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CHRONIC PELVIC PAIN: PREVALENCE, RISK FACTORS AND LAPAROSCOPIC UTEROSACRAL NERVE ABLATION

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SYNOPSIS

This thesis sheds light on chronic pelvic pain in following areas: 1. Summarising prevalence of chronic pelvic pain 2. Exploring the risk factors in chronic pelvic pain, 3. Exploring beliefs on laparoscopic uterosacral nerve ablation and 4. Developing a protocol for a Multicentre randomised controlled trial of laparoscopic uterosacral nerve ablation.

EXECUTIVE ABSTRACT

Objective

This thesis has the following objectives:

1. To estimate the prevalence of chronic pelvic pain (CPP) by means of a systematic review
2. To generate pooled evidence on the aetiology of CPP by means of systematic review
3. To undertake a questionnaire survey of practice concerning laparoscopic uterosacral nerve ablation (LUNA) in Europe
4. To undertake a questionnaire survey of beliefs concerning effectiveness of LUNA
5. To determine the effectiveness of neuroablation in CPP by means of a systematic review
6. To develop a protocol for a prospective randomised controlled trial (RCT) to assess the effectiveness of LUNA in CPP

Methods

The work undertaken in this thesis was based on prospective study protocols using the following research methodologies:

- Systematic reviews and meta-analyses to meet objectives 1, 2 and 5
- Structured questionnaires to meet objectives 3 & 4
- RCT to meet objective 6

Results

1. There was significant variation among rates of all three types of CPP. Metaregression analysis showed that this heterogeneity was mainly due to non-representativeness of study sample and inadequacy of study methods. Meta-analysis of rates amongst high quality studies with samples representative of general population showed that prevalence of dysmenorrhoea (12 studies) was 59% (95% CI 49.1-71%, heterogeneity $p<0.001$), of dyspareunia (11 studies) was 13.3% (95% CI 8.8-20.3%, heterogeneity $p<0.001$) and of noncyclical pain (2 studies) was 6.2% (95% confidence interval (CI) 3-12.6%, heterogeneity $p <0.001$).
2. Age less than 30 years, low body mass index (BMI), smoking, early menarche (<11 years), longer cycles, longer duration of bleeding or heavy menstrual flow, nulliparity, premenstrual syndrome, sterilisation, pelvic inflammatory disease (PID), sexual assault, emotional difficulties, psychological symptoms, suicidal tendency and somatisation were associated with increased risk of dysmenorrhoea. Younger age at first childbirth, exercise and oral contraceptives were associated with reduction in the risk of dysmenorrhoea. Peri/post menopausal state, PID, sexual abuse, anxiety and depression were found to be associated with dyspareunia. Drug/alcohol abuse, miscarriage, heavier menstrual flow, PID, previous caesarean section, pelvic adhesions/other pathology, childhood physical or sexual abuse, lifetime sexual abuse, anxiety, depression, hysteria, psychosomatisation were associated with an increased risk of noncyclical pelvic pain.
3. Indications for LUNA, which included noncyclical chronic pelvic pain (CPP) (68%), dysmenorrhoea (66%), dyspareunia (39%) or endometriosis (60%), were similar across UK and rest of Europe. The European group performed LUNA more often

(62% vs. 21%), completely transected the uterosacral ligaments (56% vs. 36%) and ablated at a distance of more than 2 cm from its cervical insertion (50% vs. 21%) more frequently than the UK group. More experienced gynaecologists performed LUNA more for dyspareunia (46 % vs. 26%) and endometriosis (67% vs. 47%) and they performed complete transection (45% vs.26%) more often than their less experienced counterparts.

4. The most widely held 'prior' belief, reflected in both questionnaire and numerical responses was that LUNA would have a small beneficial effect on pain. The credible limits of this belief were compatible with large reductions in pain as 60% of respondents believed a three-point improvement on VAS to be plausible.
5. For the treatment of primary dysmenorrhoea, laparoscopic uterosacral nerve ablation (LUNA) at 12 months was better when compared to a control or no treatment. The comparison of LUNA with presacral neurectomy (PSN) for primary dysmenorrhoea showed that at 12 months follow up, PSN was more effective. In secondary dysmenorrhoea, along with laparoscopic surgical treatment of endometriosis, the addition of LUNA did not improve the pain relief while PSN did. Adverse events were more common for PSN.
6. The LUNA trial protocol has been granted ethical approval. A total of 410 women have been randomised (September 2004). Interim analyses by an independent data monitoring committee have shown that the two groups are comparable in age, parity, type of CPP and baseline pain scores.

Conclusion

1. The variation in rates of CPP worldwide is explained by variable study quality. High quality literature revealed a high burden of disease.

2. Key gynaecological and psychosocial factors associated with CPP should be targeted in clinical evaluation of women with this symptom to individualise their management.
3. There is variation in the surgical techniques of performing LUNA in Europe and the techniques vary according to operator experience.
4. Among gynaecologists, there is a variation in beliefs about the effects of LUNA on pelvic pain, ranging from substantial benefit to slight harm.
5. The evidence to recommend the use of nerve interruption in the management of dysmenorrhoea, regardless of cause, is still insufficient. Methodologically sound and sufficiently powered RCTs should be undertaken in future.
6. The LUNA trial is the largest trial of neuroablation thus far. It is hoped that if the results of the trial are positive, women suffering from this common and difficult to treat condition will benefit from this simple operation. If the results are negative a reliable basis for discouraging the spread of this technique will have been provided.

DEDICATION

I dedicate this thesis to my husband, Manish and my children, Anya and Varun for giving me the time to pursue my research, my parents-in-laws for their continuing support and encouragement and to my parents who enthused me through difficult times and taught me to carry on relentlessly in the face of trying times.

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I am indebted to my research supervisor and friend, Khalid Khan, Professor of Obstetrics and Gynaecology, Clinical Sub-Dean, for the expert guidance and continued support through the years, and the many hours spent on the various research projects leading to this thesis. I would like to thank my other supervisor, Professor Richard Gray, Director of Birmingham Clinical Trials Unit, University of Birmingham for continued help and mentoring. This work would not have been possible without my co-workers especially Mr Janesh Gupta, Mr David Braunholtz, Jane Daniels, Dr. Robert Hills, Dr. Luciano Mignini and Prof. Richard Lilford. I would like to thank Mrs Mary Publicover and Mr Derek Yates of the Education Resource Centre for their assistance with the searches and obtaining articles required for the work presented in this thesis. I would like to acknowledge the friendly advice and tips from my friends Dr. Honest, Dr. Clarke and Dr. Arri Coomarsamy. Finally, I would emphasise that this work would not be complete without my co-workers on various projects (Appendix 1.1), who might or might not be mentioned in the appendix of contributions.

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LIST OF ABBREVIATIONS

AFS	American fertility score
BISS	Brief Index of sexual satisfaction
BCTU	Birmingham university clinical trials unit
CPP	Chronic pelvic pain
GP	General practitioner
5D EQ	5 dimensional European quality of life questionnaire
ITT	Intention to treat
LUNA	Laparoscopic uterosacral nerve ablation
CI	Confidence intervals
O&G	Obstetrics and Gynaecology
OCP	Oral contraceptive pills
OR	Odds ratio
PID	Pelvic inflammatory disease
RCT	Randomised controlled trial
Rev Man	Review Manager 4.2
SAQ	Sexual activity questionnaire
SR	Systematic review
UK	United Kingdom
VAS	Visual analogue scale

PUBLICATIONS FROM THIS THESIS

- **Latthe PM**, Khan KS for the LUNA Trial Steering Group: A randomised controlled trial to assess the efficacy of Laparoscopic Uterosacral Nerve Ablation (LUNA) in the treatment of chronic pelvic pain: The trial protocol [ISRCTN41196151]. BMC Womens Health. 2003 Dec 08; 3 (1): 6.
- **Latthe PM**, Powell RJ, Hills RK, Gupta JK, Gray R, Khan KS. Variation in practice of Laparoscopic uterosacral nerve ablation: A European survey. Journal of Obstetrics and Gynaecology; 2004 Aug; 24(5): 547-51
- **Latthe PM**, Khan KS. Commentary in Evidence Based O &G on the recent trials in neuroablation for pelvic pain; 2003; **11**: 6-16
- **Latthe PM**, Braunholtz D, Hills RK, Khan KS, Lilford RJ. Measurement of beliefs about effectiveness of laparoscopic uterosacral nerve ablation BJOG An International Journal of Obstetrics and Gynaecology; 2005 Feb; 112(2): 243-6.
- Proctor M, **Latthe PM,** Prof. Farquhar C.M, Johnson N, Prof. Khan KS**.** Surgical interruption of pelvic nerve pathways in dysmenorrhea: A systematic review of effectiveness (Cochrane library August 2005)
- **Latthe PM**, Proctor M, Prof. Farquhar C.M, Johnson N, Prof. Khan KS**.** Surgical interruption of pelvic nerve pathways in dysmenorrhea: A systematic review of effectiveness (Accepted for publication in Acta Obstetriticia et Gynecologica Scandinavica)
- **Latthe PM**, Mignini LM, Gray R, Khan KS. Factors predisposing women to chronic pelvic pain: A Systematic Review (Accepted for publication in BMJ)

Articles submitted for publication:

- **Latthe PM**, Latthe M, Say L, Gulmezoglu M, Khan KS. Worldwide prevalence of chronic pelvic pain: A systematic review and meta-analysis of a neglected health problem (BMC Public Health)

CHAPTER 1: INTRODUCTION

1.1 Definition of chronic pelvic pain

There are many definitions for chronic pelvic pain (CPP). An existing systematic review observed that definitions for CPP vary greatly in the published literature.[1] The definitions may consider duration of pain, location and type of pain and relationship to menstruation and sexual activity. One definition is 'recurrent or constant pain in the lower abdominal region that has lasted for at least 6 months'.[2] Another definition is: 'nonmenstrual pain of 3 or more months duration that localizes to the anatomic pelvis and is severe enough to cause functional disability and require medical or surgical treatment'. [3] Although the choice of 3- 6 months' duration within a definition is arbitrary, it does not carry the subjective anatomic or affective-behavioural assumptions that other types of definitions have used. [4]

The International Association for the study of Pain have provided a specific definition for 'CPP without obvious pathology': chronic or recurrent pelvic pain that cannot be sufficiently explained by an apparent physical cause;[5] this is sometimes also called as the 'pelvic pain syndrome'[6] or 'pelvalgia'.[7] This definition of CPP does not specifically include pain associated with the menses or sexual intercourse. A common definition, including these issues, is: constant or intermittent, cyclic or noncyclic pain that persists for 6 months or more and includes dysmenorrhoea, deep dyspareunia and intermenstrual pain'.[8] This definition will be used for CPP in this thesis.

Dysmenorrhoea is the occurrence of painful menstrual cramps of uterine origin. Dysmenorrhoea is a very common gynaecological complaint that can affect up to 50% of women,[9] and as such has a significant impact not just on personal health but also economically, through lost working hours.[10] Dysmenorrhoea is commonly defined in two

subcategories. When the menstrual pelvic pain is associated with an identifiable pathological condition, such as endometriosis, adenomyosis or pelvic adhesions reflecting previous inflammation, it is considered to be secondary dysmenorrhoea. In contrast, menstrual pain without organic pathology is considered to be primary dysmenorrhoea.[11] According to standard gynaecological texts, primary dysmenorrhoea usually occurs at or shortly after (6 to 12 months) menarche, when ovulatory cycles are established. The pain duration is typically 48 to 72 hours and is associated with menstrual flow. In contrast secondary dysmenorrhoea is more likely to occur years after the onset of menarche and occur premenstrually as well as during menstruation. In practice, the accuracy of diagnosis depends on the availability and the use of diagnostic tools.

1.2 Prevalence of chronic pelvic pain

The prevalence rate of a condition in a population is the proportion of the population that has the condition at a specific point in time (point prevalence) or at some point in a time period (period prevalence). Prevalence rates for CPP will be difficult to ascertain in light of the varying definitions used in the literature as highlighted above. In a recent UK study, women aged between 12-70 years had an annual prevalence of 38/1000 of CPP defined as recurrent or constant pain in the area from navel down in the lower belly of at least 6 months duration, unrelated to periods, intercourse or pregnancy. This compares to the rate of asthma (37/1000) and chronic back pain (41/1000) in the community. [12]

Prevalence rates for dyspareunia and dysmenorrhoea are believed to be 8% and 45-97% respectively.[1] This high prevalence reflects the disease burden in the community. Pelvic pain remains the single most common indication for referral to a gynaecology clinic accounting for

20% of all outpatient appointments. [3;13] Five percent of all new appointments are for CPP.[14] Pelvic pain has a major impact on health-related quality of life, work productivity and health care utilisation. It is also a major cause of workplace absenteeism. [15] An estimated 158 million pounds are spent annually on the management of this condition in the health service. [16] In the USA, $881.5 million are spent per year on its outpatient management. [17] From published studies it is estimated that approximately 40 per cent of all laparoscopies are done for CPP. [3]

Because CPP can reduce the quality of life and general wellbeing, there is a need to establish the true extent of the problem by performing a systematic review of all community based prevalence studies. One such review exists but it has been restricted to studies done in UK only. [1]

1.3 Aetiology of chronic pelvic pain

CPP can have pathologic causes like endometriosis, adhesions, pelvic varices, etc. In addition, various social and psychological factors are reported to be associated with CPP[18] such as personality traits, abuse in childhood or adulthood etc. [19]

The aetiology of primary dysmenorrhoea has been the source of considerable debate. Recent laboratory and clinical research have identified over-production of uterine prostaglandins as a substantial contributing factor to the painful cramps that are the major symptom of dysmenorrhoea.[20] Prostaglandins are also implicated in secondary dysmenorrhoea, however anatomical mechanisms can also be identified, depending on the type of accompanying pelvic pathology. [21] Several primary studies, many with conflicting results, have made an attempt to identify possible predisposing factors for CPP. Those assessing psychological factors have

been previously summarised in a meta-analysis,[19] which, due to, language restrictions in its search [22;23] and lack of study quality assessment, [24] could not generate robust inferences. Studies evaluating physical factors in CPP have not so far been reviewed systematically to our knowledge. If the significance of both physical and psychosocial factors purported to be associated with CPP can be evaluated reliably, these may be more effectively targeted for clinical evaluation, prevention and treatment strategies and may help in designing research studies too.

1.4 Anatomy of pain pathway and rationale for nerve ablation

Pelvic pain is poorly understood entity. Descartes originally suggested that pain was a simple signal from peripheral pain neurons to the brain (the somatic theory). Eventually it became clear that pain is much more complex. The gate theory proposes that peripheral nociceptive signals can be modulated by neurotransmitters like serotonin and endorphins that can be linked with mood states.[25] The pain may be evoked by depressive states as opposed to direct tissue irritation. Thus, interacting psychological and physical factors are likely to be present and attempt to separate one from the other is generally unrewarding.[26]

Another theory, the diathesis-stress model, proposes that some patients are at increased risk of experiencing chronic pain due to acquired pre-existing vulnerabilities e.g. history of sexual abuse.[27] The pelvic viscera receive neurons from both sympathetic (thoracolumbar) and parasympathetic (craniosacral) systems. The corpus, cervix and proximal fallopian tubes transmit pain through sympathetic fibres that arise from T10-L1. These fibres include neurons that are part of the uterosacral ligaments,[28] and eventually merge into the superior hypogastric plexus (presacral nerve). The presacral nerve does not receive fibres from the ovaries and

lateral pelvic structures and logically presacral neurectomy, which involves the total removal of the presacral nerves lying within the boundaries of the interiliac triangle, could work only in midline dysmenorrhoea.

The lateral pelvis transmits pain via nervi erigentes arising from S2-4. The presacral nerve divides into the hypogastric nerve that form the inferior hypogastric plexus, and this plexus divide into vesical, middle rectal and uterovaginal (Frankenhauser's) plexuses. Frankenhauser's plexus lies lateral to the uterosacral ligaments and medial to the uterine arteries and receives pain sensations only from the corpus and vagina. Interruption of these nerve trunks by uterosacral nerve ablation, as shown in figure 1.1 may alleviate pain.

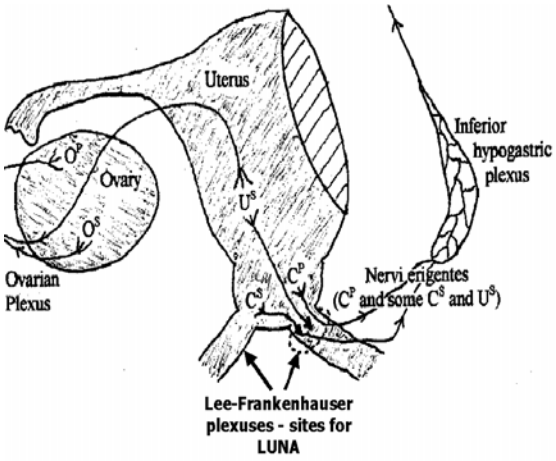


Figure 1.1: Pelvic nerve pathways and sites for laparoscopic uterosacral nerve ablation

[C= afferent nerve supply of cervix (illustrated on right side of diagram); O= afferent nerve supply of ovary (illustrated on left side of diagram); U= afferent nerve supply of uterus (illustrated on right side of diagram). The permission to publish this figure has been kindly granted by Blackwell Sciences limited]

Interruption of these nerve pathways has been used to alleviate pain by open abdominal or vaginal approach in the past, [29;30] but now this procedure can be performed less invasively via

laparoscopic approach [31;32] and is often referred to as laparoscopic uterosacral nerve ablation or LUNA in short. This procedure is a topic for evaluation of practice patterns, beliefs and effectiveness in this thesis.

1.5 Survey of Practice of LUNA

Originally laparoscopic surgical experts were of the opinion that because of the divergence of the sensory nerve fibres and their ganglia as they leave the uterus, the uterosacral ligaments should be vaporised as close to the cervix as possible.[32] However, recent anatomical studies have demonstrated that the greatest number of fibre bundles are at some distance from the site of attachment of the uterosacral ligament to the cervix [33;34]. Hence there is controversy about the optimal site for LUNA. Anatomical studies also suggest that the nerve fibres are dense at a depth of 3-15mm [33], thus the completeness of transection of the uterosacral ligament can also be expected to have an implication for the effectiveness of LUNA.

Information on prevalent variations in the techniques regarding optimal site and depth of LUNA is currently unavailable. A previous survey showed that many UK gynaecologists claimed familiarity with the operative technique of LUNA [35] but it did not explore the differences in surgical techniques with respect to the site and depth of LUNA. Thus a survey to examine the indications and different surgical techniques of LUNA is needed to establish practice patterns.

1.6 Clinicians' beliefs about effectiveness of LUNA

Clinicians have varying degrees of certainty about effectiveness of treatments. It is ethical to initiate a clinical trial when there is collective clinical equipoise about the effectiveness of the available treatments.[36] Prior beliefs are formed from indirect evidence (laboratory studies, epidemiology, extrapolation from similar treatments) and direct evidence (clinical trials, perhaps of an inconclusive nature). Surveys eliciting dichotomous 'yes' and 'no' responses to a question about effectiveness are limited because clinicians' beliefs about a treatment usually amount to rather more than just "I believe it is effective" (or the converse). They may believe the treatment to be greatly or marginally beneficial (or harmful). Some may be rather more certain than the evidence apparently warrants, others may be uncertain to a degree that they believe the treatment may, in the due course, turn out to be either greatly beneficial or harmful.

Formal measurement of beliefs about effectiveness can provide a clearer picture than the dichotomous responses. Formal measurements of 'prior belief' provide respondents with an opportunity to signal the magnitude of the expected effects and the relative probabilities of effects of different sizes. However, the published examples of collecting such information are sparse, in both obstetrics and gynaecology and in medicine.[37;38]

A recent survey has indicated that there is wide variation in the practice and use of LUNA for treatment of CPP among clinicians, suggesting that collective clinical equipoise is present. The technique has been introduced without definite evidence but opinion regarding its use has not yet solidified, as 81% of gynaecologists performing LUNA stated their willingness to recruit patients in a trial to assess effectiveness of LUNA.[35] However, this survey does not

provide information on distribution of beliefs concerning effectiveness of LUNA in alleviating CPP. A structured survey to formally document the range of beliefs on effectiveness of this surgical treatment is required.

1.7 Research Evidence on effectiveness of LUNA

An overview of effectiveness of LUNA concluded that there is insufficient evidence to guide therapeutic decision-making with regard to LUNA.[39] A systematic review of effectiveness of neuroablation undertaken in 2000 found insufficient evidence to recommend it in dysmenorrhoea.[40] It also recommended the need for future randomised controlled trials (RCTs). This information needs to be updated in view of important trials that have been published since to ascertain whether the recommendation needs to be changed.

The effectiveness of LUNA is currently being assessed in a trial. I worked as a research fellow coordinating this trial where I have helped develop and finalise the protocol. This will be presented in the thesis.

1.8 Aims and objectives

This thesis had the following objectives:

1. To estimate the prevalence of CPP by means of a systematic review
2. To generate pooled evidence on the aetiology of CPP by means of systematic review,
3. To undertake a survey of practice concerning LUNA in Europe
4. To undertake a survey of beliefs concerning effectiveness of LUNA

5. To determine the effectiveness of neuroablation in CPP by means of a systematic review
6. To develop a protocol for a prospective randomised controlled trial to assess the effectiveness of LUNA in CPP

These objectives are formulated as structured questions in table 1.1

Table 1.1: Structured questions for each chapter of this thesis

Chapter number	Population	Interventions / risk factors	Outcomes	Research designs
Section A: Prevalence and aetiology of CPP				
2	Women at risk	Prevalence by representativeness of studies	Dysmenorrhoea Dyspareunia Noncyclical pelvic pain	Systematic review (SR) of observational (cross sectional or longitudinal) studies
3	Women at risk	General (demographic) factors Gynaecological/ obstetric factors Psychological and social factors	Dysmenorrhoea Dyspareunia Noncyclical pelvic pain	SR of observational (cohort, case-control or cross sectional) studies that provide comparative information on presence of risk factors in women with or without CPP
Section B: The Practice and beliefs concerning LUNA				
4	Gynaecologists in the UK and rest of Europe	Structured questionnaire	Indications and techniques for LUNA across Europe	Survey
5	Gynaecologists collaborating in LUNA trial	Structured questionnaire	'Prior beliefs' on effectiveness of LUNA	Survey
Section C: Effectiveness of neuroablation				
6	Women undergoing laparoscopy for CPP	Neuroablative procedures (LUNA or presacral neurectomy [PSN]) versus no neuroablation	Pain relief Adverse effects	Cochrane SR
7	Women with CPP who need diagnostic laparoscopy	LUNA versus No LUNA during laparoscopy	Improvement in CPP, quality of life and sexual function	Multicentre randomised controlled trial protocol

LUNA= Laparoscopic uterosacral nerve ablation; CPP= chronic pelvic pain; SR= systematic review

SECTION A: PREVALENCE AND AETIOLOGY OF CHRONIC PELVIC PAIN

In this section, I summarise the evidence on prevalence and aetiology of chronic pelvic pain with systematic reviews of relevant studies in the following chapters:

Chapter 2. Worldwide prevalence of chronic pelvic pain: A systematic review and meta-analyses

Chapter 3: Factors predisposing women to chronic pelvic pain: A Systematic Review

CHAPTER 2: WORLDWIDE PREVALENCE OF CHRONIC PELVIC PAIN: A SYSTEMATIC REVIEW AND META-ANALYSES

2.1 ABSTRACT

Objective

A systematic literature review was performed to ascertain the prevalence of CPP according to the type of pain and to explore reasons for variation in its rates.

Methods

Medline (1966 to 2004), Embase (1980 to 2004), PsycINFO (1887 to 2003), LILACS (1982 to 2004), Science Citation index and CINAHL (January 1980 to 2004) were searched to find potentially eligible studies. Hand searching of reference lists of the relevant studies was also carried out. Studies were considered if they had non-pregnant women without cancer and other specific disorders participating in surveys about rates of CPP. There were 178 studies (459975 participants) in 148 articles. Of these, 106 studies were (124259 participants) on dysmenorrhoea, 54 (35973 participants) on dyspareunia and 18 (301756 participants) on noncyclical pain. Two reviewers, using a piloted form, extracted data independently on participants' characteristics, studies' methodological quality and rates of CPP.

Results

There was significant variation among rates of all three types of CPP. Metaregression analysis showed that this heterogeneity was mainly due to non-representativeness of study sample and inadequacy of study methods. Meta-analysis of rates amongst high quality studies with samples representative of general population showed that prevalence of dysmenorrhoea (12 studies) was 59% (95% CI 49.1-71%, heterogeneity $p<0.001$), of dyspareunia (11 studies) was 13.3% (95% CI 8.8-20.3%, heterogeneity $p<0.001$) and of noncyclical pain (3 studies) was 10.4% (95% CI 9.1-25.7%).

Conclusion

The variation in rates of CPP worldwide is explained by variable study quality. High quality literature revealed a high burden of disease.

2.2 INTRODUCTION

There is a need to establish the true extent of CPP for policy makers to consider in resource allocation and health care planning. In addition, these basic data are necessary to inform design of other research in this condition, like qualitative studies to establish well being and overall quality of life, genetic and environmental epidemiology to assess aetiology, and studies aimed at the development of new treatment strategies[41]. The epidemiological features of CPP have been generously reported in the worldwide literature. Majority of the studies are limited by small sample size and hence their inability to estimate prevalence precisely. The need to summarise this, however, has received scant attention[42].

A systematic literature review was performed to ascertain the geographical distribution of CPP, its prevalence according to the type of pain, and its variation within subgroups defined by age and development status of the country of origin whilst taking into account the quality of the studies.

2.3 METHODS

Our systematic review followed a protocol developed using widely recommended methodology. [43;44]

2.3.1 Data sources

We searched general bibliographic databases: Medline (1966-2004), Embase (1980-2004) and PSYCHINFO (1887-2004). We also searched specialist computer databases: LILACS

(Literatura Latinoamericana y del Caribe en Ciencias de la Salud 1982 to 2004), CINAHL (January 1980 to 2004) and SCISEARCH (1974-2003).

Our search term combination for electronic databases, based on published advice, was as follows: MeSH headings, text words and word variants for "pelvic pain", "dysmenorrhoea", "dyspareunia", and "low abdominal pain" were combined with terms like "prevalence", "community survey" and "incidence". These were combined with terms representing relevant study designs e.g. cross-section, survey etc. according to recent recommendations[45] for searching and the search was restricted to human and female (appendix 2.1). We also hand searched the bibliographies of all relevant reviews and primary studies to identify cited articles not captured by electronic searches. The search did not have any language restrictions.

2.3.2 Study selection

Studies on CPP were selected using the following predefined criteria:

Participants: Non-pregnant women without cancer or other specific diseases participating in surveys about rates of CPP.

Outcome: There is lack of consensus on the definition of CPP in the published literature.[46] We used a definition based on duration and nature of pain (constant or intermittent, cyclical or noncyclical pain, that persisted for 3 months or more[8]) and included three types: cyclical pain during menstruation (dysmenorrhoea), deep dyspareunia and noncyclical pelvic pain. Studies were included in the absence of information on duration of pain as long as it was explicit that cases of acute pain were excluded.

Study design: Cross sectional studies that reported the prevalence of CPP.

2.3.3 Data extraction and quality assessment

Two reviewers extracted data independently, using a piloted form, on participants' characteristics, study quality and rates of CPP. Data on studies not published in English were extracted by people with a medical background with command of the relevant language. We extracted information on whether studies evaluated dysmenorrhoea, dyspareunia and noncyclical pain symptoms individually or in combination. In some studies the existence of multiple symptoms amongst individuals could not be evaluated separately due to the structure of their questionnaires used and their manner of reporting and were excluded.

The methodological quality of all selected papers was assessed to evaluate internal validity using the following attributes[43]: (a) Study design to determine if CPP assessment had been performed prospectively to minimise recall bias; (b) Adequacy of sampling by assessing whether recruitment of participants was random or consecutive or a convenience sample; (c) Sufficiently high response rate (>80%); (d) Use of a validated measurement tool to ascertain CPP as this ensures that participants' responses are a true representation of the underlying condition; (e) Sample size calculation so as to ascertain prevalence reliably. The studies were classified into high and low quality groups based on compliance with 3/5 quality criteria or more. Representativeness of the sample for general population (source of sample) was considered separately to methodological quality as this relates to external validity. This distinction is important because internally valid studies of women attending hospitals or for private health care checks may not be biased but they are less useful due to sampling of nongeneralisable population groups.

Numerators and denominators were extracted or estimated from each study for computing rates and confidence intervals (CI). In our review, prevalence measured how many women have CPP at a single point in time, i.e. point prevalence.[47] Period prevalence, based on the number of women developing CPP during a defined period of time, was reported only in a few studies.

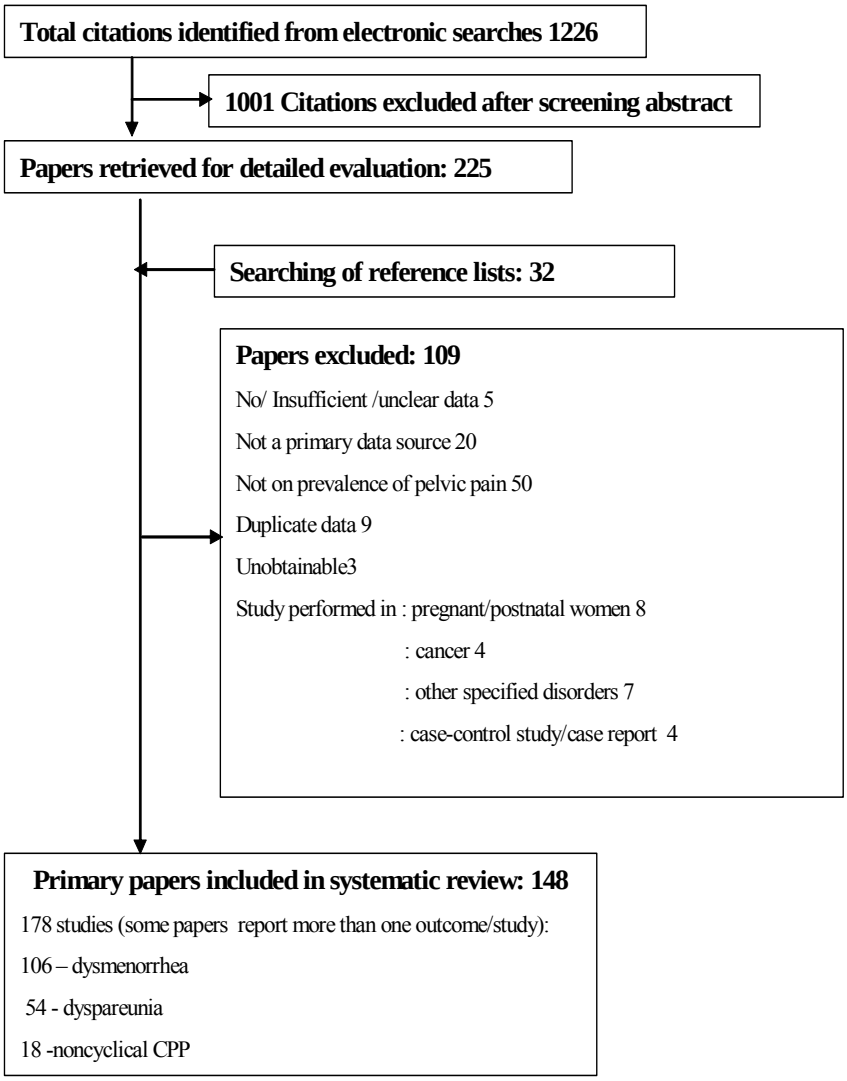
2.3.4 Data synthesis

For each study, we computed prevalence rates and their 95% CI according to the three different types of CPP. Rates of the different CPP were mapped to depict the variation in prevalence by country of origin. Heterogeneity was explored in the rates of CPP graphically using forrest plots of point estimates of rates and their 95% CI and statistically using Cochrane Q. Meta-regression explored if heterogeneity could be explained by variations in countries' development status, participants' average age, representativeness of the sample and methodological quality of the included studies.[48] For development status we used the United Nations classification (developed, less developed and least developed) for countries. Study quality was assessed separately for individual items and scores. We performed both univariate and multivariate meta-regression analysis. Only high quality, representative studies were included in the final meta-analysis. Thus none of the hospital-based studies are included in the meta-analyses as they were not representative of the general population. Meta-analyses of log rates were performed weighting each study by the inverse of its variance[49] using the random effects method[50] (Stata 8 software) and the output was exponentiated. Publication bias was examined for, by plotting log rates versus their corresponding variances in a funnel plot. Funnel asymmetry was tested for using Egger's test[51] and Begg's test.

2.4 RESULTS

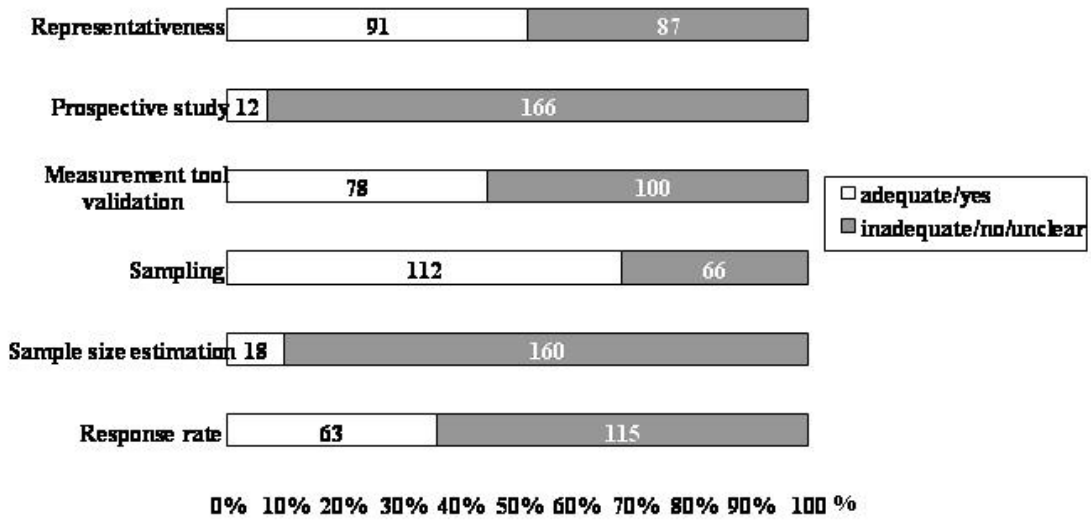
Lists of included studies (appendix 2.2) as well as each included study's salient features; methodological quality and accuracy data are given in Appendices 2.3,2.4 and 2.5 (in the accompanying CD ROM).

Figure 2. 1: Study selection for systematic review on prevalence of chronic pelvic pain



The electronic search yielded a total of 1226 citations (figure 2.1). On examination of titles and abstracts, 228 were found to be potentially relevant and their full papers were obtained. The reference lists of these revealed 32 further citations. After reviewing these, 109 papers were excluded. The remaining 148 papers met the inclusion criteria, which provided data on 459972 participants. 29 studies overlapped and reported more than one outcome. There is very little data (1/143 papers) available from the least developed countries. Study quality assessment (shown in figure 2.2 below) revealed deficiencies in many areas of methodology: Two (1.2%) studies met all five high quality criteria, 12 (7.1%) met 4/5 criteria. There were 47 studies (27.8%) that met three or more quality criteria.

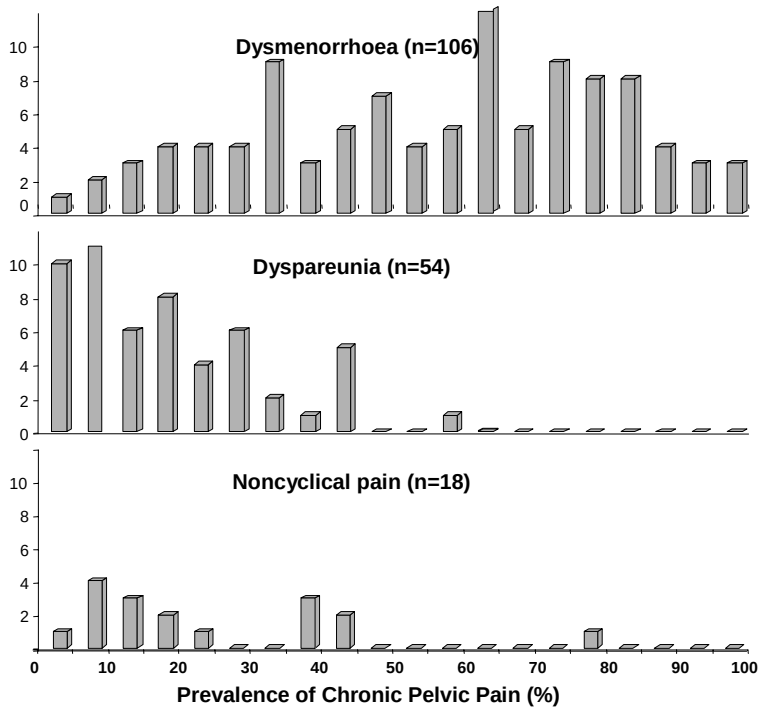
Figure 2.2: Quality of studies included in systematic review on prevalence of chronic pelvic pain (Data presented as 100% stacked bars; figures in the stacks represent number of studies).



The data on prevalence of CPP in included studies is summarised in figures 2. 3 – 2.5. Figure 2.3 depicts the range of the number of studies and the percentage of pelvic pain found in those

studies. Figure 2.4 shows the scatter of prevalence of the different types of pelvic pain with their confidence intervals. Epimaps in Figure 2.5 depict the available data on worldwide prevalence of different types of chronic pelvic pain by countries.

Figure 2.3: Prevalence rates of different types of chronic pelvic pain amongst included studies



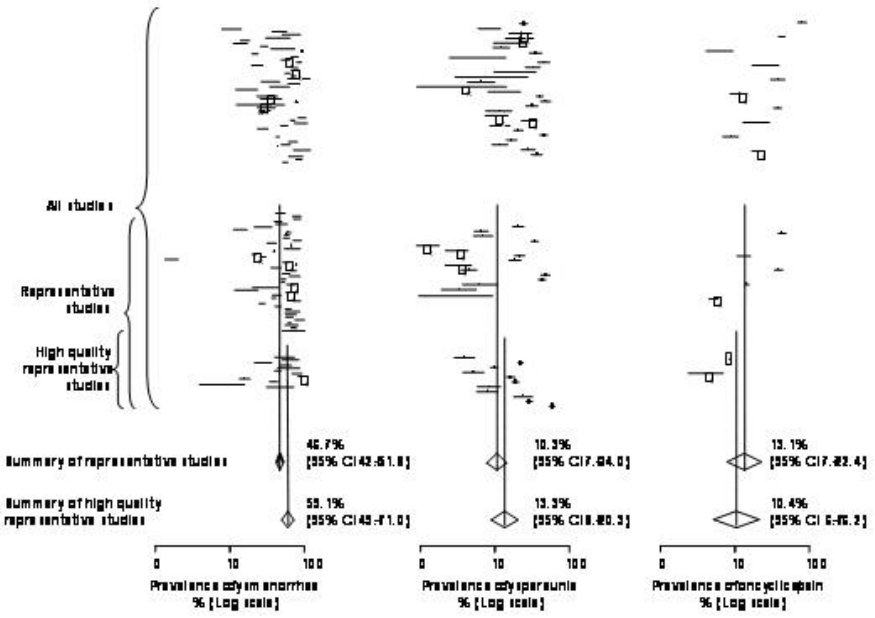
2.4.1 Dysmenorrhoea

The prevalence rates ranged from 1.7%[17] to 93.3%[52] in 106 studies including 125249 women. Prevalence rates for cyclical pelvic pain in the UK reported were between 45% (12% reporting severe)[53] to 97%[54](14% severe) for any dysmenorrhoea in community based studies and between 41-62% in hospital based studies[55;56]. In other European countries it was similar.[15;57] The lowest prevalence was reported in Bulgaria (8.8%) in women hospitalised with adnexitis between the ages of 19-41 years and the highest was in Finland (94%) in girls

aged 10-20 years.[52] There was heterogeneity and the funnel plot for dysmenorrhoea was asymmetrical (Begg's test P =0.02; figure 2.6) but not for representative studies (P=0.333) Metaregression showed validated measurement tool to be a significant factor to explain heterogeneity but not study quality score, representativeness, age< 25 years or development status of the country (developed vs. less developed vs. least developed). The prevalence of dysmenorrhoea in 54 representative studies was 46.7% (42.0-51.8%) as shown in figure 4. In 12 high quality representative studies, the pooled prevalence was 59.1 % (95% CI 49-71%)

Figure 2. 4: Data synthesis of studies on prevalence of different types of chronic pelvic pain.

(See methods for details of meta-analysis. Heterogeneity p=<0.001 for all meta-analyses)



2.4.2 Dyspareunia

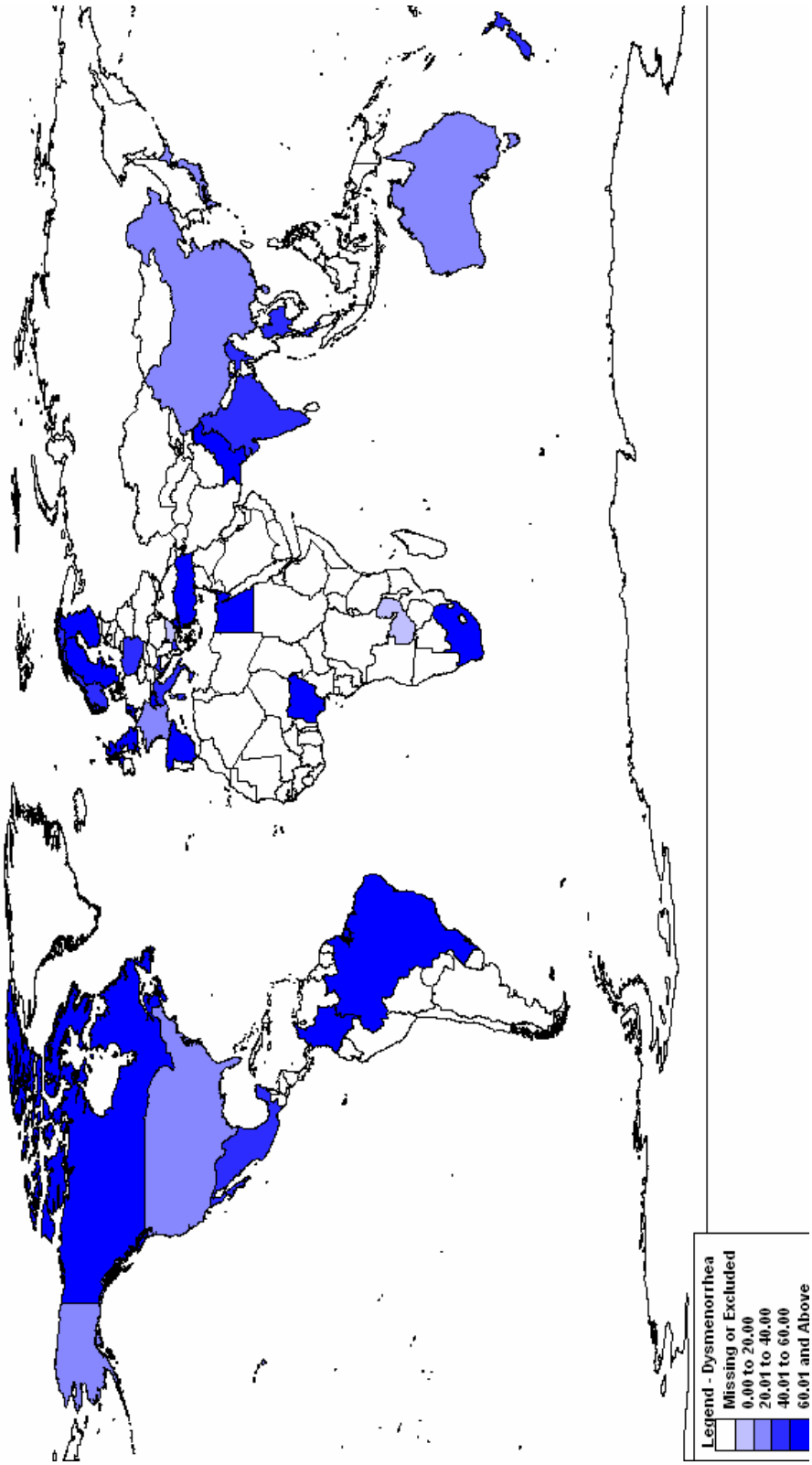
The prevalence rates ranged from 1.3%[58] to 45.7%[59] in 52 studies including 35973 women. The rates of dyspareunia varied from 1.1% in Sweden[60] to 45%[59] in US studies. In 26/52 representative studies, the overall prevalence of dyspareunia was 10.3% (95% CI 7.2-13.4%, heterogeneity p<0.001). In 11 high quality representative studies, the prevalence of dyspareunia was 13.3% (95% CI 8.8-20.3%, heterogeneity p<0.001). Studies were markedly heterogeneous (P=0.000) and the funnel plot for dyspareunia was asymmetrical (Begg's test P =0.001; figure 2.6) but not in representative studies (P=0.227). The representativeness of sample provided the main explanation for heterogeneity that was statistically significant in meta-regression analysis (appendix 2.6). Age under 60 was not a significant factor in metaregression (P=0.15).

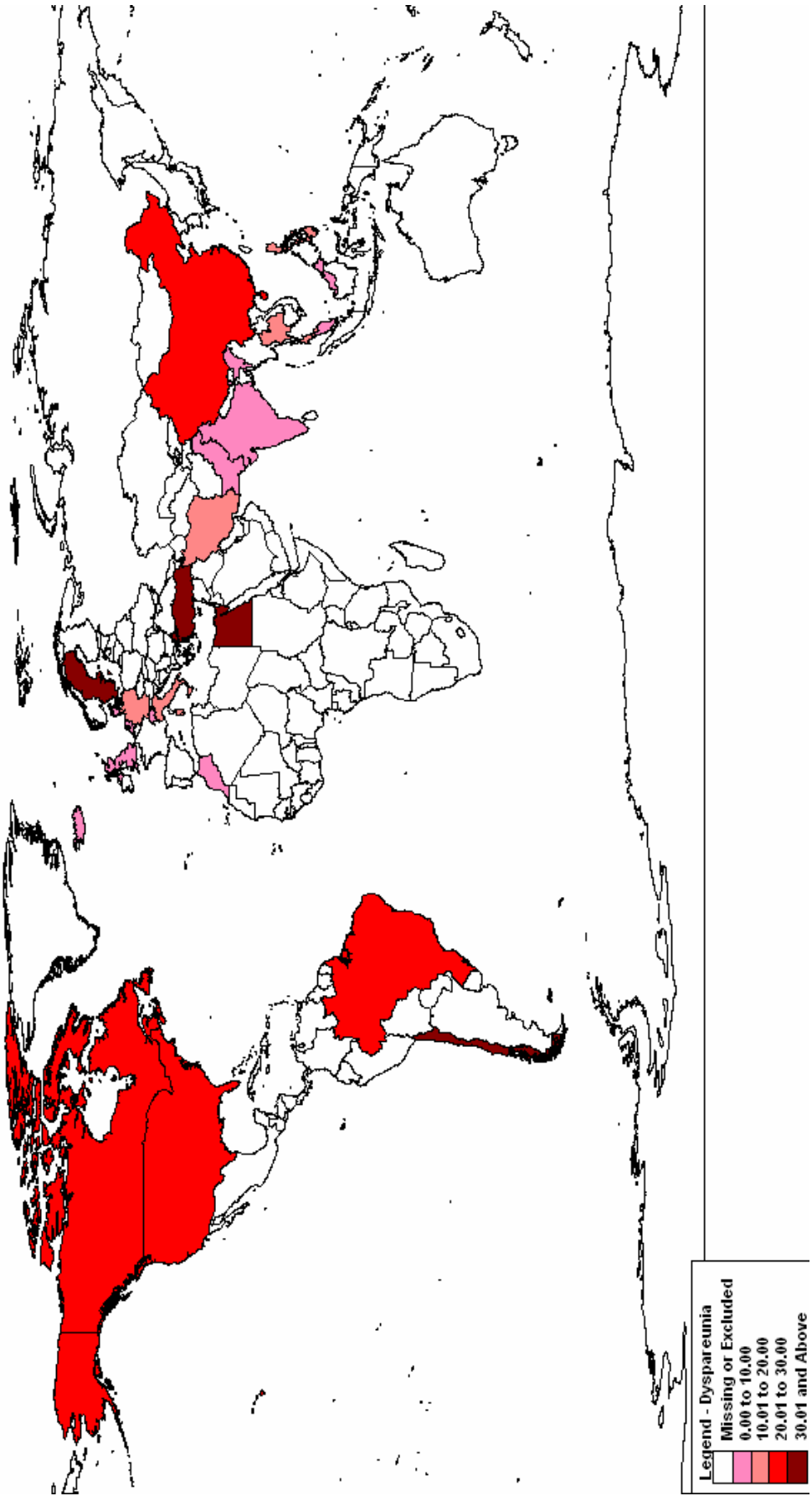
2.4.3 Non-cyclical pelvic pain

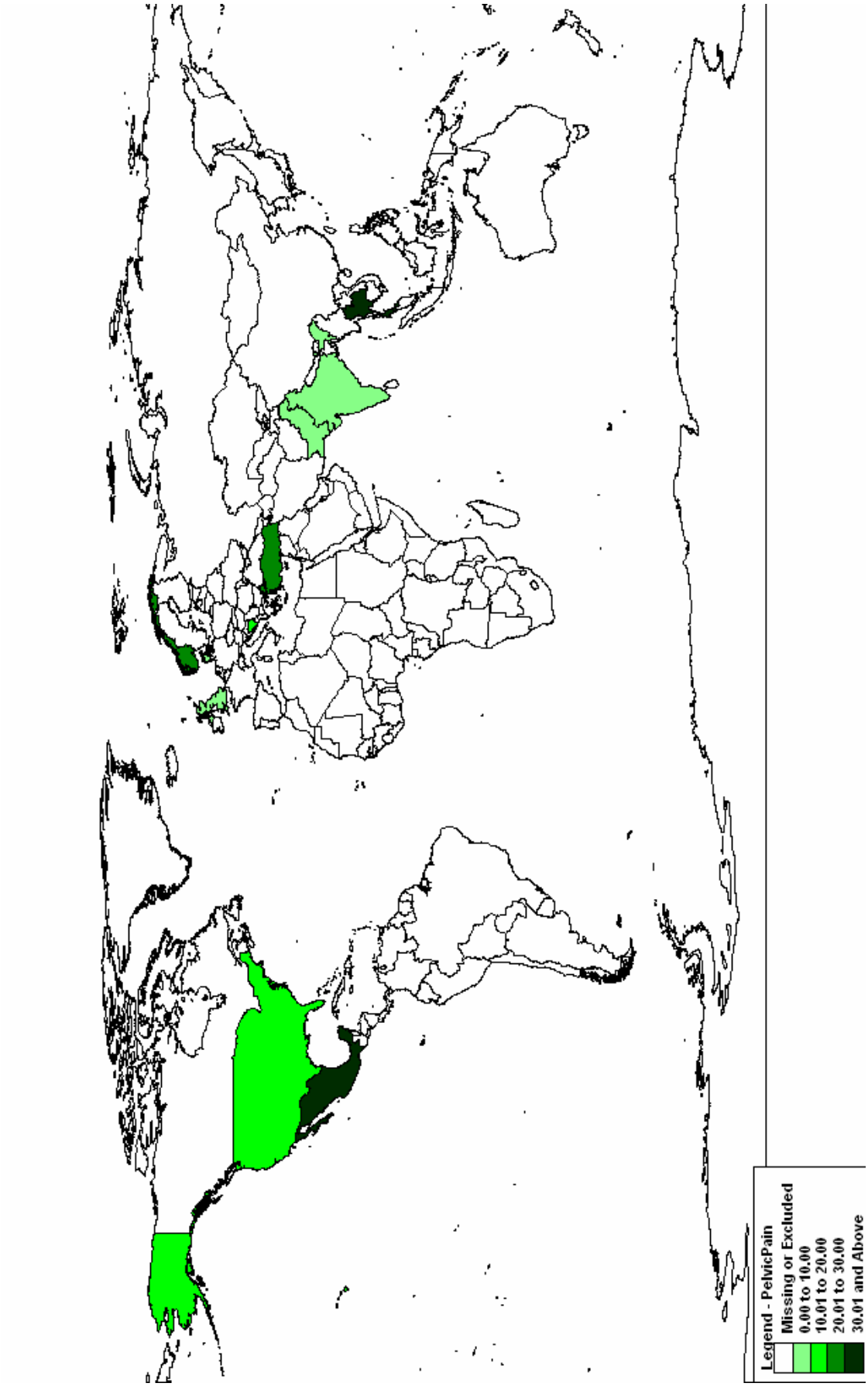
The prevalence rates ranged from 4.0%[61] to 43.4%[62] in 17 studies including 299740 women. The funnel plot for noncyclical pelvic pain was asymmetrical (Figure 2.6; Begg's test P=0.048; figure 2.6) but not for representative studies (Begg's test P=0.88). Two recent high quality studies stated a 3 month prevalence of 15% in women aged 18-50 years in the USA[17] and 24% in ages between 12-70 in the UK.[12] In less developed countries in South East Asia the prevalence rates varied from 5.2% in India, 8.8% in Pakistan to 43.2% in Thailand.[62] The overall prevalence of noncyclical pain was 13.1% (95%CI 7.7-22.4%, heterogeneity p< 0.001) in 7 representative studies. The prevalence of noncyclical pelvic pain in two high quality representative studies was 10.4% (95%CI 6.7-16.2%, heterogeneity p<0.001). The metaregression revealed that prospective design, adequate sampling strategy, sample size

estimation and high quality studies tended to describe lower prevalence of noncyclical pelvic pain though none of these were significant.

Figure 2.5 Epimaps of worldwide prevalence of different types of chronic pelvic pain (dysmenorrhoea, dyspareunia and noncyclical pelvic pain respectively)


Legend - Dysmenorrhea
Missing or Excluded
0.00 to 20.00
20.01 to 40.00
40.01 to 60.00
60.01 and Above


Legend - Dyspareunia
Missing or Excluded
0.00 to 10.00
10.01 to 20.00
20.01 to 30.00
30.01 and Above


Legend - PelvicPain
Missing or Excluded
0.00 to 10.00
10.01 to 20.00
20.01 to 30.00
30.01 and Above

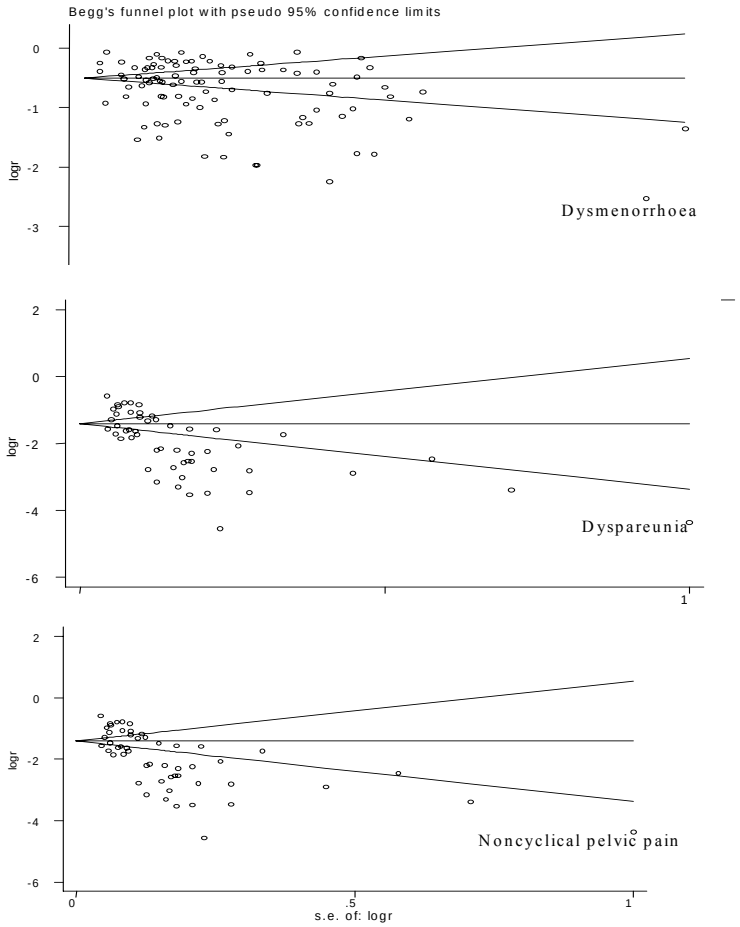


Figure 2.6: Funnel plots of the three types of pelvic pain prevalence studies

2.5 DISCUSSION

This is the first systematic review of the worldwide prevalence of CPP. It pooled rates of various types of CPP in high quality representative studies. Development status of the country did not affect the high rates of pain observed. The variation in rates of CPP worldwide is explained by variable study quality. High quality literature revealed a high burden of disease for dysmenorrhoea and dyspareunia.

We believe that the findings of our study are valid as our review methodology was rigorous. A prospective review protocol was used and a concerted effort made to identify all the available evidence without language restriction. We made concerted efforts to report this systematic review as suggested by the MOOSE consensus statement (see table 2.5).[63] Both the methodology and the rates of CPP varied among the included primary studies and explored the reasons for variations. For meta-analysis we included only high quality representative community studies in an attempt to summarise the prevalence in the general population. This review represents the best available evidence on the estimates of the prevalence of CPP at the time of writing and provides the best information available for targeting services at women suffering from pelvic pain.

The variation in geographical distribution may be related to study characteristics, study quality, age groups included and definitions used rather than intrinsic differences between the prevalence of CPP between the different populations. Other plausible explanations might be differences in the prevalence of sexually transmitted infections, availability of medical and other resources or cultural differences. Although we have included studies from 1924 onwards, majority of the studies are from 1980 onwards. The population demographics are unlikely to have undergone major changes over this period, making the studies relevant to current populations. Substantial differences or even complete absence of definitions, together with differences in age ranges of the populations studied, complicate the interpretation to a great extent.

The information on which groups have increased rate of dysmenorrhoea, dyspareunia have implication for provision of services to policymakers in terms of provision of improved

access for these women to health care resources as well as the development of appropriate treatment protocols. Future epidemiological studies should ideally be prospective, with explicit definitions of the outcome and representative of the general population. The survey should use the validated measurement tools for validity and comparability of the results.

CHAPTER 3: RISK FACTORS IN CHRONIC PELVIC PAIN: A SYSTEMATIC REVIEW AND META-ANALYSES

3.1 ABSTRACT

Objective

To evaluate the factors predisposing women to chronic pelvic pain, a common chronic condition.

Methods

Systematic review of all relevant studies without language restrictions was carried out. Studies were identified without language restrictions through Medline, Embase, PsycINFO, Cochrane Library, SCISEARCH, conference papers and bibliographies of retrieved primary and review articles (upto April 2004).

Two reviewers independently extracted data on study characteristics, quality and results. Exposure to risk factors was compared between women with and without pelvic pain. Results were pooled within subgroups defined by type of pain and risk factors. Data were pooled to produce summary estimates of Peto odds ratio (OR) or standardised mean differences (SMD).

Results

There were 122 studies (in 112 articles) of which 63 (64,286 women) evaluated 54 risk factors for dysmenorrhoea, 19 (18,601 women) evaluated 14 risk factors for dyspareunia and 40 (12,040 women) evaluated 48 factors for noncyclical CPP. Age less than 30 years, low body mass index (BMI), smoking, early menarche (<11 years), longer cycles, longer duration of bleeding or heavy menstrual flow, nulliparity, premenstrual syndrome, sterilisation, pelvic inflammatory disease, sexual assault, emotional difficulties, psychological symptoms, suicidal tendency and somatisation were associated with increased risk of dysmenorrhoea. Younger age at first childbirth, exercise and oral contraceptives and were associated with reduction in

the risk of dysmenorrhoea. Age less than 50 years, peri/post menopausal state, PID, sexual abuse, anxiety and depression were found to be associated with dyspareunia. Drug/alcohol abuse, miscarriage, heavier menstrual flow, PID, previous caesarean section, pelvic adhesions/other pathology, childhood physical or sexual abuse, lifetime sexual abuse, anxiety, depression, hysteria, psychosomatisation were associated with an increased risk of noncyclical pelvic pain.

Conclusion

Key gynaecological and psychosocial factors associated with CPP should be targeted in clinical evaluation of women with this symptom to individualise their management.

3.2 INTRODUCTION

There is wide variation in clinical evaluation of women with CPP. In some countries, like the UK, diagnostic laparoscopy is the standard investigation on referral to gynaecologists. Laparoscopy is negative in over 50% of cases, [3] so considering its invasive nature many clinicians reserve it for evaluation when non-invasive options have been exhausted.[18] Thus in some countries, like in mainland Europe, empirical treatment is the standard initial management. [64] This variation in practice is in also due to uncertainty about effectiveness of a lot of available treatments to alleviate pathologic causes. [65-67] An initial strategy to uncover and treat pathologic causes like pelvic varices, adhesions and endometriosis first is not necessarily better than psychological management first. More fundamentally, the extent to which these pathologies are causally related to pain is itself uncertain as they overlap with psychosocial factors in a majority of CPP cases.[68;69] Even laparoscopy is believed to have beneficial effects through psychological mechanisms.[70;71] A better understanding of the relative contribution of various pathological, social and psychological factors to CPP[19] may be helpful in clinical evaluation as well as in the development of prevention and treatment strategies and the design of future studies.

A number of primary studies have sought to identify predisposing factors for CPP but often with conflicting results. A previous meta-analysis [19]has summarised the evidence on social and psychological factors, but language restrictions in its search and no assessment of the quality of studies included, [24] potentially limit its findings. No systematic review of the influence of physical and environmental factors in CPP has so far been undertaken. Hence a comprehensive systematic review of all studies was performed to evaluate risk factors for CPP.

3.3 METHODS

We first developed a protocol using widely recommended methods for systematic reviews of observational studies.[44;63]

3.3.1 Data sources

We searched general bibliographic databases: Medline (1966-2003), Embase (1980-2003) and PSYCHINFO (1887-2003). We also searched specialist computer databases: the Cochrane Library (2003:1) and SCISEARCH (1974-2003). Our search term combination for electronic databases, based on published advice,[72] was as follows: MeSH headings, text words and word variants for "chronic pelvic pain", "dysmenorrhoea", "dyspareunia". Relevant terms for aetiological factors e.g. causal, odds ratio, relative risk etc. were used to combine with terms representing relevant study designs e.g. cohort, risk, case control studies, etc. and the search was restricted to human and female (see appendix 2 for details). We also hand searched the bibliographies of all relevant reviews and primary studies to identify cited articles not captured by electronic searches.

3.3.2 Study Selection

Studies on CPP that included a comparative group without pelvic pain and provided information on exposure to any risk factor were selected using the following criteria:

Participants: Women at risk.

Risk factors (exposures): *General factors*: Age, race, body mass index, smoking, occupational exposures, socio-economic status, education, sport activities etc. *Gynaecological/obstetric factors*: contraception, age at menarche, duration of menstrual flow, length of menstrual cycle, premenstrual symptoms, infertility, history of abortion or miscarriage, parity, age at birth of first child, previous caesarean section, previous pelvic

inflammatory disease (PID), presence of pelvic adhesions, varices, endometriosis, menopause etc. *Psychological and social factors*: history of childhood or lifetime physical, psychological or sexual abuse, anxiety, depression, borderline syndrome, psychosomatic symptoms, alcohol or drug abuse, unsatisfactory family relationship, history of death or divorce of parent at an early age, alcoholism in parent, disturbed puberty or childhood etc.

Outcomes: Chronic (duration 3 months or more) noncyclical pain, menstrual pain (dysmenorrhoea) and pain related to intercourse (dyspareunia) localised in the lower abdomen and pelvis.

Study designs: Observational (cohort, case-control or cross sectional) studies that provided information on the association of risk factors with CPP were included. Studies without comparative information on risk factors were excluded.

Studies were selected in a two-stage process. One of us (PML) scrutinised the citations downloaded from the electronic searches and obtained full manuscripts of all citations that were thought to meet the predefined selection criteria or if there was uncertainty whether they were eligible for inclusion. Final inclusion or exclusion decisions were made when two of us (PML and LM) examined these manuscripts. In cases of duplicate publication we used all reports to assess study characteristics and quality, but only selected the most recent and complete versions for results. We applied no language restrictions. Two of us (PML and LM) independently assessed English manuscripts. People who had command of the language to allow data extraction assessed manuscripts in other languages (Chinese, Bulgarian, French, German and Japanese). We resolved any disagreements about inclusion or exclusion by consensus or arbitration by a third reviewer (KSK).

Information on characteristics of exposures and outcomes were extracted. Some studies provided information on more than one outcome. For each of noncyclical pain, dysmenorrhoea or dyspareunia, we extracted data on separate forms. Wherever possible, exposure data and numbers of women with and without CPP were used to construct 2×2 tables. In studies where the data on exposure were continuous, we abstracted means and standard deviation and numbers in groups with and without CPP. In some studies, where both of these data was absent, significance (p) values or correlation coefficients if quoted were extracted. We pilot tested the data extraction form on primary studies related to dyspareunia using two reviewers (PML and LM). Overall, the observer agreement regarding the various components of the data extraction form was 90-100%. We attempted to obtain missing data by contacting authors via email or post wherever possible.

3.3.3 Methodological quality assessment

We assessed all manuscripts that met the selection criteria for quality. We defined quality as the confidence that the study design, conduct and analysis minimised bias in the estimation of the effect of exposure to a risk factor on CPP. Our quality items were based on existing texts and checklists.[44;63]

Bias can be associated with retrospective designs, non-consecutive or non- random participant recruitment, lack of blinding of assessors, partial verification of exposure to risk factors and outcome, overlooking temporality and lack of matching or adjusting for confounding factors. We considered a study to be of good quality if it used 1) prospective design 2) consecutive or random participant recruitment 3) ascertainment of exposures using validated instruments, 4) ascertainment of outcome by clinical evaluation with or without laparoscopy, 5) temporal relationship between exposure and outcome and 6) controlled for confounding factors. We classified studies into high or low quality categories by whether or not they fulfilled three or

more of the above six quality criteria. This is arbitrary cut off and not yet validated for non randomized studies.

3.3.4 Data synthesis

We tabulated information from each study stratified according to the three prespecified outcomes (noncyclical pelvic pain, dysmenorrhoea and dyspareunia). Results were computed separately for dichotomous and continuous data. For dichotomous data, effects in individual studies were assessed using standard Mantel Haenszel techniques, giving Peto odds ratios and confidence intervals.[73] For continuous outcomes, the outcome measure of interest was the Standardised mean difference (SMD), the difference in means divided by the pooled standard deviation, which was used to allow the synthesis of data from studies where different scales were used.[74] This method assumes that differences in standard deviations in the studies arise from differences in the scales rather than differences in population. However, even if this assumption is invalid, a consistent effect of an exposure between studies should still give qualitatively similar effects in all studies. In order to combine studies which assessed the same factors, but where some studies used continuous and some used dichotomous variables, we used the standard correction factor of $\pi/\sqrt{3}$ to convert from SMD to log odds ratio.[73] Results were displayed graphically using odds ratio (Forrest) plots with twin (continuous and dichotomous) scales where appropriate and heterogeneity between trials assessed using standard techniques.[74] In order to allow somewhat for the possibility of false positive results arising out of multiple testing, 99% confidence intervals were used in all plots.

Studies within each outcome were subgrouped according to risk factors and further according to control groups (pain free or with other pain). We also stratified by study quality. We

assessed heterogeneity of individual effects within subgroup of studies graphically (using OR plots) and statistically (using chi square test) to help us decide how to proceed with quantitative synthesis.[75;76] We explored for possible sources of heterogeneity by meta-regression analysis[77;78] using various explanatory variables defined *a priori* including age and study quality. When a variable was not explicitly mentioned, it was treated as "no" in the meta-regression analysis.

3.4 RESULTS

3.4.1 Literature identification, study characteristics and quality

Figure 3.1 summarises the process of literature identification and selection. We identified 5326 citations, from which 122 studies were selected for this review. 63 studies (64,286 women) evaluated dysmenorrhoea, [15;52;55;61;79-137] 19 studies (18,601 women) evaluated dyspareunia. [96;111;136-152] and 40 studies (12040 women) evaluated noncyclical pelvic pain.[65;68;96;108;136;138;140;142;152-181]

Summaries of each study's salient features are given in Appendix 3 (3.5-3.13 in CD ROM). In 28/40 (70%) studies on noncyclical pelvic pain, 29/63 (46.03%) on dysmenorrhoea and 13/19 (68.42%) studies on dyspareunia 3 or more quality criteria were satisfied. Multivariable metaregression analysis showed that sexual abuse was not associated with a particular type of CPP. In this analysis, poor quality studies had more prominent associations between abuse and pelvic pain than good quality studies (p=0.02). Multivariable analyses did not alter the significance of quality. Funnel plots of the analyses of abuse and pelvic pain showed asymmetry.

Figure 3.1: Study selection process for systematic review of studies of predisposing factors for chronic pelvic pain (see appendix for list of excluded studies)

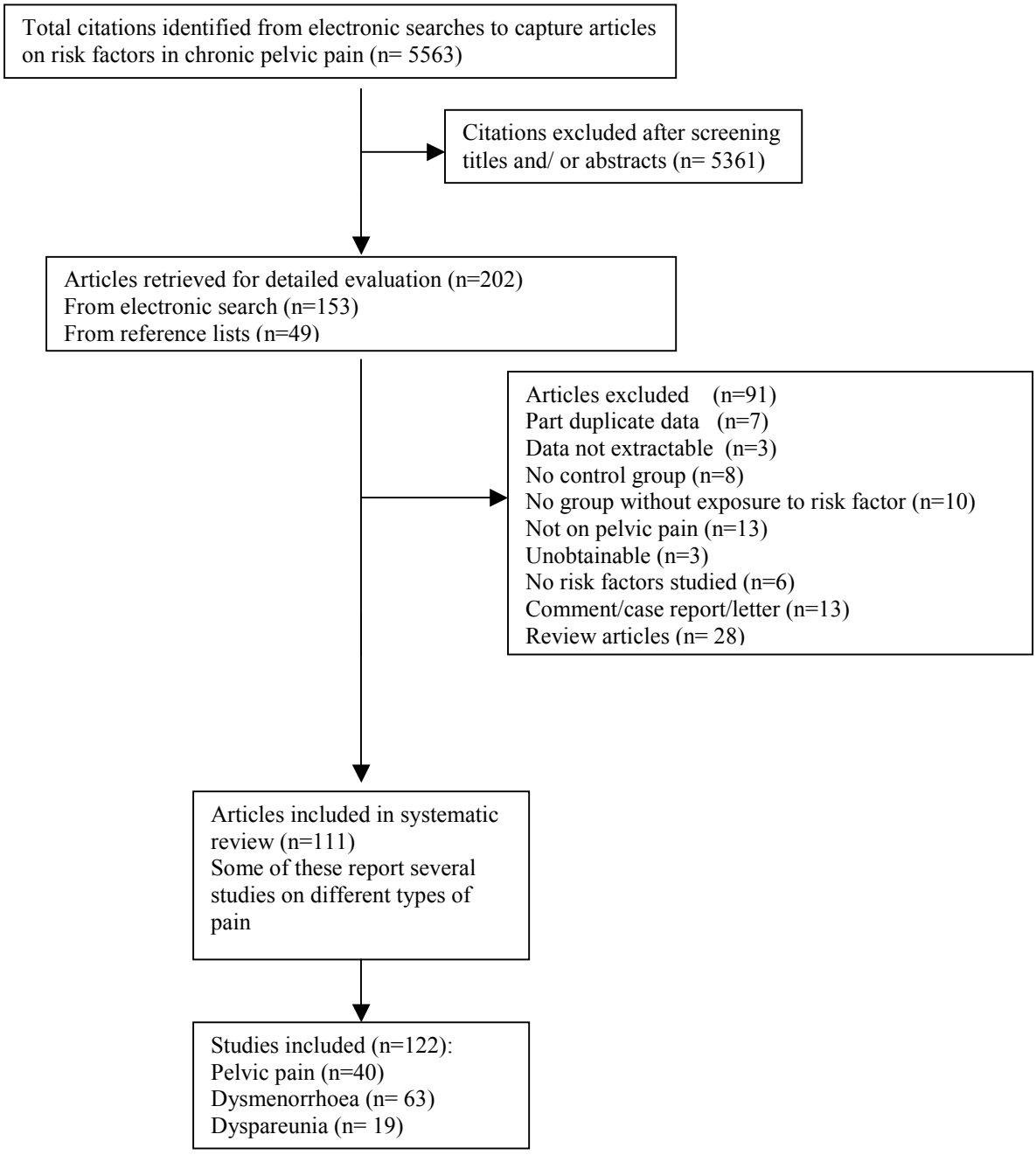
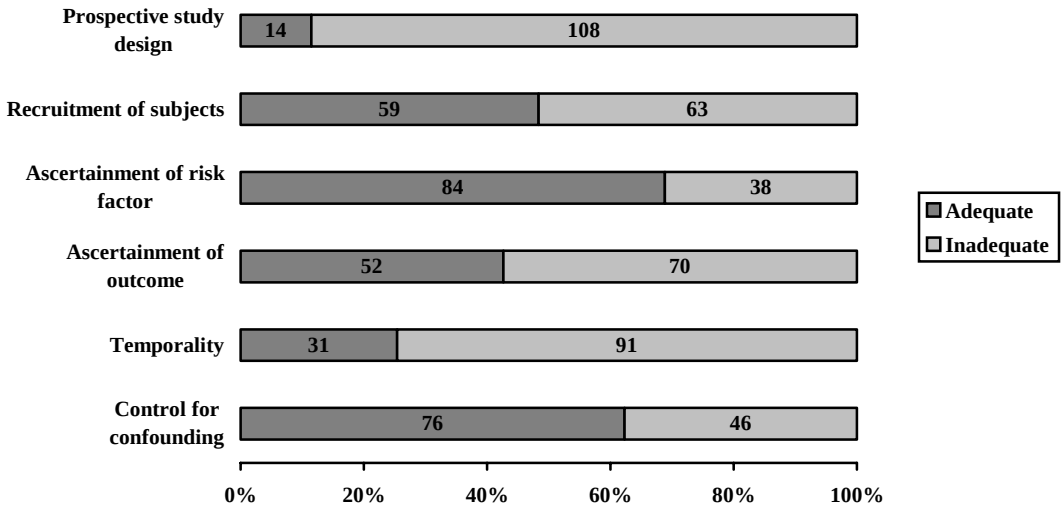


Figure 3.2: Methodological quality of studies included in the systematic review of risk factors for chronic pelvic pain

(Data presented as 100% stacked bars; figures in the stacks represent number of studies).



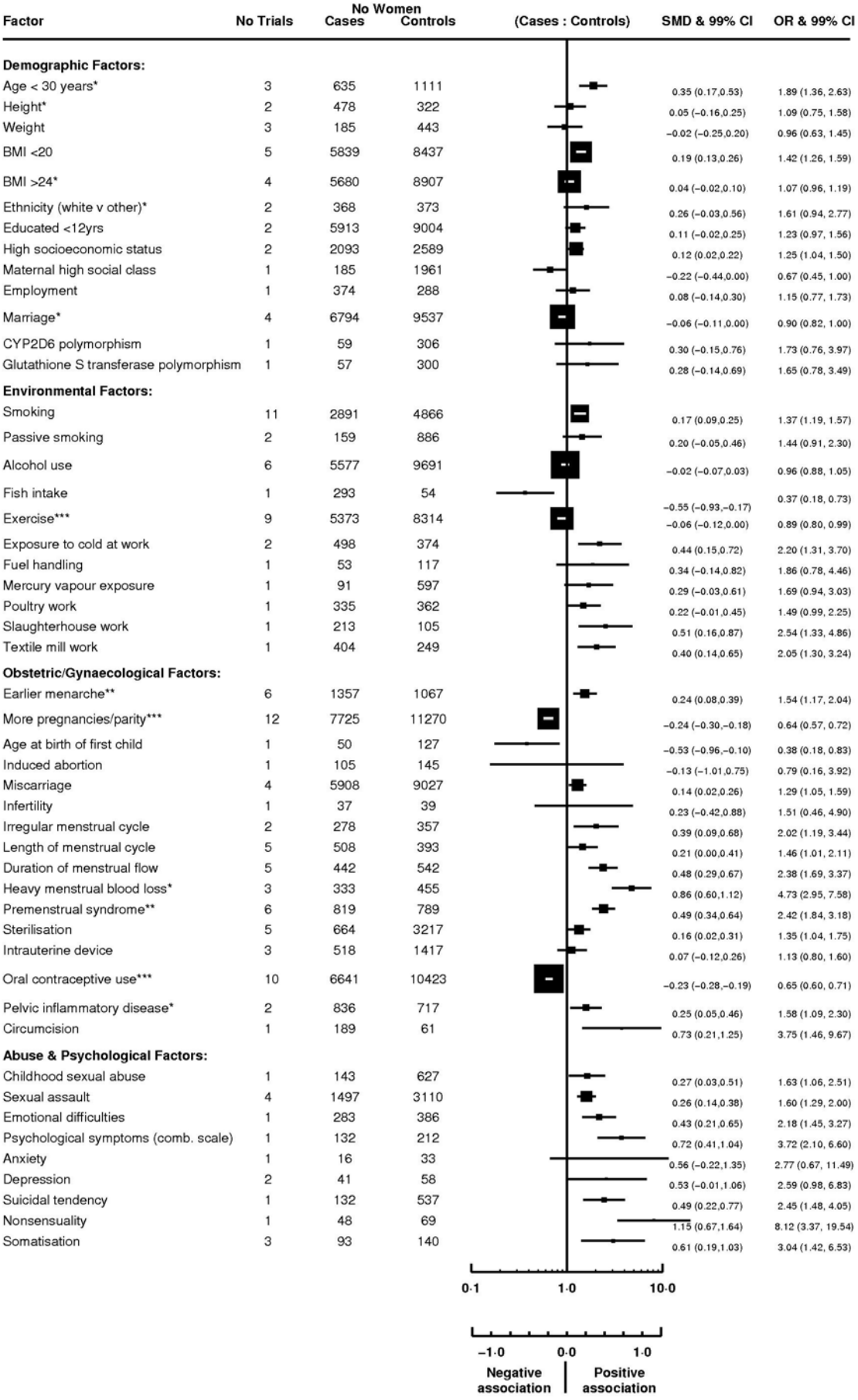


Figure 3.3: Metanalyses of risk factors associated with dysmenorrhoea

(All multiple studies are heterogeneous, *** p<0.0001; **p<0.001; p<0.01)

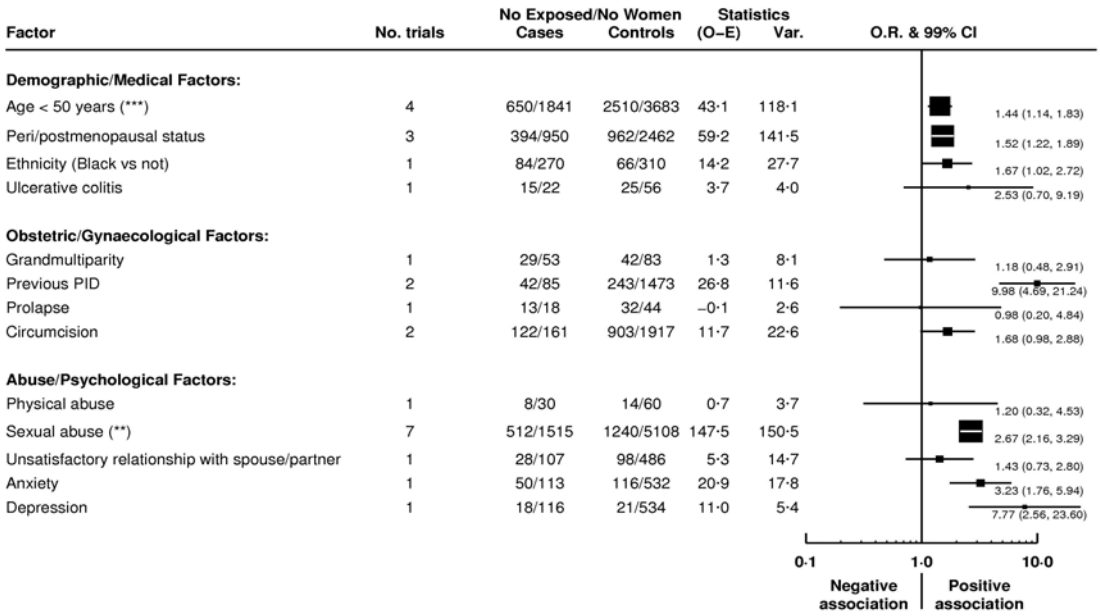


Figure 3.4: Metanalyses of risk factors associated with dyspareunia

(All multiple studies are heterogeneous, *** p<0.0001; **p<0.001; p<0.01)

3.4.2 Risk factors for CPP

Thin (BMI<19) women, less than 30 years, nulliparous, smokers, ones who had early menarche (<12 years), longer cycles / duration of bleeding, irregular or heavy menstrual flow, presence of premenstrual symptoms, PID, sterilisation and history of sexual assault presented more frequently with dysmenorrhoea (figure 3.3). The risk of dysmenorrhoea increased with the number of cigarettes smoked per day ($p<0.05$ by trend test).[89;182]. Use of oral contraceptives, physical exercise, being married or in a stable relationship and higher Dyspareunia was commoner in women less than 50 years old, history of circumcision, PID and peri/postmenopausal. Women with dyspareunia reported anxiety, depression and sexual assault more frequently (figure 3.4).

Noncyclical CPP was associated with numerous general, gynaecological and obstetric factors, abuse and psychological morbidity notably previous miscarriage, longer menstrual flow, presence of endometriosis, PID, caesarean section scar, pelvic adhesions, childhood physical or sexual abuse, lifetime sexual abuse or any abuse, anxiety, depression, hysteria and somatisation (figure 3.5). On subgroup analysis, it was found that the abuse was more strongly associated with pelvic pain when the comparison group was painfree than when the controls had other pain like backache, headache etc. On comparing women with CPP (without and with obvious pathology) with pain free groups, across studies for psychological morbidity (depression, anxiety, neuroticism and somatisation), it was noted that psychological morbidity was more in women with pelvic pain irrespective of presence or absence of pelvic pathology on laparoscopy ($p=0.03$).

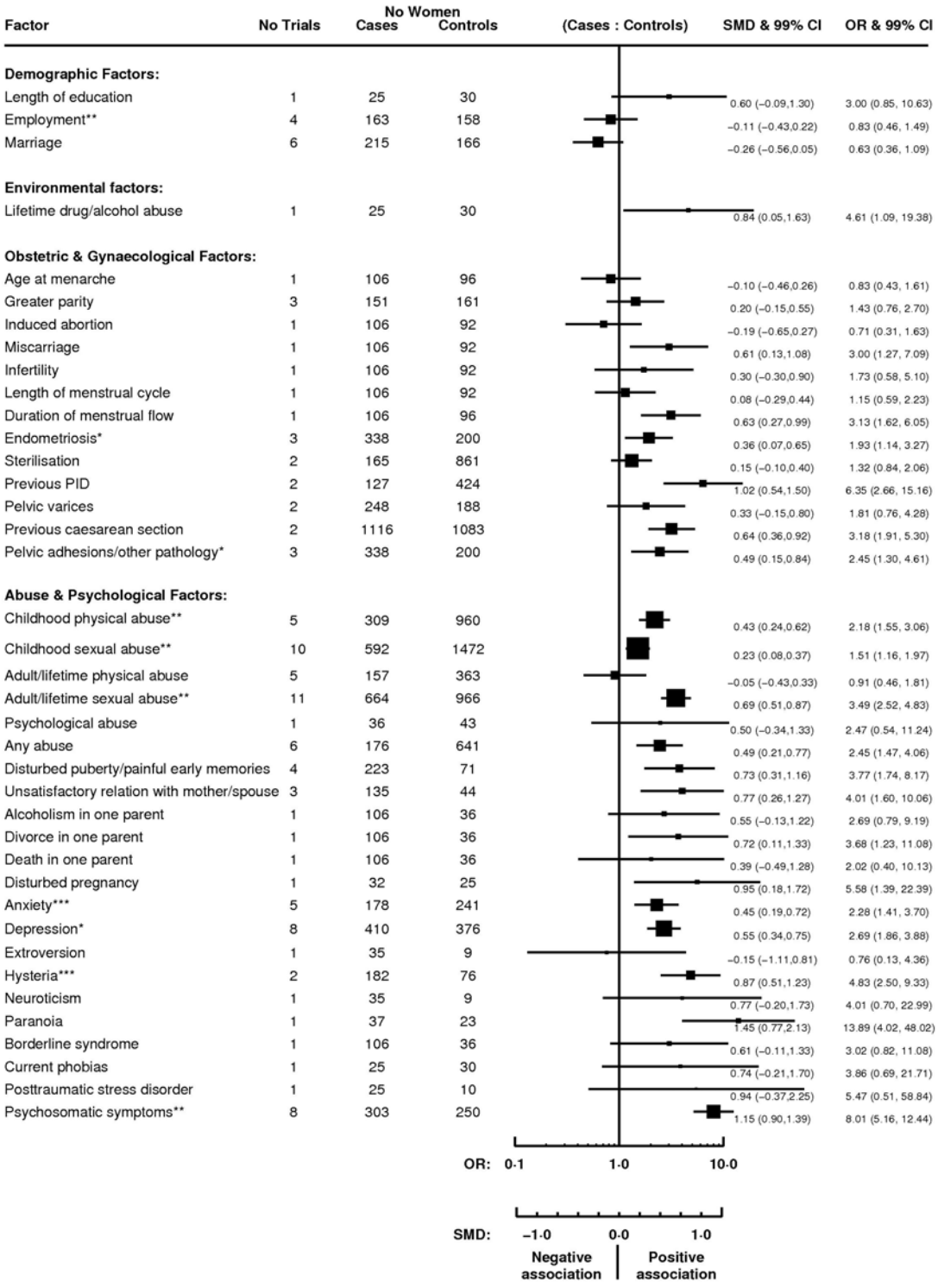


Figure 3.5: Metanalyses of risk factors in noncyclical pelvic pain

(All multiple studies are heterogeneous, *** p<0.0001; **p<0.001; p<0.01)

3.5 DISCUSSION

This review found key gynaecological and psychosocial factors that will be useful in clinical evaluation of CPP. Presence of pelvic pathology, history of abuse and coexistent psychological morbidity showed consistent associations with CPP.

This systematic review comprehensively evaluated over 60 risk factors in 122 studies related to CPP. It was rigorously carried out with an extensive literature search without foreign language restrictions and with formal assessment of study quality to evaluate bias. It met quality criteria laid down in the MOOSE statement.[63] It generated information on strength and consistency of associations of various risk factors with various types of CPP, so we could consider evaluation of some causal criteria. The variation and the poverty of methodological quality of the included studies have implications for the validity of our findings. Retrospective studies are subject to incomplete or selective recall of previous events[41]. The exposure comparisons might not have been appropriate in some studies, e.g. non-sexual abuse group may actually be a non-sexually abused group of women who have experienced physical or psychological abuse, possibly increasing psychosocial distress and diminishing clinically relevant differences between the groups.[183;184] Other concerns relate to the use of non-standard measurement tools with questionable validity or reliability to discriminate between women with and without CPP. Ascertainment bias may arise by selecting control groups from women consulting for other conditions in the same setting, who did not have assessment like laparoscopy, so in them presence of pathology could not be assessed. An explicit definition for CPP was not uniformly used. These factors reduce the ability to confidently investigate causation.[46] However, this is the best available evidence of the risk factors for CPP.

Bias in reporting is a potential problem as studies may have looked at the interaction of several risk factors with CPP but published only those that were interesting or statistically

significant. This could, conceivably, introduce bias in both directions—that is, analyses are probably equally likely to be published whether or not a particular factor indicates an abnormally high or an abnormally low risk. We decided to combine odds ratio and mean differences for risk factors where both types of results were expressed. This was done to avoid loss of strength of combined information as well as to avoid results from two analyses that could conflict and lead to an erroneous conclusion.[73]

Certain study design features may impinge on the generalisability of our findings.[41] Women included in many of the community based studies of dysmenorrhoea did not have detailed investigations to rule out pathology and so they cannot be classified strictly either as primary or secondary dysmenorrhoea.[84] The need for imaging or laparoscopy to identify pathology in hospital setting means that in some studies, [99;118;185] associations between risk factors and CPP may be due to differences in health care seeking behavior and referral patterns compared to community settings.[41] We feel that the associations observed for abuse, pathology and psychosocial morbidity are generalisable, because these were consistent across the studies from different geographical and age groups.

Abuse was consistently and strongly associated with all types of CPP highlighting a possible causal role for it. Similar effect of these exposures on controls with other pain in contrast with painfree controls reflects the complex psychological interactions involved in the pain process or pathway.

The mechanisms through which various pathologies might cause pain are not entirely clear. Pelvic inflammatory mediators and congestion may lead to all kinds of CPP in PID. Premenstrual symptoms are often associated with ovulatory cycles and hence release of

prostaglandins might explain the increased incidence of dysmenorrhoea in these women. Perimenopausal/postmenopausal states related hypoestrogenism is one of the explanations for dyspareunia in these women.

Women with CPP had higher neuroticism, anxiety and depression scores and more sexual problems[186] than controls, but this could be either a consequence of their pain or could increase the reporting of the pain. The case-control study design makes it difficult to distinguish between cause and effect. It seems the association of psychological morbidity with CPP could be due its link with non-organ specific pain, a conclusion supported by another meta-analytic review of psychological factors. [19]

In recent studies, abuse has been shown to be strongly associated with depression in women attending general practice,[187] so one might find that women who are abused are depressed and hence report pain more often. Similarly, it may be worry over menstrual distress that leads to heightened anxiety rather than anxiety itself that prompts dysmenorrhoea. It could also be that pathology, the root cause of dysmenorrhoea, may contribute to somatic imbalance that is expressed in raised scores on personality inventories.[188] Our review, due to the study-level nature of its analysis, is unable to disentangle these relationships. However, on the basis of strength and consistency of association we believe abuse and psychological morbidity to be at least as important as pathology for increasing the risk of CPP.

Prospective cohort studies would be ideal study designs for delineating relationship between various exposures and CPP. Sexual abuse victims have been shown to use dissociative defenses to a greater degree[189] and this increases the importance of using validated, structured assessment instruments while conducting future research on this group of women. As abuse

seems to be commoner in control groups with other pain, to elicit the true association it might be necessary to perform future studies with pain free controls only. The development of non-invasive diagnostic tools for some of the underlying somatic conditions that may account for CPP will help with unraveling of some of the risk factors further. If treatment of pathology in CPP shows no better outcome than without treatment, then probably there is a role for trials in psychological interventions. It would be rational to design intervention studies of use of psychological counseling, antidepressants and other modifiable factors in chronic pelvic pain. PID has emerged as a bigger risk factor than previously realized and it seems logical to establish this definitively and then explore preventative measures for CPP in women with definitive PID. One study design example is to measure chlamydia titers in women visiting STD clinic, treating those with high titers and then following all these women to establish whether the women who received antibiotics have reduced incidence of pelvic pain. Robust evidence from future aetiological studies could provide clues to experiment relevant treatment strategies for millions of pelvic pain sufferers.

Key gynaecological and psychosocial factors associated with CPP should be targeted in clinical evaluation of women with this symptom to individualize their management and achieve a satisfactory outcome.

(PML- Pallavi Latthe; LM- Luciano Mignini; KSK- Khalid Khan)

SECTION B: SURVEY OF PRACTICE OF LAPAROSCOPIC UTEROSACRAL NERVE ABLATION

In this section, I examine the variation in current indications and surgical techniques for performing laparoscopic uterine nerve ablation (LUNA) in Europe assess the effect of operator experience on practice. I also explore gynaecologists' 'prior' beliefs on effectiveness of laparoscopic uterosacral nerve ablation (LUNA)

Chapter 4: Variation in practice of Laparoscopic uterosacral nerve ablation: A European survey

Chapter 5: Measurement of 'prior' beliefs about effectiveness of laparoscopic uterosacral nerve ablation

CHAPTER 4: VARIATION IN PRACTICE OF LAPAROSCOPIC UTEROSACRAL NERVE ABLATION: A EUROPEAN SURVEY

4.1 ABSTRACT

Objective

To examine the variation in current indications and surgical techniques for performing laparoscopic uterine nerve ablation (LUNA) in Europe and to assess the effect of operator experience on practice.

Methods

Two groups were surveyed: I) UK gynaecologists (n=1569) and II) European Gynaecologists (n=301). A structured questionnaire was sent to the UK group and an identical email survey was sent to the European group.

Results

The questionnaire was returned by 719 (38% of 1870) of the gynaecologists contacted and 173 (24%) performed LUNA. Indications for LUNA, which included noncyclical chronic pelvic pain (CPP) (68%), dysmenorrhoea (66%), dyspareunia (39%) or endometriosis (60%), were similar across UK and rest of Europe. The European group performed LUNA more often (62% vs. 21%), completely transect the uterosacral ligaments more frequently (56% vs. 36%) and more frequently ablated at a distance of more than 2 cm from its cervical insertion (50% vs. 21%) than the UK group. More experienced gynaecologists performed LUNA more for dyspareunia (46 % vs. 26%) and endometriosis (67% vs. 47%) and they performed complete transection (45% vs.26%) more often than their less experienced counterparts.

Conclusion

There is variation in the surgical techniques of performing LUNA in Europe and the techniques vary according to operator experience.

4.2 INTRODUCTION

Chronic pelvic pain (CPP) is frequently investigated by laparoscopy. Interruption of the nerve pathways in the uterosacral ligaments has been used to alleviate pain by open abdominal or vaginal approach in the past,[29;30] but now this procedure can be performed less invasively via laparoscopic approach.[32] Originally laparoscopic surgical experts were of the opinion that because of the divergence of the sensory nerve fibres and their ganglia as they leave the uterus, the uterosacral ligaments should be vaporised as close to the cervix as possible.[32] However, recent anatomical studies have demonstrated that the greatest number of fibre bundles are at some distance from the site of attachment of the uterosacral ligament to the cervix [33;190]. Hence there is controversy about the optimal site for laparoscopic uterosacral nerve ablation (LUNA). Anatomical studies also suggest that the nerve fibres are dense at a depth of 3-15mm,[33] thus the completeness of transection of the uterosacral ligament can also be expected to have an implication for the effectiveness of LUNA.

Information on prevalent variations in the techniques regarding optimal site and depth of LUNA is currently unavailable. A previous survey showed that many UK gynaecologists claimed familiarity with the operative technique of LUNA [35] but it did not explore the differences in surgical techniques with respect to the site and depth of LUNA. Thus I undertook a large survey to examine the indications and different surgical techniques of LUNA among European gynaecologists. I was also interested in the preferences of gynaecologists for treating minimal-mild endometriosis in the context of LUNA.

4.3 METHODS

A postal survey of 1569 gynaecologists who were on the consultants' database of the Royal College of Obstetricians and Gynaecologists (RCOG) was carried out between September-October 2002 (henceforth referred to as the UK group). I emailed the same survey to 301 members of the European Society of Gynaecological Endoscopy (ESGE) who were on their email list (henceforth referred to as the European Group). I included a personalised letter to the clinicians informing them of the objective of the survey.

The survey was designed to explore the differences in practice between the UK and the rest of Europe and between gynaecologists with varying levels of experience. To obtain information on various issues relating to the practice of LUNA, I included questions on indications, number of LUNA procedures performed, willingness to participate in a randomised trial to assess effectiveness of LUNA, techniques with regard to cutting modality, distance and depth of uterosacral ligament transection and any complications they had encountered. I also asked them about their routine practice of management of minimal-mild endometriosis encountered at laparoscopy.

A Microsoft Access database was used to store the responses. The number of procedures undertaken by the gynaecologist defined experience. Following discussion with some RCOG gynaecologic endoscopy preceptors, I decided to use 20 procedures as a threshold to distinguish more from less experienced gynaecologists.

4.4 RESULTS

4.4.1 Questionnaire responses

As shown in table 4.1, of the 1569 questionnaires posted to the consultants on the database held by the RCOG, 661(42%) were returned. Of 301 email questionnaires sent to ESGE members, 58 (19%) were returned. The combined response rate was 38%. The UK group was three times more likely to respond than the European group (P<0.001). Responses to individual items were missing from some respondents. In total, 146 of the 173 (85%) respondents (86% and 83% in the UK and Europe respectively) who performed LUNA were willing to recruit women in a randomised trial to assess effectiveness of LUNA.

4.4.2 Geographical variation in practice

As shown in table 4.1, 137/ 661 UK respondents (21%) performed LUNA in contrast to 36/58 (62%) of the European group (P<0.001). Indications for LUNA included chronic pelvic pain (68%), dysmenorrhoea (66%), dyspareunia (39%) and endometriosis (60%). The indications for LUNA were similar across UK and rest of Europe as shown in table 4.2. The different cutting modalities were used in similar proportions across the continent as is evident from the results shown in table 4. 3. As compared to 32% and 75% rates (some used both) of use for laser and electrodiathermy in the UK, the rates were 36% and 78% respectively in the rest of Europe. Compared to the UK group, the European group performed complete transection of the uterosacral ligament more often (56% vs. 36%; P = 0.05) and also transected it farther away from its cervical insertion more often (50% vs. 21%; P = 0.006).

Table 4.1: Responses to the questionnaires on practice of Laparoscopic Uterosacral Nerve Ablation (LUNA) in the UK and the rest of Europe

	UK n (%)	Europe n (%)	Total n (%)
Number of questionnaires sent	1569	301	1870
Number of questionnaires received (% of sent)	Q661 (42)	58 (19)	719 (38)
Number that do LUNA (% of Q received)	**137** (21)	**36** (62)	**173** (24)
Number Willing to Enter Patients into Trial (% of those who perform LUNA)	116 (86)	30 (83)	146 (85)
Speciality: Obstetrics Gynaecology	128(93)	29 (81)	157 (91)
Other	09 (07)	07 (19)	16(09)
Number of Procedures Performed in Career			
Fewer than 20	45 (33)	13 (36)	58 (32)
20-49	60 (44)	10 (28)	70 (42)
50-99	16 (12)	4 (11)	20 (12)
100 or more	16 (12)	6 (17)	22 (13)
Not stated	0	3 (8)	3(2)

4.4.3 Complications of LUNA

Of the 173 gynaecologists who performed LUNA, 169 responded to the question regarding complications with LUNA. Of these, 18 (13%) had encountered complications of LUNA; 16 had come across short-term problems and 2 had seen long-term complications. The commonest complication stated was bleeding by six respondents and two respondents reported persistent pain. No one reported ureteric damage, prolapse or laparotomy.

Table 4.2 Comparison of indications for laparoscopic uterosacral nerve ablation (LUNA)

Indications	UK N (%) 137	Europe N (%) 36	Total N (%) 173	More Experienced (112)	Less Experienced (58)
Chronic Pelvic Pain	92 (67)	25 (69)	117 (68)	72 (64)	42 (72)
Dysmenorrhoea	93 (68)	21 (58)	114 (66)	74 (66)	38 (66)
Dyspareunia	52 (38)	16 (44)	68 (39)	52 (46)	15 (26)
Endometriosis	82 (60)	21 (58)	103 (60)	75 (67)	27 (47)
Endometriosis: mild only	24	01	25	15	10
Endometriosis: mild or moderate	14	03	25	14	03
Endometriosis: moderate only	07	01	08	05	03
Endometriosis: moderate or severe	10	05	15	13	02
Endometriosis: severe only	08	07	15	07	07
Endometriosis: any severity	19	04	23	21	02
Other Pelvic Pain	03 (2)	01 (3)	04 (2)	04 (2)	00

4.4.4 Effect of experience on practice

Table 4.3 compares various aspects of LUNA studied in the survey with respect to experience of the operating gynaecologist. Gynaecologists who had performed more than 20 LUNA operations used it more for dyspareunia (46% vs. 26%; P=0.01) and for endometriosis (67% vs. 47%; P = 0.01) than less experienced gynaecologists. They performed complete transection more often (45% vs.26%; P=0.02) than their less experienced counterparts.

Table 4.3: Laparoscopic uterosacral nerve ablation (LUNA) techniques, management of minimal-mild endometriosis and comparison of techniques by experience

	UK N (%) 137	Europe N (%) 36	Total N (%) 173	More Experienced 112	Less Experienced 58
Treatment of minimal-mild endometriosis					
Ablation with other modality	108 (79)	25 (69)	133 (77)	88 (79)	43 (74)
Ablation exclusively	76 (55)	15 (42)	91 (53)	59 (53)	31 (53)
Excision	23 (17)	15 (42)	38 (22)	27 (24)	10 (17)
Excision exclusively	8 (06)	5 (14)	13 (08)	10 (9)	3 (05)
Medical treatment	39 (28)	7 (19)	46 (27)	29 (26)	16 (28)
Medical treatment exclusively	17(12)	0	17 (10)	11 (10)	06 (10)
Cutting modality used					
Laser	44(32)	13 (03)	57(33)	41 (37)	14 (24)
Laser exclusively	20 (15)	8(22)	28 (16)	21 (19)	7 (12)
Electrodiathermy	103(75)	28 (78)	131(76)	82 (73)	46 (79)
Electrodiathermy exclusively	62 (45)	15 (42)	77 (45)	43 (38)	32 (55)
Scissors	20 (15)	8 (22)	28 (16)	19 (17)	9 (16)
Scissors exclusively	3 (02)	6 (17)	9 (05)	1 (01)	2 (03)
Harmonic Scalpel	15 (11)	03 (08)	18 (10)	13 (12)	5 (09)
Harmonic scalpel exclusively	8 (06)	00	8 (05)	5 (04)	3 (05)
How uterosacral ligaments (USL) are transected					
Completely	47 (36)	20 (56)	67 (41)	50 (45)	15 (26)
Partially	82 (64)	16 (44)	98 (59)	58 (52)	39 (67)
Distance from cervix for USL transection					
Less than 1cm	32 (23)	04 (11)	36 (21)	27 (24)	9 (16)
1-2 cm	75 (55)	14 (39)	89 (51)	54 (48)	34 (59)
More than /= 2 cm	30 (21)	18 (50)	48 (28)	31 (28)	15 (26)

(The responses to some items were missing or more than one and hence the figures do not add up to the total number of respondents for some questions)

4.4.5 Practice in minimal-mild endometriosis

The approach to treatment of minimal-mild endometriosis encountered at laparoscopy was in favour of ablation. Of the 173 respondents, 133 (77%) ablated endometriosis. However 38/173 (22%) excised it and 46/173 (27%) treated it medically. Some used one or more of the

above options concurrently. Compared to 108/137 (79%) of the UK gynaecologists, 25/36 (69%) of the other European gynaecologists performed ablation in mild endometriosis. In the UK, 23/137 (17%) performed excision of which 8 respondents (6%) exclusively did only this for mild endometriosis. In contrast, the comparable figures for the rest of Europe were 15/36 (42%) and 5/36 (14%) respectively. Among the UK group, 39/137(28%) offered medical treatment and 17(12%) of these offered only this option of treatment. In the European group, 7/36 (19%) offered medical treatment but none of them offered it exclusively without surgical option.

4.5 DISCUSSION

A previous survey on this topic [35] was carried out on a limited sample of members of the British Society of Gynaecological Endoscopy only. It did not collect details of the methods of performing LUNA or current methods of managing minimal-mild endometriosis. The current survey was designed to obtain more in-depth knowledge of the practice across Europe. I used a short questionnaire and prepaid envelopes. I did not have enough resources to implement other strategies like coloured ink for the questionnaires, recorded first class post delivery for questionnaires, reminder letters with questionnaires for non respondents, monetary incentives and other such factors known to be associated with higher response[191]. This has a potential for introduction of bias by the "responding group". There has been a trend towards reduction in response to questionnaire surveys.[192] Thus it is not surprising that although I made all efforts within our means to enhance the return rate, I received replies from only 38% of gynaecologists.[193;194]

This analysis and interpretation are limited due to a differential and low response rates. This is also the reason for inability to stratify the results by individual countries. The most likely reason for the differential responses between UK and the rest of Europe is the difference in the types of groups surveyed. All O & G consultants in the UK most of who are generalists were surveyed in contrast to gynaecological endoscopists in the rest of Europe. The differences in response rates could be due to the different methods of returning the questionnaires, which was by freepost in the UK whereas it was by email, or fax in the rest of Europe. There are several plausible reasons for non-response, including out of date addresses, lack of time in busy practice. It could also reflect on the poor general attitude of the specialty towards surgical research and evidence based practice. I observed that the proportion of gynaecologists in the UK performing LUNA in this survey was 24% compared to 45% in the last survey. An important difference between this survey and the previous one[35] is that the first survey was on members of the BSGE which is a more focused group with special interest in Endoscopy than the group in the current survey comprising of all the UK consultants in obstetrics and gynaecology. The absolute numbers performing LUNA were 137 in the current survey versus 113 in the previous survey[35] indicating that perhaps the UK consultants who are members of BSGE continue to perform LUNA while other non-member UK consultants rarely do so. Our finding that higher proportions of European gynaecologists perform LUNA and excision of endometriosis could be due to the differences in the groups surveyed as alluded to before. It could also indicate different pattern of training in minimal access surgery. The difference in the depth and the distance of transection between the UK and the rest of Europe is difficult to explain but perhaps implies differences in the beliefs regarding the anatomy of the nerve plexuses. It is important to emphasise the apparent safety of the LUNA

procedure from the fact that none of the respondents reported ureteric damage or prolapse or laparotomy to control bleeding, which have been reported anecdotally.[195;196]

A high proportion of gynaecologists wish to participate in a clinical trial to assess the clinical effectiveness of LUNA. This indicates that there is widespread clinical uncertainty in that the technique has been introduced without reliable evidence of effectiveness and so the opinion regarding its use is uncertain and variable. There is a need for an adequately powered, properly randomised trial to assess effectiveness of LUNA, a message that has been highlighted in several recent publications.[39;197;198] This survey suggests that such a trial should also take into consideration the impact of differing prevalent techniques for this procedure.

CHAPTER 5: MEASUREMENT OF 'PRIOR' BELIEFS ABOUT EFFECTIVENESS OF LAPAROSCOPIC UTEROSACRAL NERVE ABLATION

5.1 ABSTRACT

Objective

To explore gynaecologists' 'prior' beliefs about effectiveness of laparoscopic uterosacral nerve ablation (LUNA).

Methods

A structured survey was used to gather information from participants on the distribution of their prior beliefs regarding the effects of LUNA on pelvic pain using a 10 point visual analogue scale (VAS). 'Prior' beliefs were captured both graphically and textually by responses to a questionnaire.

Results

None of the 25 gynaecologists responding to the questionnaire stated that LUNA would increase pain, while 2/25 gave numerical answers suggesting they believed that the intervention would worsen the pain. The most widely held 'prior' belief, reflected in both questionnaire and numerical responses was that LUNA would have a small beneficial effect on pain. The credible limits of this belief were compatible with large reductions in pain as 60% of respondents believed a three-point improvement on VAS to be plausible. The standard deviations of expected mean change in VAS due to LUNA ranged from 0.52 to 1.64.

Conclusion

Among gynaecologists, there is a variation in beliefs about the effects of LUNA on pelvic pain, ranging from substantial benefit to slight harm.

5.2 INTRODUCTION

It is ethical to initiate a clinical trial when there is collective clinical equipoise about the effectiveness of the available treatments.[36] Prior beliefs are formed from indirect evidence (laboratory studies, epidemiology, extrapolation from similar treatments) and direct evidence (clinical trials, perhaps of an inconclusive nature). Surveys eliciting dichotomous 'yes' and 'no' responses to a question about effectiveness are limited because clinicians' beliefs about a treatment usually amount to rather more than just "I believe it is effective" (or the converse). They may believe the treatment to be greatly or marginally beneficial (or harmful). Different clinicians will admit varying degrees of uncertainty. Some may be rather more certain than the evidence apparently warrants, others may be uncertain to a degree that they believe the treatment may, in due course, turn out to be either greatly beneficial or harmful.

Observing differences in practice or, as explored here, formal measurement of beliefs about effectiveness can provide a clearer picture than the dichotomous responses. Formal measurements of 'prior' belief provide respondents with an opportunity to signal the magnitude of the expected effects and the relative probabilities of effects of different sizes. However, the published examples of collecting such information are sparse, in both obstetrics and gynaecology and in medicine.[199]

A recent survey has indicated that there is wide variation in the practice and use of laparoscopic uterosacral nerve ablation (LUNA) for treatment of chronic pelvic pain among clinicians, suggesting that collective clinical equipoise is present. The technique has been introduced without definite evidence but opinion regarding its use has not yet solidified, as 81% of gynaecologists performing LUNA stated their willingness to recruit patients in a trial

to assess effectiveness of LUNA.[35] However, this survey does not provide information on distribution of beliefs concerning effectiveness of LUNA in alleviating pelvic pain. Therefore a structured survey to formally document the range of beliefs on effectiveness of this surgical treatment was undertaken.

In this chapter, I illustrate a method of collecting 'prior' beliefs of clinicians about possible effectiveness of an intervention.

5.3 METHODS

A survey was administered with oral explanation to a 'captive' group of participants in a Collaborators' meeting of the LUNA trial[200] in November 2002. The survey questionnaire is provided in the appendix. The aim was to obtain distribution of their beliefs about the likely effectiveness of LUNA in alleviating pelvic pain, compared to placebo i.e. laparoscopy alone. An example of how the survey of beliefs was explained is as follows: Suppose a clinician is asked to predict what the true benefit of LUNA is likely to be in reducing pain in suitable patients. Pain is to be measured using a Visual Analogue Scale (VAS) from 0 to 10, with 0 indicating no pain and 10 indicating greatest conceivable pain. The outcome to be predicted is the mean extra change (before - after) in VAS scores in patients receiving LUNA, compared to the mean change in patients receiving placebo treatment i.e. laparoscopy alone. Thus, if the true mean change in VAS score in patients treated with LUNA is a reduction of 1.3 in pain score, while the true mean change in similar patients treated with placebo is an increase of 0.2, then the true benefit from LUNA would be 1.5. On this scale, it is arbitrarily decided that the improvement of 0.5 to 1.5 points would be a small benefit, an improvement of 1.5 to 2.5 points to be a moderate benefit, and an improvement of 2.5 points or more to be a substantial benefit.

Figure 5.1: A sample of a graphical elicitation of beliefs about the likely true effect of laparoscopic uterosacral nerve ablation (LUNA) compared to placebo (laparoscopy alone), in patients with chronic pelvic pain, as measured by change in 10-point visual analogue scale (VAS) scores (see text for details). This approach provided numerical estimation of 'prior' beliefs.

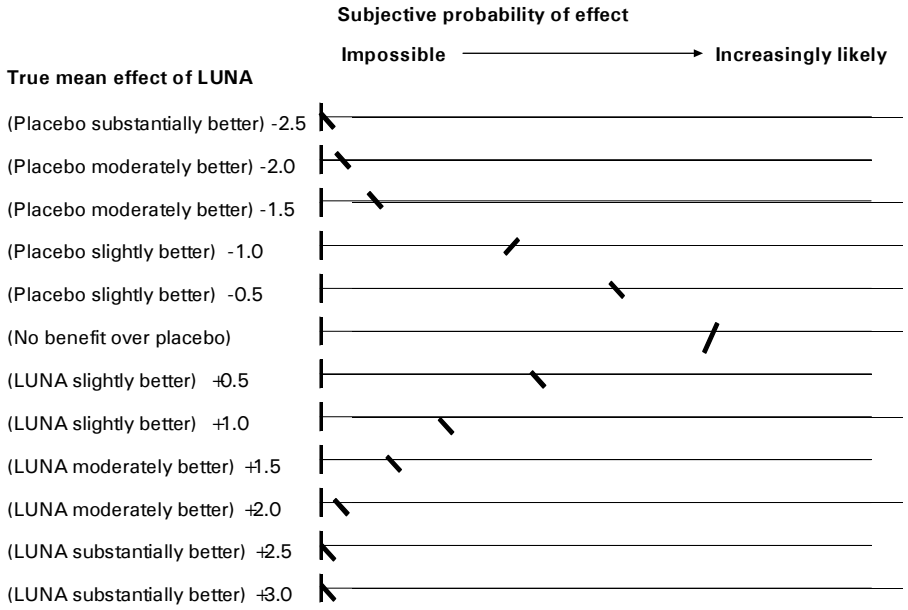


Figure 5.1 provides an example of how the plots of beliefs were drawn. The participants were briefed on filling the numeric scale as follows: If the participant believes that the most likely benefit from LUNA in suitable patients is (on average) zero (i.e. negligible benefit or harm), then he/she should first mark the zero benefit line somewhere towards the right of the page. If he/she believes that a mean 1.5 point or more disadvantage (i.e. LUNA moderately worse compared to placebo) is extremely unlikely, she should mark the –1.5 and –2.0 lines at or very close to the left end. Similarly, if he/she believes a mean benefit of 3.0 points or more (i.e. LUNA substantially better compared to placebo) is extremely unlikely, he/ she would mark the last line at the left-hand end. He/she then needs to consider how much less likely than zero

are mean changes of –0.5 and +0.5 are. Suppose he/she thinks +0.5 (i.e. a small benefit) is about half as likely, while –0.5 (i.e. a small harm) is about a quarter as likely, then he/she should mark these lines accordingly. All of the above details were briefly explained by a short presentation in the meeting. This procedure produced a distribution that represents the respondent's beliefs - a "Bayesian prior".

We also asked the participants to describe their beliefs on the true mean effect of LUNA on pain, compared to standard treatment, by selecting a response from a number of statements or writing their own statement of beliefs. The graphical representations of the beliefs were 'triangulated' with the textual statements to assess their compatibility. We used the respondent's chosen statement describing their beliefs as a way of checking whether an elicited graphical representation really could be said to represent the respondent's beliefs. To this end, three assessors (see acknowledgement) independently assessed the compatibility of textual statement and graphical representation for each respondent. The responses were processed and analysed using a spreadsheet. The mean weighted change in VAS was calculated for each respondent by multiplying the VAS with its likelihood (distance from left end in cm) and then taking average of all the values obtained.

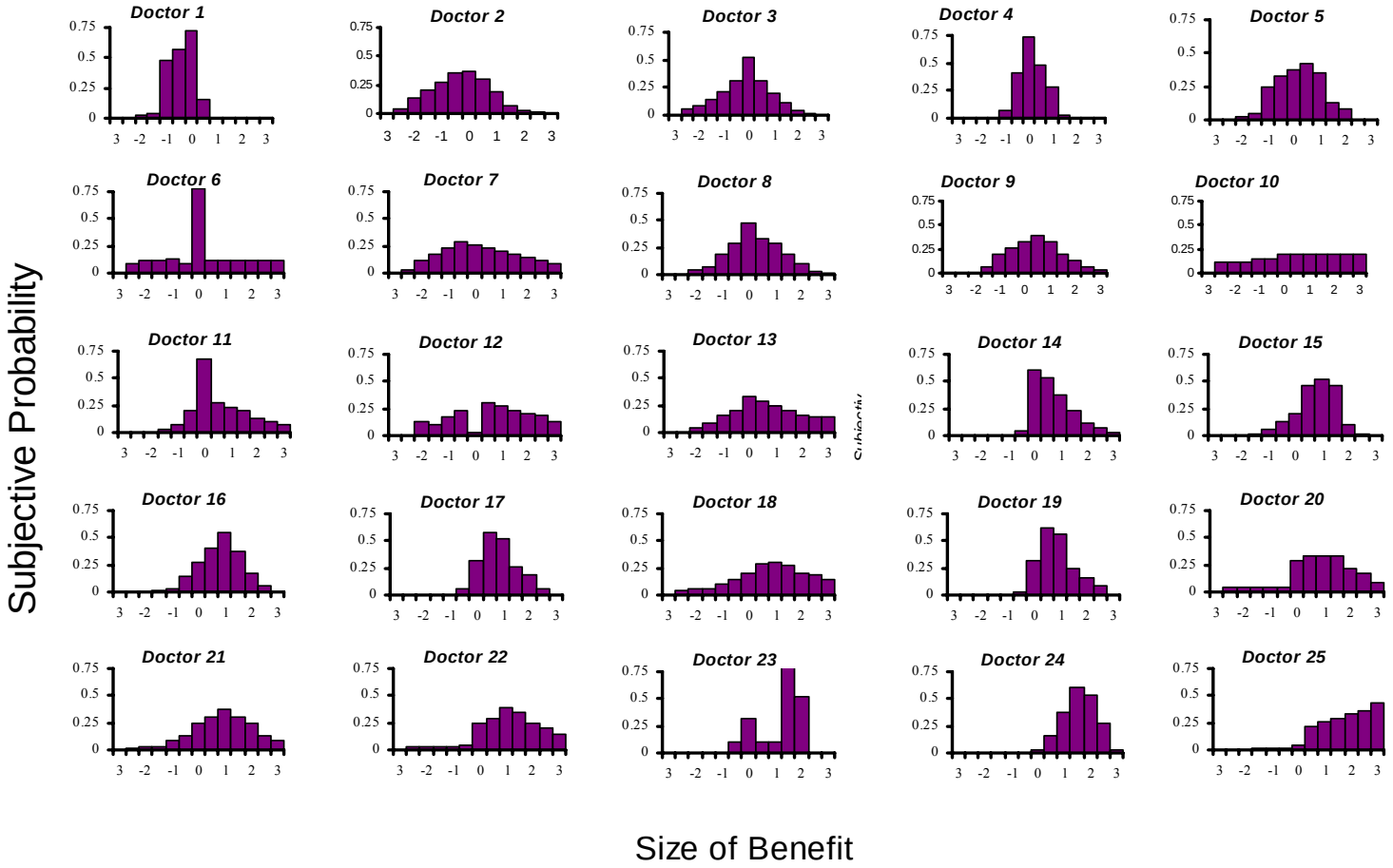
5.4 RESULTS

The survey was distributed to 30 gynaecologists of whom 25 responded. Their distribution of the beliefs on basis of the textual responses is given in table 5.1. The distribution of numerical 'prior' beliefs by graphical representation is summarised in figure 5.2. The range of means was –0.40 to 1.81. The standard deviations of expected mean change in VAS due to LUNA ranged from 0.52 to 1.64.

Table 5.1: Clinicians' textual 'priors' beliefs on the effect of laparoscopic uterosacral nerve ablation (LUNA) on pain

Response	Number of clinicians (N=25)
Harmful or no benefit	0
Negligible benefit or harm (near 0 on VAS)	5
Slightly beneficial (0.5 to1.5 reduction)	12
Moderately beneficial (1.51-2.5 reduction)	4
Substantially beneficial (2.5 or more reduction)	2
Beneficial but unsure how much	0
Unsure whether beneficial or not, but not harmful (0 or more reduction)	1
Unsure whether harmful or beneficial	1
Other (own description if none fits well)	0

Figure 5.2: Graphical representation of numerical ‘prior’ beliefs

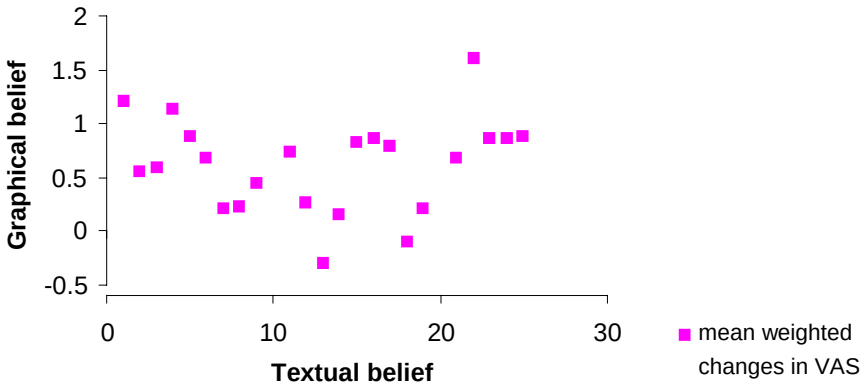


The graphical representations of the beliefs when 'triangulated' with the textual statements as shown in figure 5.3, showed reasonable compatibility in that none were judged to be totally incompatible by any of the three assessors.

The observed difference in mean change in VAS between the 'compatible' and 'some incompatibility' group was 0.27. The mean changes in VAS in both groups, however, is less than 2 points change on the VAS, which is the minimal clinically relevant difference assumed in the LUNA trial. The following results pertain to those respondents judged compatible on numeric and textual descriptions by all three assessors (10/25): expected mean change in VAS ranged from a small (0.1 points) increase to a substantial decrease (1.8 points). The expected mean change in VAS due to LUNA on the numerical representation was 0.8 points reduction. The most pessimistic of these respondents predicted a mean change of 0.1 increase while the most optimistic respondent predicted a mean change of 1.8 point reduction in VAS scores. In responses where some incompatibility (15/25) between graphical and textual representation was observed (7/25 were thought to be compatible by two of the three assessors), the mean benefit was slightly less at a 0.51 point decrease on VAS. The observed difference in the mean change in VAS between the groups was 0.27 (confidence interval –0.17 to 0.72) with the 'compatible' group being more optimistic of the benefits of LUNA than the incompatible group, but this could simply be due to chance (P = 0.21).

Figure5. 3 shows the correlation of textual and graphical beliefs with regards to the effects of LUNA.

Figure 5. 3: Agreement between graphical and textual representation of beliefs of effects of laparoscopic uterosacral nerve ablation (LUNA)



5.5 DISCUSSION

There is variation in beliefs on the effectiveness of LUNA in pelvic pain, ranging from substantial benefit to slight harm. This study represents one of the very few attempts at formal collection of 'prior' beliefs from participants in a randomised controlled trial and possibly the first in gynaecological surgery. There might have been more variation if the sample surveyed was more representative of the general clinical opinion. The majority of respondents felt that LUNA would benefit the patient in terms of change in VAS but there was wide variation in the expected level of benefit. The clinicians did not agree about the benefits of LUNA and there was collective and reasonably balanced uncertainty[201] - the main requirement for a randomised trial.[36] The measurement of prior beliefs can be used for calculation of sample sizes as well as in Bayesian analysis of clinical trials.[202;203] A double blind randomised controlled trial to assess effectiveness of LUNA is currently recruiting women with pelvic pain in the UK.[200] We will be able to update these beliefs when the LUNA trial results are available and see whether clinicians' beliefs change in line with Bayesian formulae.

The elicitation process used in the study was designed to be quickly self-completed with a minimum of exploration. The use of a textual statement to 'triangulate' with graphical priors is, a useful avenue to pursue, but one that is in need of further work. About half of elicited 'priors' were unanimously agreed to be compatible with the textual statements. This performance may be in part due to remediable problems with the elicitation process, but it may point to a more fundamental truth - that for many respondents, substantial effort (from researcher and respondent) may be required before a valid prior can be elicited. The effort may include any or all of the following: re-examination of the evidence, extensive exploration of the task, feedback of the implications of elicited priors with the opportunity for revisions, discussion with colleagues etc. It would also have been useful to know at what expected level of benefit would the clinicians be inclined to offer LUNA to their patients.

Methods of documenting distribution of beliefs about likely effects of a treatment need further development.[204;205] Our survey is one such step in this direction. It would also be interesting for methodological researchers to compare the graphical and textual methods of collecting "Bayesian priors" and explore the factors that potentially will lead to better representation of the clinicians' opinions.

SECTION C: EVIDENCE ON EFFECTIVENESS OF LUNA AND LUNA TRIAL PROTOCOL

In this section I have endeavored to determine the effectiveness of neuroablation in CPP by means of a Cochrane systematic review and develop a protocol for a prospective randomised controlled trial to assess the effectiveness of LUNA in CPP

CHAPTER 6: EFFECTIVENESS OF NEUROABLATION IN RELIEVING CHRONIC PELVIC PAIN (DYSMENORRHOEA): UPDATE OF COCHRANE SYSTEMATIC REVIEW

6.1 ABSTRACT

Objective

To assess the effectiveness of surgical interruption of pelvic nerve pathways as treatment for chronic primary and secondary dysmenorrhoea.

Methods

The Cochrane Menstrual Disorders and Subfertility Group trials register (searched 9 June 2004), CENTRAL (The Cochrane Library Issue 2, 2004), MEDLINE (1966 to Nov 2003), EMBASE (1980 to Nov 2003), and CINAHL (1982 to Oct 2003) were searched. Attempts were also made to identify trials from the metaRegister of Controlled Trials and the citation lists of review articles and included trials. The inclusion criteria were randomised comparisons of surgical techniques of interruption of the pelvic nerve pathways (both open and laparoscopic procedures) for the treatment of primary and secondary dysmenorrhoea. The main outcome measures were pain relief and adverse effects. The data was pooled in meta-analysis to obtain Peto odds ratios with 95% confidence intervals.

Results

Nine RCTs were included in the systematic review. There were two trials with open presacral neurectomy (PSN); all other trials used laparoscopic techniques. For the treatment of primary dysmenorrhoea, laparoscopic uterosacral nerve ablation (LUNA) at 12 months was better when compared to a control or no treatment (Odds Ratio or OR 6.12; 95% confidence interval /CI 1.78-21.03). The comparison of LUNA with PSN for primary dysmenorrhoea showed that at 12 months follow up, PSN was more effective (OR 0.10; 95% CI 0.03-0.32). In secondary dysmenorrhoea, along with laparoscopic surgical treatment of endometriosis, the addition of

LUNA did not improve the pain relief (OR 0.77; 95% CI 0.43-1.39) while PSN did (OR 3.14; 95% CI 1.59-6.21). Adverse events were more common for PSN than procedures without PSN (OR 14.6; 95% CI 5-42.5).

Conclusion

The evidence to recommend the use of nerve interruption in the management of dysmenorrhoea, regardless of cause, is still insufficient. Methodologically sound and sufficiently powered RCTs should be undertaken in future.

6.2 INTRODUCTION

Dysmenorrhoea is a very common gynaecological complaint that can affect up to 50% of women. Although the use of both OCPs and NSAIDS[206;207] has been very successful, there is still a 20 to 25% failure rate.[21;208] Surgery has been a treatment for cases of dysmenorrhoea that fail to respond to medical therapy. When diagnostic laparoscopy is indicated, laparoscopic uterine nerve ablation (LUNA) and presacral neurectomy (PSN) are two surgical treatments that have become increasingly utilised in recent years and as described in chapter 1 (section 1.4), both interrupt the majority of the cervical sensory nerve fibres, thus diminishing uterine pain.[32] Observational studies have supported the use of LUNA for both primary and secondary dysmenorrhoea with either complete relief or substantial reduction in menstrual pain in the majority of subjects.[209-215] PSN involves the interruption of a greater number of nerve pathways than LUNA, therefore it is a more complex procedure than LUNA, and entails more operative risk.[216] However, despite these drawbacks the use of PSN is also supported by observational studies showing similar results to that of LUNA for both primary and secondary dysmenorrhoea. [217;218]

In order to determine the effectiveness of surgical interruption of pelvic nerve pathways (both open and laparoscopic UNA or PSN), I compared UNA/PSN to no treatment (where the control group is either no treatment or a recognised treatment which is also performed in the intervention group) and also explored if the effects varied according to: 1) primary or secondary dysmenorrhoea and 2) UNA or PSN.

6.3 METHODS

A protocol for updating Cochrane reviews was adopted.[219]

6.3.1 Data sources

All reports that described (or might describe) randomised controlled trials of surgical interruption of pelvic nerve pathways (both open and laparoscopic) in the treatment of dysmenorrhoea were obtained using the search strategy developed by the Menstrual Disorders and Subfertility Group. Following were searched:

(1) The Cochrane Menstrual Disorders and Subfertility Group trials register (searched 9 June 2004).

(2) The Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, Issue 2, 2004.

(3) The electronic databases MEDLINE (1966 to April 2004), EMBASE (1980 to April 2004), and CINAHL (1982 to April 2004) using OVID software.

(4) The metaRegister of Controlled Trials.

(5) Citation lists of review articles and all included and excluded trials.

In most cases, the first or corresponding authors of included trials were contacted for additional information. The following keywords were used to search the above databases: dysmenorrhea, dysmenorrhoea, painful menstruation, pelvic pain/surgery/, laparoscopy, surgical procedures, laparoscopic denervation, uterine nerve ablation, presacral neurectomy.

6.3.2 Study selection

All prospective randomised controlled trials comparing surgical interruption of pelvic nerve pathways (both open and laparoscopic UNA and PSN) to no treatment, or other treatment, for

women with primary or secondary dysmenorrhoea were considered. Two reviewers (MP and PL) performed the selection of trials for inclusion after employing the search strategy described above. These trials included women of reproductive years with primary dysmenorrhoea (no identifiable organic pathology) or secondary dysmenorrhoea (identifiable specific pathology). Laparoscopic and open techniques are combined for these interventions, as there is some evidence to suggest they have similar ranges of pain relief for dysmenorrhoea.[211;217] The outcome measures we looked at were: (1) Pain relief after treatment (at 6 months and more): Measurement with the VAS or other validated pain scales were studied and where these are not used other scales or dichotomous data as well as changes in pain intensity were also considered. (2) Adverse effects from the treatment (dichotomous data, number of participants with side effects) (3) Quality of life

6.3.3 Quality assessment of included trials

All assessments of the quality of trials and data extraction were performed independently by the two reviewers (MP and PL) using forms designed according to Cochrane guidelines. A third reviewer (NJ) resolved any discrepancies. Additional information on trial methodology and/or actual original trial data was sought from the authors of trials which appeared to meet the eligibility criteria but had aspects of methodology that were unclear, or where the data were in a form unsuitable for meta-analysis.

We assessed the trials for the following quality criteria: method of randomisation, quality of allocation concealment until randomisation, presence or absence of blinding to treatment allocation after randomisation, explicit statement about the number of women randomised,

excluded or lost to follow up, whether an intention to treat analysis was done and whether a power calculation was done.

6.3.4 Data synthesis

Attempts were made to dichotomise the pain relief data in order to do sub-group analyses. Other pain scales were collapsed into dichotomous outcomes, pain relief or no pain relief. For example. if pain relief was measured on a scale of 0 (no pain)-5 (maximum pain imaginable), 0-2 was considered as pain relief. [11]

Statistical analyses were to be performed according to the statistical guidelines for reviewers in the Menstrual Disorders and Subfertility Review Group.[220] For the dichotomous data, results of each study were expressed as an odds ratio with 95% confidence intervals and combined for meta-analysis with RevMan software using the Peto-modified Mantel-Haenszel method. The outcome of pain relief is considered a positive consequence of treatment therefore a higher proportion of women with pain relief is considered a benefit (OR>1), whereas the outcome of adverse effects is a negative consequence therefore higher numbers are considered to be detrimental (OR <1). This needs to be taken into consideration when the summary graphs are viewed.

6.4 RESULTS

6.4.1 Literature identification, selection and characteristics

A total of 288 articles were identified. Ten RCTs involving surgical interruption of the pelvic nerve pathways as treatment for dysmenorrhoea were selected. Out of these, one trial was

excluded from the review. The excluded trial[221] compared laser laparoscopy (involving LUNA and surgical treatment of endometrial implants) to no treatment (expectant management only). Therefore due to the lack of a control group that had laser vaporisation only, the outcome data as a result of LUNA surgery could not be distinguished from the outcomes resulting from the laser vaporisation.

Nine RCTs met the criteria for inclusion in the review. All the studies described clear inclusion and exclusion criteria (see appendix Table 7.1 of characteristics of included studies). All the trials included women between the ages of 18 to 50 years of age, and the majority of the studies' participants appear to have sought medical assistance for dysmenorrhoea. None of the trials gave clear information on the source of their women or how they were recruited into the studies. Two of the studies[11;222] looked exclusively at women with primary dysmenorrhoea, excluding all participants with any pelvic pathology using a diagnostic laparoscopy. One study included women with dysmenorrhoea related to uterine myoma.[223] One study included two patient groups, women with primary dysmenorrhoea and women with secondary dysmenorrhoea associated with endometriosis.[224] The other studies included women with secondary dysmenorrhoea associated with endometriosis. Two of the included studies involved women with endometriosis included those with an AFS classification of stage III - IV endometriosis [225;226] one trial included women with only stage I – III, [227] and the other trials included all stages I – IV. [224;228;229]

Two trials[11;224] compared laparoscopic uterine nerve ablation with diagnostic laparoscopy only, for women with primary dysmenorrhoea. Three trials [224;227;228] combined LUNA and laser treatment of endometriosis implants as surgical techniques and compared them with laser

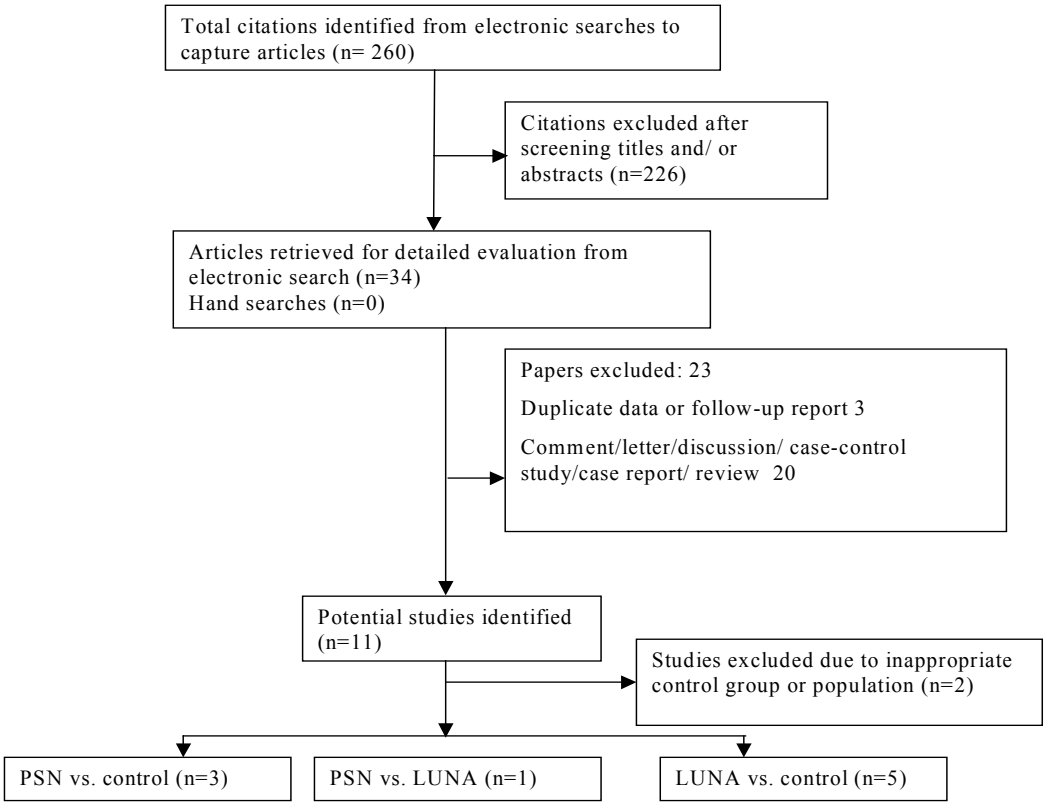
treatment only, for women with secondary dysmenorrhoea. One trial compared LUNA and laparoscopic bipolar coagulation of uterine vessels with laparoscopic bipolar coagulation of uterine vessels only in women with dysmenorrhoea secondary to uterine myomas.[223] Three trials compared presacral neurectomy combined with surgical treatment of endometriosis versus surgical treatment of endometriosis only as a control for treatment of secondary dysmenorrhoea. [225;226;229] The final included trial compared LUNA and LPSN as treatments for primary dysmenorrhoea. [222]

The primary outcome in all trials was pain relief. This was measured and reported in a variety of ways. Two studies used a 5-point pain scale.[11;222] VAS were also used in some of the trials, however the length of the scales varied. One trial used a 10cm VAS as well as a 10-point pain scale.[227] One study used a 10 point VAS (but only reported dichotomised data) and a multidimensional scale. This scale comprised 3 components: limitation of working ability, coexistence of systematic symptoms and need for analgesics.[225] One study used a 100mm VAS[230], and another simply reported whether pain relief did or did not occur. [226] The majority of studies also reported side effects; these were reported as the number of women who suffered any specific adverse events for example constipation.

Outcomes were assessed at various time periods following surgery. In two trials [223;226], participants were assessed at 6 months, although one trial[226] stated that participants were followed for a minimum of 42 months. One trial assessed participants at 3 and 6 months.[227] In two trials [222;224] participants were assessed at 3 and 12 months. Two trials[228;229] assessed participants at 6 and 12 months, although one of this[228] extended follow up of some women for

up to 36 months. In the final two trials [11;225] all participants were followed up for at least 12 months.

Figure 6.1: Study selection process for systematic review of neuroablation in dysmenorrhoea (LUNA- laparoscopic uterosacral nerve ablation; PSN- presacral neurectomy)



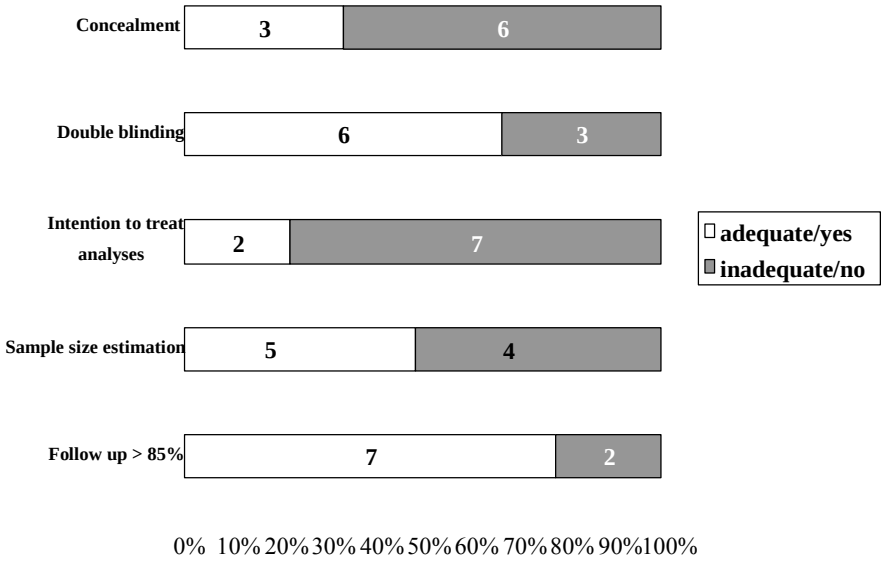
6.4.2 Methodological quality of included studies

All the included studies assessed comparability of the treatment and control groups at baseline, no appreciable differences in age, parity, condition or pain scores were reported.

Five of the trials had adequate concealment prior to allocation. [224;226-229] Two studies had inadequate concealment, [11;223] due to the use of case numbers in the allocation process. Double blinding was used in six studies with blinding of the patient and the investigator, [11;223;224;227-229] one was single blind, [226] and for the other trials blinding was unclear. Two trials [224;228] included an intention to treat analysis. A power calculation was performed in five studies. [224;225;227-229] In

one study, although the power calculation was done, the trial was stopped before the number of women needed was reached. [226]

Figure 6.2: Methodological quality of studies included in the systematic review of effectiveness of neuroablation in dysmenorrhoea (data presented as 100% stacked bars; figures in the stacks represent number of studies).



Follow up and withdrawal rates varied among trials. Two trials reported no withdrawals or losses to follow up.[222;226] In four trials less than 15% of randomised participants withdrew or were lost-to-follow up.[223;225;227;229] In one trial of 180 participants only 116 were analysed; 29 became pregnant, 14 used OCP, 15 (8%) were lost-to-follow up, six women withdrew for other reasons. [228] In another trial of 18/39 women (46%) were excluded from analysis due to pathology at follow up. [11]

There were two trials with open PSN and none of open uterosacral nerve ablation.

6.4.3 Effectiveness of neuroablation

6.4.3.1 LUNA versus control

There were two studies comparing LUNA versus control for primary dysmenorrhoea.[11;224] At 6 months or less follow up there was no significant difference in pain relief (2 RCTs; n = 68; OR 1.43, 95% CI 0.56 to 3.69). However longer-term pain relief (assessed at 12 months) showed a significant difference between the experimental and control groups (2 RCTs; n = 68; OR 6.12, 95% CI 1.78 to 21.03).

One trial [224] reported additional outcomes related to quality of life following treatment. Satisfaction rates at 12 months showed no difference between the groups (LUNA 15/18 vs. control 22/32; p>0.05). Information on the need for further surgery (one hysterectomy in the LUNA group and 2 in the control group), and the need for additional treatment (3 women in the no LUNA group were using OCP or Mirena), also indicated no difference between the two groups.

There were three trials that compared LUNA with surgical treatment of endometriosis versus surgical treatment of endometriosis only. [224;227;228] At 6 months or less follow up there was no significant difference in pain relief (3 RCTs; n = 190; OR 1.03, 95% CI 0.52 to 2.02). Longer-term pain relief also showed no significant difference between groups (2 RCTs; n = 217; OR 0.77, 95% CI 0.43 to 1.39).

One trial [227]reported comparable baseline pain scores, and at six months post-operative showed no significant difference between the experimental and control groups for dysmenorrhoea pain scores on the VAS scale (Mann-Whitney test, p=0.21). On the 10cm VAS

scale the experimental group pain scores at 6 months had a median of 4.8 (range 1-9.0), while the control pain scores had a median of 3.0 (range 0-9.8).

Another trial found no significant difference in pain relief between the treatment and control group following extended follow up of up to 36 months (1 RCT; n=116; OR 0.84, 95% CI 0.39 to 1.80)[228]. The 12-month Kaplan-Meyer cumulative probability of recurrence of moderate to severe dysmenorrhoea was 33.7% for the experimental group and 27.55% for the control group. An intention to treat analysis on subject satisfaction showed that 68% of the experimental group and 73% of the control group were very satisfied or satisfied with treatment, while 32% of the experimental group and 27% of the control group were uncertain, dissatisfied, or very dissatisfied with treatment. No adverse effects were reported for either group. In this trial, additional quality of life data was collected. There were significant mean improvements in all scales; however at one year follow up the trial reported that there were no significant differences between groups.

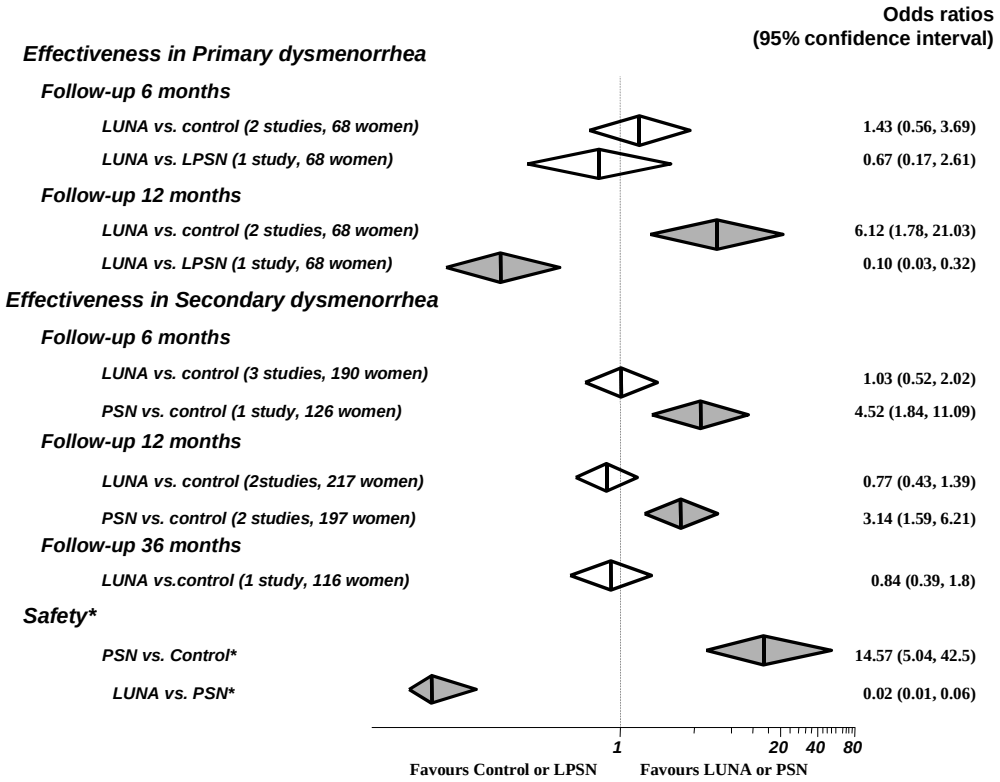
6.4.3.2 PSN versus control

Three trials compared PSN with surgical treatment of endometriosis versus surgical treatment of endometriosis only.[225;226;229] At 6 months (or less) follow up there was no significant difference in pain relief (1 RCT; n = 126; OR 1.23, 95% CI 0.50 to 3.00). Pain relief measured up to 12 months following treatment also showed no significant difference between treatment groups (2 RCTs; n = 197; OR 1.38, 95% 0.67 to 2.83). However in one trial, the authors originally collected information on the incidence, site and severity of pain and in analysis split their results into separate areas of pain.[225] They interpreted their findings as showing a significant difference in the recurrence of midline abdominal dysmenorrhoea, with the

experimental group reporting what the authors interpreted as a significantly lower recurrence (p=0.06). There was a strong significant difference in the proportion of women with adverse effects from the treatment; the control group reported none but the PSN group reporting 13 women with constipation, 3 with urinary urgency and 2 experienced a painless first stage of labour (OR 14.6, 95% CI 5.0 to 42.2). This trial also evaluated dysmenorrhoea on a multidimensional scoring system that included limitation of working ability, systemic symptoms, and need for analgesics. There was no significant difference between the treatment and control groups with both group showed a large reduction in symptoms (absent or mild symptoms - PSN 30/35 women, control 29/36 women). In another trial, where information on location of pain was collected, it was found that the experimental and control groups were significantly different in pain relief for midline abdominal pain (Fisher exact test, p= .028). However for back pain or lateral pain associated with dysmenorrhoea there were no significant differences between the groups. These results are based on only the eight randomised participants[226].

Figure 6.4: Results of metanalyses of effectiveness of neuroablation in dysmenorrhoea

(LUNA- laparoscopic uterosacral nerve ablation, PSN- presacral neurectomy; shaded diamonds= statistically significant result; safety*: OR<1= LUNA is safer than LPSN and OR>1 = PSN has more adverse effects than control/no PSN)



6.5 DISCUSSION

This review assessed the effectiveness of surgical interruption of pelvic nerve pathways in the treatment of dysmenorrhoea. There is insufficient evidence to recommend the use of nerve interruption in the management of dysmenorrhoea, regardless of cause. Adverse events were significantly more common for presacral neurectomy, however the majority were complications such as constipation, which may spontaneously improve.

The systematic review was rigorously carried out with an extensive and rigorous literature search without foreign language restrictions and with formal assessment of study quality to evaluate bias. It met most of the quality criteria laid down in the QUOROM statement (see appendix 6.2).[23] The review has been done adhering to a strict protocol.

Due to a small number of participants and predictable allocation of randomisation the results should be treated with caution. In the evaluation of the effectiveness of LUNA in treating secondary dysmenorrhoea a meta-analysis of the data is to be viewed with caution due to the relevant studies being heterogeneous in the baseline characteristics and stages of endometriosis. Quality of life measures were reported in only one study[225] though improvement of this is the ultimate goal for the patient and the clinician. Overall the small number of participants who have been entered into randomised controlled trials on LUNA and PSN make it difficult to assess effectiveness in treating dysmenorrhoea. In the trials with negative results, inadequacy of power to detect a clinically important difference is an issue of concern. Overestimation of the expected clinical difference at the time of power calculation can lead to underestimation of the sample size, with the observed effect size showing wide confidence intervals indicating a potential for benefit as well as harm at the extremes of the confidence intervals. The other drawbacks of the included studies are single (fixed) block randomisation, lack of intention to treat analysis and limited generalisability of results due to a single centre trial.

Laparoscopic PSN is a surgical procedure that requires a high degree of skill by an experienced pelvic laparoscopic surgeon trained specifically in this retroperitoneal operation. The presacral region may be highly vascular and the procedure carries major potential hazards for the unwary or inadequately trained surgeon. Conversely, although laparoscopic UNA must be performed precisely to avoid complications it should be within the scope of all competent pelvic laparoscopic surgeons. Not withstanding this fact, there is insufficient evidence to recommend the use of nerve interruption in the management of dysmenorrhoea and data from methodologically sound trials must be awaited before changing current practice.

There is a lack of good quality RCTs in all the comparisons examined in this review. The main issues are sample size and trial methodology. To help resolve the issue of effectiveness of neuroablation, clinicians may initiate good quality and adequately powered trials or participate in the ongoing multicentre trials. An individual patient data metanalysis may address the uncertainty by combining raw data from various studies included in this review as well as the data from ongoing studies.[231]

CHAPTER 7: A RANDOMISED CONTROLLED TRIAL TO ASSESS THE EFFECTIVENESS OF LAPAROSCOPIC UTEROSACRAL NERVE ABLATION (LUNA) IN CHRONIC PELVIC PAIN: THE TRIAL PROTOCOL

7.1 ABSTRACT

Objectives

The principal objective of the trial is to test the hypothesis that in women with chronic pelvic pain in whom diagnostic laparoscopy reveals either no pathology or mild endometriosis laparoscopic uterosacral nerve ablation (LUNA) alleviates pain and improves life quality at 12 months follow up.

Methods

A multi-centre, prospective, randomised-controlled-trial will be carried out with blind assessment of outcomes in eligible consenting patients randomised at diagnostic laparoscopy to LUNA (experimental group) or to no pelvic denervation (control group). Postal questionnaires including visual analogue scale (VAS) for pain (primary outcome), an index of sexual satisfaction and the EuroQoL 5D-EQ instrument (secondary outcomes) will be administered at 3, 6 and 12 months. The sample size has been estimated as 450 patients in total using the hypothesis that LUNA will moderately alleviate pain symptoms (i.e. 0.3 SD difference in the pain scores on a VAS) compared to no intervention at one-year with 80% power at p= 0.05 and taking into consideration 20% loss to follow-up. The primary assessment of the effectiveness of LUNA will be from comparison of outcomes at the one-year follow-up using intention to treat analysis. The medium-term and longer-term risks and benefits of LUNA will also be evaluated at 2, 3, 5 and 10 years.

Results

Interim analyses in 2004 have recommended continued recruitment. A total of 410 women have been randomised (September 2004). The two groups are comparable in age, parity, type of chronic pelvic pain (CPP) and VAS baseline scores.

Conclusion

The LUNA trial is the largest trial of neuroablation thus far. It is hoped that if the results of the trial are positive, women suffering from this common and difficult to treat condition will benefit from this simple operation. If the results are negative a reliable basis for discouraging the spread of this technique will have been provided.

7.2 INTRODUCTION

The transection of the uterosacral ligaments and the nerve plexuses it contains is a simple surgical procedure for pelvic pain. The original work by Doyle described vaginal and abdominal approaches to divide the attachments of the uterosacral ligaments to the cervix.[29;30] With the wider use of minimal access therapy there is a renewed interest in the division of the Frankenhauser nerve plexus in the uterosacral ligaments laparoscopically using lasers or electro-diathermy. In an attempt to relieve patients' symptoms clinicians frequently perform laparoscopic uterosacral nerve ablation (LUNA).

However the effectiveness of this procedure has not been assessed objectively using methodologically sound research. I conducted a survey of UK O&G consultants and European gynaecologists associated with the European Society of Gynaecological Endoscopy in 2002 (chapter 4) to determine the extent to which LUNA was being used in practice as also the differences in indications and techniques across Europe. I also conducted a survey of 'prior beliefs' (chapter 5) to measure beliefs about effectiveness of LUNA. The survey indicated that despite the lack of definitive evidence, many gynaecologists familiar with the technique were using LUNA as a therapeutic option. The systematic reviews to date[39;232] have indicated the need for good quality trials to answer the question of effectiveness of this procedure in CPP. Crucially, the surveys conducted in 1998[35] and 2002, both indicated that 93 of 108 (86%) gynaecologists currently performing LUNA were willing to recruit patients in a randomised trial of LUNA. In this situation equipoise applies i.e. the technique has been introduced without definite evidence but opinion regarding its use is not yet solidified.

Health technology assessment in surgical interventions requires an initial evaluation of the safety and stability of new interventions followed by randomised trials [233]. The initial evaluative evidence [32;212] alone is not sufficient to assess the clinical effectiveness of LUNA for which randomised research remains the gold standard.

Update of the Cochrane review (see chapter 6) has shown that the currently available randomised research evidence on LUNA is also inconclusive. Therefore further research is required to generate effectiveness evidence in the form of a high quality randomised controlled trial.

7.3 METHODS

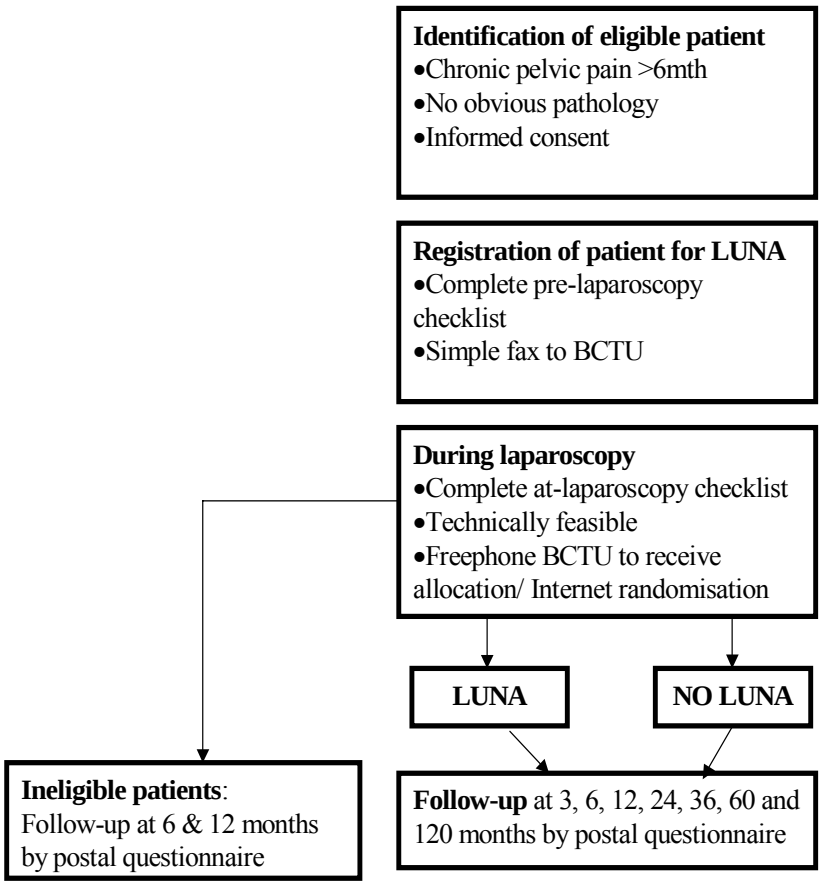
7.3.1 The LUNA trial Objectives

1. To test the hypothesis that in women with chronic pelvic pain in whom diagnostic laparoscopy reveals either no pathology or mild endometriosis (American Fertility Society score ≤ 5) LUNA alleviates pain and improves life quality at 12 months (principal objective).
2. To test the hypothesis that response to LUNA differs according to the site and cause of the pain by two secondary analyses: (i) Women with central pain, (ii) women with no visible pathology.
3. To explore the variation in LUNA's effectiveness and side effects at different periods of follow-up (3, 6, months and 1, 2, 3, 5 and 10 years).

To meet the above objectives, a multi-centre, prospective, randomised-controlled-trial funded by WellBeing (CF/371),[231] involving centres in the UK is being carried out with blinded assessment of outcomes in eligible consenting patients randomised and blinded at diagnostic

laparoscopy to LUNA (experimental group) or to no pelvic denervation (control group). Postal questionnaires including visual analogue scale for pain (primary outcome), a sexual activity questionnaire (SAQ) and the EuroQol 5D-EQ instrument (secondary outcomes) will be administered at 3, 6 and 12 months. The primary assessment of the effectiveness of LUNA will be from comparison of outcomes at the one-year follow-up, although the medium-term and long-term risks and benefits of LUNA will also be evaluated by postal questionnaires to the women at 2, 3, 5 and 10 years after laparoscopy.

Figure 7.1: The laparoscopic uterosacral nerve ablation (LUNA) trial schema



7.3.2 Participants

All new patients presenting to the Gynaecology outpatient clinic with pelvic pain (cyclical or noncyclical) and/or dyspareunia, and requiring diagnostic laparoscopy for evaluation of these conditions, will be invited to participate[200].

Inclusion criteria

- Pelvic pain of longer than 6-month duration.
- Pain located within the true pelvis or between and below the anterior iliac crests.
- Associated functional disability.
- Lack of response to medical treatment.
- Diagnostic laparoscopy planned.

Exclusion criteria

- Previous LUNA.
- Mild, moderate and severe endometriosis (AFS score >5).
- Previous surgery for endometriosis.
- Previous surgery for pelvic inflammatory disease.
- Previous hysterectomy.
- Adnaexal pathology.

7.3.3 Interventions

Diagnostic laparoscopy plus uterosacral nerve ablation (experimental group) or laparoscopy without pelvic denervation (control group).

LUNA will be carried out in a uniform manner by named surgeons in each of the participating centres following a common protocol as described in the standard surgical text.[32] Routine

preparation will be made for a diagnostic laparoscopy with the patient under general anaesthesia. Following pneumoperitoneum, a laparoscope will be used to visualize the pelvis. Before embarking on operative laparoscopy an anatomical pelvic assessment will be performed to identify pelvic structures and pathology. At this stage patients with pathology outlined in the exclusion criteria will be excluded. It is expected that around 30% of women will be unsuitable for LUNA at operation. Women who are ineligible for the LUNA trial because of moderate to severe endometriosis, significant adhesions, significant pelvic inflammatory disease, other significant pathology or those for whom LUNA is not technically feasible should be registered with the Trial Office for follow-up only. The woman should be told that she was not eligible for the trial randomisation and the reasons why, and asked if she would agree to complete the follow-up questionnaires at 6 and 12 months. This non-random cohort will provide comparative data on the natural history of patients with chronic pelvic pain with significant pathology. Eligible patients will be randomised by a telephone call to the BCTU.

Clear identification of the uterosacral ligaments is a prerequisite to treatment with lasers or electro-diathermy. The posterior leaf of the broad ligament will be carefully inspected to identify the course of the ureters, which on rare occasions could be particularly close to the uterosacral ligaments. Care will also be taken to note thin walled pelvic veins, which often lie lateral to the uterosacral ligaments. If accidentally punctured, they may cause troublesome bleeding requiring further endoscopic endocoagulation. The uterosacral ligaments will be identified by manipulation of the uterus in the right and left lateral planes. The ligaments will then be ablated with laser or micropoint electro-diathermy or endocoagulation depending upon the surgeons' preference. The variation in the surgical techniques is as noted in Chapter

4. In a typical case, the ablation will start as close to the posterior aspect of the cervix as possible and continue for a minimum of 1 cm posterolaterally on either side. The aim of the procedure is to destroy the sensory nerve fibres and the secondary ganglia as they leave the uterus and come to lie within the uterosacral ligaments.

The safe conduct of operative laparoscopy for LUNA requires the use of two ports, one for delivery of the energy source (laser or diathermy) and another for manipulation. These are in addition to the umbilical port used for the laparoscope itself. In contrast, diagnostic laparoscopy in women with no pathology requires only one port in addition to the umbilical laparoscopic port. This difference in number of ports has potential for introducing bias by compromising patient blinding to group allocation. A sham incision (see discussion) in the control group is used to overcome this problem.

7.3.4 Trial procedures

Consenting eligible patients will be randomised to diagnostic laparoscopy plus uterosacral nerve ablation (experimental group) or to no pelvic denervation at the time of diagnostic laparoscopy (control group).

The subjects will be allocated to groups using a chance procedure, blocking and stratification. [234] Stratified block randomisation will be employed to ensure that there will be nearly equal numbers of patients in the two groups within the prognostic subgroups, even if the study ends prematurely. Variable block size will be used to avoid any possibility of foreknowledge.

Randomisation will be conducted using minimisation, stratified by the four variables:

a. Presence or absence of some minimal pathology (minimal endometriosis ± ablation; adhesions requiring adhesiolysis only; minimal pelvic inflammatory disease)

b. Site of pain (presence of central pain or not)

c. Parity of the woman (nulliparous or parous)

d. Whether the woman is sexually active or not

The first two variables form the prespecified subgroup analyses, and the other two variables are included as having impact on dysmenorrhoea and dyspareunia respectively.

Treatment allocation will be issued at diagnostic laparoscopy, after the surgeon has inspected the pelvis and ensured that the patient fulfils *all* of the inclusion criteria and she does not have *any* of the exclusion criteria. Women may be randomised or registered into the study by telephoning the toll free Randomisation Line on 0800 953 0274 (+44 121 687 2319 from outside the UK) or by Internet randomisation at http://www.trials.bham.ac.uk/luna and clicking on the randomisation button. Passwords for Internet randomisation will only be allocated to centres with ethical approval.

Following surgery, the surgeon fills in operation details on a post-surgery form. (Appendix 6) Patients will be kept blind to their treatment allocation until the follow-up in the trial is complete. However, there is a potential problem in the maintenance of blinding in the LUNA trial. As mentioned earlier, patients allocated to have LUNA will have the standard operative laparoscopy with three ports (one 10mm umbilical port and two 5mm lateral ports), whereas patients allocated to the control group under normal circumstances would have standard diagnostic laparoscopy with two ports (one 10mm umbilical port and one 5mm lateral or midline port). By noting the different number of incisions some patients might become aware of their group allocation and this might alter their response. In order to maintain patient

blinding, a sham 5mm skin incision is made superficially in a lateral port site. This approach in avoiding bias due to lack of blinding has been used in a previous trial of laparoscopic nerve ablation [221] and has also received ethical approval in this trial.

The trial is being managed from the BCTU. Each investigating centre will carry out the study in accordance with the study protocol and to the Medical Research Council guidelines on Good Clinical Practice in Clinical Research (1998). Patients will be invited to participate if they fulfill all the inclusion criteria and do not have *any* exclusion criteria. They will be provided with a laparoscopy and LUNA trial information leaflet and signed consent obtained prior to laparoscopy. Consenting patients will be asked to complete the Enrolment Questionnaire and On Study Form. The final decision to enroll patient in the trial will depend on the findings at laparoscopy when the surgeon will perform LUNA or not after determining eligibility as shown in Eligibility Checklist and Randomisation Form. At the end of the procedure the surgeon will complete the Post Surgery Form (Appendix 6 contains all the forms used in this trial). All the three forms for each patient enrolled will be photocopied to keep a record at the participating centre and the originals will be sent to the BCTU, which will act as the coordinating centre. At 3, 6 and 12 months after enrolment, the Follow-up Questionnaire will be mailed to the patients with a pre-paid self-addressed envelope. Recruitment is expected to take 12 months (upto September 2005) and follow up for the main endpoints another 12 months. At completion of the main study further follow-up questionnaires will be mailed out at 24 and 36 months.

Table 7.1: Study Flow Chart

Form/Questionnaire	**Gynaecology Clinic**	**Operating Theatre**	**Postal Follow up (months/ years)**						
			3	6	12	2	3	5	10
Patient information and consent (Appendix 6.1)	X								
Eligibility Checklist and Randomisation form (Appendix 6.2)	X	X							
Enrolment Questionnaire (Appendix 6.3)	X								
Surgery Form (Appendix 6.4)		X							
Letter to GP (Appendix 6.5)	X								
Follow-up Questionnaire (Appendix 6.6)			X	X	X	X	X	X	X

7.3.5 Outcomes

The primary outcome measure will be based on VAS for assessment of pain.[235] This technique involves use of a 10 cm line on a piece of paper representing a continuum of the patients' opinion of the degree of pain. It is explained to the patient that the one extreme of the line represents “no pain at all” while the other represents “as much pain as she can possibly imagine”. The subject rates the degree of pain by placing a mark on the line and scale values are obtained by measuring the distance from zero to that mark.

The secondary outcome measures will be assessment of sexual function and quality of life. The Sexual Activity Questionnaire (SAQ)[236] will replace the Brief Index of Sexual Satisfaction (BISS) [237] for the assessment sexual function. This has been necessitated due to the poor acceptability and compliance with BISS in the pilot study. The SAQ has excellent internal consistency and test retest reliability. It also has excellent concurrent and construct validity and has been shown to be acceptable to women in other clinical trials. [238] In the questionnaire it will be clearly stated that the measure of sexual function covers material that is sensitive and personal. Participants will be reassured that their responses will be kept completely confidential and that if they do not wish to answer any questions, they will be allowed to leave the questionnaire blank.

Health-related quality of life (HRQL) instruments are becoming powerful tools for outcome assessments in randomised trials. Quality of life instruments assess aspects of patient's health status usually not grasped by conventional clinical indices; hence, they can be applied as complementary assessments together with VAS and SAQ. Quality of life has to be defined clearly and patient's perception of normal performance serves a pivotal role in this context. HRQL instruments are administered with questionnaires assessing a number of different domains, i.e. areas of behavior or experience that the instrument is attempting to measure. [239]

Economic outcomes are often considered in clinical trials. LUNA is a quick, safe and inexpensive procedure for women already undergoing diagnostic laparoscopy. Our hypothesis is about a clinically important effect without an excess of complications. If the hypothesis is confirmed, then any benefits will essentially be "dominant" outweighing the relatively small costs of intervention. Therefore, we do not plan a formal economic evaluation at this stage. However, data on health resource use will be collected partly as effectiveness outcome measures (i.e. less need for medical care for pelvic pain indicates greater effectiveness), and

partly to allow an economic evaluation to be carried out, should significant complications occur. Other measures will include analgesic use, consultations at general practice and hospital, and time off work. Again these are both economic outcomes and indicators of residual pain.

Postal Questionnaires to assess pain and sexual function will be administered at enrolment in the trial and then at 3, 6, 12, 24 and 36 months after laparoscopy. The outcomes at 12 months will be used to address the primary research question. This time interval is chosen because laparoscopy alone has a placebo effect for up to 3-6 months in some patients. [71;240] The 24 and 36-month follow up will be used to monitor medium-term effects of the intervention. Existing participants in the trial who consented to 3 years of follow-up will be asked to consent to long-term follow-up (10 years) once they have reached the 3 year follow up time-point. Participants randomised after June 2003 are asked to consent to 10 years of follow-up at entry for long term follow up.

The centres have been advised to fill an “adverse event form” in case of immediate and delayed complications if any are associated with the procedure.

7.3.6 Sample Size and Power Considerations

The sample size for this trial has been estimated using the hypothesis that LUNA will alleviate pain symptoms (i.e. reduce pain scores on a VAS) more often than no intervention at one-year following diagnostic laparoscopy. Cohen describes 'effect sizes' of 0.2 and 0.5 standard deviations (SD) as 'small' and 'medium'.[241] Interim analyses of the pilot study indicate that the SD of the difference in change in VAS scales between LUNA and no pelvic denervation groups will be about 4.0. This corresponds to small and medium effect sizes on

VAS of 0.8 and 2.0 respectively and is consistent with other studies of chronic pelvic pain, where clinically important symptom alleviation has been defined as a reduction in pain score of 2 or more [242]. To confirm or refute a small to medium effect of LUNA (0.3 SD difference or 1.2 VAS points), based on α=0.05 and β=0.2 (80% power), 175 patients in each group (i.e. 350 patients in total) will be required. Considering a 20% loss to follow-up, the sample size is inflated to 210 patients in each group (i.e. 420 patients in total).

7.3.7 Data Analysis

The type of analysis will be based on Intention to treat principles. The main analysis to address the principal research questions will be conducted using the one-year follow-up data. The mean differences in VAS pain scores; sexual satisfaction and life quality scores in the two groups will be compared using a two-sample t-test. The rates of women with clinically significant (2 VAS point) alleviation of pain symptoms will also be compared producing a relative risk estimate with 95% confidence intervals (Mantel-Haenzel test). Baseline characteristics of the patients enrolled in the two groups will be compared to ensure that randomisation has produced comparable groups of patients. The use of additional treatment (co-intervention) for pelvic pain following LUNA or no pelvic denervation will be assessed for any systematic difference between the two groups.

Subgroup analyses are limited by statistical power and can produce spurious results particularly if many are undertaken. Our literature review [39] and consultation with gynaecologists [35] suggests that the effectiveness of LUNA may be greater for central compared to non-central pain and if there is no associated pathology (i.e. no endometriosis). Therefore, we have chosen to limit secondary analyses to these subgroups only. The LUNA trial is powered to detect a small to medium overall difference and if a larger treatment benefit

is found then other subgroup analyses will be undertaken, appropriately cautiously. The LUNA trial is powered overall at 80% to detect a 0.3 SD difference in effect. Our pilot study shows that 60% patients have mainly central pain and 70% have no pathology. Hence, in the subgroup with central pain the power will be 80% to detect a 0.4 SD treatment effect. In the subgroup with no pathology the power will be 80% to detect a 0.35 SD treatment effect.

7.4 RESULTS

A study was undertaken with the objective of assessing its feasibility of a trial of LUNA. It has shown acceptability to patients. It has also established trial management procedures, piloted questionnaires, measured compliance and standardised operating procedures. A confidential interim analysis was reviewed by an independent data monitoring committee when the first 60 patients had completed 6 months follow-up (March 2001). The committee recommended that a larger study is needed for adequate statistical power in the trial to evaluate LUNA reliably.

Bi-annual analyses of recruitment, compliance and loss to follow-up are being carried out for LUNA Trial Management Committee. An annual interim analysis of effectiveness was done in March 2003 and 2004 for confidential review by independent Data Monitoring Committee to determine whether the principal question has been answered and to monitor adverse events. It confirmed sample size estimation and recommended continued recruitment into the trial.

Interim analysis has provided with the details of the baseline characteristics of women recruited in the trial upto August 2004 as described in the table below.

Table 7.2: Baseline characteristics of participants in the LUNA trial. Items marked * were, until recently, asked on the "On Study Form" rather than the randomisation form, and would therefore only be present if such a form were returned. Items marked ** were not asked on all versions of this form so information is necessarily not complete.

	LUNA	**No LUNA**
Number randomised	200	206
Treatment received*		
LUNA	182	0
No LUNA	3	186
Unknown	15	20
Age:		
17-19	7	6
20-29	64	74
30-39	89	83
40-49	40	43
Adhesions Present	40	35
Endometriosis		
None	150	142
Minimal	32	42
Minimal, Ablated	18	22
Pelvic Inflammatory Disease	3	9
Gravida*		
0	56	75
1	27	24
2	36	31
3	26	18
4+	22	26
Unknown	33	32
Para*		
0	71	75
1	31	33
2	43	43
3	18	19
4+	13	14
Unknown	24	22
Sexually Active*		
Yes	160	152
No	30	33
Unknown	10	21
Dysmenorrhoea*		
Present	146	144
Absent	43	51
Unknown	11	11
Dyspareunia*		
Present, Sexually Active	127	110
Absent, Sexually Active	29	41
Not Sexually Active	30	33
Unknown	14	22
Non-menstrual pain*		
Present	125	126
Absent	58	67
Unknown	17	13

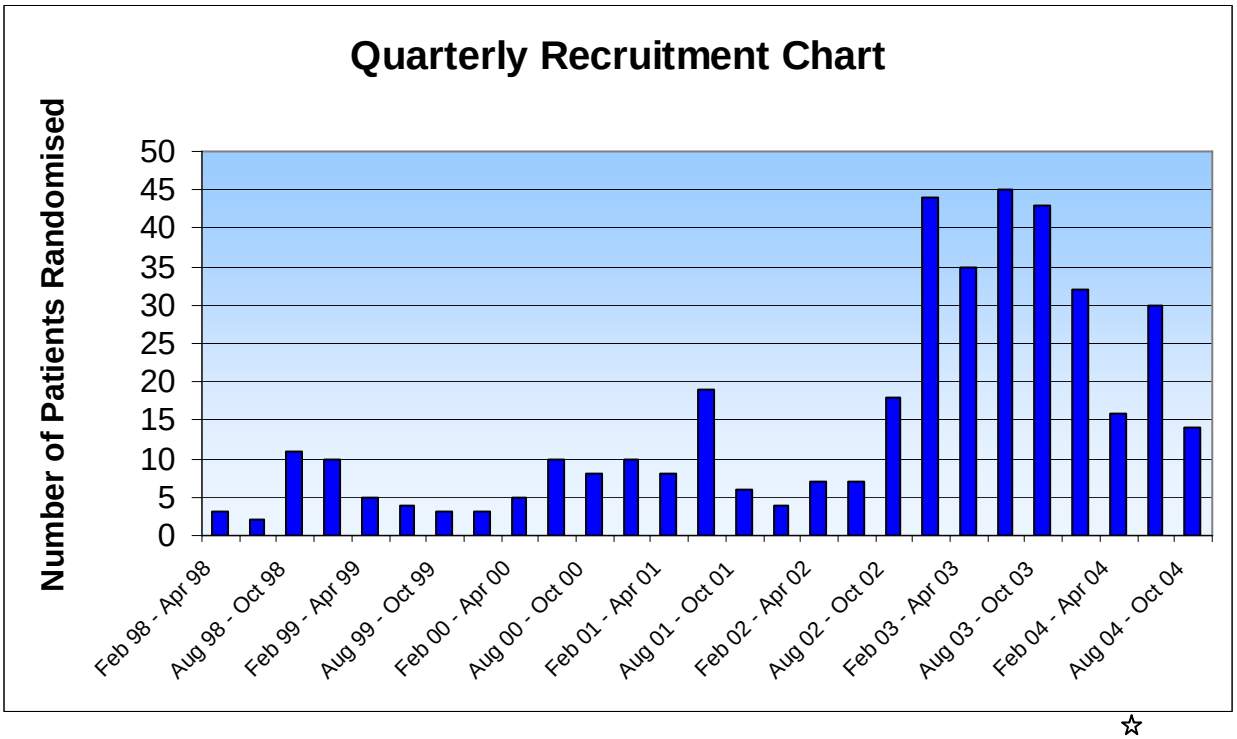
	LUNA	No LUNA
Any visible pathology:		
Yes	15	11
No	185	195
Central dysmenorrhoea*		
Yes	93	96
No	92	96
Unknown	15	14
Central dyspareunia*		
Yes	92	89
No	88	105
Unknown	20	12
Central Non-cyclical pain*		
Yes	54	58
No	126	132
Unknown	20	16
Irritable Bowel Syndrome**		
Yes	1	0
No	76	82
Unknown	123	124
Previous Laparoscopy**		
Yes	1	3
No	42	45
Unknown	157	158
Previous Surgery**		
Yes	0	2
No	78	81
Unknown	122	123
Central pain: Any*		
Yes	130	136
No	52	54
Missing/Unclear	18	16

Table 7.3: **Baseline VAS scores of pain, EUROQoL scores and sexual satisfaction scores of participants in the LUNA trial**

	LUNA	**No LUNA**
Baseline VAS - dysmenorrhoea		
N	170	176
Mean, SD	6.56 (2.63)	6.7 (2.39)
	7.2 (5 – 8.6)	7.1 (5.2 – 8.4)
Baseline VAS - dyspareunia		
N	156	169
Mean, SD	5.9 (3.1)	5.3 (2.97)
	6.5 (4 – 8.5)	5.7 (3 – 7.7)
Baseline VAS – other pain		
N	167	177
Mean, SD	5.7 (2.7)	5.9 (2.73)
	5.8 (4.1 – 8)	6.5 (4.3 – 8)
Baseline EuroQol Thermometer		
N	153	161
Mean, SD	65.8 (22.75)	67.9 (21.13)
	70 (50 – 85)	75 (50 – 85)
Baseline EuroQoL Health Status		
N	167	167
Mean, SD	0.56 (0.32)	0.58 (0.3)
	0.72 (0.23 – 0.8)	0.73 (0.23 – 0.8)
Baseline Sexual Satisfaction Score		
N	136	130
Mean, SD	21.7 (14.85)	23.8 (16.29)
	18 (9 – 31)	21 (21 – 34

EuROQoL-European Quality of life questionnaire; SD- standard deviation; VAS- visual analogue scale

Figure 7.3: Quarterly recruitment progress in the LUNA trial



* Indicates incomplete quarter

The graph above indicates the rate of recruitment divided in quarters in the LUNA trial. As seen in the graph, the recruitment increased once a dedicated research fellow was appointed to coordinate the trial. The recruitment is above target in most months (target is 15/month at present) and is expected to finish by April 2005 if the recruitment is carried on at the current rate of approximately 18/ month. This projection of recruitment is illustrated in the graph below (figure 7.5).

The recruitment is highest in the centres where there is a Research fellow or funded research nurse sessions (BWH, Forth Park Hospital, Royal Hallamshire Hospital)

Figure 7.5: Recruitment Projection in the LUNA trial

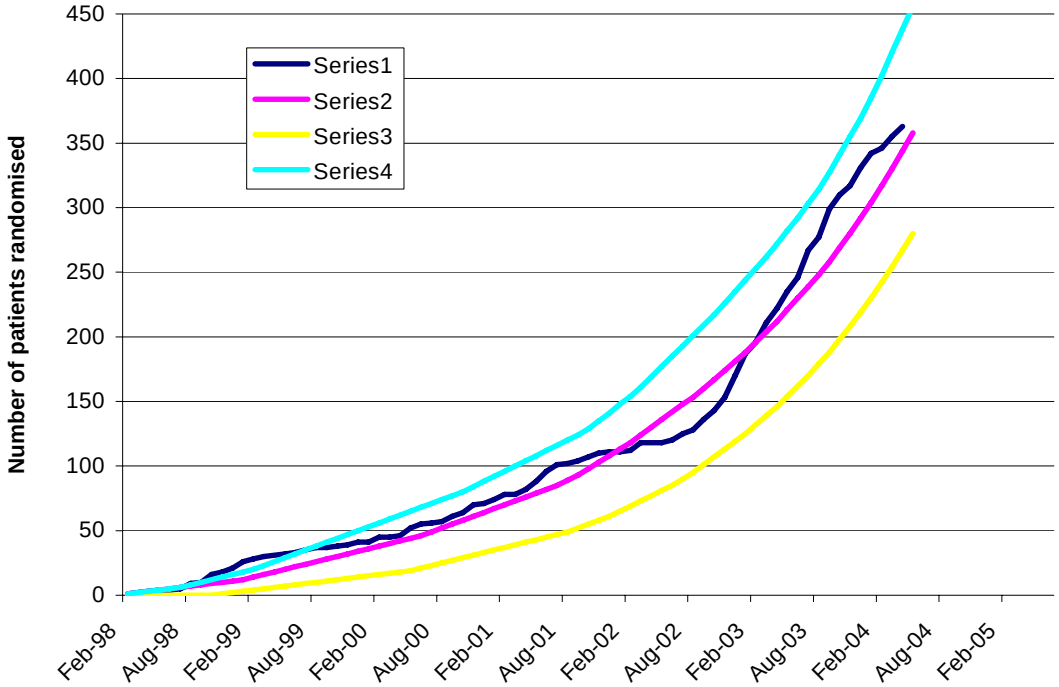
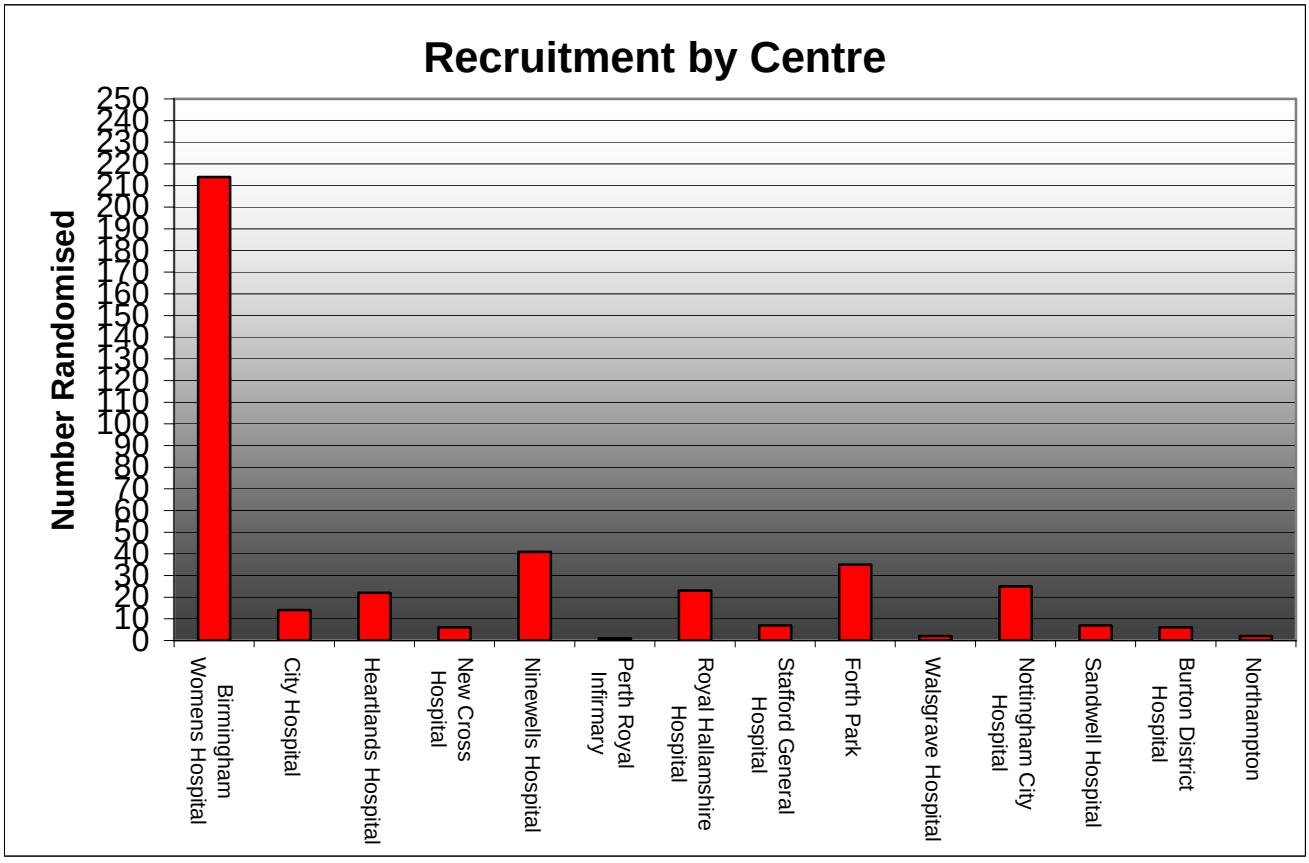


Figure 7.4: Recruitment by collaborating centres until August 2004



7.5 DISCUSSION

7.5.1 Main findings

The acceptance rate for women invited to participate in the trial currently is 70%. The baseline characteristics of women randomised in the trial are not appreciably dissimilar. The follow up rate at present is 71% and efforts are being made to improve it.

7.5.2 Quality of the trial

The trial report will aim to convey to the reader the information needed to make informed judgments regarding the internal and external validity of the trial. LUNA trial complies with all the quality criteria laid down in the CONSORT checklist[243] as is shown in table7.4

LUNA Trial design ensures adequate methodological quality as it has taken care of selection bias (secure randomisation and allocation of participants), performance bias (blinding), measurement bias (valid and reliable pain measurement over long term) and statistical uncertainty (use of a power calculation) amongst other features. Stratified allocation is used so that chance imbalances in the stratification variable do not have an effect on the outcome. As has been previously pointed out in chapter 4, there are several acceptable variations in the practice and techniques of LUNA. Since response to treatment may depend on the surgeons' technique for laparoscopic uterosacral nerve ablation, analyses will be retrospectively stratified according to the surgeons participating in the trial. Allocation concealment is a crucial factor in avoiding bias in randomised trials.[244] Although it is not possible to blind the surgeon, it is essential to keep the surgeon blind to the group allocation until after the irrevocable decision to enter the woman into the trial has been made.

Table 7.4 Consolidation of standards for Reporting Trials (CONSORT) checklist applied to the LUNA Trial Protocol

Heading	Subheading	Descriptor	Reported
Title		Identify the study as a RCT	√
Abstract		Use a structured format	√
Introduction		State prospectively defined hypothesis, clinical objectives and planned subgroup analysis	√
Methods	Protocol	Describe: Planned study population with inclusion and exclusion criteria Planned intervention and their timing Primary and secondary outcome measures and minimum important differences and indicate how the target sample was projected Rationale and methods of statistical analysis, detailing main comparative analyses and whether they were completed on ITT basis Prospectively defined stopping rules (if warranted)	 √ √ √ √ √ √
	Assignment	Describe Unit of randomisation Method used to generate allocation schedule Method of allocation concealment and timing of assignment	 √ √ √
	Blinding	Describe mechanism, allocation schedule control and evidence of successful blinding among participants, outcome assessors, and data analysis	√
Results	Participant Flow& Follow up	Provide a trial profile summarizing participant flow, numbers and timing of randomization assignment, interventions, and measurements for each randomized group	N/A
	Analysis	State estimate effect of intervention on primary and secondary outcome measures including a point estimate and measure of precision (confidence interval) Describe prognostic variables by treatment group and any attempt to adjust for them	√ √
Comment		State interpretation of study findings, including source of bias and imprecision (internal validity) and discussion of external validity including appropriate quantitative measures when possible	√

Patients may also show a placebo effect if they know they have received the active treatment. The magnitude of placebo effects should not be underestimated. There is clear evidence that inadequacies of blinding in randomisation lead to exaggeration of treatment effect in randomised trials. A

second purpose of blinding is to prevent differences in other aspects of patient management introducing biases affecting the results.[244] The patient's GP will therefore be kept blind to treatment allocation. Double blinding is not possible in LUNA, however, as the surgeons performing the surgical intervention on the patients will be aware of the group allocation. However, the likelihood that this will lead to bias in outcome assessment is low as the patient outcome assessments in this study will be conducted by self-administered questionnaires, avoiding any possible bias from surgeons' knowledge of group allocation.

Pain is difficult to measure, partly because it is accompanied by other sensations and partly because the reaction component affects the judgment of the pain regardless of the intensity of the stimulus. A measure of pain is nevertheless essential to the outcome of this clinical trial. VAS originally devised as measures of well being,[245] have been successfully adapted to measure pain and have been established to be reproducible and accurate.[235;246] VAS has commonly been used in measurement of chronic pain. [247] All the studies of LUNA included in systematic reviews so far have used this measure, or its variation, for assessing outcome. Individual pain scores have sufficient psychometric strengths to be used in chronic pain research involving group comparison designs.[248] Sexual function is an important aspect of life quality in patients with pelvic pain. Pain itself is an anti-aphrodisiac, and together with discomfort and altered self-image, it impacts upon sexual function. [249] Its assessment in an objective manner is therefore an important part of the LUNA trial. There are several sexual function instruments, with high levels of reliability, validity and responsiveness, which yield comparable results across

occasions and individuals, making them suitable for monitoring therapeutic progress in randomised research. [249]

When there is uncertainty about the appropriate therapy, scientific clinical trials are the best scientifically ethical way to resolve uncertainty and thereby benefit both the individual patients and all others concerned in their care. [250] The need for a "sham" incision in this trial is the main ethical issue and it is required because without it the patients cannot be kept blinded. The purpose of blinding is to prevent various biases from affecting the results. The need for blinding in surgical trials has been emphasized in the medical literature [251] and there is empirical evidence that inadequacies of blinding in randomisation lead to exaggeration of therapeutic efficacy in randomised trials.[244] Blinding of patients in surgical trials is clearly indicated when the intervention primarily treats symptoms and when the outcomes are based on patients' own assessment. LUNA is an intervention for treating chronic pelvic pain (a diagnosis based on symptoms) and the outcome assessment is based on patients' responses on a VAS and a quality of life instruments. Hence, the use of a "sham" incision is justified if bias is to be avoided in the LUNA trial and this approach has been used in a previous trial of LUNA.[221] Ethical approval for the LUNA trial procedures has already been obtained from the Multicentre Research Ethics Committee.

The LUNA trial is already the largest trial of neuroablation. It is hoped that if the results of the trial are positive, women suffering from this common and

difficult to treat condition will benefit from this simple operation. If the results are negative a reliable basis for discouraging the spread of this technique will have been provided.

CHAPTER 8 SUMMARY

8.1 Summary of findings

In this thesis, I have collated existing knowledge on prevalence and aetiology of chronic pelvic pain and effectiveness of pelvic neuroablation by means of thorough systematic reviews. I have surveyed practice of LUNA in Europe, developed questionnaire to collect 'prior beliefs' on effectiveness of LUNA and LUNA trial protocol. Below, I reproduce the table of structured questions from Chapter 1 (Table 1.1), adding a final column of results from the various chapters of this thesis:

Table 8.1: Findings of the objectives in the thesis

Objective A: To summarise the evidence on prevalence and aetiology of chronic pelvic pain with systematic reviews of relevant studies

Chapter	Population	Comparison	Outcomes	Research Design	Findings
2	Women at risk	Prevalence by representativeness of studies	Dysmenorrhoea Dyspareunia Noncyclical pelvic pain (CPP)	Systematic review (SR) of observational (cross sectional or longitudinal) studies	There was significant variation among rates of all three types of CPP. Meta-analysis of rates amongst high quality studies with samples representative of general population showed that prevalence of dysmenorrhoea (12 studies) was 59% (95% CI 49.1-71%), of dyspareunia (11 studies) was 13.3% (95% CI 8.8-20.3%) and of noncyclical pain (2 studies) was 6.2% (95% confidence interval (CI) 3-12.6%, heterogeneity p for all three values was <0.001).
3	Women at risk	General, Gynaecological/ obstetric, Psychologic and social factors	Dysmenorrhoea Dyspareunia Noncyclical pelvic pain	SR of observational (cohort, case-control or cross sectional) studies that provide comparative information on presence of risk factors in women with or without CPP	There were 122 studies (in 111 articles) of which 63 (64,286 women) evaluated 54 risk factors for dysmenorrhoea, 19 (18,601 women) evaluated 14 risk factors for dyspareunia and 40 (12,040 women) evaluated 48 factors for noncyclical CPP. Age less than 30 years, low BMI, smoking, early menarche (<11 years), longer cycles, longer duration of bleeding or heavy menstrual flow, nulliparity, premenstrual syndrome, sterilisation, PID, sexual assault, emotional difficulties, psychological symptoms and somatisation were associated with increased risk of dysmenorrhoea. Younger age at first childbirth, exercise and oral contraceptives and were associated with reduction in the risk of dysmenorrhoea. Age less than 50 years, peri/post menopausal state, PID, sexual abuse, anxiety and depression were found to be associated with dyspareunia. Drug/alcohol abuse, miscarriage, heavier menstrual flow, PID, previous caesarean section, pelvic adhesions/other pathology, childhood physical or sexual abuse, lifetime sexual abuse, anxiety, depression, hysteria, psychosomatisation were associated with an increased risk of noncyclical pelvic pain

Objective B: To examine the variation in current indications and surgical techniques for performing laparoscopic uterine nerve ablation (LUNA) in Europe and assess the effect of operator experience on practice as also to explore gynaecologists' 'prior' beliefs on effectiveness of LUNA					
4	Gynaecologists in the UK and rest of Europe	Structured questionnaire	Indications and techniques for LUNA across Europe	Survey	The questionnaire was returned by 719 (38% of 1870) of the gynaecologists contacted and 173 (24%) performed LUNA. Indications for LUNA were similar across UK and rest of Europe. The European group performed LUNA more often (62% vs. 21%), completely transected the uterosacral ligaments (56% vs. 36%) and ablated at a distance of more than 2 cm from its cervical insertion (50% vs. 21%) more frequently than the UK group. More experienced gynaecologists performed LUNA more for dyspareunia (46 % vs. 26%) and endometriosis (67% vs. 47%) and they performed complete transection (45% vs.26%) more often than their less experienced counterparts.
5	Gynaecologists collaborating in LUNA trial	Structured questionnaire	'Prior beliefs' on effectiveness of LUNA	Survey	The most widely held 'prior' belief, reflected in both questionnaire and numerical responses was that LUNA would have a small beneficial effect on pain. The credible limits of this belief were compatible with large reductions in pain as 60% of respondents believed a three-point improvement on VAS to be plausible. The standard deviations of expected mean change in VAS due to LUNA ranged from 0.52 to 1.64.

Objective C: To determine the effectiveness of neuroablation in CPP by means of a systematic review and develop a protocol for a prospective randomised controlled trial to assess the effectiveness of LUNA in CPP					
6	Women undergoing laparoscopy for CPP	Neuroablative procedures (LUNA or presacral neurectomy [PSN]) versus no neuroablation	Pain relief Adverse effects	Cochrane SR	Nine RCTs were included in the systematic review. There were two trials with open presacral neurectomy (PSN); all other trials used laparoscopic techniques. For the treatment of primary dysmenorrhoea, LUNA at 12 months was better when compared to a control or no treatment (OR 6.12; 95% CI 1.78-21.03). The comparison of LUNA with PSN for primary dysmenorrhoea showed that at 12 months follow up, PSN was more effective (OR 0.10; 95% CI 0.03-0.32). In secondary dysmenorrhoea, along with laparoscopic surgical treatment of endometriosis, the addition of LUNA did not improve the pain relief (OR 0.77; 95% CI 0.43-1.39) while PSN did (OR 3.14; 95% CI 1.59-6.21). Adverse events were more common for PSN than procedures without PSN (OR 14.6; 95% CI 5-42.5).
7	Women with CPP who need diagnostic laparoscopy	LUNA versus No LUNA during laparoscopy	Improvement in CPP, quality of life and sexual function	Multicentre randomised controlled trial protocol	Interim analyses in 2004 have recommended continued recruitment. A total of 410 women have been randomised (September 2004). The two groups are comparable in age, parity, type of chronic pelvic pain (CPP) and VAS baseline scores.

8.2 Implications for clinical practice

- Prevalence of dysmenorrhoea (12 studies) is 59% (95% CI 49.1-71%), of dyspareunia (11 studies) is 13.3% (95% CI 8.8-20.3%) and of noncyclical pain (2 studies) is 6.2% (95% CI 3-12.6%). This precise estimation of disease burden should be considered by policy makers when planning gynaecological services.
- Key gynaecological and psychosocial factors associated with CPP should be targeted in clinical evaluation of women with this symptom to individualize their management.
- There is variation in the surgical techniques of performing LUNA in Europe and the techniques vary according to operator experience. This variation may impact on

effectiveness of LUNA. LUNA trial when completed will shed light on effectiveness according to technique.

- Among gynaecologists, there is a variation in beliefs about the effects of LUNA on pelvic pain, ranging from substantial benefit to slight harm. Gynaecologists may take this into account when judging the results of the LUNA trial, which may affect the uptake of LUNA trial's findings.
- The evidence to recommend the use of nerve interruption in the management of dysmenorrhoea, regardless of cause, is currently insufficient. This information should form part of patient's counselling at present.

8.3 Implications for research practice

- Substantial differences or even complete absence of definitions, together with differences in age ranges of the populations studied, complicate the interpretation of prevalence of CPP. The surveys should use the validated measurement tools for validity and comparability of the results
- Use of retrospective studies which are subject to incomplete or selective recall of previous events, inappropriate exposure comparisons in some studies, use of non-standard measurement tools with questionable validity or reliability, selecting control groups from women consulting for other conditions in the same setting, who did not have assessment like laparoscopy, non use of explicit definition for CPP and other such factors reduce the ability to confidently investigate causation. Future epidemiological studies should ideally be prospective, with explicit definitions of the outcome and representative of the general population.

- The development of non-invasive diagnostic tools for some of the underlying somatic conditions that may account for CPP will help with unraveling of some of the risk factors further. If treatment of pathology in CPP shows no better outcome than without treatment, then probably there is role for trials in psychological interventions. It would be rational to design intervention studies of use of psychological counseling, antidepressants and other modifiable factors in chronic pelvic pain.
- Methods of documenting distribution of beliefs about likely effects of a treatment need further development. It would also be interesting to compare the graphical and textual methods of collecting "Bayesian priors" and explore the factors that potentially will lead to better representation of the clinicians' opinions
- The uncertainty about the effectiveness of neuroablation in CPP indicates that scientific clinical trials are the best way to resolve uncertainty. Another efficient alternative would be an individual patient data metanalysis of all the existing trials and ongoing studies

TABLE OF CONTENTS OF APPENDICES

(Appendices appear in the accompanying CD ROM)

LIST OF REFERENCES

Reference List

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