management to be unacceptable; two women reported that the abdominal pain was unbearable while

passing the products of conception, the third woman considered that waiting for two weeks was too long, and the fourth gave no reason why conservative management was unacceptable. Of the 122 women in the surgical group one woman (1%) had considered the management to be unacceptable as she suffered from abdominal pains for duration of eight days.

Outcome measures for women with incomplete miscarriage and non-viable pregnancy managed conservatively:

Women with incomplete miscarriage managed conservatively showed higher incidence of complete miscarriage rate, lower incidence of drop in Hb and lower score on blood loss charts when compared with women with non-viable pregnancy managed conservatively. The incidence of women who had positive swabs of bacterial vaginosis and women prescribed antibiotics was higher in the former than the latter. The emergency referral rates were significantly higher in the non-viable group than in the incomplete miscarriage group [Fisher's Exact 0.047, 95% C.I. 0.029 – 1.39)] (table 16).

Histopathological examination:

Histopathological examination was carried out routinely for the tissues retrieved at surgical uterine evacuation and for those women (n = 52) in the conservative group who brought tissues to the hospital. Histopathological examinations confirmed the presence of chorionic villi in 97% of women in the former group and 98% of the latter group.

Predictors of the incidence of complete miscarriage following expectant management: Each ultrasound measurement taken for RPOC was assessed as an independent prognostic variable in relation to the incidence of complete miscarriage in all women managed conservatively (Table 17). The continuous data of each variable was divided arbitrarily using fixed increment(s) to determine the different cut off points, followed by comparing the complete miscarriage rates for any significant differences between women with measurements less than the index cut off point and those with measurements at and above the same cut off point. An inverse relationship between the different ultrasound measurements and the incidence of complete miscarriage was observed. Complete miscarriage was significantly commoner below the following: (1) **for all women managed conservatively**; (a) a volume of the products of conception of 31 cc^3 or less *[Fisher's Exact, P= 0.0028, 95% CI (1.87-6.77)]*, (b) an AP diameter of retained products of conception of 35 mm or less measured in the sagittal plane *[Fisher's Exact, P=0.0088, 95% CI (1.53-5.2)]* (2) **for women managed conservatively who initially presented with a diagnosis of non-viable pregnancy** (a) a mean sac diameter of 29 mm or less *[Fisher's Exact, P=0.0083, 95% CI (0.35-1.02)]*, (b) a gestational sac volume of 10 cc^3 or less *[Fisher's Exact, P=0.0072, 95% CI (1.58-5.86)]*. Other parameters assessed, as potential predictors, such as age, period of amenorrhoea, parity (P = 0.3) and βhCG levels at recruitment, did not demonstrate a cut off level, which can be used to predict the outcome of conservative management.

Non-randomised groups: A summary of the different outcomes for women who chose their management is given in table (18). The complete miscarriage rate for women who

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chose conservative management in the non-randomised groups was 90% (28/31) as compared to 93% for those who chose surgical uterine evacuation.

Four (7%) women from the surgical non-randomised group presented with evidence of retained products of conception and requested to have a repeat procedure. Three of them presented as emergencies before their scheduled appointment with heavy bleeding and crampy abdominal pains. The fourth while attending her first follow-up visit admitted to having experienced heavy irregular bleeding for 7 days and the ultrasound examination suggested the presence of retained products of conception.

At the end of 14 days from recruitment 25 (81%) women of the group who chose to be managed conservatively had achieved complete miscarriage. By the end of 8 weeks from recruitment the total complete miscarriage rate was 90% and only three women required surgical evacuation. The first woman suffered heavy bleeding before the passage of the intact gestational sac, the second had suffered heavy bleeding after a week from the passage of the gestational sac which was confirmed to be due to incomplete miscarriage and the third requested to have surgical evacuation when she did not pass the products of conception after four weeks from recruitment. The complications evident in the conservative non-randomised group were mainly related to heavy blood loss (10 – 16%), emergency referrals for heavy bleeding (16%) and the need for iron supplementation (16%). On the other hand women opted to have surgical evacuation had experienced less problems with bleeding but similar or higher rates of positive swabs (15%), antibiotic treatment (24%) or emergency referrals for PID (4%). The mean duration of pain for

women in the non-randomised groups was shorter than the duration of pain for women in the randomised groups. The reasons for this difference are not clear, it, however, could be attributed to the fact that women who chose their management were anticipating some of these symptoms.

Discussion

This large randomised study has compared conservative management with surgical evacuation of the uterine cavity for women with retained products of conception following first trimester miscarriage.

This study has demonstrated that conservative management of women presenting with early pregnancy failure is associated with similar rates of complication and morbidity to those associated with routine surgical uterine evacuation of residual intrauterine tissues. The difference in complete miscarriage rates between the two study arms was marginally significant in favour of women managed by surgical uterine evacuation. This difference happened mainly because eight of the eleven women who had surgical uterine evacuation from the conservative group did not want to wait for spontaneous expulsion of their gestational sacs and requested to change their management. They did not encounter any complications while they were managed conservatively and their surgical management was uneventful. Furthermore, despite the significant difference of 5% (CI 0.04 – 0.12) in the incidence of complete miscarriage rate between the two study arms, still a large percentage of women in the conservative group [93% (CI 0.88 – 0.96)] managed to avoid surgical management with all its possible sequelae. These findings

call into question the appropriateness of routine policies of surgical evacuation, which continue to be favoured in the United Kingdom as previous studies describing a conservative approach to the management of women with residual intrauterine tissues did not persuade clinicians in UK to change their policies.

A preliminary report by Nielsen et al (1995) who managed conservatively women with a diagnosis of either incomplete or inevitable miscarriage for three days achieved a success rate of 79% (Nielsen et al., 1995). That study was comparatively small and was criticised for recruitment bias and lack of diagnostic precision (Ankum et al., 1995). The period of three days of expectant management was also thought to be too short to demonstrate the required success of conservative management as an alternative to surgical management. Later reports on the role of conservative management for women with non-viable pregnancy in the first trimester gave conflicting results. While Jurkovic et al., 1998, reported a success rate of only 24% other researchers (Schwarzler et al., 1999) reported a success rate of 84% when expectant management was adopted for a period of four weeks. Both studies were small and non-randomised based on women's choice for the type of management offered

Our study had strict selection criteria. We used only transvaginal scanning to establish the diagnosis and serial βhCG assessment to screen for women with missed ectopic pregnancy. The accuracy of the chosen ultrasound criteria for detection of residual intrauterine tissues was confirmed by its high positive predictive value for detection of

chorionic villi of 98% as assessed by the histopathological examination of the tissues retrieved by suction evacuation or brought to the hospital by women in the conservative group. We also followed up women, who declined randomisation and chose their own management, using the same protocol instead of applying a nonflexible randomised approach. This allowed the majority of women with residual intrauterine tissues referred to the hospital during the period of the study to take part and consequently led to a more generalized assessment of the performance of the two managements and in particular the safety of conservative management. Our data suggest that conservative management is more successful in women with incomplete miscarriage than in women with non-viable pregnancy.

Different waiting periods were used by other investigators for expectant management of women with residual intrauterine products of conception (Nielsen et al., 1995; Schwarzler et al., 1999; Jurkovic et al., 1998). We felt at the beginning of the study that two weeks of expectant management would be a reasonable cut off interval to advise women with persistent retained products to have surgery. Some women in our population requested to continue with conservative management beyond these initial two weeks. The psychological impact of the length of the waiting period needs to be assessed, and this is advised in chapter III.

Although women allocated to conservative management showed a high self-referral rate as compared to women managed by surgical evacuation, reassurance and explanation of the possible physical symptoms that might be experienced can result in a drop in the rate

of self-referrals and help women to cope with their symptoms at home. Also, a small number of women who were managed conservatively encountered some complications of prolonged vaginal bleeding or significant drop in Hb, these were transient and the vast majority of women in the conservative group (97%) reported that their management was acceptable to them.

On the other hand, while the incidence of pelvic infection in the surgical evacuation group was 2%, which was similar to that of 2.3% reported by Filshie et al. (1973), none of the women managed conservatively developed PID and the effect of conservative management on future fertility had also been previously assessed (Ben-Baruch et al., 1991; Kaplan et al., 1996; Blohm et al., 1997) and found to be reassuring. The higher incidence among women treated surgically compared to women managed conservatively was also previously reported by Nielsen's et al (1995).

This study challenges the established practice of routine surgical evacuation of the uterus in cases of incomplete and non-viable pregnancy in the first trimester. Although the conservative group had a higher incidence of bleeding and anaemia, these were generally minor and transient problems. The more worrying complication of pelvic sepsis was only confirmed among women managed by surgical uterine evacuation both in randomised and non-randomised groups (n = 3). In addition there seemed to be a significant possibility that uterine perforation had occurred in two women in the same group, although this was not confirmed laparoscopically.

Because the planned sample size was large and the study was unmasked, therefore, it was preferred to use complete randomisation rather than blocked randomisation to allocate women to the different management options as the former provides optimal protection against various experimental biases, while the latter is vulnerable to experimental biases especially in an unmasked trial (Lachin et al. 1988). We were aware from the beginning of the small imbalance in the sample size (56 v. 44%) and we chose to have the bigger proportion for the newly studied treatment (conservative management). Such a small imbalance, as described by Lachin (1988) should not affect the statistical power of the study or the accuracy of any statistical analysis (Pocock, 1985).

Overall we conclude that conservative management can be offered for women with incomplete miscarriage and nonviable pregnancy as an alternative to surgical uterine evacuation. This policy seems to be acceptable, safe and effective with more work required to determine the absolute safety of conservative management on future fertility and to establish whether offering conservative management as an alternative to routine surgical uterine evacuation can have any potential savings in terms of cost, staff time and resources.

CHAPTER III

Evaluating Psychological Morbidity Following Conservative Management of

Spontaneous Miscarriage

Introduction

A number of studies have emphasised the impact of early miscarriage as an adverse life event on women's psychological welfare (Seibel & Graves, 1980; Friedman & Gath, 1989; Hamilton, 1989; Neugebauer et al., 1992, Robinson et al., 1994; Cecil, 1994). In a prospective study by Prettyman et al. (1993) the incidence of different psychological adverse reactions varied between 22 – 40% of all women who experienced miscarriage and were recruited into their study.

The majority of the studies, which compared between conservative and surgical management did not assess the differences in psychological outcomes in relation to the type of management offered (Ben-Baruch et al, 1991; Mansur, 1992; Rulin et al, 1993; Haines et al, 1994; Kaplan et al, 1996, Hurd et al. 1997; Chipchase and James 1997; Jurkovic et al. 1998; Schwarzler et al. 1999)

Surgical management may subject women to the discomfort of separation from their families and of receiving inpatient management at a time when they need the support of their families and general practitioners (Henshaw, et al, 1993). But the non-selective use of surgical uterine evacuation for women with spontaneous miscarriage over the past 60 years did not allow the effect of this procedure on women's psychological reactions to be challenged.

On the other hand, there is a scarcity of data available on the psychological outcomes following a conservative approach for the management of women with spontaneous

miscarriage who have retained products of conception. Firstly, the impact of the length of the period of expectancy on women's feelings is not known. Secondly, following this period of expectancy women may have to go through the physical experience of miscarriage. Thirdly, women may also need to handle the POC themselves. The aim of this report is to assess the psychological morbidity for women with retained products of conception following spontaneous miscarriage, who were randomised to conservative management in comparison to the standard management surgical uterine evacuation.

Methods

Participants. Women randomised (n = 283) to receive either expectant or surgical evacuation management in the original clinical trial were invited to take part in this study. They had a brief history taken in relation to their miscarriage and also to enquire about any past medical history of psychiatric illnesses or antipsychiatric treatment or consultations. They also had general and pelvic examination with bacteriological screening for chlamydia, gonorrhoea and other relevant microbes. Women in both groups were given the hospital emergency telephone numbers and scheduled for their follow up visits after one and two weeks. Women managed conservatively were allowed home following recruitment. Women who underwent surgical evacuation were admitted to the hospital as day cases within 24 hours from recruitment. Evacuation of retained products of conception was carried out under general anaesthesia by suction curettage. Further episodes of clinical intervention involved weekly follow-up visits to screen for the presence of retained products of conception or the incidence of pelvic inflammatory disease as explained in Chapter II.

As soon as women were discharged from our care to the community, a questionnaire was sent to all general practitioners. This questionnaire was designed to collect information on any community care episodes, in relevance to the woman's recent miscarriage, within short or intermediate periods of time starting from their recruitment into the study until two weeks following the completion of the hospital-based care, provided that a minimum period of four weeks from recruitment has been covered.

Assessment of psychological reactions

Depressive reactions were described by previous investigators to be the most commonly experienced feelings associated with miscarriage. Therefore, we chose to focus on the effect of management especially the conservative approach on these depressive reactions. *The Edinburgh Postnatal Depression Questionnaire (the ten factors version by* Cox et al., 1987), which was previously tested in a number of studies, was used to assess depressive reactions. It was revised by rewording the questions to represent women suffering from spontaneous miscarriage before it was used in this work (Appendix 2). The new questionnaire was used to address women's feelings such as ability to laugh, enjoying things, feelings of blame, anxiety, panic, inability to coop, sadness and inability to sleep, feeling miserable or even crying and finally the thought of harming themselves.

Assessment of psychological reactions was carried out both cross-sectionally while women were receiving their hospital-based care for their miscarriage and also longitudinally after 12 weeks from recruitment, following discharging them into the

community. These were achieved by using **three sets** of the same questionnaire; EPD1, EPD2 and EDP3 at different times. Women were, initially, asked to complete the **first set (EPD1)** at the recruitment visit, to provide a baseline assessment of their psychological reactions before allocating them to the two managements. At the completion of their management and before discharging them into the community women were asked to complete **EPD2**. After 12 weeks from recruitment, women were sent the third set of the **questionnaire (EPD3)** for assessment of their psychological reactions after they have been sent to community. At this stage, women were also sent a demographic assessment questionnaire to enquire about their marital status, education, employment and the household income.

All completed questionnaires were scored at the end of the study according to a standard scoring system (Cox et al., 1987). A threshold total score of 13 in any of the completed questionnaires was used to define women suffering from significant psychological morbidity such as depressive reactions.

Statistical tests

Comparisons between randomised groups for any statistical differences in psychological outcomes were carried out using either t-test and the confidence interval approach or Mann-Whitney test where relevant. Comparisons between proportions in relation to the number of women who were depressed in the two study groups were performed by Fisher's exact test, which is a non-parametric test. Two-tailed tests were used and P <0.05 was considered significant (Brown et al., 1990).

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Results

Studied numbers: Of the 283 randomised women (161 managed conservatively and 122 managed by surgical uterine evacuation) 19 did not take part in this study representing five women who did not speak fluent English (two from the conservative group and three from the surgical group) and fourteen women who did not want to contribute to the study (seven from each group).

Women characteristics: Women managed either conservatively or by surgical uterine evacuation were similar in age, parity, gestational age of the pregnancy, antero-posterior diameter of products of conception, volume of products of conception, volume of gestational sac, haemoglobin (Hb) and haematocrit (Hct) values, serum hCG concentration (Chapter II). The average age of women managed conservatively was 29 (SD 7) compared to 29 (SD 6) for women managed by surgical uterine evacuation. Three women were born outside UK, one woman managed conservatively and two women managed surgically. The studied groups included five women who had previously received antidepressant treatment (two from the conservative group and three surgical evacuation group).

Comparable numbers of women in the two treatment groups completed their demographic assessment questionnaire, 105/161 (65%) women from the conservative group as compared to 88/122 (72%) women in the surgical group. Women in both

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groups were comparable in their demographic characteristics. The breakdown of these demographic characteristics is given in table (19).

Almost two-thirds of the subjects were married (63%) (122/193). The greatest proportion (69%) (134/194) described themselves as being employed or self-employed at the time of this survey. Sixty-eight percent (128/187) of all women who filled their demographic questionnaire in relation to their household income estimated their household income to be over £15,000 per year.

The index pregnancy was the first pregnancy for 92 women (92/283) (51 of women managed conservatively and 41 of women managed by surgical uterine evacuation) and ninety nine percent of the couples were planning to continue the pregnancy before the occurrence of the miscarriage. Three women were planning to terminate the pregnancy before they discovered that they had a spontaneous miscarriage, (1 woman from the conservative group and 2 women from the surgical group).

The clinical outcome parameters for those who took part in this psychological assessment from both groups have been summarized in table (20).

Assessment of psychological outcomes:

The incidence of significant depressive reactions, among women who completed EPD1 at recruitment was 22% in each management group [Fisher's Exact Test, P = 1.0] as shown in table (21).

The number of cases following receiving the management and while still coming for follow-up visits (scored ≥13 in EPD2) remained comparable between women in the two groups (36 of 161 managed conservatively and 26 of 122 managed by surgical evacuation) [Fisher's Exact Test, P = 0.9].

The total number of cases, scored ≥13 in EPD1, EPD2 or both (i.e., from recruitment visit till the last visit), was 55 of 161 [34%, 95% CI (27% - 42%)] women managed conservatively and 43 of 122 [35%, 95% CI (27% - 44%)] women managed by surgical evacuation [Fisher's Exact Test, P = 0.9].

At 12 weeks following recruitment and after women were discharged to the community those managed conservatively showed lower [4%, 95% (CI 1% - 6%)] incidence of significant depressive reactions as compared to women managed by surgical evacuation [9%, 95% CI (5% - 16%)] [Fisher's Exact Test, P = 0.08], which could be suggestive of a trend towards a quicker psychological recovery for women managed conservatively. This needs to be assessed in future prospective research studies.

The total number of women scored ≥13 in one or more of the questionnaires (EPD1, EPD2 and EPD3) was equivalent for the women in the two management groups; 57 of 161 [35%, 95% CI (28% – 43%)] as compared to 46 of 122 [38%, 95% CI (29% – 47%)] for women managed by surgical evacuation [Fisher's Exact Test, P = 0.7].

Longitudinal analysis of depressive reactions in the study population:

The breakdown concerning the longitudinal assessment from recruitment (EPD1) till the completion of the hospital-based care (EPD2) is given in figure (4) and table (22) and from filling EPD2 until 12 weeks after recruitment is given in figure (5) and table (23).

Table (22) and figure (4) explain that the number of women who scored ≥13 in EPD1 and continued to suffer from significant depressive reactions while filling EPD2, were comparable between the two management groups, 47% (17/36) for the conservative group and 37% (10/27) for the surgically managed group [Fisher's Exact Test, P =0.6].

The number of cases scored ≥13 in EPD2, who initially scored <13 in EPD1 was also comparable between the two management groups, 15.5% (17/109) for women managed conservatively and 20% (16/79) for those managed by surgical evacuation [Fisher's Exact Test, P = 0.4].

Table (23) and Figure (5) explain that for women who scored ≥13 in EPD2, 8.3% (3/36) from conservative group and 11.5% (3/26) from surgical group continued to suffer from significant depressive reactions at 12 weeks from recruitment (scored ≥13 in EPD3). A comparable proportion from the two management groups reported recovering from their adverse psychological symptoms; 44.4% (16/36) from the conservative group as compared to 50% (13/26) from the surgical group [Fisher's Exact Test, P = 0.7]. The number of women who did not respond represents 47.3% (17/36) from the former as compared to 38.5% (10/26) from the later.

The number of women scored ≥13 in EPD3, who initially scored <13 in EPD2 were significantly higher among women managed by surgical evacuation (7/76) [9%, 95% CI (3.7% – 18%)] as compared to women managed conservatively (2/106) [2%: CI 0.2% - 6.6%] [Fisher's Exact Test, P = 0.035, 95% CI (1.31 – 2.89)].

Analysis of the individual questions of each questionnaire: No differences were observed when the score of the individual questions and the total score of each set of the three questionnaires (EPD1, EPD2 and EPD3) was compared between women in the two management groups as shown in table (24) and figures (6 - 8).

Length of the expectancy period among women with successful outcome:

A further analysis was carried out among women managed conservatively, to assess the impact of the length of the expectancy period (≤14 days of expectancy period as compared to >14 days) on the psychological reactions (Table 25). This showed no differences in the number of women scored ≥13 at EPD2 [Fisher's Exact Test, P = 1.0] or EPD3 [Fisher's Exact Test, P = 0.5] between women with successful outcome who had different periods of expectancy.

Similarly, no significant differences in the number of cases were observed after completing EPD2 [Fisher's Exact Test, P = 0.7] or EPD3 [Fisher's Exact Test, P = 1.0] among women who were initially managed conservatively and eventually required

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surgical uterine evacuation as compared to other women in the conservative group who were managed successfully.

General practitioners support for psychological matters:

The response of the general practitioners in completing and returning the community care-episodes questionnaire was 89% (252/283), representing 87% (140/161) of all general practitioners of women managed conservatively as compared to (112/122) 92% for women managed by routine surgical evacuation. Eight women [5%, 95% CI (2% - 10%)] from the conservative group required their family doctor support as compared to 16 women [13%, 95% CI (8% - 20%)] from the surgical evacuation group [Fisher's Exact Test, P = 0.02]. The breakdown of the type of the psychological care required is given in table (26), which included prescribing antidepressants, emotional support and counselling.

Discussion

Miscarriage is usually accompanied by a profound sense of loss, which is similar to grief reaction that commonly follows bereavement. The physical experience of miscarriage, the trauma of separation from family, hospital admission for surgery and receiving potentially unnecessary surgical and anaesthetic procedures were among different factors thought to contribute to the high frequency of psychological distress among women with pregnancy failure (Levy, 1987). The total number of women who suffered significant depressive reactions in this work regardless of the type of the management offered was 36% (103/283), which was much higher than the levels reported in general

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population of 10 – 12% (Surtees, 1990). These findings were closely correspond with the findings of Prettyman et al. (1993) than with the findings of Lee et al. (1996) who reported an incidence of 8% of their population.

The results of this study do not show any differences in the psychological outcomes of women managed conservatively as compared to women managed by surgical uterine evacuation. At recruitment 22% of women in each study group showed evidence of depressive reactions. The experience of symptoms of miscarriage was enough to trigger these psychological reactions because women were anticipating the bad news of the occurrence of pregnancy failure.

The passage of fetal tissues, as well as the possibility of seeing the remains was previously reported to strongly affect the women experiencing miscarriage (Oakley et al., 1986; Thapar and Thapar, 1992; Lasker and Toeder, 1994). However, at the completion of the hospital-based care, there were no differences in relation to the psychological reactions observed between the two groups. Moreover, the majority of women managed conservatively did not raise any concerns about handling the POC but three women mentioned that it was a difficult experience for them to flush the POC down the toilet. Similarly some women from the surgical group felt unhappy about the fact that the products of conception were treated as medical waste. These concerns need to be addressed during the clinical counselling of women with miscarriage.

There was a general improvement in the psychological outcome among women from both groups after 12 weeks from recruitment, which was also reported to happen in Prettyman et al. (1993). The total number of women who remained psychologically depressed (scored ≥13 in EPD3) was comparable among women from both groups (4% for women managed conservatively as compared to 9% for women managed by surgical evacuation).

Nielsen et al. (1996) reported less psychological distress in women managed successfully by an expectant approach within three days from diagnosis as compared to those initially recruited to conservative management but who required surgical evacuation after three days. For women managed conservatively in our report, neither the period of expectancy nor the final outcome of the clinical management seemed to have a detrimental effect on the women's psychological reactions. Moreover, conservative management was not accompanied by an increased demand on community psychological services. On the contrary, higher number of women from the surgical evacuation group required their general practitioners care and support as compared to women from the conservative group.

The impact, of the clinical care provided during the follow-up visits through clinical, ultrasound examination and the discussion provoked by the research team with all women in relation to the miscarriage experience, on the psychological outcomes could not be assessed in this work, as all women were followed up using the same protocol. It is more likely in the future that only women who will be managed conservatively are

going to receive these follow-up visits. Therefore, it would be of interest to study the effect of this provisional follow-up care on the psychological outcomes, to see whether it would be advantageous to review all women with miscarriages regardless of the type of the management offered.

Apart from the GP questionnaire used, to document community care episodes, it was difficult to assess any other sources of intervention in the community, which might have affected the psychological outcomes of women in both management groups.

Conclusion

Based on the results of this study, conservative management does not seem to have a negative effect on the feelings and the psychological reactions of women with retained products of conception following spontaneous miscarriage.

The length of the expectancy period and the final outcome of the conservative approach did not appear to increase the depressive reactions in women with miscarriages.

CHAPTER IVa

Follicular Growth and Return of Ovulation Following Conservative

Management and Surgical Uterine Evacuation of Spontaneous Miscarriage

Introduction

Although the return of cyclical ovarian function following term delivery has been widely discussed in the literature, the endocrine profile after the interruption of early pregnancy has been less extensively investigated. Keye et al. (1976) has confirmed that the resumption of cyclical ovarian activity following term delivery usually takes place within three months. The available evidence on the length of the period required for the return of cyclical ovarian function following early pregnancy interruption is rather controversial.

Cameron and Baird (1988) reported an incidence of ovulation of 91% in the first cycle following the interruption of an early viable pregnancy <8 weeks of gestation by either prostaglandins or surgical evacuation. The mean time to ovulation was 24 (16 – 32) days and 29 (16 - 37) days following prostaglandins and surgical evacuation respectively. They emphasized in their report on the necessity for the use of a reliable contraception within a week or two following the termination of pregnancy.

On the other hand Nakajima et al. (1991) reported that 75% of all endometrial biopsies taken during that first menstrual cycle following miscarriage were abnormal with luteal insufficiency, proliferative endometrium, endometritis, and decidualised stroma. Their findings were supported by Elkas and Cunningham (1995), who studied the return of ovulation in 35 women with spontaneous miscarriage and reported that the first menstruation occurred within 42 ± 17 days and the first ovulation was detected after 67

± 16 days. They concluded that the return of the hypothalamo-pituitary-ovarian axis following spontaneous miscarriage usually happens within two menstrual cycles.

It is not clear whether the differences between the findings of Cameron and Baired as opposed to those of Elkas and Cunningham are due to the differences in the presenting diagnosis of the women in the two studies or due to the use of an active management as surgical evacuation or prostaglandins in the former study as compared with a non-intervention approach in the latter. Theoretically, a conservative approach can lead to a slower passage of the chorionic villi and pregnancy deciduas than surgical evacuation of the uterine cavity.

Moreover, if conservative management is becoming an alternative management to surgical evacuation, women should be made aware of any possible drawbacks on the resumption of the cyclical ovarian activity following conservative management.

The aim of this study was to assess the resumption of ovarian follicular activity, following conservative management of retained products of conception as compared to surgical evacuation, by carrying out an assessment of the daily urinary excretion of luteinizing hormone (LH), pregnanediol (P_4) and total urinary oestrogen (E_2) following miscarriage and also to monitor follicular and endometrial development using transvaginal ultrasound scanning.

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Methods

Participants: Women recruited into the original study (randomised groups) who lived within 10 miles distance from the hospital were invited to take part in this study. Sixty women, 30 in each group completed the study.

Urine collection:

The participants collected daily early morning urine samples starting seven days following their recruitment into the study and until the onset of their first menstrual period following miscarriage, or in case of pregnancy till the diagnosis of pregnancy using a urine pregnancy test. The urine samples were frozen immediately without preservatives at -10°C till the time of the analysis.

Drop in serum pregnancy hormones:

Following confirmation of the passage of POC at the weekly follow-up visits, venous blood sample were collected on weekly basis to assess serum levels of the following pregnancy hormones: βhCG, P_4 and E_2.

Monitored ovarian activity and follicular growth:

Women were scanned regularly and as frequent as every other day once a follicle of 12 mm or more in size was observed on ultrasound examination and until follicular rupture occurred or until diagnosis of unruptured follicle was made or when vaginal bleeding commenced. The ultrasound examination was carried out as a transvaginal ultrasonic examination *(Toshiba TOSBEE with 6 MHZ vaginal probe)* and each follicle was

measured in two planes and the measurements were repeated and photographed. Once a dominant follicle had evolved (>16 mm in diameter) smaller follicles were not measured. Follicular rupture was diagnosed ultrasonically by marked reduction in follicular size associated with the presence of free fluid in the pouch of Douglas or around the ovary (Hall et al., 1979; Queenan et al, 1980; Renaud et al., 1980).

Signs of Ovulation:

For the purpose of this study ovulation was considered to have taken place if a rupture of a leading follicle was noted ultrasonically and coincided within 48 hours following the onset of LH peak (Lenton et al, 1984) as revealed later following the analysis of the collected early morning samples.

Signs of luteinised unruptured follicle (LUF):

The diagnosis of LUF was entertained when the follicle failed to rupture despite a normal endogenous LH surge. Thereafter the follicular volume can remain unchanged (Coulam et al, 1982), or undergo a rapid increase (Hamilton et al, 1985). These patients may have normal luteinization (Kerin et al, 1983) or a poor progesterone surge (Coutts et al, 1982; Hamilton et al, 1985).

Hormonal assays:

Urinary oestrone-3-glucuronide levels were measured using a specific radioimmunoassay (RIA) (Samarajeewa and Kellie, 1975). The sensitivity of the assay, defined arbitrarily as the mass of analyte producing a 10% reduction in specific binding,

was 0.35 nmol/l; the intra- and interassay coefficients of variation (CV) were 7.9% and 15% respectively. **Pregnanediol-3-glucuronide** (p-3-G) was measured in urine using an enzyme-linked immunosorbent assay (ELISA). The enzyme-labelled mixed anhydride reaction (Erlanger et al., 1959) followed by Sephadex G-25 chromatography and cold acetone precipitation. Enzyme label and primary antibody (rabbit anti-P-3-G-BSA, MRC/AFRC Comparative Physiology Research Group, London) were incubated for 2 h with appropriate dilutions of urine or standard in micro-titre plates (Immulon A, Dynatech Laboratories, Chantilly, Virginia) pre-coated with the IgG fraction of donkey steroid was prepared by conjugating P-3-G to horseradish peroxidase by the anti-rabbit second antibody (SAPU, Carluke, Scotland, UK) (Steinbuch and Audran, 1969). The enzyme substrate was hydrogen peroxide with O-phenylendiamine as chromogen and the coloured endpoint was detected spectrophotometrically at 492 mm using a Titretek Multiskan plate reader (Flow laboratories, Herts, UK) Accuracy was assessed in two ways: (i) recovery samples prepared by adding P-3-G standard to analyte-free urine over the range 2 –30 µmol/l gave 99.5% recovery (range 96 – 105) of added hormone and (ii) correlation with gas liquid chromatography (GLC) gave a correlation coefficient of 0.94 with ELISA giving values approximately twice the GLC results (due to a 50% procedural loss in the GLC method at the acid hydrolysis and extraction stages). The assay sensitivity was 0.5 nmol/l; intra- and interassay CV were 10% and 12% respectively. Urinary steroids were expressed as a ratio of the creatinine concentration measured colorimetically (Jaffe reaction).

Serum hormone assays:

Human chorionic gonadotropin was measured with a kit for plasma hCG β-subunit (NIAMDD), NIH, Bethesda, MD) essentially as described by Vaitukaitis et al (1972). Measurement of E_2 in the serum was done using a radioimmunoassay kit (SB-ESTER) purchased from CIS (Italy). Values are expressed as pmol/l. P_4 was measured in serum using the Amerlex-M progesterone RIA kit (Amersham, UK). Results are expressed as nmo/l. The interassay and intra-assay coefficients of variation were 9.8 and 7.6% for E_2 and 6% and 10.9% for P_4 (Messinis et al, 1988).

Data analysis:

The accumulated data for all women in each study group were normalized around the day of the LH peak (day 0) to calculate the mean and the confidence interval (C. I.) for each day. Then each patient's endocrine data were compared to the accumulated data's reference value (mean and 95% C.I.) for each day in the same treatment group.

Statistical Analysis:

Comparisons between groups for any statistical differences in relation to the levels of serum or urinary hormones, rate of drop of serum hormones were carried out using either paired or unpaired t-test and the confidence interval approach or Mann-Whitney test where relevant. Comparisons between proportions of women in the two study groups according to the type of ovarian cycle were performed by Fisher's exact test,

which is a non-parametric test. Two-tailed tests were used and P <0.05 was considered significant (Brown et al., 1990).

Results

The characteristics of the women who contributed to this study are given in table (27). Given the evidence of ovulation according to the criteria defined above and with the comparison of each patient's endocrine findings against the accumulated data's reference value (mean and 95% C.I.) for each day for the same treatment group, the cycles observed were described as ovulatory (normal and abnormal), LUF and anovulatory. The cycles were considered to have abnormal ovulation if they showed evidence of ovulation but abnormal events in the cycle like mid-follicular rise in progesterone levels (Ayers et al; 1987), bi-or multi-phasic LH surge (Cheesman et al; 1982; Williams et al, 1986) and/or premature follicular rupture (Lenton et al, 1983) at the start of the LH surge. All women who contributed to this study achieved complete miscarriage without surgical evacuation for those managed conservatively or a repeat surgical evacuation for those who were initially randomised to surgical management. The comparative breakdown of the type of the cycles observed following miscarriage according to these criteria is given in table (28).

The results are described in the following sections: (i) comparison of ovulatory cycles for women managed conservatively with those of women managed by surgical evacuation. (ii) Comparison of women who suffered LUF and women with normal ovulation for each management group. (iii) Comparison of women with normal and

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abnormal ovulation for each treatment group. (iv) Description of the scan findings and the hormonal profile in women with anovulatory cycles.

Section I: Comparison between ovulatory cycles for women managed conservatively and those managed by surgical evacuation: There were 18 [60%, 95% CI (41% - 77%)] spontaneous normal ovulatory cycles in the conservative group as compared to 22 [(73%, 95% CI (54% - 88%)] in the surgical evacuation group [Fisher's Exact Test, P = 0.4]. The accumulated data for these ovulatory cycles for each treatment group has been shown in figure (9) and table (30).

Durations until the incidence of LH surge and the return of menstruation: The duration following the miscarriage till the return of menstruation was similar in the two management groups as shown in table (29). Six women experienced durations longer than 42 days, three (17%) in the conservative group with durations varied between 45 – 58 days and three (14%) in the surgical evacuation group with durations varied between 43 and 48 days [Fisher's Exact Test, P = 1.0].

No differences between the two treatment groups were observed in the interval from the retrieval of the RPOC (or spontaneous expulsion of POC) until the occurrence of the LH surge (within 24 - 36 hours prior to ovulation) and the second part of the cycle measured from the LH surge till the commencement of menstruation.

Three women in the conservative group compared to none from the surgical group had a luteal phase <8 days duration from the day of the LH surge until the occurrence of menstruation. The luteal phase durations for them varied between four and seven days. Women with a luteal phase length between 8 - 10 days from the day of the LH surge represented one woman in the conservative group as compared to three women in the surgical evacuation group. They all had a luteal phase of nine days long.

The total interval till menstruation and the length of the luteal phase could not be calculated for one woman in the conservative group who fell pregnant immediately after the miscarriage and she was having an ongoing pregnancy at the time this report was written. Her ovulation happened 22 days from the date of the expulsion of the retained products of conception.

Drop in pregnancy hormones. There was no significant difference, in the serum levels or the rates of drop of βHCG, P_4 and E_2 at the end of the first and second follow-up weeks between women in the two groups as shown in table (29).

Urinary hormones. The difference in the urinary levels of LH between the two treatment groups was found to be significant *(Wilcoxon matched pairs signed ranks test, P = 0.002)*. Women managed conservatively had higher follicular levels of LH [Paired t test = 3.0, P = 0.02], higher surge levels and also higher levels in the first few days in the luteal phase when compared to women in the surgical evacuation group. The differences

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in the urinary levels of E_2 [Paired t test = 1.91, P = 0.07] and Pregnanediol [Paired t test = 1.6; P = 0.1] between the two treatment groups were insignificant.

Follicular Growth & Endometrial Thickness: The follicular growth in women managed conservatively was comparable to that in women managed by surgical evacuation [Paired t test = 1.1, P = 0.3]. The mean (SEM) diameter of the follicles at ovulation for women managed conservatively was 23.3 mm (2.4) as compared to 16.9 mm (3.04) for women managed by surgical ovulation. The double thickness of the endometrium was greater in the conservative group *(Mean 11 mm)* than in the surgical evacuation group *(Mean 7.9 mm)* [Mann-Whitney Test, Mann-Whitney U-statistic = 30.0, P = 0.0002].

Section II: Comparison between women managed conservatively who had ovulatory cycles and those who had LUF cycles: There were nine [30%, 95% CI (0.15 - 0.49)] cycles with LUF as compared to 18 [60%, 95% CI (.041 – 0.77)] spontaneous normal ovulatory cycles in women managed conservatively. Women with LUF cycles had shorter cycles of 29 days (SEM 3) as compared to women with ovulatory cycles 34 days (SEM 2.3) [Unpaired t test = 1.47, P = 0.15].

Drop in pregnancy hormones: Significantly slower rates of drop and consequently higher serum levels of βHCG, were observed at the end of the 2nd week of follow-up for women with LUF cycles as compared to women with ovulatory cycles in the

conservative group (Table 31). Also significantly higher levels of progesterone, at the end of the first week of follow-up, were observed for the former 7.2 (Range 2.5 – 14.3) as compared to the latter 1.95 (Range 0.7 – 46.3) [Mann-Whitney U-statistic = 30.5, P = 0.01]. No differences were observed in relation to the rate of drop or the serum levels of E_2 between the two groups.

Urinary hormones: The difference in the urinary levels of LH between women with LUF cycles and women with ovulatory cycles in the conservative group was found to be insignificant [Paired t test = 1.8, P = 0.07]. The comparison at the first [Paired t test = 2.2, P = 0.058] and second [Paired t test = 0.5, P = 0.6] part of the cycle was also insignificant (Table 31).

The differences in P_4 at the follicular [Paired t test = 3.9, P = 0.001] and the luteal phase [Paired t test = 2.7, P = 0.01] were found to be significant between women with LUF cycles and women with ovulatory cycles. The urinary P_4 levels were higher in the former than in the latter during the follicular phase and higher in the latter compared to the former in the luteal phase [Figure 10 and table 32]. Urinary levels of E_2 were significantly higher in LUF than in ovulatory cycles in the conservative group [Paired t test = 3.5, P = 0.001]. The paired difference in the follicular [Paired t test = 0.58, P = 0.56] was insignificant but in the luteal phase [Paired t test = 4.2, P < 0.001] was found to be significant.

Follicular Growth & Endometrial Thickness: A rapid rate of follicular growth was observed for women with LUF as compared to women with ovulatory cycles in the conservative group [Paired t test = 4.6, P < 0.001]. No significant differences were found in the double endometrial thickness between women in the two treatment groups [Figure 10 and table 32].

Section III: Comparison between women managed by surgical evacuation who had ovulatory cycles and those who had LUF cycles:

There were five [17%, 95% CI (0.06 - 0.34)] cycles with LUF as compared to 22 [(73%, 95% CI (0.54 – 0.88)] spontaneous normal ovulatory cycles in the surgical evacuation group. Similar durations of the total cycle length (Mann-Whitney Test, P = 0.27) and the length of the different components of the cycles were observed following surgical evacuation in women who had cycles with LUF as compared to women who had normal ovulatory cycles (Table 33).

Drop in pregnancy hormones: There were insignificant differences in the rate of drop and the actual serum levels of the βHCG at the end of first and second week of follow-up between women with LUF cycles and women with ovulatory cycles in the surgical evacuation group. Similar findings were also observed in relation to the rate of drop and the serum levels of E_2 and P_4 at the end of week one for LUF cycles as compared with ovulatory cycles (Table 33).

Urinary hormones: Insignificant differences were observed between LUF cycles and ovulatory cycles in the urinary levels of LH [Paired t test = 0.7, P = 0.4)] and Pregnanediol [Paired t test = 0.4; P = 0.6] [Figure 11 and table 34].

Urinary levels of E_2 were significantly lower for LUF cycles as compared to ovulatory cycles in the surgical evacuation group [Paired t test = 2.1, P = 0.04]. Urinary levels were low in the follicular phase [Paired t test = 2.0, P = 0.09], and significantly lower in the luteal phase [Paired t test = 10.1, P = 0.0005] for LUF cycles as compared with ovulatory cycles [Figure 11 and table 34].

Follicular Growth & Endometrial Thickness: A rapid rate of follicular growth was observed for LUF cycles as compared with normal ovulatory cycles for women managed by surgical evacuation [Paired t test = 3.2, P = 0.01]. Comparable findings in relation to the double-endometrial thickness were observed for women with LUF cycles and women with normal ovulatory cycles [Unpaired t test = 0.12, P = 0.9] [Figure 11 and table 34].

Section IV: Women managed conservatively who had ovulatory cycles but abnormal peripheral hormonal events: Two [7%, 95% CI (0.008 - 0.22)] women managed conservatively had ovulatory cycles but with abnormal hormonal events. The duration of the cycle for the first woman was 52 days, 40 days for the follicular phase and 12 days for the luteal phase. The duration of the cycle for the second woman was unknown as she had a chemical pregnancy after a follicular phase of 51 days.

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Urinary hormones:

First case: Analysis of the urinary LH levels showed a multi-phasic LH surge. However, the urinary levels of LH in general were comparable with the reference values in the ovulatory group [Paired t test = 1.4, P = 0.17]. The urinary levels of E_2 were significantly lower for this woman as compared with the accumulated data of the ovulatory cycles in this group [Paired t test = 6.5, P < 0.0001]. However, comparable levels of urinary P_4 were detected [Paired t test = 0.22; P = 0.8] [Figure 12 and table 35].

Second case: The urinary LH levels showed a biphasic LH surge. The urinary levels of LH [Paired t test = 2.2; P = 0.04] and E_2 [Paired t test = 2.9, P = 0.01] were higher for this woman as compared to the accumulated data of the ovulatory cycles in this management group. However, comparable levels of urinary P_4 were detected [Paired t test = *1.9*; P = *0.07*] [Figure 13 and table 36].

Follicular Growth & Endometrial Thickness: Data of follicular growth and the double-endometrial thickness for the two cases are shown in table (36).

Section V: Women managed by surgical evacuation who had ovulatory cycles but abnormal peripheral hormonal events: Two [7%, 95% CI (0.008 - 0.22)] women managed by surgical evacuation had ovulatory cycles but with abnormal hormonal events. The durations of the cycles for these two women with an abnormal ovulation were 50 days and 86 days. The follicular phase for the former was 39 days and for the

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later was 74 days. The length of the luteal phase of the cycle was 11 and 12 days respectively.

Urinary hormones:

First case: The urinary levels of LH [Paired t test = 0.2, P = 0.8] were comparable for this woman and the ovulatory cycles in the surgical evacuation group but the urinary levels for E_2 [Paired t test = 2.3, P = 0.03] and P_4 [Paired t test = 3.8; P = 0.002] were found to be significantly different as shown in figure (14) and table (37).

Second case: The urinary LH levels were higher for this woman as compared to the accumulated data's reference value of ovulatory cycles in this management group [Paired t test = 2.9; P = 0.009]. The difference also in the urinary levels of Pregnanediol was found to be significant [Paired t test = 6.0; P = 0.0009] [Figure 15 and table 38]. The difference in the urinary levels of E_2 was found to be insignificant [Paired t test = 1.0, P = 0.3].

Follicular Growth:

First Case: Following a normal follicular development of a leading follicle there was a decline in the follicular diameter with an irregular appearance of the follicle and these signs were considered corresponding to ovulation but they were not accompanied by an LH surge, which followed these events by another 6 days and the menstrual bleeding commenced 11 days after the surge (Table 37).

Second case: The second patient had three separate LH surges within a period of four weeks. The first two surges were accompanied with leading follicle(s), which had undergone follicular atresia and were not followed by menstrual bleeding until after another 30 days from the second surge, which was followed by a third surge 12 days prior to the commencement of the menstrual bleeding (Table 38).

Section VI: Women with anovulatory cycles: Two women, one from each group had anovulatory cycles. The duration of the cycle was 28 days (for the woman managed conservatively) and 24 days (for the woman managed by surgical evacuation). Despite a normally growing leading follicle and thickening endometrium, there was an absent LH surge in both cases and no increase in serum P_4 one week before the commencement of the period. The peripheral hormonal events and data for follicular growth and double endometrial thickness are shown in table (39) for the woman managed conservatively and table (40) for the woman managed by surgical uterine evacuation.

Discussion

The data from this work showed that the majority of women with spontaneous miscarriage in the first trimester had experienced spontaneous ovulation (67% 95% CI: 0.53 to 0.78) in their first cycle regardless of the type of management offered with a mean time to ovulation of 22 (SEM 1) days. Women in our population had lower incidence of ovulation in the first cycle following receiving their management as compared to those reported by Cameron and Baird (1998) and higher rates when compared to those of Elkas and Cunningham (1995).

The type of management offered whether conservative or surgical evacuation did not have a significant influence on the percentage of women who experienced ovulatory cycles, the time to ovulation and the return of menstruation. Also, similar number of women from the two management groups showed similar incidence of abnormal ovulation and anovulatory cycles. However, the incidence of LUF was higher in women managed conservatively (30%) as compared to women managed by surgical evacuation (17%).

Only seven (12%: CI 5% - 23%) of the women who had ovulatory cycles from the two management groups experienced luteal phase length <11 days. In the study of Cameron and Baird (1988) the number of women who experienced luteal phase length <11 days following the interruption of an early pregnancy was 45% (30% in the surgical evacuation and 56% in the prostaglandin group).

The hormonal profile of the ovulatory cycles for women managed conservatively showed higher LH, but comparable E_2 and P_4 levels when compared to women managed by surgical evacuation. The reasons for these differences in the LH urinary levels are not clear.

Women who experienced LUF cycles in the conservative group showed higher levels of βHCG and P_4 at the end of the second and first follow-up weeks, respectively, as

compared to women with ovulatory cycles in the same group. This might support Cameron and Baird's suggestion that normalization of the P_4 levels is important for the resumption of normal follicular activity. However, these differences in the serum levels of βHCG and P_4 were not shown among women managed by surgical evacuation who had LUF versus ovulatory cycles. This trend still needs to be reassessed in future studies with larger numbers and also women with LUF need a longer follow-up to assess the resumption of normal ovulation in them.

The occurrence of successful gestation immediately following first trimester loss was reported before in the literature and as early as 19 days following miscarriage (Ali et al., 1994). Two women who were managed conservatively in our study fell pregnant before they experienced their first menstrual bleeding following their miscarriage. This suggests that a reliable contraception needs to be used by couples, if they do not desire a pregnancy immediately following the miscarriage.

Conclusion

The follicular activity, return of ovulation and time to menstruation for women managed conservatively following spontaneous miscarriage was comparable to women managed by surgical evacuation of the retained products of conception. This is a reassuring finding indicating that conservative management dose not appear to impair women's future reproductive function.

CHAPTER IVb

Future Fertility following Conservative Management and Suction

Evacuation of Spontaneous Miscarriage

Introduction

Several encouraging preliminary reports (Nielsen et al., 1995 and Schwarzler et al., 1998) confirmed the safety of conservative management of women with spontaneous miscarriage in short and intermediate terms when compared to surgical uterine evacuation. However, the possible impairment of future fertility following conservative management has been responsible for the reluctance from the clinicians side to encourage women to select expectant management especially when retained products of conception complicate their miscarriage.

Preliminary reports, by Ben-Baruch et al. (1991) and Kaplan et al. (1996) on future fertility following conservative management of complete miscarriage were reassuring in relation to subsequent pregnancy rate, miscarriage rate and the incidence of ectopic pregnancy. However, the former report by Ben-Baruch et al. (1991) was of small number and the later report by Kaplan et al. (1996) did not emerge from a randomised study.

Blohm et al. (1997) reported on future fertility following conservative management of incomplete miscarriage in comparison to surgical uterine evacuation. Their data were collected retrospectively two years following the original randomised study. The cumulative conception rates in women managed by primary surgical evacuation or expectantly only, and for those managed expectantly first and who eventually required surgical evacuation were 88%, 91% and 93% respectively. There is, however, a scarcity of data in relation to the effect of conservative management on future fertility of women with non-viable pregnancies.

The aim of this study was to assess prospectively the reproductive performance following conservative management of women with incomplete and missed miscarriage in comparison to the 'gold standard' surgical uterine evacuation.

Methodology

All women who took part in the original study 283 randomised or chose their management 85 non-randomised, as described in the second chapter of this thesis, were followed up in relation to their future fertility performance.

Assessment of Reproductive Performance: All women recruited for the original study were contacted 6 – 8 weeks following their miscarriage by the research nurse to enquire about the return of their menses, discuss their intention to conceive or use contraception and were offered an early ultrasound examination when they became pregnant (positive pregnancy test) to confirm the viability of the pregnancy and to exclude the possibility of an ectopic pregnancy.

After nine months from their recruitment all women but those who reported falling pregnant were sent a questionnaire to enquire about period of unprotected intercourse and whether they had conceived following their miscarriage. Women who desired to become pregnant and did not achieve a pregnancy after 18 months from trying were invited to come for a review visit and if a diagnosis of secondary infertility was made they were referred to a specialised infertility clinic.

Those who conceived spontaneously following their participation in this study were followed up in relation to the outcome of their pregnancies. If they received their antenatal and intrapartum care in the local hospital (Forth Park Maternity Hospital) the data for the outcome of their pregnancies were obtained through the hospital computerized patient administration system (PAS) or from their family doctors. Those who had their subsequent pregnancies following the miscarriage followed up in other hospitals were asked to contact the Research team to update them with the outcome of their pregnancies. Only the data for the randomised groups were used to compare between the two management options.

For the purpose of this study miscarriage was defined as the unplanned loss of pregnancy before the age of viability. Ongoing pregnancy was defined as a viable pregnancy at the time of the routine fetal anomaly scan, and live birth was defined as the birth of a live child of more than 24 weeks of gestation (Williams Obstetrics, 1993). Secondary infertility was defined as no pregnancy achieved despite unprotected coitus for at least 12 months.

Statistical Analysis:

Comparisons between randomised groups and subgroup analysis for any statistical differences in return of menstruation and length of follow up periods were carried out using either t-test and the confidence interval approach or Mann-Whitney test where relevant. Comparisons between proportions in relation to the different reproductive outcomes for women who desired to become pregnant were performed by Fisher's

exact test, which is a non-parametric test. Two-tailed tests were used and P <0.05 was considered significant (Brown et al., 1990).

Results

Randomised groups:

Of the 283 women who were randomised one hundred and seventy nine women desired to become pregnant (179/283) representing one hundred and three women (103/161) randomised to conservative management and seventy six (76/122) randomised to surgical uterine evacuation. The characteristics of these women are given in table (41). The breakdown of women who did not desire to become pregnant, or moved from the area or were lost to contact is given in table (42).

There was no difference between the two groups in the length of the period between receiving their management and the return of their menstruation being 35 (SEM 1.3) days for women randomised to surgical management and 37 (SEM 1.4) days for women randomised to conservative management (Unpaired t test = 1.07, P = 0.3).

Similar periods of follow-up were employed for both groups to study their future fertility; 697 days [Range (166 – 1037)] for conservative group and 630 days [Range (86 – 993)] for women in surgical group (Unpaired t test = 1.2, P = 0.2).

The median duration to achieve a pregnancy (calculated from the date of the occurrence of the miscarriage to the LMP of the subsequent pregnancy) for all women who desired to become pregnant in the randomised groups was 158 days (0 –

830). The median duration for women managed conservatively was 160 days (0 – 591) as compared to 155 days (18 – 830) for women managed by surgical evacuation (P = 0.6, Mann-Whitney test = 2932).

A summary of the different reproductive outcomes for the randomised groups is given in table (43). Of 103 women managed conservatively who were contacted and desired to become pregnant nine [8.7% (CI 4 - 16%)] women suffered from secondary infertility as compared to four out of 76 [5% (CI 1 – 13%)] from the surgical group [Fisher's Exact Test, P = 0.5]. The median age in years for the former group was 35.5 (Range 22 - 41) as compared to 32.5 (Range 29 - 39) for the later group.

Of the 103 women from the conservative group who were contactable and tried to become pregnant 94 became pregnant [91%, CI (84 – 96%)] as compared to 72 of 76 women [95%, (CI 87 – 99%] from the surgical group. The cumulative pregnancy rates for women who achieved pregnancies in the two treatment groups are shown in figure (16).

There was no significant difference in the number of live births for women in both groups: 60 of 103 [58%, (CI 48 – 68%)] women randomised to conservative management who desired to become pregnant as compared to 38 of 76 [50%, (CI 38 – 62%)] women randomised to surgical uterine evacuation [Fisher's Exact Test, P = 0.4].

The numbers of ongoing pregnancies when this report was written were also similar in both groups: 17 of 103 [17%, 95% CI (0.10 – 0.25)] women randomised to conservative management who desired to become pregnant as compared to 15 of 76 [19.7%, 95% CI (0.11 – 0.30)] women randomised to surgical uterine evacuation [Fisher's Exact Test, P = 0.5].

The total numbers of pregnancies achieved following receiving management as described in the original trial were 102 and 77 for women who were managed conservatively or by surgical uterine evacuation respectively. The number of women who conceived only once was 86 and 69 for conservative and surgical groups respectively (Table 43).

Women who moved from the area after confirmation of the presence of a viable intrauterine pregnancy were 2% (2/103) of all women randomised to conservative management and 5% (4/76) of all women randomised to surgical uterine evacuation.

The occurrence of subsequent miscarriage was similar in the two treatment groups, 18 of 102 pregnancies achieved [18%, 95%CI (0.11 – 0.26)] by the women randomised to conservative management as compared to 13 of 77 pregnancies achieved [17% CI (0.9 – 0.27)] by the women randomised to surgical uterine evacuation [Fisher's Exact Test, P = 1.0]. There was only one woman managed by surgical uterine evacuation who had an intrauterine death (IUD) at 38 weeks of gestation. The postmortem examination did not reveal any reasons and it remained unexplained.

The incidence of ectopic pregnancy was higher among women managed conservatively as compared to women managed surgically. Of the 103 women randomised to conservative management who desired to become pregnant three [3%, 95% CI (0.006 – 0.08)] had ectopic pregnancy as compared to none from the surgical group. None of these three women showed any evidence of PID or tubal pathology at the time of their surgery and their tubes were preserved through the performance of salpingostomy by three different surgeons. Negative bacteriological screening was reported for all these three women while receiving their conservative management.

In the conservative group two women [1% (CI: 2 – 7%)] had their pregnancy terminated, one because of the presence of fetal anomalies and the second was according to her request. However, of the 77 pregnancies achieved in the surgically managed group six women [8% (CI: 3 –16%)] requested to terminate their pregnancies which was significantly higher when compared to only one woman in the conservative group who requested to terminate her pregnancy (1/102) [Fisher's Exact test, P = 0.04].

Of the three women managed by surgical evacuation, who developed PID following their operative procedures, two were lost to follow-up; one moved from the area and the second was lost to contact. The third woman achieved an ongoing intrauterine pregnancy. Of the two women suspected to have PID in the conservative group one was lost to contact and the second had a miscarriage followed by a live birth.

A subgroup analysis, of the reproductive outcomes following conservative management of women recruited with non-viable pregnancy as compared to those of women recruited with incomplete miscarriage, has shown similar outcomes in terms of time till pregnancy, incidence of live births and miscarriage rates (Table 44). The incidence of secondary infertility was higher among women with incomplete miscarriage (20%) as compared to women with non-viable pregnancy (5%) [Fisher's Exact test, P = 0.03]. However, the incidence of ectopic pregnancy was higher (3.8%) in the non-viable pregnancy group as compared to incomplete miscarriage group (0%) [Fisher's Exact test, P = 1.0].

The breakdown of the reproductive performance of women who had successful expectant management but periods of expectancy longer than two weeks (n = 18) and for those who were initially managed conservatively and subsequently required surgical uterine evacuation (n = 11) is given in table (45). The incidence of pregnancy among those who desired to become pregnant was 81.8% for the former and 83% for the latter.

Comparing the effect of different periods of expectancy on the future reproductive outcome did not show any statistically significant differences between women completed their management in ≤14 days of recruitment compared to those who completed their treatment after 14 days of recruitment (Table 46). The incidence of pregnancies in the former was 93% as compared to 80% of the latter (P = 0.1). The numbers for these subgroup analyses were small.

A summary of the different reproductive outcomes for women who chose their management is given in table (47). All women who were desired to become pregnant (20 in the conservative group and 32 in the surgical evacuation group) in the non-randomised groups became pregnant, with the total number of pregnancies achieved of 21 pregnancies in the conservative group and 36 in the surgical evacuation group. The number of ongoing pregnancies, livebirths and those who moved from the area while pregnant was comparable between the two groups, 60% (12/20) for those managed conservatively and 78% (25/32) for the surgical evacuation group.

Discussion

Subsequent reproductive performance following miscarriage, for women with retained products of conception, did not seem to be affected by the type of the management offered. Our data has shown no differences in the probability of conception between women in the conservatively randomised group when compared to women randomised to routine suction evacuation of the uterine cavity. Women from both groups also had comparable outcomes in relation to the return of their menses, the time to conception, the cumulative pregnancy rates, the incidence of a subsequent miscarriage and the number of the live births achieved.

Kaplan et al, 1996, reported that 67.8% of all women who desired to become pregnant in their population conceived within six months following the miscarriage and another 5.5% within the next 12 months. The median duration from miscarriage to achieving a pregnancy for all randomized women who desired to become pregnant in our population was 158 days (Range 0 – 830).

The miscarriage rate in all the women recruited into the randomised group who desired to become pregnant was 17% (31/179) (Table 43) similar to the incidence in normal population (McBride 1991 and Giacomucci et al., 1994) and lower than the incidence reported by Kaplan et al. (1996) (29.7%) and by Ben-Baruch et al. (1991) (27.6%) who had a higher number of women with recurrent miscarriages in their population.

Previous workers reported similar incidences of secondary infertility for women managed conservatively when compared to women managed by surgical uterine evacuation. Ben-Baruch et al. (1991) reported an incidence of secondary infertility of 22.9% in the conservative group and 25% in surgical groups. Blohm et al. (1997) reported an incidence of 8% and 12% for conservative and surgical groups respectively. Kaplan et al. (1996) who followed only women managed conservatively reported an incidence of 26.7% of secondary infertility.

This study has addressed for the first time the effect of a conservative approach on the future fertility of women with non-viable pregnancy, which represented 76% of the randomised group and also of all women who desired to become pregnant in this group. Comparable findings between women recruited with incomplete miscarriage and women recruited with non-viable pregnancy were found. The higher incidence of secondary infertility for incomplete miscarriage and ectopic pregnancy rate for women with non-viable pregnancy could not be explained.

Data for women managed conservatively, who had periods of expectancy longer than 14 days or failed their management showed higher incidence of secondary infertility of 13% as compared with those who had successful outcome in < 15 days of expectancy period (6%). The numbers were small for this comparison and this needs to be assessed in future studies or hospital-based audits with bigger numbers.

The incidence of ectopic pregnancy in the conservatively randomised women was 3% (3/103), as compared to 3.7% (1/27) in Ben-Baruch et al. (1991) and 1.7% (2/161) in Kaplan et al. (1996). Women managed conservatively who subsequently developed an ectopic pregnancy in our study showed no signs suggestive of the occurrence of pelvic infection as an underlying reason for their tubal pregnancy as indicated by a normal bacteriological screening at the time of receiving their management and normal findings of Fallopian tubes at the time of the surgical management of the ectopic pregnancy. There was also one case of an ectopic pregnancy, which appeared among women who chose surgical management. So, it remains unclear whether these ectopic pregnancies have resulted from a subclinical infection or just by chance.

The higher incidence of pregnancy termination in the surgical group also needs a thorough clinical evaluation of the possible underlying reasons to see whether this can be dealt with before attempting to conceive following miscarriage.

A possible criticism of this work could be the inability to provide data on the results of the investigations in the infertile couples referred to infertility clinics for further investigations.

CHAPTER V

A Prospective Economic Evaluation Comparing Conservative

Management versus Surgical Uterine Evacuation of Spontaneous

Miscarriage

Introduction

Reporting on economic evaluation of medical management and surgical vacuum aspiration for women undergoing pregnancy termination, Henshaw et al. (1994) concluded that the widespread introduction of medical abortion services would be unlikely to achieve substantial savings. It would seem reasonable therefore, to expect that medical management of women with retained products of conception would also be unlikely to lead to substantial cost-savings.

Conservative management has been shown through the previous work carried out in this thesis to be as safe and as effective as surgical management in all aspects of clinical management of women with retained products of conception. However, economic evaluation of this newly suggested management has to prove its cost-effectiveness in comparison to the 'gold standard' management.

Despite potential cost benefits of conservative management, there is scarcity of data available on the economic aspects of this management. There are not so far any systematic reviews of the impact of conservative management on the resources of women undertaking an expectant approach and also on NHS resources. Therefore, the aim of this study was to try to assess the differences in costs both to women and to NHS resources following either conservative management or surgical uterine evacuation.

Subjects and methods

This economic evaluation was undertaken as part of the study designed to assess and compare the effectiveness and safety of conservative management in comparison to surgical suction evacuation (Chapter II).

Main outcome measures: the two main outcomes of this analysis are: (1) the total cost incurred by the woman undergoing either conservative management or surgical uterine evacuation for retained products of conception, (2) the total costs incurred by the NHS in providing care for women undergoing conservative management of retained products of conception v. surgical uterine evacuation using vacuum aspiration. All vacuum aspirations were performed under general anaesthesia.

Three hundred and sixty eight women (283 randomised and 85 chose their management) were recruited at the time; all pregnancies were less than 13 weeks of gestation. The statistical rationale for sample size and the characteristics of the study subjects have been described in chapter II.

Women with a preference to a particular management were allowed to undergo that management, whilst allocating women without preferences at random to either conservative management or surgical evacuation of the uterine cavity.

At the recruitment visit TVS and pelvic examination with bacteriological screening for chlamydia, gonorrhoea and other relevant microbes were carried out. Blood

samples were also taken to estimate full blood count (FBC), C-reactive protein (CRP), serum human chorionic gonadotrophin (HCG).

Women managed conservatively were allowed home following recruitment. Women who underwent surgical evacuation were admitted to the hospital as day cases within 24 hours from recruitment. Evacuation of retained products of conception was carried out under general anaesthesia by suction curettage. Rhesus negative women in both treatment groups were given an intramuscular dose of 250 IU of anti-D immunoglobulin following surgical procedure or within 72 hours from the occurrence of spontaneous miscarriage.

During planned inpatient treatments it was assumed that every woman was accompanied to and from the hospital, but that the accompanying person did not lose any earnings (the majority of women were admitted prior to the start of the working day and collected later)

Arrangements were made for all women to attend for at least 2 hospital-based follow-up visits. Of all women recruited to the study 92.7% attended for at least one follow-up visit. Bacteriological swabs and blood samples similar to those taken at recruitment were obtained at each follow up visit. A transvaginal ultrasonic examination was routinely carried out at the follow-up visits to look for retained products of conception, blood clots and/or deciduas.

As soon as women were discharged from our care to the community, a questionnaire was sent to all general practitioners. This questionnaire was designed to collect information on any community care episodes, in relevance to the woman's recent miscarriage, within short or intermediate periods of time starting following recruitment and until two weeks following the completion of the hospital-based care, provided that a minimum period of four weeks from recruitment has been covered. The response of the general practitioners to completing and returning the community care episode-questionnaire was (252/283) 89%, representing (140/161) 87% of all general practitioners of women managed conservatively as compared to (112/122) 92% for women managed by routine surgical uterine evacuation.

Data concerning resources used by women.

Resources used by women include those used to attend for outpatient consultations, for routine inpatient treatments and for the inpatient treatment of complications. The following factors were also taken into account when calculating resources used:

1- Traveling expenses incurred by the woman, and costs of caring for children or significant others during absence;

2- Time spent in hospital for planned treatments, attending for consultations and for the management of complications;

3- Time spent to recover and return to work or to routine daily activity following allocation to management.

4- Other expenses for sanitary towels, analgesia and any other medications required.

Data on these items (1 - 4) were collected by questionnaire filled during the first and the second follow-up visits.

The costs incurred by women to attend their family doctors' clinics for treatment of complications could not be measured and also the cost of time taken off work, lost gross income and travelling expenses of the woman's companion at any of the care episodes provided were not estimated in this work.

Evaluation of resources used by women. For economically active women performing regular office hours the amount of time lost was calculated in days and for those doing shifts the lost time was calculated in hours lost (Henshaw et al., 1994). Resources were measured in units of time and were valued by using *standard labour wages (Luce et al., 1990)*. Accordingly the time costs were calculated using average gross weekly female earnings without overtime payments (£5.89 per hour or £47.12 per day) (as published in the New earnings survey by the Department of Employment in London 1991).

We chose to calculate the time for economically inactive women (in full time education or engaged in home care duty) by estimating the earnings foregone had the person elected to join the wage-earning population. An alternative to this would have been the use of central government standard appraisal of non-working time (£2.41 per hour) (as published in the Value of journey time savings and accident prevention by the Department of Transport in 1987). Therefore, the cost incurred by time taken off work by women was calculated as average number of hours lost by a working

women multiplied by the total number of women recruited into a particular management.

If a woman was treated as a day case it was assumed that a whole day's employment was lost (equivalent to eight hours). Days taken off work and time taken to return to normal activities were calculated starting from the time taken off following the recruitment visit.

Travel costs were estimated directly by taxi, bus or other public transport fare paid. Costs of travel by a private car were calculated using standard mileage charge of £0.33 (as published in the Automobile Association Technical Services in London in 1991).

Child care or the care of significant others was calculated by taking into account fees paid and/or travelling expenses incurred in taking the child to child minder. All costs were inflated to 1998 prices. Costs of analgesia and sanitary towels were estimated directly during filling the relevant questionnaire at the end of the follow-up visits.

Data concerning resources used by the NHS. Resources used by the NHS include those used in providing outpatient consultations (staff cost, investigations cost and the cost of any treatment required), resources used in providing planned inpatient treatment (hotel cost, operating theatre costs, drug cost and cost of histopathological examination of the retained products of conception) and resources used in treating complications (including complications treated in hospital and in the community).

Evaluation of resources used by the NHS. Data on hospital costs were provided by Fife Acute Health Trust accountants and also by individual departmental heads or by the Pharmacy Drugs Information service.

Only average costs were used and included, where appropriate, staffing costs, materials, capital charges, hospital and departmental overheads, tax and administration charges. Staff cost of providing outpatient consultations, inpatient care and operating theatre facilities and so are not documented separately but incorporated in the total cost of the episode of care described. The breakdowns of these episodes were provided by the Fife Acute Heath Trust Finance Department accountants (Table 49).

Measuring the length of the time spent caring for a random sample of ten women at different episodes of care including initial consultation; inpatient-care and follow-up appointments was used to estimate medical and nursing staffing time spent during these care-episodes and subsequently the staffing costs.

Resources used for the initial consultation. It includes staff cost of an E-grade nurse and a registrar, cost of ten minutes work of an ultrasonographer, cost of investigations, cost of TVS and cost of medications given at the outpatient visit. Cases, which were recruited from the gynaecology ward, had the costs of NHS resources adjusted accordingly.

Resources used for Follow-up appointments. These were similar to the initial visit but with less time required from the nurse and the registrar.

Resources used for inpatient day-case. The break down of the cost of the hospital stay and the overnight stay is shown in table (49) as provided by Fife Acute Health Trust Finance Department accountants.

Resources used for inpatient management of complications. All emergency referrals, which ended up by discharging the patient within few hours, were considered as day-cases. If women were admitted overnight or in the early hours of the day they were considered as a full-day stay. Emergency admissions to the gynaecology ward were considered either a day case or an inpatient stay depending on the length of stay. Finally, data on the use of general practitioner resources were based upon the duration and cost of treatments instituted.

Results

Data for the randomized groups were used to compare the cost of the two managements both for women and for NHS.

Resources used by women. Overall costs incurred by the women randomised to the two management groups are summarized in table (48). Of all women recruited to conservative management 52% were working when they received their management as compared to 61% of women randomised to surgical management [Fisher's Exact Test, $P = 0.1$].

Costs incurred in attending hospital for consultations are shown in table (48). The cost to women of the initial consultations and the follow-up visits included the cost incurred by women to travel to the hospital and the lost wages due to the time taken off for consultation. The latter was calculated as average number of hours lost by working women multiplied by the total number of women recruited into a particular management.

The cost of attending for consultations represents 17% of the total cost incurred by women managed conservatively as compared 16% of the total cost incurred by women managed by surgical evacuation.

The cost of consultations for women managed surgically was 27% less compared to women managed conservatively as women randomised to conservative management required longer follow-up and higher number of follow-up visits (n = 359) than women randomised to surgical management (n = 223).

All women who required surgical uterine evacuation had to travel to the hospital to receive their treatment. Also women who were seen as emergencies required transport to travel to be checked over (20 women in the conservative group and two women in the surgical group). The total cost of travelling to the hospital to receive treatment either routine or for complications was three times higher for women in the surgical group as compared to women in the conservative group.

The cost of travelling for receiving treatment or for complications represents 0.3% of the total cost incurred by women managed conservatively as compared to 1% of women managed by surgical evacuation.

The average time taken off work by working women recruited to conservative management was higher 43.2 working hours (Range 0 - 96) as compared to the time taken off by the working women recruited to surgical management 35.5 working hours for women in the surgical evacuation group (Range 0 - 96) [Mann-Whitney U-statistic = 2639.0, P = 0.06]. It includes time taken to receive inpatient treatment or inpatient treatment of complications and time taken off to recover and return to work.

The cost incurred by time taken off work by women was calculated, as if all women recruited to the study were working and it was also assumed as if all women lost wages in relation to the time taken off work and there were no paid sick leaves. The cost related to the lost wages to return to work was 22% higher in women managed conservatively as compared to women managed by surgical evacuation. The time taken to recover following hospital treatment of complications was not measured separately from the time taken to recover following allocation to different management.

The cost of time taken off work represents 79% of the total cost incurred by women managed conservatively as compared to 80% of women managed by surgical evacuation.

Other expenses incurred (the cost of child minding, cost of analgesia, cost of sanitary towels and any other costs) for women in the conservative group were 36% higher than for women managed by surgical uterine evacuation. Childcare did not represent a significant source of expenses to women as it was usually arranged and organized by the relatives of the couple. It represents 3% of the total cost incurred by women managed conservatively and also 3% of women managed by surgical evacuation.

In this study the total mean cost incurred by women managed by surgical evacuation was 19% less than the cost incurred by women managed conservatively.

Resources used by the National Health Services.

Overall resources consumed by the NHS are summarized in table (50).

Cost of outpatient consultations: The cost of all consultations represents 80% of total cost of NHS resources used by women managed conservatively as compared to 44% for women managed by surgical evacuation.

Costs of initial outpatient consultations were similar in the two treatment groups. Costs of follow-up visits were higher for women managed conservatively as compared to women managed surgically. Number of follow-up visits was significantly higher for women randomised to conservative management as compared to women randomised to surgical management [Mann-Whitney U-statistic = 7854.5, P = 0.003].

Cost of management of inpatient treatment: The cost of inpatient treatment represented 8% of total costs NHS resources used by women managed conservatively as compared to 52% for women managed by surgical evacuation. This was significantly higher for women managed by routine surgical evacuation as compared to women managed conservatively. An average cost of £295.49 per woman recruited to surgical management as compared to £27.3 per woman recruited to conservative management.

Of the 32 women in the conservative group who were admitted as inpatients 26 (26/161, 16%) women were admitted as emergencies to the gynaecology ward by their general practitioners prior to recruitment and they were allowed home following their recruitment to the study. Three of them had a hospital stay of > 12 hours (they were admitted over the weekend or preferred to stay for observation) and 23 were for periods < 12 hours. The remaining six (6/161, 4%) women who were initially recruited from the clinic to receive conservative management, requested surgical evacuation after few hours from recruitment and were admitted on the following day to the gynaecological ward for surgical evacuation of retained products of conception. All of them had periods of stay <12 hours.

All women managed by surgical evacuation as day cases but 16 (13%) women spent >12 hours in the hospital, the reasons were mainly late operating time (n = 15) and one for heavy vaginal bleeding (n = 1).

Inpatient management of complications: The cost of inpatient management of complications represented 10% of total cost of NHS resources for women managed conservatively as compared to 2% for women managed by surgical evacuation.

Of all women recruited to conservative management 11 (11/161, 7%) had failed their management and had surgical evacuation of the retained POC. Three of them were admitted as emergencies (3/161, 2%), and the rest (8/161, 5%) were arranged admissions. Of these 11 three had > 12 hours stay and the rest <12 hours. Another 17 (11%) women were admitted as emergencies, ten were for < 12 hours and seven for > 12 hours and they all were allowed home. Only one of them received blood transfusion. The cost of the management of complications accounted for 9% of the total costs of NHS resources used by women managed conservatively.

Four women in the surgical evacuation group came back as emergencies, two had re-evacuation one of them spent >12 hours and the rest less than 12 hours. The cost of management of complications represented only 1% of the total cost of NHS resources used by women managed by surgical evacuation.

Cost of community care: The cost of community care represented 2.3% of total cost of NHS resources by women managed conservatively as compared to 1.8% of women managed by surgical evacuation.

The costs of consultations and medication were similar in both treatment groups. The cost of providing such consultations was generally low and has little impact of the

total cost of the management. The cost of community care was £8.4 per woman recruited to conservative management and £10.5 per woman recruited to surgical uterine evacuation.

Discussion

During this study it was assumed that the theatre time, which was freed by the use of conservative management instead of surgical evacuation was fully utilized. We did not attempt to measure alternative uses of theatre time in a systematic way. Depending on local facilities, conservative management may release theatre resources, thus allowing a reduction in gynaecological waiting lists. Conservative management may also help releasing the pressure on ward bed space without any noticeable increase or shifting of early pregnancy services into the community services. Community services for women managed conservatively represented 2.3% of the total NHS resources used and were similar to women who had surgical evacuation.

This study was conducted in a Scottish District General Hospital and the population served had a higher rural component than many other areas. These factors may make it difficult to directly compare costs incurred by women or the NHS with other units. However, the study was comparative in nature and the conclusion that 38% (CI 33% - 42%) less NHS resources were used by conservative management as compared to surgical management is likely to be applicable to similar generalists units.

As experience as well as acceptance of conservative management grows, follow up visits will be delegated to general practitioners or other community based services, as already happen in charitable sector, thus reducing costs to both women and NHS.

Further reductions in the costs of conservative management are possible; the number of routine visits can be minimized and kept only for one visit immediately following the passage of the retained products of conception to check on the completeness of miscarriage. Routine screening for infection can also be reduced to be only carried out around the time of the passage of the POC. Since Bacterial vaginosis has been the most commonly reported finding on routine screening using HVS (16/19, 84% of all positive swabs), as an alternative a single prophylactic course of Flagyl (£1.6) can be given at the time of the occurrence of miscarriage. The necessity of repeating serum levels of pregnancy hormones can also be minimized by following clear accurate clinical guidelines of diagnosing early fetal demise. Likewise, the cost of surgical uterine evacuation can be reduced by undertaking the procedure on an outpatient basis with local anaesthesia, or in dedicated units.

A possible criticism of this study in assessing both resources consumed by women and NHS was the inability of measuring all costs in a systematic way e.g. separating time required for recovery from complications from time needed to recover from the physical experience of miscarriage or following surgical evacuation of the retained POC. Assumptions have had to be made about fixed costs, and average, not marginal, costs were used to estimate resource use. Other costs such as operating theatre and hotel costs have not been measured directly but taken from other sources;

their validity has not been confirmed. Finally the costs related to complications occurring beyond four weeks post complete miscarriage were not measured.

While the original study intended comparing the safety and efficacy of conservative management against routine surgical evacuation, this cost analysis has assessed the difference in cost between the two management options according to the protocol designed for the original study. Therefore, care has to be taken while drawing conclusions from this chapter as some of the episodes of the care-format provided in the original study and consequently included in this economic evaluation might not be practiced in routine daily clinical practice. As a result, the costs for surgical evacuation could have been exaggerated by the cost of some of the initial investigations following the diagnosis of miscarriage such as the assessment of βhCG levels (especially in cases of non-viable pregnancy), CRP and the triple swabs to screen for infection (HVS, ECS and Chlamydia). Similarly the cost of the follow-up visits to the hospital could be considered completely avoidable in routine clinical practice.

However, it can be argued that the cost of assessing βhCG and CRP has been added to all women entered the study and in this way it should not effect comparing the costs of the two management and also the need for screening for infection could be beneficial and probably will be recommended for future management of women who would opt to surgical evacuation especially after five women from treated initially by surgical evacuation developed PID (three from the randomised group and two from the non-randomised group). In relation to the cost of the follow-up visits, it is true

that we do not know the impact on community services should women managed by surgical evacuation were not invited for these follow-up visits. However, the costs of the follow-up visits remain unjustifiable in assessing future savings that can be brought into the NHS by recommending a conservative approach rather than surgical evacuation to women with miscarriages.

In the same caveat, for women in the conservative group the costs of the second follow-up visits for all women who achieved spontaneous expulsion of the retained products during the first week following recruitment (75% of all women managed conservatively) as confirmed by ultrasound examination could be considered preventable. Similarly, following the confirmation of the safety of conservative management especially in relation to the development of PID, clinicians in the future might prefer to review women fortnightly instead of weekly the impact of this on future potential savings related to conservative management makes the need for further economic evaluations essential.

If we assess the differences in the costs between the two management options assuming that women in the surgical group will only have the cost of their initial visit including the costs of consultation, ultrasound examination, FBC, G & S, HVS, ECS and Chlamydia but not βhCG and CRP, to be followed by receiving their treatment and then they will be discharged to the community, the cost of the surgical management will be only £401.00 (Table 51).

Similarly, for women managed conservatively assuming that the cost of the initial visit will only include the cost of the consultation ultrasound examination, FBC, G & S, HVS, ECS and Chlamydia but not βhCG nor CRP to be followed by weekly visits until an ultrasound confirmation of achieving complete miscarriage, the cost of conservative management could drop to £255.00, which represents the cost of conservative management in the original study without the costs of the second follow-up visits offered to those who miscarried during the first week following recruitment (75% of all women randomised to conservative management) (Table 51). Despite these new cost values for the two management options, it was noted that conservative management still offers 37% reduction (instead of 38% as described above) in the cost of the management of miscarriages as compared to conservative management.

Conclusion

In this study conservative management used 38% less of NHS resources (£355 *vs* £567) but 19% more of the women's resources (£ 322 *vs* 262) when compared to surgical uterine evacuation.

Substantial NHS resource savings are likely to follow the widespread introduction of conservative management of women with retained products of conception following spontaneous miscarriage.

CHAPTER VI

SUMMARY AND FINAL CONCLUSION

During the last decade preliminary work on non-surgical options (medical and expectant management) demonstrated the safety and efficacy of these options for the management of women with retained products of conception. However, following a thorough review of the available literature the conclusion was that surgical uterine evacuation of the uterine cavity remains the 'Gold Standard' management of women with retained products of conception especially when the retained products of conception represent the intact gestational sac. This was based on the lack of randomised controlled trials of appropriate size, power and design to confirm or refute whether other management options can be safely and successfully offered as alternatives to surgical evacuation. Most of the previous reports concerning the role of conservative management of women with retained products of conception were either of small numbers or non-randomised.

The work carried out and reported in this thesis represents a large randomised trial for women with incomplete and missed miscarriage in the first trimester of pregnancy, where an expectant approach was directly compared with the "Gold Standard" management, surgical uterine evacuation under general anaesthesia by using suction evacuation.

This study has demonstrated that conservative management was less effective in achieving complete miscarriage when compared with surgical evacuation at the end of the second week. The difference between the two management options was 14% and could have been as great as 21% (upper 95% of 14.7%). This difference was mainly because of the higher proportion of cases with intact gestational sac included

in the study. However, by adopting a longer period of conservative management, up 49 days, more women achieved complete miscarriage. It was reassuring to note that women whose expectant management lasted for longer than two weeks did not suffer any complications. The effectiveness of conservative management was also related to the original diagnosis, being higher among women with incomplete miscarriage than among women with non-viable miscarriage at different periods of expectancy. The success rate for women with non-viable pregnancy is 91% at the end of seven weeks of conservative management. The effectiveness of conservative management was directly related to the length of the expectancy period. The effectiveness of conservative management could also be predicted by the use of ultrasound measurements such as AP diameter and volume of retained POC and in case of non-viable pregnancy through measuring of the mean sac diameter and gestational sac volume.

Since the success of a conservative approach has been found to be related to the length of the waiting period, it would be important to assess the uptake of this approach by women suffering from non-viable pregnancy. At present, there are no studies reporting on women views about prolonged periods of expectant management as long as 49 days as reported in this study. It is true that similar periods of expectancy (up to 49 days) were reported for management of women with RPOC, but we can only be confident in saying that all women recruited to conservative management in our study were prepared to wait for at least two weeks. The long waiting period of seven weeks might be discouraging for some women to adopt an expectant approach especially when the original diagnosis is non-viable pregnancy

and limit its use for those who are motivated or for those who would like some time to come into terms with their miscarriage in the first place. The uptake of conservative management for periods longer than two weeks remains to be assessed in future research.

Women who had conservative management had higher self-referral rate compared to women in surgical evacuation group. Majority of these self-referrals were in the first half of the study. However, with cumulative experience of the study group in the second half, there was a dramatic fall in the number of women with self-referrals. The higher incidence of emergency referrals in our study (12%) as compared to the incidence given in the literature, which varied between 1.3% and 5.9% (Nielsen et al., 19995, Schwarzler et al., 1999, Sairam et al., 2001, Luise et al., 2002) in different reports, is partially due to the criteria we used to define this outcome, involving all unscheduled reviews rather than reviews for clinical indications only and also because of the large number of women with nonviable pregnancies who took part in this study. These self-referrals mainly presented as emergencies for vaginal bleeding and/or abdominal pains and by in large they did not require surgical intervention and a few only had a short-hospital stay. Despite the above troublesome symptoms 98% of all women managed conservatively were satisfied with their management. Therefore, it is important to counsel women opting for conservative management about the occurrence of the above symptoms.

Our data suggests that women presenting with RPOC and managed conservatively had comparable rates of complication to those managed with surgical evacuation but

nature of complications varied. Previous researchers reported that the overall incidence of emergency curettage for haemostatic uterine evacuation, suspected genital tract infection or any other complications for women managed conservatively varied between 0.2% - 8.5% Nielsen et al., 1995, Schwarzler et al., 1999, Chipchase et al., 1997, Jurkovic et al., 1998, Luise et al., 2002, Hurd et al., 1997) In general in our study only a small proportion of women managed conservatively suffered transient but easily managed complications related to longer and/or heavier periods of bleeding. The incidence of haemorrhagic expulsion of the retained products of conception requiring surgical evacuation was small in this study (less than 1%) and the need for emergency surgical evacuation/re-evacuation was similar for the women in the two management groups. Conservative management did not increase the incidence of pelvic sepsis nor the number of women treated with antibiotics. On the other hand, women managed surgically had different type of complications such as PID and uterine perforation, (although the latter was not confirmed laparoscopically). Comparing the incidence of pelvic infection following the two management options showed higher incidence among women managed surgically (0 – 10%) when compared to women managed conservatively (0 – 5%) (Nielsen et al., 1995, Schwarzler et al., 1999, Chipchase et al., 1997). The risk of PID with surgical management was also higher following the use of conventional sharp curettage rather than the use of suction evacuation (Verkuyl et al., 1993, Beric et al., 1997, Filshie et al., 1973). Neilsen et al (1995) has previously reported similar findings in relation to safety of conservative management in comparison to "standard management" by surgical evacuation. They quoted a 10% risk of PID with surgical evacuation as compared to only 3% with conservative management. In their opinion surgical

intervention even if aseptic precautions were taken still carries a risk of introducing pathogens into uterine cavity from lower genital tract through use of instruments. This is contrary to an established belief that an expectant approach carries higher risk of sepsis in comparison to surgical uterine evacuation, which had been cited in several case reports (Dunn, 1937, Heritage et al., 1959, Hartman, 1953, Russell, 1947). In our study the incidence of positive swabs for different pathogens and the rate of prescribing antibiotics was comparable between the two management options. To summarise, the high complete miscarriage rate achieved following surgical evacuation should be considered along with a risk of developing PID and its possible long term sequelae. Conversely, women managed conservatively although had a lower complete miscarriage rate at the end of the 2nd week, but none of the women suffered from significant morbidity.

Based on the results of this randomised study we conclude that conservative management represents an alternative non-invasive approach to surgical uterine evacuation for women with incomplete or non-viable miscarriage in the first trimester. Clinicians and patients should be aware of the success rates and the possible complication rates for both treatment options in order to make an informed choice.

There is little information in the literature concerning *women's satisfaction* with an expectant approach. Nielsen, et al. (1996) reported on the incidence of depression and anxiety among women with incomplete miscarriage who were expectantly managed for a short period of three days. In Nielsen's et al. (1996) report, assessment

of women's psychological reactions was only carried out for two weeks following assignment to management. They reported increased incidence of adverse psychological reactions in women who were initially managed conservatively but eventually required surgical uterine evacuation.

Assessment of the quality of life as a reflection to women's satisfaction with the type of management offered by using a self-administered questionnaire (a modified version of Edinburgh Postnatal Depression) was carried out for the population studied in this thesis to compare the psychological impact following conservative management as compared to surgical evacuation.

Women managed conservatively had similar incidence of adverse psychological reactions when compared to women managed by surgical evacuation both at the completion of the management (at the end of the follow-up visits) and after being discharged into the community (12 weeks from recruitment into the study). Moreover, analysis of the individual questions of each questionnaire filled at different stages of this study (EPD1, EPD2 and EPD3) demonstrated that the average score for women managed conservatively was comparable or even less than the score for women managed by surgical evacuation.

Since it was demonstrated in the original work that the effectiveness of conservative management was related to the length of period of expectancy, determining the impact of expectancy period and the final outcome of conservative management on psychological outcomes became necessary. It was found that waiting periods longer

than two weeks or failed conservative management were not accompanied by any increased incidence of psychological reactions among women managed expectantly. The numbers of these subgroup analyses were small and further audits or research will be required to answer this question.

Elkas and Cunningham (1995) reported that the return of the hypothalamo-pituitary-ovarian axis following spontaneous miscarriage usually happens within two menstrual cycles. Since it was, theoretically conceivable that, a conservative approach can lead to a slower passage of the chorionic villi and pregnancy deciduas than surgical evacuation of the uterine cavity with possible delay in the resumption of ovulatory cycles, it was important to clarify the effect of a conservative approach on the return of cyclical ovarian function. This was carried out by assessing daily urinary hormone levels of LH, E_2 and pregnanediol, which was accompanied by transvaginal ultrasound scanning to monitor follicular growth and ultrasound evidence of ovulation.

It was shown that the incidence of ovulation was comparable between women managed conservatively and women managed by surgical evacuation. Two-thirds (60%) of women from the conservative group (n = 30) recruited to this study had normal ovulatory cycles and 17% showed evidence of LUF cycles, two more women showed evidence of ovulation but abnormal hormonal events (abnormal ovulatory cycles) and only one woman did not show evidence of ovulation. Two women from the conservative group fell pregnant in the first cycle, which emphasize the need of a

reliable contraception when the couple do not desire to become pregnant immediately following the management of their spontaneous miscarriage.

Longer follow-up for women managed conservatively to investigate the effect of management on future reproductive potential as compared to surgical evacuation showed no difference between the two management groups in relation to the return of menstruation, time till pregnancy, the incidence of live births, ongoing pregnancies and miscarriage rates. The incidence of ectopic pregnancy (3%) following conservative management was similar to the incidence reported in previous studies. It was very difficult to be certain whether these ectopic pregnancies resulted from a subclinical infection or a non-infectious process or even a chance finding. Further assessment of this risk should continue in future studies or hospital-based audits.

The evidence in the literature on the use of medical abortion predicts no substantial cost savings with the wide spread use of medical management. Success with medical management is even lower in women with retained products of conception. So, it seemed unlikely that medical management of spontaneous miscarriage would provide any benefit to the NHS resources.

Evaluation of the *health-economic aspects* of conservative management was systematically assessed for the first time in this thesis. The effect of conservative management on both women's and NHS resources was compared with surgical evacuation. Women managed conservatively incurred a higher cost of 19% than women managed by surgical evacuation, which was related to higher number of

follow-up visit, and the longer periods required before returning to work. On the contrary the effect of conservative management on NHS resources showed savings of about 38% when compared with surgical management. It seems possible for the first time that substantial savings will follow the widespread use of conservative management.

The conclusion from the work carried out in this thesis is that conservative management is a safe non-surgical alternative of surgical evacuation of the uterine cavity. The success rate for women with retained products of conception is higher among women with incomplete miscarriage than among women who present with the intact gestational sac. The effectiveness of conservative management is directly related to the length of the expectancy period with 82% complete miscarriage rate after two weeks of conservative management and 93.2% after seven weeks of expectancy. In other words the longer are the policies for conservative management, the better is the overall success rate. It was also demonstrated that a conservative approach is a manageable domestic experience without any increased risk of psychological adverse reactions due to seeing or handling the expelled products of conception. The resumption of normal ovulation and the incidence of subsequent successful pregnancies did not seem to be affected by offering conservative management. Moreover, a substantial cost savings are likely to be gained with the widespread use of conservative management. Therefore, it would be recommended to offer conservative management as an alternative option to all women with incomplete and nonviable spontaneous miscarriage.

We therefore feel justified in offering a choice of conservative or surgical management to women presenting with either incomplete miscarriage or non-viable pregnancy. In some of the cases of incomplete miscarriage excluding the possibility of an ectopic pregnancy is of a paramount importance before offering women conservative management. Hospital guidelines should aim to exclude these cases depending on the available facilities both of the ultrasound scan department in terms of equipment and expertise and the availability of laboratory facilities of offering serial assessment of βhCG. The RCR/RCOG guidelines should be found very useful for confirming the diagnosis of a non-viable pregnancy when it is suspected and two scans to be offered, which should be at least one week apart to exclude the possibility of wrong dates.

Women should be allowed to make an informed choice based on the facts and the uncertainties revealed in this work. It would be advisable that women who chose conservative management need to have access to transport if they need to travel to the hospital as emergencies. An initial assessment of haemoglobin and Rhesus factor are prudent to allow further assessment of blood loss following the expulsion of retained POC and the need for anti-D cover for Rhesus negative women. Screening for infection is also advisable at that stage until the confidence of the clinicians and the women is gained in favour of offering conservative management to women with uncomplicated spontaneous miscarriage.

Women who would chose an expectant approach must also be made aware with the symptoms that they are likely to experience and be counselled about the simple oral

analgesia that they can use at home. As part of clinical governance policy, there should be written information sheet about the complications, their symptoms and how to contact clinical teams if symptoms worsen, possibly through dedicated telephone lines.

An ultrasound examination to confirm the passage of retained products of conception is preferable with a repeat FBC to check whether they would require iron supplementation. For those who would present with heavy bleeding following the confirmation of the passage of the products of conception the possibility of a molar pregnancy should be kept in mind and assessment of the serum βhCG level should be carried out.

Couples would also need an advice about the different means of contraception that they can use until they feel psychologically ready to try for another pregnancy and this should be used even before the menstrual bleed commences.