Chronic pelvic pain and menorrhagia: Assessing treatment effectiveness
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Chapter 12

Summary and Discussion
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Discussion

The first part of this thesis presents the results of the LUNA trial to determine the efficacy of laparoscopic uterosacral nerve ablation (LUNA) for chronic pelvic pain (CPP), a multicentre trial coordinated by the University of Birmingham Clinical Trials Unit, and the subsequent individual patient data (IPD) meta-analysis of this and all other comparable trials. A review of psychological therapies is also presented. The second part of the thesis was undertaken as part of a commissioned project from the National Institute for Health Research Health Technology Assessment programme and assessed, by systematic review, the effectiveness of the levonorgestrel releasing intra-uterine system (LNG-IUS, Mirena®), hysterectomy and endometrial ablation in the treatment of heavy menstrual bleeding (HMB). The measurement properties of a quality of life instrument for heavy menstrual bleeding were also assessed.

The introduction (Chapter 1) defines the two benign gynaecological conditions, chronic pelvic pain and heavy menstrual bleeding, highlighting the burden to women and health care systems and describes the symptoms, aetiology and epidemiology for both.

Chapter 2 provides a complete clinical overview of chronic pelvic pain. The importance of taking a careful and thorough history to prompt further investigations is emphasised, particularly in view that an organic cause is not found at laparoscopy in at least a third of women with chronic pelvic pain. The biopsychosocial model of pain is discussed and consideration of psychological symptoms highlighted. The absence of effective gynaecological treatments is discussed and a multidisciplinary approach is recommended.

Chapter 3 sets the scene for the randomised trial by describing the state of clinical practice in the UK gynaecological community. We undertook a national survey and found around 45% of respondents performed LUNA, of whom three quarters used the procedure for chronic pelvic pain and just under two-thirds employed it for endometriosis. However, 81% of surgeons were prepared to randomise patients into a clinical trial of LUNA versus no intervention, demonstrating that equipoise existed amongst gynaecologists and a clinical trial was warranted.

The protocol for the LUNA trial is detailed in Chapter 4. Women with chronic pain of greater than 6 months duration, in whom diagnostic laparoscopy revealed either no pathology or mild endometriosis, were eligible. Consenting, eligible women were randomised during laparoscopy to undergo immediate uterosacral nerve ablation or no LUNA. Women were blinded to the allo-
cation by use of a sham incision in the no LUNA group. Pelvic pain was measured using a visual analogue scale, with general quality of life and sexual activity as secondary outcomes. Women responded by postal questionnaire at 3, 6 and 12 months after randomisation. Pre-specified sub-groups included the presence or absence of some minimal pathology, the site of pain and parity. Analysis was by intention to treat. The sample size required to detect a difference of two points on a ten centimetre scale, allowing for 20% loss to follow-up, was 440 participants.

Chapter 5 reports the results of the LUNA trial. After a median follow up of 69 months, there were no significant differences between the visual analogue pain scales for the worst pain reported (mean difference (MD) between LUNA group and No LUNA group -0·04cm, 95% confidence interval (CI), -0·33 to 0·25cm; p=0·80), non-cyclical pain (-0·11cm, 95%CI -0·50 to 0·29cm; p=0·60), dysmenorrhea (-0·09cm, 95%CI -0·49 to 0·30cm; p=0·60), or dyspareunia (0·18cm, -0·22 to 0·62cm; p=0·40). No differences were observed between the LUNA group and the No LUNA group for quality of life. We concluded LUNA did not result in improvements in pain, dysmenorrhea, dyspareunia or quality of life, compared to laparoscopy without pelvic denervation.

Chapter 6 describes the protocol for a meta-analysis collecting IPD from the existing trials, to provide a comprehensive assessment of the effectiveness of LUNA. We updated searches, contacted the authors of identified trials to obtain IPD and explored any heterogeneity. Pain scores were calibrated to a 10 point scale and were analysed using a multilevel model allowing for repeated measures.

Chapter 7 reports the results of the IPD meta-analysis. Raw data were available from 862 women randomised into five trials. There was no significant difference between LUNA and No LUNA for the worst pain recorded over a 12 month time period (MD: 0.25 points in favour of No LUNA on a 0-10 point scale, 95% CI: -0.08 to 0.58; p=0.1). This IPD meta-analysis reinforces the conclusions drawn from our LUNA trial that the procedure is not effective in alleviating pain within one year of treatment.

The effectiveness of psychological therapies for CPP was evaluated in a systematic review, described in Chapter 8. The selected four studies involving women with CPP were randomized controlled trials of psychological therapies compared to no treatment or standard gynecological treatment. Compared to no psychological intervention, therapy produced a standardized mean difference (SMD) of -3.27 (95% CI -4.52 to -2.02) and 1.11 (95% CI -0.05 to 2.27) at 3 months and -3.95 (95%CI -5.35 to -2.55) and 0.54 (95%CI -0.78 to 1.86) at 6 months and greater, based on a visual analog scale score of 0-10. The current evidence does not allow us to conclude whether psychological interventions have an effect on self-reported pain scores in women with CPP.
In Chapter 9, we undertook an IPD meta-analysis to evaluate the relative effectiveness of hysterectomy, endometrial destruction (both ‘first generation’ hysteroscopic and ‘second generation’ non-hysteroscopic techniques) and LNG-IUS for HMB. Data on 2814 women were available from 17 of the 30 randomised controlled trials identified. At around 12 months, 7.3% (12.6% vs 5.3%) more women were dissatisfied with outcome of first generation hysteroscopic techniques than hysterectomy (Odds Ratio (OR): 2.46, 95%CI:1.54-3.93, p=0.0002), but hospital stay (Weighted Mean Difference (WMD): 3.0 days, 95%CI:2.9-3.1, p<0.00001) and time to resumption of normal activities (WMD: 5.2 days, 95%CI:4.7-5.7, p<0.00001) were longer for hysterectomy. Unsatisfactory outcomes were comparable with first and second generation techniques (OR: 1.20, 95%CI:0.88-1.62, p=0.2), although second generation techniques were quicker (WMD:14.5 minutes, 95%CI:13.7-15.3, p<0.00001) and women recovered sooner (WMD: 0.48 days, 95%CI:0.20-0.75, p=0.0008) with fewer procedural complications. More women are dissatisfied following endometrial destruction than hysterectomy. However, dissatisfaction rates are low after all treatments and hysterectomy is associated with increased hospital stay and recovery period. Definitive evidence on effectiveness of LNG-IUS compared to more invasive procedures is lacking.

In chapter 10, we extended the previous review to determine the relative effectiveness of second generation ablation techniques in the treatment of heavy menstrual bleeding. Nineteen randomised controlled trials (involving 3287 women) were identified. Of the three most commonly used techniques, network meta-analysis showed that bipolar radiofrequency and microwave ablation resulted in higher rates of amenorrhoea than thermal balloon ablation at around 12 months (OR: 2.51, 95%CI 1.53 to 4.12, p<0.001; and 1.66, 1.01 to 2.71, p=0.05, respectively), but there was no evidence of a convincing difference between the three techniques in the number of women dissatisfied with treatment or still experiencing heavy bleeding. Compared with bipolar radio frequency and microwave devices, an increased number of women still experienced heavy bleeding after free fluid ablation (OR: 2.19, 95%CI 1.07 to 4.50, p=0.03; and 2.91, 1.23 to 6.88, p=0.02, respectively). Compared with radio frequency ablation, free fluid ablation was associated with reduced rates of amenorrhoea (OR: 0.36, 95%CI 0.19 to 0.67, p=0.004) and increased rates of dissatisfaction (OR: 4.79, 95%CI 1.07 to 21.5, p=0.04). We concluded bipolar radio frequency and microwave ablative devices are more effective than thermal balloon and free fluid ablation in the treatment of heavy menstrual bleeding with second generation endometrial ablation devices.

Finally, in Chapter 11, the reliability and validity of the Menorrhagia Multi-Attribute Scale (MMAS), a menorrhagia-specific quality of life instrument, was investigated. The MMAS was found to have good measurement properties and is therefore an appropriate condition-specific instrument to measure the outcome of treatment for HMB.
Chronic Pelvic Pain

CPP represents a significant disease burden in both primary and secondary care\(^1\). A diagnosis of idiopathic CPP is arrived at once all other organic causes of pain are excluded by diagnostic laparoscopy. That is not to say that idiopathic CPP is a psychogenic condition. Endometriosis, pelvic adhesions, chronic pelvic inflammatory disease, and ovarian cysts were the pathologies most frequently observed at laparoscopy in women with CPP in the LUNA Trial.\(^2\) Moreover, the severity of pain is not related to severity of underlying pathology, as illustrated by endometriosis, where stage of disease is poorly correlated with reported pain.\(^3\) CPP is seldom caused by a single factor alone and psychological symptoms may be both causative and associative.

A troublesome clinical issue is the lack of an accurate tool to efficiently diagnose and direct cases of patients.\(^4\) The Royal College of Obstetricians and Gynaecologists (RCOG) guidelines provide a number of suggested initial investigations, including history, microbiological screening and vaginal examination, all with weak evidence for utility.\(^5\) If no cause of the pain is found, the first port of call would usually be to perform a diagnostic laparoscopy, although the RCOG guidelines now suggest it may be better seen as a second line investigation if other therapeutic options have failed.\(^5\)

The parasympathetic ganglia and nerve plexuses in the uterosacral ligaments are believed to carry the somatic pain from the pelvis to the pain, thus theoretically, ablation of these nerve trunks should offer pain relief. Neuroablation at the time of diagnostic laparoscopy was widely practiced in the UK,\(^6\) but its efficacy was never reliably demonstrated prior to our work. Our IPD meta-analysis reinforced the conclusions drawn from the LUNA trial that the procedure is not effective in alleviating pain within one year of treatment. Subgroup analysis did suggest a benefit of LUNA in those without visible pathology, consistent with the Cochrane review, although this effect was only seen at 12 months and was of borderline statistical significance.\(^7\) Conversely, the IPD meta-analysis of those with visible pathology showed greater decrease in pain in the No LUNA group, contradicting the Cochrane review. These subgroup effects lack biological plausibility and are likely to have arisen by chance.

The failure to demonstrate an improvement in pain relief or quality of life in women who had the LUNA procedure illustrates the importance of rigorous assessment in the pursuit of evidence based medicine. Negative results are equally important as data supporting a procedure. LUNA is not without risks and costs and the findings of our research here should discourage the use of an ineffective procedure. Conversely, there is still a lack of evidence regarding the effectiveness of adhesiolysis in reduction of CPP.\(^8\) There is insufficient evidence to comment on pain relief after hysterectomy, and reflecting similar guidelines for heavy menstrual bleeding, such a major operation perhaps should not be considered as a first line solution to pelvic pain.
We postulate that the initial general improvement seen over the first 6 months is attributable to the reassurance derived from being told that no serious cause had been found for their pain. A study identified in our review of psychological therapies found no difference in pain between women debriefed after laparoscopy with a photograph of their pelvis, compared with those that did not receive a photograph. Grace, in her reflections from interviews with women with CPP, observes that women expect the source of pain should be “visible”, in the form of pathology, and in the absence of a laparoscopic diagnosis, tend to normalise the pain. Yet women continue to refer in their thoughts about the cause of pain to biological mechanisms, for example hormonal imbalance or pelvic trauma due to childbirth. Living with chronic pelvic pain requires women to develop coping strategies to maintain their daily family and working lives. Cognitive behavioural therapy (CBT) may help with this. CBT involves encourages women to first assess the thoughts associated with pain, and the extent and consequences of such thinking. The goal then is to develop adaptive coping behaviour that seeks to achieve positive goals. CBT has demonstrated to be effective in improving mood and may be useful in reducing pain and disability in a review of many musculoskeletal chronic pain, but the effectiveness for CPP is unproven.

Future research in the management of CPP

CPP can be viewed in a ‘biopsychosocial’ model, in which underlying ‘disease’ states interact with psychological and social factors to produce the symptoms experienced. This approach demands a multidisciplinary approach to management and there is some evidence that this results in improved quality of life, if not reduced pain, but further health service research is required. Such multidisciplinary care should be considered as a complex intervention, built up from a number of components, each of which may act both independently and inter-dependently. The components usually include treatment activities e.g. psychological therapy, parameters of these activities e.g. frequency, timing in relation to other aspects of management and methods of organising those activities e.g. group sessions or CBT by telephone. Sometimes is difficult to identify the most efficacious components within a multidisciplinary care approach and it is not necessarily enough to conduct randomised trials of individual components and assume that putting together those activities that are of benefit will produce a synergistic effect. Optimisation of a multidisciplinary approach will require a coordinated programme of research, modelled upon the Medical Research Council’s Framework for the development and evaluation of complex interventions.

Future trials should also consider the recommendations of the IMMPACT initiative and employ outcome measures that not only capture the intensity of pain, but the effect on physical and emotional functioning. If pharmacological treatments are to be assessed, the use of titrated dosing and a minimum treatment period of 3 months are recommended in order to identify responders. New trials should have larger numbers, aiming to recruit 350 or more patients to detect...
a more realistic, but worthwhile, effect of any intervention. To explore when the benefit emerges and whether it is maintained, longer follow-up of participants is recommended. In chronic conditions where outcomes may vary over time, repeated measures analyses will maximize statistical power from the trial sample. Finally, to truly capture the impact of CPP on a woman’s life, a disease specific instrument, developed and validated by rigorous methods, and driven by accounts of symptoms and burden from women with CPP, needs to be develop in order to assess the effectiveness of future treatments.

**Heavy Menstrual Bleeding**

Heavy menstrual bleeding (HMB) is a common problem that can significantly impact on women’s lives, and burden individuals and healthcare systems.19,20 A range of non-hormonal and hormonal medical treatments are available as first line therapy for women presenting with HMB in primary care. ECLIPSE, a recent large, pragmatic randomized trial found both LNG-IUS and usual medical treatments reduce the adverse impact of HMB on women’s lives over two years, but LNG-IUS is the more effective.21 Discontinuation rates for LNG-IUS in our review were 28% by two years, comparable to ECLIPSE where 31% of those who had the system fitted had it removed, predominantly for perceived lack of effectiveness or irregular or prolonged bleeding.

When medical treatments fail to provide adequate relief, surgical interventions, including hysterectomy or endometrium destruction, can be considered.22 A rapid decrease in the number of hysterectomies has been observed in the UK,23 with a corresponding rise in the number of endometrial ablations,24 but overall, surgical procedures are decreasing, which can perhaps be ascribed to the increasing use of LNG-IUS over the last decade. This is reflected in the ECLIPSE trial, where 6% (32 of 571 women randomised) had hysterectomies within 2 years, yet 5% (28/571) had endometrial ablation. Our review found that both first and second generation endometrial destruction techniques are associated with higher dissatisfaction rates than hysterectomy, although all three procedures provided high levels of satisfaction, with small absolute differences. The predicted dominance of endometrial destruction is neither being witnessed nor may be warranted.24 The results of an current randomised trial of LNG-IUS compared with a second generation endometrial device also help resolve the question as to first line treatment.25

Technological developments may influence the further uptake of endometrial destruction. Whilst our review found no statistically significant difference in amenorrhea rates between first and second generation techniques, the latter were clearly quicker to perform, and enabled women to return to work and normal activities more quickly.26 Comparing second generation techniques, bipolar radiofrequency ablation seems to offer benefits over thermal balloon in terms of amenorrhea rates and is procedurally quicker than thermal balloon and microwave ablation.27 Again, this
is reflected in UK usage data, with radiofrequency ablation techniques being the most rapidly rising procedure. Whether this market share is sustained will depend on the emergence of simpler, next generation devices, the replacement chosen by users of the microwave ablation system and the increasing pace of out-patient based procedures.

Pain, from cervical dilation and vasovagal reactions are limiting factors for the wider use of out-patient procedures. Only two studies have evaluated the use of any endometrial device under local anaesthesia, both of which employed intracervical anaesthesia. The efficacy of intra- and paracervical anaesthesia in reducing pain during diagnostic hysteroscopy has been demonstrated, but data on the most effective anaesthetic for interventional procedures is lacking. Other aspects, such as the distension media, diameter of the ablative device, and the use of speculum and other cervical instruments may also influence patient discomfort with the procedure. Ultimately, the decision should be left to the women's preference and the operator’s experience.

There has been a long term interest in progesterone antagonists and selective progesterone receptor modulators for treatment for idiopathic HMB and HMB associated with uterine fibroids. Recently, a pair of randomised trials has recently demonstrated the effectiveness of the ulipristal acetate in reducing fibroid size and quickly inducing amenorrhea. However, reversible changes to the endometrium have been witnessed, limiting their indication to short-term pre-operative use. There is potential for use of ulipristal as a first line, long term treatment for heavy menstrual bleeding associated with uterine fibroids, but not without further data on the long-term safety in this population.

**Future Research in Heavy Menstrual Bleeding**

Any further developments in endometrial ablation devices should be compared against the bipolar radiofrequency procedure before widespread adoption. New thermal balloon devices are now on the market which are suitable for the out-patient setting and have shorter treatment cycles. Evidence-based improvements in pain management for diagnostic hysteroscopy should be explored in interventional procedures.

The UK guidelines for heavy menstrual bleeding recommend that for women with a normal uterus, endometrial ablation should be considered preferable to hysterectomy, whilst our review indicates higher levels of dissatisfaction with endometrial ablation. It has been suggested that this difference might be amplified if laparoscopic sub-total hysterectomy was performed, in contrast to the total hysterectomies predominant in the contributing studies. However, a Cochrane review failed to corroborate anecdotal evidence of improved sexual, bowel or urinary outcomes after sub-total hysterectomy. A randomized trial of sub-total hysterectomy compared with second generation ablative techniques would address this uncertainty.
The current epidemiological data on the prevalence of heavy menstrual bleeding are derived from regional surveys and are out-of-date. It is also likely that those presenting in primary care represent only a minority of women experiencing difficulties with their periods. A shift in emphasis away from menstrual blood loss to a more patient-centred definition of HMB that interferes with women’s physical, emotional and social life, is advocated. Thus, the priority for healthcare providers should be to respond to the impact of HMB on women’s day-to-day lives, basing treatment decisions on evidence using patient reported outcomes, such as the validated Multi-attribute Menorrhagia Assessment Scale.