An Investigation of the Surgical Treatment of Endometriosis

by

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Statement of Originality

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Abstract

Background

The surgical treatment of endometriosis has developed in recent decades alongside the development of laparoscopic surgery and has been directed towards understanding and improving the outcomes related to fertility and pain. Little is known about the techniques and instruments actually used by gynaecological laparoscopic surgeons in relation to the evidence available. Furthermore, it is still not clear whether vaporisation or ablation of lesions is as efficacious as excision.

Objectives

Firstly, to internationally survey the views of gynaecologists to find out how they surgically treat endometriosis. Secondly, to determine whether excision or vaporisation is the optimal surgical technique for minimal to moderate endometriosis.

Methods

A 34 question web-based survey was constructed, piloted and sent out by email to the members of the BSGE, ESGE and AAGL to get a snapshot of current practice. A randomised blinded trial of harmonic scalpel excision versus carbon dioxide laser vaporisation for the treatment of minimal to moderate endometriosis in women with pelvic pain was carried out, using as a primary outcome measure EHP-30 Core pain domain, and secondary outcomes for VAS scores for dysmenorrhoea, dyspareunia, chronic pelvic pain and dyschezia, EHP-30 HRQoL measures, and HADS.

Results

From the survey, the predominant view is that endometriomas should be excised and that bowel resection should be avoided if possible in recto-vaginal disease. For minimal to moderate disease, superficial disease can be treated with a combination of excision or vaporisation depending on the case, but that deep disease should be excised.

The trial results show that both excision and vaporisation result in an equally significant proportion of patients showing some level of pain improvement at 12 months (85.4 v 72.9%). However, excision results in a significantly greater extent of improvement for both superficial and deep disease than vaporisation ($p=0.008$). In addition, for deep disease, the extent of improvement in pain with vaporisation is not significant ($p=0.262$). Overall 20% of patients stay the same or get worse.

Conclusions

Excision results in greater pain and quality of life improvement than vaporisation for minimal to moderate disease, and is the optimal technique for the surgical treatment of all types of endometriosis. However it must be taken into account that the range of improvement is wide and a proportion of patients will continue to deteriorate.

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Chapter 1 - Introduction

In the surgical treatment of endometriosis there are two views that favour either vaporisation or excision as the optimal means of treatment. There exist various instruments to carry out these treatments. The “excisers” tend to use electrosurgical or ultrasound instruments to cut around the lesion and remove it along with the underlying fibrotic tissue. The “vaporisers” tend to use lasers, electro-surgery or modified electro-surgical techniques to vaporise the lesion and underlying fibrosis.

The “excisers” claim that the vaporisation of endometriosis is too superficial and does not go deep enough to remove infiltrating tissue. The risk of inadequate treatment or recurrence of symptoms may be greater. The “vaporisers” claim their technique is faster and more efficient for the removal of widespread disease and just as effective. It is unclear why surgeons use one approach or the other and how many are using each approach.

There is only one randomised trial comparing the two approaches. This compares the treatment of rASRM (revised American Society for Reproductive Medicine) (1979) stage 1-2 minimal and mild endometriosis by excision or vaporisation. This trial shows no difference in the two modalities in terms of pain outcome (Wright et al., 2005), although it did not include stage 3 moderate disease. The “excisers“ claim that the more advanced the disease, and the more infiltrating and nodular it becomes, the more important excision becomes. This disease “progression” culminates in the most extreme form of pelvic

endometriosis: the recto-vaginal nodule. This is probably treated by excision, with or without bowel resection, by all endometriosis surgeons. The vaporisation/excision debate is not an issue here.

In our unit we use both vaporisation and excision to treat rASRM stage 1-3 endometriosis. By vaporisation, we mean complete destruction or vaporisation of endometriosis and fibrotic tissue down to underlying normal tissue, not just a superficial treatment as often seen with ablation. At the end of treatment the macroscopic appearance is identical for both excision and vaporisation. With the correct surgical approach, both techniques can be used around sensitive structures including ureters, bladder and vessels. We use CO2 laser for vaporisation and the harmonic scalpel for excision.

The CO2 laser can be used both as a vaporisation and excision tool. At Guildford, Professor Chris Sutton carried out the first randomised double blind controlled trial of ablative surgery using a CO2 laser (Sutton et al., 1994). Harmonic (ultrasound generated) energy has been around for more than a decade as a cutting tool (Feil, 2005). In comparison to electrical energy, it removes the risk of electrical injury and results in less thermal spread to adjacent tissues.

A review of the endometriosis literature in chapter 2 reveals gaps in our knowledge and capabilities in many areas. I have attempted to present a rationale for surgical therapy as the current optimal treatment for endometriosis in most cases. 82% of cases of endometriosis fall into stages 1-3 (Redwine,

1990b). It therefore seems most logical to mainly concentrate on this group in my thesis.

In particular I wish to focus on the fundamental question of whether or not there is a difference between the excision or vaporisation of minimal to moderate endometriosis in terms of improvement in pain scores. To achieve this I aim to critically review the literature for the surgical treatment of endometriosis to see if there is any evidence in favour of one technique over another. I then aim to compare this with the *actual* use of techniques and instruments used by gynaecological laparoscopists. This will be determined by a web-based survey. My thesis therefore divides into the three areas that are listed below:

1. A literature review of the diagnosis, management and treatment of endometriosis with particular reference to surgical management (an earlier version of this review was published in a peer reviewed journal and is at Appendix A) (Barton-Smith et al., 2006).

2. An international survey of techniques and instruments used in the treatment of endometriosis: who is using what and why?

3. A randomised blinded trial of carbon dioxide laser vaporisation versus harmonic scalpel excision of rASRM stage 1-3 endometriosis in women with pelvic pain.

Chapter 2 - Literature Review

A general review

Endometriosis is a common condition of unknown aetiology that can cause pain and infertility in women. It is defined as the presence of endometrial glands and stroma present outside of the uterus (Olive and Schwartz, 1993). It is most commonly found in pre-menopausal women but rarely can also occur in postmenopausal women or pre-menarchal girls.

Prevalence

The prevalence of endometriosis has probably increased over the last one hundred years or so for several reasons. Modern women have many more menses than their predecessors as they spend less of their reproductive lives in a state of pregnancy. Women now have an estimated 450 menses in their lifetime compared to the 100 that their Victorian forebears had. Consequently the frequency of dysmenorrhoea has increased. The introduction of laparoscopy over the last three decades has allowed us to diagnose endometriosis more easily, and nowadays most gynaecologists are able to perform a diagnostic laparoscopy at least. The current prevalence is estimated to be up to 10% (Vessey et al., 1993, Kjerulff K. H., 1996, Vigano, 2004). Vercellini stated in his address to the World Congress on Endometriosis in Maastricht in 2005 that the incidence has not increased in the last thirty years and remains at 2.37-2.49 per 1000 women per year, equating to an approximate prevalence of 6-8% (Hummelshoj, 2006, Leibson et al., 2004). A national epidemiological study of endometriosis within a community based

sample, revealed that the prevalence of diagnosed endometriosis in women aged 18-50 is 1.5% (Ballard et al., 2009). This lower prevalence can be explained by the sample being drawn from women attending primary rather than secondary care.

Localisation and Appearance

Endometriosis is most commonly found in the pelvis (Jenkins et al., 1986). More rarely it is found in remote sites like the lungs and brain (Di Palo et al., 1989, Thibodeau et al., 1987). It has even been found in men (Oliker and Harris, 1971). In the pelvis, it is more frequently left sided (Vercellini et al., 2004). The reason for this left sided dominance is unclear, although the direction of flow of peritoneal fluid been proposed as a possible cause (Chapron et al., 2003).

Endometriotic lesions can infiltrate any structure in the pelvis. They are seen more commonly on the pelvic peritoneum, utero-sacral ligaments, bladder, sigmoid colon and rectum, the most severe presentation being the recto-vaginal nodule. On the ovaries, endometriotic cysts can form that contain a thick “chocolate-like” substance formed from old blood. These cysts are often adherent to the pelvic side-wall. Rarely, the ureter can be infiltrated with endometriosis itself, though stenosis is more commonly due to fibrotic impingement by a proximal uterosacral nodule (Lucero et al., 1988).

Endometriotic deposits can appear in a range of colours and textures from transparent vesicles and white fibrotic plaques to red haemorrhagic flares and blue/black nodular lesions, first systematically described by Martin et al in 1987 (Martin and Vander Zwagg, 1987). These may be superficial or described as

deep if they extend more than 5mm beneath the peritoneal surface. This wide variety of appearance is not always recognised by the general gynaecologist and the diagnosis may be easily missed. Overall appearance may vary from the barely visible through to the “frozen pelvis”.

Epidemiology

There are several large epidemiological studies detailed below that give us an insight into the disease (Hummelshoj, 2006, Treloar, 2005b). The results reveal the depth of the problem for women, their families and society in general, as well as highlighting the current inadequacy in management.

The All Party Parliamentary Group in the UK has so far collected epidemiological data via its on-line questionnaire from 7025 women from 52 countries. It estimates that two million women in the UK suffer from endometriosis. The results of this survey to date show a delay in diagnosis in this cohort averaging 8.3 years. 65% of women complained of being wrongly diagnosed initially. Only a third believed their treatment to be effective. A startling 78% took an average of 5.3 days off work per month and 72% reported relationship problems (Hummelshoj, 2006). These results are similar to those found in a recent Australian genetic epidemiological study of 3895 women diagnosed with endometriosis where the average age of onset of endometriosis symptoms was 20.1 $\pm$6.8 years (Treloar, 2005b). The youngest diagnosed participant in this study was 13 years old. The disease or its antecedent has been diagnosed in females as young as eight years old (Marsh and Laufer, 2005).

Endometriosis is less common in black African women compared with Caucasians and more common in East Asians, but is found in all ethnic groups (Sangi-Haghpeykar and Poindexter, 1995, Hasson, 1976).

Endometriosis is found in 40-60% of women with pelvic pain and in 20-30% of women suffering from infertility (Mahmood and Templeton, 1991, Eskenazi and Warner, 1997, Ajossa et al., 1994). Women with more advanced disease have a higher rate of infertility (19.5% for rASRM stage 1 versus 28.7% for rASRM stage 2-4) (Plumb, 2005).

Risk factors for endometriosis include early age of menarche, short menstrual cycles, long duration of menstrual flow, a family history of endometriosis, and there is an inverse relationship with parity (Vigano, 2004).

Aetiology

Many theories of the aetiology of endometriosis have been postulated since Rokitansky first described the disease in 1860 (Von Rokitansky). Meyer proposed the theory of coelomic metaplasia in 1909 and postulated that tissue, with the potential to develop into endometrial-like cells later in life, was laid down in the trans-embryonic coelom (Meyer, 1909). Halban proposed the possibility of haematological or lymphatic spread from the endometrium in 1924 (Halban, 1924). Sampson proposed the theory of retrograde menstruation in 1927 (Sampson, 1927) and this has become the “default” explanation.

However, there remain several problems with Sampson’s theory. There is little doubt that reflux menstruation occurs. Bloody peritoneal fluid is found in 80-

90% of menstruating women (Blumenkrantz et al., 1981, Halme et al., 1984) compared with only 15% of women with occluded fallopian tubes. However, most women do not develop endometriosis. Moreover, the cells found in endometriosis are not identical to normal endometrium (Redwine, 2002) and endometriosis does not generally recur if treated surgically as one might expect if retrograde menstruation was to continue (Abbott et al., 2003, Redwine, 1991). Also, it does not explain the small, but nevertheless relevant, occurrence in men, pre-menarchal girls and post-menopausal women.

Consequently, all of the above theories remain in the frame to this day with no clear evidence having emerged for either one. Despite being the dominant theory, it seems likely that Sampson's view was over simplistic.

More recent advances in technology have permitted the emergence of new theories. Altered immune function has gained credibility with those seeking to find a basis for the discrepancy between the frequency of retrograde menstruation and the infrequency of endometriosis. This theory was first postulated in 1987 by Gleicher (Gleicher et al., 1987), who suggested that immune system alterations result in a failure to "mop up" ectopic endometrial cells and therefore allow them to infiltrate at the site of disease. Immune system alterations in endometriosis sufferers have been shown in natural killer (NK) and cytotoxic T cells, and aberrations have been found in immune mediators such as tumour necrosis factor-α, Interferon-γ and polyclonal B-cell auto antibodies (Kitawaki et al., 2002).

Simpson first suggested a genetic basis for endometriosis in 1980 (Simpson et al., 1980). This is likely to be complex and polygenic in nature. Linkage study work has now shown a susceptibility locus on Chromosome 10q26 (Treloar, 2005a). Work is also progressing in other areas including studies of expression profiling, tumour genetics and functional candidate genes (Barlow and Kennedy, 2005).

There is evidence suggesting that endometriosis may increase the risk of cancer. Brinton's work looking at cancer risk after a diagnosis of endometriosis shows a relative risk of 1.18 for developing cancer of any form, and a relative risk of 1.92 for developing ovarian cancer (Brinton et al., 1997). The K-ras oncogene and P-ten tumour suppressor gene appear to be involved in this process. Mice with either of these gene mutations developed endometriosis, and mice with both gene mutations simultaneously produced endometrioid ovarian adenocarcinoma (Dinulescu, 2005). Clinically, the endometrioma is of most concern as far as malignancy risk is concerned; a risk of 0.7% has been suggested (Nishida et al., 2000), and in one more recent report, 7% of endometriomas contained a neoplastic process (Bedaiwy et al., 2009).

The theory of progesterone resistance is the most recent to emerge. In his review, Osteen has suggested that the impaired regulation of matrix metalloproteinases, that has already been shown to increase the implantation potential of the endometrial tissue (Bruner-Tran et al., 2002), may be due to a decreased responsiveness to progesterone (Osteen et al., 2005).

Other aetiological theories rely on environmental factors. Nutritionally, wheat has been implicated as a potential source of exacerbation in endometriosis. Manipulation of the diet in endometriosis sufferers resulted in an improvement in prospectively collected “measure yourself medical outcome profile scores” (MYMOP) that measure symptom improvement (Shepperson Mills, 2004). Other potential environmental agents include organochlorines (PCBs and dioxins). In rodents and primates these promote the development of endometriosis and have been found in higher concentrations in human sufferers (Heilier, 2004).

Whilst endometriosis has been shown to be a predominantly oestrogen dependent disease, the underlying pathophysiology that creates the conditions for oestrogen to drive the development of endometriosis is likely to be multi-factorial and include many of the above possibilities.

Diagnosis

The main clinical symptoms of endometriosis are infertility, dysmenorrhoea, dyspareunia, dyschezia, and chronic pelvic pain (defined as pain of greater than six months duration and not cyclical in nature) (Jantos, 2007). Other symptoms seen less commonly include haematuria and rectal bleeding. Making a diagnosis purely on presenting symptoms is difficult as there is considerable overlap with other conditions. This often results in a delay in diagnosis of between five and ten years (Treloar, 2005b, Hadfield et al., 1996, Husby et al., 2003, Arruda et al., 2003, Ballard et al., 2006). This is an important finding when one considers that endometriosis is a progressive disease that worsens with time (Koninckx et al., 1991, Matsuzaki, 2004). The delay in diagnosis may also result in associated psychological morbidity (Jones et al., 2004b).

Clinical signs on examination can also be difficult to elicit. Endometriotic nodules on the utero-sacral ligaments or in the recto-vaginal septum may be palpable and are easier to feel on a combined vaginal-rectal examination. These are most reliably palpated if the examination is undertaken during menstruation (Koninckx et al., 1996). In some cases endometriosis invading through the vaginal mucosa may be visible on speculum examination. It remains to be seen whether symptom profile questionnaires alone, without invasive testing, will be able to improve diagnosis (Ballard et al., 2009).

The gold standard for diagnosing endometriosis in the abdomen and pelvis is the visual identification of characteristic lesions at laparoscopy. In one study, this means of diagnosis was shown to be 97% sensitive and 77% specific (Buchweitz et al., 2003). Lesions may also be visually confirmed on vaginal speculum examination, in the bladder at cystoscopy or in the bowel mucosa at sigmoidoscopy. It is considered good clinical practice that the diagnosis is confirmed by histology of at least one lesion (Kennedy, 2004).

However, negative histology does not exclude the diagnosis as explained by Clement who describes the potential alterations in glandular and stromal components of endometriosis, especially in small biopsy specimens resulting in false negative results (Clement, 2007, Shafik A, 2000). A correlation of 88% was found by Ballard between visual inspection and positive histology (Ballard et al., 2009). It should also be noted that visual inspection alone can produce false positive diagnoses as lesions may be mimicked by psammoma bodies caused by old haemorrhage or suture material from previous surgery for example (Martin and Vander Zwagg, 1987).

It is recommended that histology should be obtained for endometriomas of >3cm diameter and deep disease, to exclude rare cases of malignancy (Kennedy, 2004). Disease sites and depths should be mapped and recorded (Kennedy, 2004) to allow adequate reassessment of the disease subsequently.

Many other tests have been employed to aid in diagnosis without resorting to surgery. CA125 is raised in some cases, but the test remains non-specific. Most endometriosis sufferers are pre-menopausal and there are many other causes, both pathological and physiological, for a raised CA125. Therefore it has been argued that, compared with laparoscopy, CA125 has no value as a diagnostic tool in endometriosis (Mol et al., 1998). Furthermore, if the level is raised in an endometriosis case and applied to a risk of malignancy index, then there remains the possibility of the woman being subjected to an unnecessary laparotomy for a high-risk score. If a laparoscopy is carried out first then a laparotomy may be avoided.

New serum tests are being developed. One such test is based on the detection of autoantibodies against Thomsen-Friedenreich antigen bearing proteins found in endometriosis. Current sensitivity and specificity results are 80% and work to improve these is underway (Hummelshoj, 2006). Also, gene expression analysis is beginning to identify potential markers of endometriosis in peripheral blood samples as well as in endometriotic lesions (Hornung, 2005, Van Langendonckt, 2004).

Ultrasound is commonly used as a diagnostic tool in most gynaecological departments. Trans-vaginal ultrasound (TVS) is not a useful tool in the

diagnosis of peritoneal endometriosis although it is useful for diagnosing endometriomas, disease infiltrating the bladder (Moore et al., 2002, Bazot et al., 2004b) and is becoming a more successful tool for the diagnosis of recto-vaginal disease too (Hudelist and Keckstein, 2009). Also, trans-rectal ultrasound is a useful tool in diagnosing deep infiltrating disease in the recto-vaginal septum (Chapron et al., 2004).

Magnetic resonance imaging (MRI) has been shown to be of use in diagnosing the extent of deep nodular disease, particularly in the recto-vaginal septum (Bazot et al., 2005, Bazot et al., 2004a). Fat suppression MRI films and the use of phased array coils appear to offer even better images that can show the level of invasion into the bowel wall itself. In the future this may help tailor how radical the excision of recto-vaginal nodules should be prior to surgery. A recent report from Bazot suggests “MRI provides a more reliable map of DIE than physical examination, TVS or trans-rectal ultrasound” (Bazot et al., 2009).

CT scans do not offer the required resolution to do this, although spiral CT may be better. Double contrast barium enema alone has been shown in two recent studies to have close to 90% sensitivity, and specificity ranging from 54 to 88% (Ribeiro et al., 2008, Faccioli et al., 2008). For suspected ureteric involvement, an intravenous urogram (IVU) or MRI may be used and a cystoscopy may be required to assess the bladder mucosa (Bazot et al., 2008).

Staging the disease in a way that gives useful information about the extent of pain or fertility, its management and prognosis, has so far eluded us. With endometriosis, the extent or type of disease is not clearly correlated with pain

levels. Several systems have been attempted, often based upon the visual findings during laparoscopy, histological examination or a combination of the two (Acosta et al., 1973, Batt and Mitwally, 2003, Adamyan et al., 1993). The most commonly used one to date is the revised American Society for Reproductive Medicine (rASRM) originally produced in 1979 (1979) and revised in 1985 (1985) and 1997, which grades endometriosis as minimal (stage 1), mild (stage 2), moderate (stage 3) and severe (stage 4) (1997).

Chapron argued that all of these systems fail to correlate well with symptoms of pain and fertility (Chapron et al., 2003, D'Hooghe et al., 2003) or aid in prognosis. He argued that including palpation to assess depth clinically was required. This concept of considering depth further was picked up in the Enzian system (Tuttlies et al., 2005). Further elucidation of the pathophysiology of the disease will hopefully facilitate the development of more useful scoring systems.

We have begun to speak more about two types of disease, superficial and deep infiltrating endometriosis (DIE), as evidence emerges that these two forms of the disease may behave differently from each other (Garry, 2004). That superficial endometriosis is less severe in its symptoms and complexity of management, is one of the subjects to be considered in this thesis. In the light of all this evidence, future scoring or staging systems may be more appropriately aimed at predicting surgical morbidity or the appropriateness of radical surgery as Wright suggested in his unpublished thesis on surgical endometriosis. That being said, a new validated endometriosis fertility index (EFI) has been developed by Adamson (Adamson and Pasta, 2009). It is designed for patients who are attempting spontaneous conception and is an

intra-operatively derived score from visual assessment of the ovary, tube and fimbria, the patient's age, years of infertility and previous pregnancies to give a graphical display of the chances of spontaneous conception over time. Its full evaluation in clinical practice is awaited.

Medical treatment

In most cases, women who reach the gynaecology clinic will already have been treated with non-steroidal anti-inflammatory drugs (NSAIDs) in primary care. Although there is some evidence that these drugs reduce endometriosis-related pain (Kauppila et al., 1979), the majority of women presenting to the gynaecologist in secondary care will report little benefit from this therapy.

In the first half of the twentieth century the treatment and diagnosis of endometriosis had been surgical. In this era it became apparent to some observers, like Meigs, that there was a lower rate of pregnancy amongst endometriosis sufferers. He theorised that pregnancy itself was a prophylaxis or even treatment for endometriosis (Meigs, 1922). From this observation there grew attempts to hormonally create a "pseudo-pregnancy state" as a treatment (Kistner, 1958). This is the basis for the use of progestogens and combined oral contraceptives (COCP) in medical therapy.

Similarly, it was noted that endometriosis is a disease of predominantly pre-menopausal women. Therefore castration was recommended as a therapy to remove the oestrogen source driving the disease (Cattell R., 1936, Fallon, 1946). From this developed the theory of creating a "pseudo-menopausal state" to treat endometriosis, and this forms the other cornerstone of current medical

therapy. Danazol and gonadotrophin-releasing hormone agonists (GnRH agonists) are employed along these lines (Audebert et al., 1977, Shaw, 1992). Cochrane reviews suggest that there is no benefit, in terms of pain relief, in favour of the pseudo-pregnancy over the pseudo-menopausal treatment strategy (Moore, 2004, Selak, 2004). All approaches appear equally efficacious and provide benefit for up to six months following the cessation of treatment. Consequently, the choice of drug will be driven more by the side effect profile and contraceptive requirements of the women. The levonorgestrel intrauterine system (LNG-IUS) also appears to be of equal benefit as well (Vercellini et al., 1999a, Petta et al., 2005).

The optimum duration of GnRH therapy is unclear. Extending GnRH therapy beyond three months up to six months does not seem to confer greater benefit in terms of sustained pain relief (Hornstein et al., 1995). However, extension of treatment up to two years appears to be safe, in terms of bone protection, if add-back hormone replacement therapy is used (Surrey et al., 2002). Also, GnRH analogues used as a post operative adjunct to surgical treatment delay the recurrence of pain compared with expectant management after surgery (Vercellini et al., 1999b).

In terms of actual disease regression, medical therapies have been shown to reduce the extent of disease found at laparoscopy (Telimaa et al., 1987, Fedele et al., 1989, Cedars et al., 1990), but not to eradicate it entirely.

The European Society of Human Reproduction and Embryology (ESHRE) guidelines for the management of endometriosis, suggest that it is good clinical

practice to use counselling, analgaesia and nutritional therapy combined with progestogens, the COCP or GnRH analogues, as an empirical treatment for pelvic pain presumed to be endometriosis (Kennedy, 2004). If a laparoscopy is carried out, ESHRE guidelines then logically recommend that, as the gold standard for diagnosis is laparoscopy, *ideal* clinical practice should be to surgically remove endometriosis at the same time. Surgery is the only means of ensuring complete removal of visible disease.

Whilst a laparoscopy undoubtedly carries risks, endometriosis is a progressive disease and delaying surgical intervention might lead to a greater risk of compromised fertility as well as pain although there is no direct evidence of this. Most women have already tried analgaesia and hormonal intervention in primary care, so in such cases ideally an operative laparoscopy should be carried out as first line treatment if symptoms have been sufficient enough to warrant referral to a gynaecologist.

As understanding of the pathophysiology behind endometriosis improves, novel medical therapies are emerging. These include GnRH antagonists (Kupker et al., 2002), mifepristone (RU486) (Kettel et al., 1996), TNFα inhibitors (Falconer et al., 2006), angiogenesis inhibitors (Becker and D'Amato, 2007), matrix metalloproteinase inhibitors (Osteen et al., 2003), pentoxifylline (Creus et al., 2008) and aromatase inhibitors (Nawathe et al., 2008). These agents are mostly in the experimental stage of use.

Where pelvic clearance is performed, and hormone replacement therapy (HRT) required, then a theoretical benefit exists for including progesterone in the form

of combined HRT. Firstly, the addition of progesterone may prevent recurrence of endometriosis. Secondly, a lack of protective progesterone may result in endometrial carcinoma arising from endometriotic lesions after total abdominal hysterectomy and bilateral salpingo-oophorectomy (Ulrich, 2005). However, this has to be weighed against the possible increased risk of breast cancer in combined versus Oestrogen only HRT (Beral, 2003).

Measuring outcome

Second look laparoscopy to assess the state of the pelvis requires another surgical procedure that is most likely unnecessary, and does not give information on improvement in pain and quality of life issues. Therefore other measures are required to assess improvement peri-operatively. Visual analogue scores for pain, quality of life measures, mental state and sexual function questionnaires have been used. There is an endometriosis-specific validated questionnaire, called the Oxford EHP30 questionnaire (Jones et al., 2001), that assesses the impact of endometriosis on different aspects of life.

Multidisciplinary approach

Pelvic pain is not exclusive to endometriosis and there is a degree of crossover with other conditions like interstitial cystitis and irritable bowel syndrome. There is also a degree of psychological morbidity. Specific pelvic pain clinics that adopt a multidisciplinary approach encompassing a wider range of pathologies and treatments are more likely to offer improved support and relief to women (Metzger, 1997). They can also develop links with infertility clinics, colorectal surgeons, urologists, anaesthetist-run pain clinics, psychologists and patient support groups. Multidisciplinary pain clinics have been shown to be effective in

the management of other chronic conditions such as back pain (Guzman et al., 2001). Endometriosis UK, the patient support group, now helps run a Department of Health sponsored Expert Patient Programme to teach women how to live with their symptoms (www.expertpatients.co.uk).

A critical review of the surgical treatment for endometriosis

There are no clinical trials directly comparing surgical and medical treatment for endometriosis. As no direct comparisons are available we must rely on other evidence to weigh up the pros and cons of each approach.

Unlike medical therapy, surgery can diagnose and remove all macroscopic disease at the same procedure in the majority of cases. Even severe macroscopic disease can be entirely removed surgically. Remember also that surgery is the gold standard for diagnosis of most endometriosis. Surgical therapy compared to placebo can result in a continuing positive effect on pain at 6 months after surgery (Sutton et al., 1994, Abbott et al., 2004). Both authors also have data suggestive of this effect lasting even longer (Sutton et al., 1997b, Abbott et al., 2003). Treatment at laparoscopy seems to also improve rates of spontaneous conception for infertility associated with endometriosis (Marcoux et al., 1997). The evidence for this is analysed in greater detail below.

The development of techniques to remove endometriosis surgically has been governed by the development of energy sources used in surgery. Most surgeons would regard complete excision or complete vaporisation as the preferred techniques for removing endometriosis surgically. These remove the

active lesion and the underlying fibrosis, both of which are considered to have a causal link to pain. Only normal tissue remains. Superficial electro-coagulation with diathermy may destroy the active lesion but may also leave the treated tissue and the underlying fibrosis. Applying prolonged diathermy may also increase the risk of collateral damage.

Cold scissors may be used to excise endometriosis. However, most surgeons prefer an energy source that gives them a degree of haemostasis as well as the precision of cold scissors. Electrical energy is most effectively used in its monopolar form to excise endometriosis. For example, 3mm monopolar scissors used at a high power of 90 Watts are a precise means of excision (Redwine, 1993). Electro-surgical energy essentially cuts and coagulates by applying high levels of heat to the target area. There is a potential of collateral damage by heat spread proximal to the target area, insulation failure, direct coupling or capacitive coupling. Bipolar energy is not a useful energy source for effective excision or vaporisation.

Several modified electro-surgical devices have been developed to reduce the amount of electrical energy required to cut or coagulate. These devices include the argon beam coagulator (Daniell et al., 1994) and Helica Thermal Coagulator (Nardo et al., 2005). Both have been used for the coagulation of superficial deposits of endometriosis.

Ultrasound generated energy is also a precise means of excision with simultaneous haemostasis. Ultrasound energy is converted to high-speed motion in an active blade. This cuts and causes haemostasis, by coaptation

more than coagulation, at a lower temperature than electrosurgical energy. Consequently there is a trend towards less heat damage to adjacent tissues in human and animal studies (Awadzi, 2005, Meltzer, 1994). Also, ultrasound energy devices are free from the risks of insulation failure, direct coupling and capacitive coupling as no electrical energy passes down the instruments. Haemostasis is good but not as effective as electro-surgery.

Lasers can be used for either the excision or vaporisation of endometriosis (Bruhat et al., 1989, Sutton, 1989). The common lasers employ carbon dioxide (CO2 laser) or yttrium aluminium garnet modified with potassium tinanyl phosphate (KTP laser) to create a highly focused visible light beam that cuts tissue precisely by heat. Excision is precise and quick however haemostasis is not as good as electrical or ultrasound energy. Vaporisation is achieved by moving the beam around over the target area until only an underlying area of normal tissue remains. With the Swiftlase function on Sharplan CO2 lasers, the beam is automatically rotated around the aiming point, making vaporisation easier.

The choice of energy source, instrument and technique is probably controlled by various factors, including what the surgeon is comfortable with, what they believe to be best, what they have available, whether the instruments are safe, and the cost. However, there exists no data on why surgeons use which technique or which instrument.

In addition to different techniques, there are three distinct areas of surgical treatment for endometriosis: minimal to moderate endometriosis, endometriomas, and lastly, recto-vaginal nodules.

Surgical treatment of peritoneal endometriosis for Infertility

As yet there has been no direct causal link established between sub-fertility and endometriosis (Vercellini et al., 2009). According to Hughes Cochrane review of the subject (Hughes et al., 2003) there is no evidence to suggest that medical therapy with hormonal drugs is beneficial for women with endometriosis-associated infertility. Hughes, in a separate paper reviewing 5 cohort studies and a quasi-randomised study, suggests that laparoscopy is superior to Danazol by an odds ratio of 2.7 in terms of pregnancy incidence (Hughes et al., 1993). Evidence does exist to suggest that surgical treatment may be of benefit in all stages of the disease including endometriomas (Jacobson et al., 2004b, Adamson et al., 1993, Guzick et al., 1997, Osuga et al., 2002).

Jacobson's Cochrane meta-analysis of minimal to mild endometriosis, "Laparoscopic surgery for sub-fertility associated with endometriosis" (Jacobson et al., 2004b) since updated in 2009 with no significant changes, includes the EndoCan trial of 341 patients (Marcoux et al., 1997), which shows a beneficial effect for laparoscopic treatment, and the Italian Group trial which shows no significant difference and a slight negative effect on live births (dell'Endometriosi, 1999). The meta-analysis of the two trials shows an improvement in fecundity with surgical therapy with an odds ratio 1.6 (95%CI 1.05 to 2.57) of pregnancy progressing beyond 20 weeks gestation or live birth.

Jacobson has commented that this result should be treated with caution, as the two results are contradictory.

On further analysing the two trials we find that both had strict eligibility criteria at the outset. Both had power calculations (although the Italian Group trial ended up being underpowered as it was attempting to show the 2.7 odds ratio suggested by Hughes above). The entry criteria for the Italian Group trial were two years of infertility, versus one year for the EndoCan trial. The Italian Group subjects probably reflect a group of patients with poorer prognosis at the outset as a result. There were also more stage 2 cases of disease in the Italian Group that may have disadvantaged it. The eligibility for the EndoCan trial restricted the visual diagnosis of endometriosis to blue or black lesions only and so missed a whole cohort of other appearances. Neither trial confirmed the presence of endometriosis with histology and so the possibility of false positive diagnoses exists. Surgical technique is not clearly explained in either trial and with the number of centres and surgeons involved there is a distinct possibility that the quality of treatment between the two trials was not consistent. Neither trial was blinded, so there were potential performance biases involved in that patient knowledge of which treatment had been received may have affected the sexual behaviour of participants subsequent to surgery. The two trials had different follow-up periods: 9 months for the EndoCan trial and 12 months for the Italian Group. However, about half of the Italian Group patients had 3 months of adjuvant GnRH analogue treatment after surgery, meaning that there were also 9 months available to them to conceive in half of the cases. This addition of adjuvant therapy also created new subgroups of treatment though no significant differences were shown in any of them in the analysis.

On balance there appears to be some positive effect on fertility with laparoscopic surgery for treating endometriosis but it may be less substantial than originally suggested and recent reviews appear to be downplaying the positive benefits (Vercellini et al., 2009). In addition, the EndoCan group calculated from their data that one in eight women should benefit from laparoscopic treatment of endometriosis. In Jacobson's meta-analysis (Jacobson et al., 2004b), the suggestion was that the number needed to treat for one additional ongoing pregnancy beyond 20 weeks lies somewhere between 3 and 100. Therefore, this evidence does not clearly indicate that all women suffering from infertility should undergo laparoscopy to purely look for endometriosis alone, as potentially only 1 in 8 of the 20% to 68% likely to have infertility associated with the presence of endometriosis are likely to benefit (1994, Koninckx et al., 1991, Mahmood and Templeton, 1991, Matorras et al., 1995). However, in the absence of gamete problems, laparoscopic treatment of endometriosis can be recommended for endometriosis found at laparoscopy in association with infertility, especially if it can be removed at the same time as diagnosis.

Endometriomas

Medical treatment has shown a significant reduction in the size of endometriomas (Schenken, 1990, Batioglu et al., 1996) but there remains the risk of ovarian torsion, a small risk of malignancy, continued pain and the effect on fertility to consider. Surgery had already been touted as beneficial for fertility as far back as 1957 (Fredrikson, 1957). Furthermore, in modern times laparoscopy has not been shown to be disadvantageous compared with laparotomy, as shown by the many reports that considered this during the rise

of laparoscopy in the 1990s (Daniell et al., 1991, Donnez et al., 1996, Adamson et al., 1992, Sutton et al., 1997a). Research then moved on to consider the technique that should be used to best treat endometriomas considering the outcomes in respect to pain, recurrence, reoperation, ovarian function and fecundity. It became clear that fenestration alone was inadequate (Vercellini et al., 1992) and so the front runners became either straight excision of the pseudo-cyst capsule or some combination of fenestration and coagulation involving varying energy sources and the possibility of staged procedures with adjuvant GnRH analogue therapy. Energy sources for ablation have included electro-cautery (Beretta et al., 1998, Alborzi et al., 2004b), CO2 laser (Donnez et al., 1996) and KTP laser (Sutton and Jones, 2002). The two-staged procedure allows for initial drainage, followed by down regulation for several months with GNRH analogue, to then permit definitive coagulation of the capsule and treatment of peritoneal lesions (Donnez et al., 1994).

Randomised evidence appeared in three trials since 1998 (Beretta et al., 1998, Alborzi et al., 2004b, Alborzi et al., 2007b) that were considered together by Hart in his Cochrane review (Hart et al., 2008). On reading the methodologies for the 1998 and 2004 trials by two separate authors they appear to be very much based on each other, with some small variations. Fecundity seemed to be the primary outcome variable though this was not stated in either trial and neither was a power calculation done. Both trials appeared to have rigorous eligibility for infertility. It should also be noted that in neither trial were patients blinded from the treatment, and the investigators did not appear to be blinded from follow-up either. Pain outcomes were only judged by a single VAS for varying types of pain and were dichotomised into levels of severity. It is not

clear from either paper how recurrence of pain was derived and objective pain results are not described. In both trials fertility was judged by positive pregnancy on ultrasound, and not by pregnancy outcome. Recurrence of disease was judged by the recurrence of probable endometriomas greater than 3cm diameter on ultrasound. Pain is a subjective measure, and the lack of blinding of patients is particularly concerning in this respect despite excision resulting in a significant reduction in recurrent pain. That being said, the evidence for fertility improvement and reduced recurrence with excision is strong in Hart's meta-analysis: the spontaneous conception rate was OR 5.21, 95%CI 2.04 to 13.29, and the reduced recurrence rate of OR 0.41, 95%CI 0.47 to 4.15. The combination of evidence was compelling in favour of excision when electro-surgery is used for coagulation. With KTP laser there is a suggestion that pregnancy rates may be more comparable with excision (57% for KTP versus 59% in Alborzi's trial) (Jones and Sutton, 2002, Alborzi et al., 2004a). This has some logical credibility, though the evidence is not strong enough to draw firm conclusions, as the KTP laser penetrates well on the wet surface of an endometrioma, whereas CO2 laser penetration is stopped at a liquid interface, suggesting that the KTP may be more effective at destroying the pseudo-cyst.

More recently research has shifted towards concern regarding damage caused by excision that might compromise ovarian blood supply, ovarian reserve and the potential success of assisted conception techniques. Consequently Canis has suggested a combination of excising the outer part, and ablating the deep inner part of the capsule proximal to the hilum (Canis et al., 2003), but there is no evidence yet for this approach and coagulating the hilar area may potentially cause more damage than excision of the capsule from this area. Current

research is beginning to be directed towards Anti-Mullerian Hormone as a marker for ovarian reserve and variations that may be found between excision and ablation (Lemos et al., 2008). All this being said, the Cochrane evidence still supports the evidence that higher spontaneous pregnancy rates result from excision, and even that the follicular response of ovaries to GnRH analogue after excision is higher for assisted conception (Alborzi et al., 2007a). However there is no evidence of improved outcomes of IVF following excision of endometriomas (Garcia-Velasco and Arici, 2004). There probably does remain a small risk of significant ovarian damage and potential ovarian failure from over-aggressive excision treatment with a rate of up to 2.6% in a retrospective review by Busacca (Busacca et al., 2006).

Recto-vaginal nodules

These cases present the ultimate surgical challenge for gynaecological laparoscopists in centres specialising in the treatment of endometriosis. The presence of a recto-vaginal nodule is not always obvious, either on recto-vaginal examination or at laparoscopy. Deep infiltrating disease is under-diagnosed as it may appear to be minimal disease if one only assesses its surface appearance (Koninckx et al., 1994). Usually there is obliteration of the Pouch of Douglas to a greater or lesser extent that can be easily missed by inexperienced eyes.

Radical excision of recto-vaginal disease was known to carry a high morbidity and mortality and so was still regarded as less preferential to menstrual suppression in the mid part of the 20th century. However, evidence of bowel resection being used by some surgeons does exist coming into the 1970s

(McSwain et al., 1974, Gray, 1973, Cromer, 1967). Weed published his series of 163 cases of resection of bowel endometriosis at laparotomy in 1987, as laparoscopy began to develop (Weed and Ray, 1987). It is interesting that this series, and the 72 women undergoing bowel resection in Coronado's series in 1990 (Coronado et al., 1990), made no report of significant morbidity. Crosignani and Vercellini reviewed the relative benefits of laparoscopy and laparotomy in 1995 and found no difference between the two in terms of endometriosis outcome suggesting that technological advances in laparoscopy were already advanced enough to allow comparable results for even this complex area of surgery (Crosignani and Vercellini, 1995). Also, the benefits of laparoscopy over laparotomy in terms of recovery, pain and hospital stay were already becoming apparent (Luciano et al., 1992).

The literature then continues in a procession of case series reports to the present day, here reviewed in a table constructed by Wright and presented at the ESGE Annual Meeting in Florence in 2009:

Table 1. A summary of case series for the treatment of recto-vaginal endometriosis

Authors	Date and Number of cases	Reported Bowel fistulae/leaks n (%)	95% confidence limits
McSwain	1974/14	0	0-0.215
Weed	1987/53	0	0-0.068
Chen	1989/2	0	0-0.658
Coronado	1990/76	0	0-0.048
Redwine	1999/5	0	0-0.053
Nezhatz	1986/22	0	0-0.068
Bailey	1994/130	0	0-0.029
Donnez	1995/231	0	0-0.016
Koninckx	1994/285	1 (2.85)	0.001-0.02
Jerby	1999/12	1 (8)	0.015-0.354
Verspyck	1997/6	1 (16)	0.030-0.564
English	2004/100	4 (2.5)	0.016-0.098
Darai	2007/71	6 (8.5)	0.039-0.172
Keckstein	2005/202	6 (2.9)	0.014-0.063
Slack	2007/32	3 (9.3)	0.032-0.242
Waters	60	5 (8.3)	0.036-0.181
Possover	2000/34	0	0-0.102
Total	1335	28 (0.21)	0.015-0.03

(Bailey et al., 1994, Chen et al., 1989, Coronado et al., 1990, Darai et al., 2007, Donnez and Nisolle, 1995, Ford et al., 2004, Jerby et al., 1999, Keckstein and Wiesinger, 2005, Koninckx and Martin, 1994, McSwain et al., 1974, Nezhat et al., 1994, Possover et al., 2000, Redwine et al., 1996, Slack et al., 2007, Verspyck et al., 1997, Weed and Ray, 1987).

This review by Wright considers a total of 948 cases of endometriosis undergoing surgical treatment for their disease. The overall complication rate was calculated to be 1.7% (95%CI 1 to 2.7). However, the more recent series in table 1 above seem to be showing up a higher frequency of bowel leaks and fistulas. This is an interesting finding that may reflect the fact that complication data was previously under-reported, or that the complexity of cases attempted has increased. Women presenting with recto-vaginal nodules need to be carefully counselled and prepared if surgery is being considered, as there now appears to be a genuine 4-10% risk of major complications associated with sigmoid and rectal surgery that is confirmed in the experience of general surgeons treating rectal cancer too (Canis, 2005, kenney, 2005). Acutely, these

include anastamotic leaks, fistulas and urinary system damage as well as the chronic bowel morbidity resulting from strictures and short bowel syndrome. It appears that these strictures may be more common in endometriosis patients than in those undergoing rectal resection for rectal cancer (Waters N, 20008) representing possibly the underlying fibrotic nature of endometriosis. Despite Dubernard reporting an improvement in all items of SF-36 for a series of 58 colorectal resections of endometriosis, the major complication rate was 15.5% and tenesmus, constipation and bowel frequency were not improved in the long term (Dubernard et al., 2006).

Surgically, a combined approach with a laparoscopic colorectal surgeon may be undertaken. The sigmoid colon and rectum are dissected away from the ureters, pelvic side-walls, uterus, cervix and vagina. Following this the endometriotic nodule or nodules are removed from the bowel. In the most conservative technique this is done by shaving the nodule off the bowel, thereby avoiding perforation of the bowel mucosa. However, if entering the bowel is necessary to remove the disease a disc resection may be performed that is subsequently closed by primary laparoscopic suturing. In cases where a nodule is deeply infiltrating over a larger area, and it is considered that disc resection could result in stricture, anterior or segmental resection may be carried out. Multiple sites of disease, that would otherwise require multiple disc resections, may also be treated by segmental resection. Recommending surgery as the main primary treatment is by no means the only option. With the risk of complications, patients may prefer to consider long-term medical therapy instead. Or, if pregnancy is the main requirement, then IVF may be preferential as a first line treatment.

We do not know which is the optimum technique to surgically remove recto-vaginal disease. There are no RCTs and it would be very difficult to produce a robust trial to investigate this. Some surgeons advocate segmental resection in all cases as they believe that it is the only way to remove all disease, especially as there is evidence to suggest that up to 68% of patients have multiple lesions (Keckstein, 1999). Others believe that there is gene-profiling evidence emerging to suggest that the nodules are cervical in origin, and so surgery should be more radical on the cervico-vaginal side and less radical on the rectal one in order to decrease bowel complications and risk of recurrence (Van Langendonckt, 2004). Overall success rates of surgery for recto-vaginal nodules in terms of pain relief are in the region of 85-95% with recurrence rates of 5-15% (Canis, 2005) though the positive effects on fertility are less clear. Pain recurrence was estimated at 28% in Dubernard's series despite colonic resection (Dubernard et al., 2006). In addition to this, Abbott showed in his 2-5 year follow up of women undergoing laparoscopic excision for all stages of endometriosis that the risk of requiring subsequent surgery was 33%, estimated at 36% over 5 years, and that women with deep infiltrating stage 4 disease were significantly more likely to be in this group showing that their risk of re-operation was even higher (Abbott et al., 2003).

In summary, despite favourable improvement in pain symptoms after radical surgery, the acute complication risk, long-term bowel morbidity and the risk of recurrence tend to favour a more "conservative" radical approach, whereby as much endometriosis as possible is removed with the least risk of sustaining bowel complications. The level of pain improvement has not been shown to be

any worse for a more “conservative” approach. This seems particularly important in view of the fact that endometriosis is not lethal and has a substantial likelihood of recurrence despite how aggressive the resection is. In addition to this, the progress in robotic surgical techniques, allowing state-of-the-art 3D vision and unparalleled precision, may allow for more accurate excision of recto-vaginal endometriosis with reduced bowel morbidity (Magrina, 2007).

Surgical treatment of minimal to moderate endometriosis for pelvic pain

In the laparoscopic era of surgery for endometriosis, various techniques for operating on minimal to moderate endometriosis developed side by side, but can broadly be put into the categories of excision, vaporisation or ablation/coagulation. Excision is in a clear category of its own with no doubt over the technique of staying in normal tissue and excising around the suspected lesion. Ablation and coagulation are terms that have been used frequently to describe the application of heat energy to a lesion to result in its destruction. These terms reflect a wide range of resulting effects from just applying heat to the surface of a lesion leaving a charred area of tissue that probably represents sub optimal treatment, through to full destruction of tissue resulting is an appearance of normal tissue similar to excision. For that reason the use of the word “vaporisation” is perhaps more appropriate to describe the technique where energy is applied to a lesion where the outcome appears similar to excision. These varying approaches were reported in various case series throughout the 80s and 90s (Redwine, 1996, Candiani et al., 1986, Lomano, 1987, Martin and Vander Zwagg, 1987, Redwine, 1991).

Sutton then produced the first RCT looking at the surgical treatment of minimal to moderate endometriosis for relief of pelvic pain in 1994 with a series of 63 patients (Sutton et al., 1994). Patients underwent laser vaporisation of all lesions with or without the addition of adhesiolysis and utero sacral nerve transection or had diagnostic laparoscopy alone. Patients completed VAS pain scores based on their worst symptom from dysmenorrhoea, dyspareunia and pelvic pain (which was dysmenorrhoea in all cases), at 0, 3 and 6 months. Scores were not significantly different at 3 months but became significant at 6 months with 62.5% of the treatment group improving. There was no power calculation included in the report, no information on allocation concealment and no data on quality of life, yet this gave the first substantial evidence that surgical treatment was effective. However, it has subsequently been established that there is no evidence that laparoscopic uterine nerve ablation (LUNA) by itself or combined with surgical removal of endometriosis is of benefit for women with pelvic pain and endometriosis (Vercellini et al., 2003, Johnson et al., 2004, 2003, Daniels, 2009).

However, many gynaecologists continued with excision, presumably because they felt they were achieving the same effect, if not better, and were also saving the substantial cost of investing in a laser. More critical evidence for the effect of excision, including quality of life data, did not really arrive until Abbott's paper of 2003, prospectively looking at the outcome of patients for pain and quality of life at 2-5 years post laparoscopic surgical excision. This was a more substantial look at the evidence than their group's previous report by Garry in 2000 (Garry et al., 2000). The findings showed that the most common symptom at presentation was non-menstrual pain (74%), 67% were improved (though a

disturbing 25% were worse), there was a significant risk of re-operation (33%), analgaesia was still required for 35%, and hormonal therapy in 26%. Median pain scores were significantly improved for all pain modalities and quality of life was significantly improved though not to normal population levels. Dysmenorrhoea remained the most common symptom at follow up. It must be noted that this sample of women appears to be skewed towards more advanced disease (41% had stage 4 disease) suggesting that these outcomes are those one may expect in a tertiary referral practice and not necessarily the general population of endometriosis sufferers.

This prospective study was followed up with the first RCT for excision therapy by the same group published in 2004 (Abbott et al., 2004). This included 39 women (just missing their power calculation of 40), again with all stages of disease that seems once more to be biased towards more complex disease compared with the general endometriosis population, with 17/39 (43.6%) of patients having stage 4 disease, in what was presumably a tertiary referral practice. Comparative data for excision versus control is available at 6 months, as in the Sutton trial, and showed that 80% (versus 32% in the control group) of patients in the immediate surgery group had some form of pain improvement, with a median improvement of 30 points on a 100-point VAS of overall pain improvement. Interestingly, for individual pain modalities of dysmenorrhoea, dyspareunia, non-menstrual pain and dyschezia, there was no significant difference in direct score comparison between excision and controls groups at 6 months. However, within each group, excision significantly improved for all 4 modalities and the controls for dysmenorrhoea and CPP only. The placebo effect noted by Sutton at 3 months appears to extend, to some extent, to 6

months in the Abbott trial. That the comparatively significant improvement in overall VAS for pain did not correlate with the individual pain modalities is disappointing and casts some doubt on the overall result at 6 months. The authors themselves call into question the potential limitations of VAS pain scores alone to interpret outcomes as they are probably subject to significant intra-observer error. Ideally, additional validated outcome measure instruments need to be used looking at HRQoL as was done in Abbot's trial with EQ-5D and SF-12. This trial raised the question of whether 6 months follow up was really long enough to pick up a significant difference as suggested by Sutton's trial. Sutton's follow up report on his trial at 12 months also suggested that 90% of those who responded at 6 months had continued symptom relief, although the blinding was now broken (Sutton et al., 1997b). 12 months of direct comparative follow up was the logical next step.

Jarrell et al attempted to look at 12 month follow up and simultaneously overcome the VAS problem above by taking repeated daily VAS pain scores for a month pre-operatively and at 3 monthly intervals up to one year (Jarrell et al., 2005). Sadly only 16/29 women completed the rigorous follow up protocol, resulting in a significantly underpowered trial. The other two potential trials, by Tutunaru and Lachlandani, considered by Jacobson in his updated Cochrane review (Jacobson et al., 2009) were data presented from conferences, are unpublished in full form, and should be treated with caution. The meta-analysis of the advantage of laparoscopic treatment versus diagnostic laparoscopy alone at 6 months suggests an odds ratio of 5.72 (95%CI 3.09 to 10.60).

These trials did not attempt to compare excision and vaporisation, the two leading forms of surgical treatment for minimal to moderate endometriosis. Only one published trial of 24 women exists from Wright, comparing excision and

ablation with monopolar electro-surgery for superficial minimal to mild endometriosis (Wright et al., 2005). A significant improvement was found for symptoms and signs in both groups but no significant difference between the two groups at 6 months. This trial was small and confined to only rASRM stage 1 and 2 superficial disease, and perhaps the sensitivity of the 1 to 5 ordinal scale used is limited in being able to differentiate between treatments.

There is currently insufficient evidence to differentiate between excision and vaporisation in the treatment of minimal to moderate endometriosis. It would seem logical to assume that, provided all endometriosis and fibrosis is removed leaving only normal tissue, then there should be no difference between the two.

Conclusion

Endometriosis is almost certainly under diagnosed and under treated and much more research is needed. The development of the World Endometriosis Society (WES), the availability of Internet information from quality websites like *endometriosis.org*, and the rapid development of patient-support groups are all helping to raise the profile of the disease. This in turn will hopefully lead to a better understanding of the aetiology and effectiveness of treatments. Ultimately however, it will be informed patients demanding high quality evidence-based treatment that will drive progress. The British Society of Gynaecological Endoscopy (BSGE) is also developing a national treatment database and network of accredited centres with the aim of improving standards of treatment and collecting data for research. Ten centres are currently accredited on the BSGE website (www.bsge.org.uk).

150 years after the disease was first described, we are still debating its aetiology. The rise of laparoscopic surgery has raised the profile of the disease over the past 30 years and this has led to a corresponding increase in our understanding of the underlying processes. As the evidence currently stands, laparoscopic surgery appears to be the most logical approach to treatment provided women accept the risks of surgery especially for complex disease. There is little evidence to support the use of one technique or instrument over another, and there are insufficient centres and surgeons capable of dealing with the problem. This thesis will hopefully be able to assess more clearly the currents trends in practice for all forms of the disease, and perhaps throw more light upon whether one technique or other is advantageous for minimal to moderate disease.

Chapter 3 - Methodology

An International Survey of Surgical Techniques used in the Treatment of Endometriosis

Introduction

When the patient comes to the operating theatre there are many factors that have influenced the procedure that they will actually undergo. These include:

1. Factors related to the surgeon themselves including their training, experience and character.
2. Factors related to the evidence for the procedure including the medical literature and guidelines.
3. Factors related to economics and availability of instrumentation pertaining to the hospital in which the surgery is being carried out.

This complex inter-relationship is often not developed in a systematic way and instead is the result of a series of coincidences influenced in varying degrees by the factors listed above. Dealing with each of these factors in turn we can see more clearly the complexity of the issue.

Part of why surgeons choose to use different instruments or techniques will be based upon their own character. Some may be more risk averse and more inclined to carry out less invasive and radical techniques than others who are more aggressive in nature. Some may be more driven by ambition and discovery and inclined to explore and develop their own new techniques that result in a change in widespread practice. The training that a surgeon has

received will vary considerably from a standard-type training path to a specialist Fellowship or postgraduate degree. Their theoretical and practical ability will vary widely as a result. The influence of the teacher in this process is likely to be significant in affecting the method that the surgeon ultimately applies on his or her own patient. Experienced surgeons are likely to be more confident and may be more likely to be more aggressive and innovative, or conversely may be stuck in their ways in outdated techniques.

The medical literature for the surgical treatment has been outlined in detail in Chapter 2 but in summary suggests that the gold standard for the diagnosis of endometriosis is laparoscopy (Kennedy et al., 2005). This is not necessarily required if medical therapy controls pain symptoms, fertility is not an issue at that moment, and the woman is comfortable without a definitive diagnosis. This guideline was developed on the basis of RCT evidence summarized in the Cochrane database (Hart et al., 2008, Jacobson et al., 2009, Jacobson et al., 2004b) as well as large numbers of non-randomised studies. There is no clear evidence that one technique or instrument is better than any other, and so factors 1 and 3 above play a larger part in influencing what happens to the patient on the operating table than they would if there was a definitive procedure with overwhelming evidence supporting it.

Economical issues in health care play a large role in determining what is available to the surgeon. There are many instruments capable of carrying out excision, vaporisation or ablation of endometriosis with varying costs and characteristics. Less economically restricted hospitals, with visionary chief executives may be more likely to invest in the latest developments. Others will

wait until there is more evidence, or even till there is no choice once the evidence for a procedure is overwhelmingly in favour of it.

This study looks at which instruments and techniques are currently being used and why. It is therefore an exploratory study to attempt to understand more about surgeons choices in instrument and technique in relation to the three factors listed above.

Study design

The survey was administered and designed to collect reliable, valid and unbiased data from a representative sample, in a timely manner and within the given resource constraints.

In questionnaire design, certain methods have been identified that have been shown to help achieve this (Boynton, 2004, R Nakash, 2006). For administration these include:

1. Saliency of the questionnaire to the responder
2. Linguistic ability of the responders
3. Efficient means to complete the questionnaire
4. Will to complete the questionnaire
5. Clear aim of survey conveyed to responders by covering letter
6. Pre notification
7. Reminders
8. Use of incentives
9. Available researcher to answer questions

10. Pilot study
11. Efficient data entry and cleaning

For design these include:

1. Clear design and layout
2. Visually appealing
3. Short questionnaires
4. Question wording
5. Question ordering
6. Question form

Objectives

Primary endpoints

To discover the type of surgical techniques and instruments used in treating different types of endometriosis, including superficial minimal to moderate disease, deep minimal to moderate disease, endometriomas and recto-vaginal nodules, within the study population.

Secondary endpoints

1.The characteristics of the laparoscopic surgeons using these techniques and instruments defined by region, experience and training.

2.The geographical distribution of the use of these techniques and instruments, and why the surgeons are choosing them.

Population

The survey was sent to members of the British Society of Gynaecological Endoscopy (BSGE), European Society of Gynaecological Endoscopy (ESGE), and the American Association of Gynecologic Laparoscopists (AAGL). The Australian Gynaecological Endoscopy Society (AGES) was approached but declined to participate for data protection reasons. These societies had email addresses for 4878 medical members in total.

Type of survey

This was an international web-based self-completed survey with a large target population of nearly 5000. Clearly a self-administered questionnaire was preferable to an interviewer-administered approach for numerical and geographical reasons. An electronic web-based rather than postal distribution was chosen for several reasons:

1. An electronic survey would be less expensive, saving on postal costs.
2. Answering is controlled, by stopping responders from moving on until they have completed certain questions.
3. Out of range answers are prevented from being entered in error.
4. Response collation and transfer to a statistical database is electronic.
5. A sampling frame existed, as each society maintained a member email address database.
6. Electronic surveys are easy to distribute with less risk of postal failure provided that email addresses are accurate.
7. Electronic surveys are efficient to complete in the presence of a good Internet connection.

8. Responders, being doctors in mainly developed countries, were likely to have easy access to computer and Internet facilities.

Survey Administration

Covering letter and invitation to participate

Each Society agreed to distribute the survey by an invitation covering letter, stating the clear aim of the survey, with an electronic link into the questionnaire. This confirmed the bona fide credentials of the survey, and was presented with headings and logos. It also guaranteed confidentiality. The BSGE and ESGE agreed to do this by an individual email invitation to each member on their databases. The AAGL would only agree to do this by including the invitation in the monthly newsletter. No other pre-notification technique was used. A copy of the invitation letter for the main survey is at appendix K.

Use of incentives

All responders email addresses were included into a post-survey raffle. The winner received an iPod Nano. This was stated clearly on the invitation email.

Available researcher to answer questions

On the bottom of each questionnaire page the researcher's email address was included so that responders could ask questions.

Pilot Study

A pilot study was sent to a representative sample of 12 gynaecologists from the main study population. They were also sent a covering invitation email directly to their address, which allowed them to click on an electronic link into the pilot

questionnaire. The results of the pilot study were analysed to assess issues regarding layout and design, non-responses due to poor language or signposting, relevance, ambiguities and its ability to hold interest. An open free text box was included for responders to comment on the survey. A copy of the pilot invitation and pilot questionnaire are at appendices J and L.

Data handling and record keeping

All data responses were transferred to a secure central database operated by the commercial web survey system until the survey was closed. This was then transferred electronically into an Excel database. From there, the Excel database was copied manually into SPSS for further analysis. The SPSS database was held on a password protected laptop. No paper records of responders' personal details were kept. All data was handled in accordance with data protection legislation.

Reminders

Both the BSGE and ESGE agreed to send out a reminder one month after the initial send out of the invitation email. The same invitation covering letter as before was emailed out to each individual member. The AAGL declined to send out a reminder, or to include the invitation in their next monthly newsletter.

Questionnaire software

The initial pilot study survey was set up using the Panorama© online survey system that was developed at the School of Management, University of Surrey. The system was registered for copyright in 2004. It was compatible for PC and Apple Mac users and worked in common web browser systems including

Internet Explorer. For the pilot survey it was very successful, but unfortunately restrictions forced upon the IT Department at the University of Surrey in 2007 resulted in this study needing to find a new distribution system. The survey was switched to the commercial system Zoomerang, which was recommended by the Sociology Department. It was simple, intuitive and straightforward to transfer the questionnaire from Panorama©. Consequently, the main survey was sent out using Zoomerang.

In Zoomerang, results are collated for each question and simple descriptive statistical outcomes are tabulated automatically. Responses are broken down by date and hour of the day allowing analysis of response patterns. Unlike Panorama, data was not broken down by the browser system that the responder uses, to rule out browser system bias. Also unavailable in Zoomerang were:

1. Drop out analysis showing data on whether particular parts of the survey were repeatedly not completed to help identify problem areas.
2. Duration analysis showing the time taken to complete the survey.
3. Automatic coding for export into SPSS for further statistical analysis.

Questionnaire development

Initially a list of questions was generated from using the literature and the known instruments and techniques used for the surgical treatment of endometriosis in order to cover all of the areas for which information was required. Meetings were held with supervisors to ensure the validity of the coverage. The ideas and topics were then developed into open and closed

questions of varying types. Initially these were pre-piloted on members of the research group, and then formally piloted in electronic form as described above. They were then refined, and a questionnaire was created that took about 10 minutes to complete and was subdivided into the following subsections:

1. A profile of the respondent.
2. The responders' management of minimal to moderate endometriosis.
3. The responders' management of endometriomas.
4. The responders' management of recto-vaginal nodules.

Clear design and layout and visual appeal

The Zoomerang survey system produced a very clear, professional design and layout. It had varying designs that could be selected from, and had enough flexibility in question generation to be able to produce a simple, visually appealing result. An introductory welcome page gave clear instructions and a thank you statement was included at the end. Any filter questions were clearly marked. Lower case letters were generally used to avoid the appearance of shouting. Numbering was clear, and response categories were never split over two pages. A paper copy of the main questionnaire is at appendix M (however it was not possible to print this out from the Internet with the page breaks in the correct place).

Questionnaire length

The questionnaire was kept a short as possible to get the required information, and was 34 questions long. No questions were added or removed after the pilot study and the main questionnaire remain the same length.

Question form

The questionnaire mainly employed closed type questions with pre-coded scaled or dichotomous response choices. Some questions had small open response text boxes to account for response alternatives missed in the pre-coded list. Closed type questions were used as they are simpler and quicker to administer and code, as well as being appropriate to the information required from the survey. However, it was appreciated that they can also give clues about the type of response expected, and this was minimised where possible.

Response scales in Likert format (5 point scale, strongly agree to strongly disagree) were used for questions about why responders used the techniques they chose. They are commonly used, easily understood and analysed, and are more sensitive and precise than dichotomous responses. Creating categorical scales, by using words in the Likert scale, shows a similar responsiveness to visual analogue scales (Jaeschke, 1990) with less ceiling and floor effects than dichotomous responses. Neutral responses in the scale were felt to be important and so were included.

Question ordering

An advantage of electronic questionnaires is that responders are unable to read through them and assess questions in the light of ones further on in the questionnaire. A funnel approach was taken to question order, starting with broad questions in logical categories, filtering out responders who these questions were irrelevant to, and then progressing onto more detailed questions within that category. Responders who were filtered out were automatically taken onto the next question that applied to them.

Question wording

The wording, format and direction of response were varied where possible to make responders think about the question and avoid a “response set”. Wording was also aimed to be as non-confrontational as possible. Double-negatives and colloquialisms were avoided. Complex questions about the management of recto-vaginal nodules were broken up into a series of simpler questions that were more easily understood. There were no double-barrelled questions (two questions in one sentence) and ambiguity was avoided where possible. Wording was aimed to draw specific answers rather than general ones, and was not “loaded”.

Ethics

Ethical approval was gained from the University of Surrey Ethics Committee. Responders were emailed in their independent capacities as members of Gynaecological Societies. No resources or information directly related to the NHS were used and so ethical approval from the NHS was not required.

Statistical analysis

Simple descriptive statistics were used for response rate and demographic factors with means and standard deviations used where appropriate for continuous variables, and median and range used for skewed continuous, or discrete variables. To test for differences between proportions Pearson’s Chi-square test was used and, where the groups were small, Fisher’s Exact test was employed. For testing differences in mean values between multiple groups an Anova was used. For testing differences in median values between multiple groups Kruskal-Wallis test was used.

Financing and insurance

The only financial outlay for the study was the subscription for the Zoomerang survey system. This was $198 for 6 months use and was funded from a gynaecological endoscopy fund based at the Royal Surrey County Hospital. The author's salary was 50% funded by the Minimal Access Therapy Training Unit with funds provided by Ethicon Endo-Surgery from October 2004 until April 2008.

A Randomised Blinded Trial of Carbon Dioxide Laser Vaporisation versus Harmonic Scalpel Excision of rASRM Stage 1-3 Endometriosis in Women with Pelvic Pain.

Participants

Patients were recruited from General Practitioner NHS referrals to the Royal Surrey County Hospital (RSCH) and private referrals to a Surrey based private practice. The sample was therefore not self-selected. RSCH is a UK District General Hospital that has a history of performing tertiary referral-type gynaecological laparoscopy. The other site, The Guildford Nuffield Hospital, is a small private institution attached to the RSCH. Although consultation and surgery took place in more than one hospital, it was under the care of only one Consultant. From these, patients with pelvic pain who were booked for a laparoscopy for known or suspected endometriosis were judged against the inclusion-exclusion criteria and were then verbally invited to take part in the trial and given an information leaflet explaining the trial (appendix B). This was done either in the outpatient setting or on admission to the hospital prior to laparoscopy by one of the three surgeons taking part in the trial. The County of Surrey, in which the practice is based, has an “average” population with little evidence of poverty or other major public health problems, and is well connected by public transport.

Eligibility

Inclusion criteria

- Patients in whom surgical treatment of the endometriosis is considered the treatment of choice.

- Patients consented to participate in the trial.
- Patients who are 18 years old or older.
- Patients who have no contraindications to either of the treatment modalities proposed.
- Endometriosis stage I-III according to the revised American Society for Reproductive Medicine scoring system (rASRM) found on visual inspection at laparoscopy (Appendix H).

Exclusion criteria

- Patients who do not wish to participate or have not signed the informed consent form.
- Pregnancy or breastfeeding.
- Patients who are unable or unwilling to discontinue hormonal treatment for six months post-operatively.
- Patients who have received additional treatment for their endometriosis within three months of surgery.
- Patients with other known conditions causing pelvic pain other than endometriosis. For example, conditions of the gastrointestinal or genito-urinary system.

If patients agreed to participate they signed consent forms for admission to the trial (appendix C). All pre-op questionnaires were completed in hospital on the day of surgery and kept in an individual trial folder for each patient. The trial folder contained their personal details, consent forms, questionnaire replies, rASRM score sheet and any correspondence generated during the trial. The Senior Research Sister held all files secured in a filing cabinet in the team

office. Patients returned at 3, 6, and 12 months for follow-up appointments and were seen by the research Sister, or a deputising clinic, to fill in their post-op questionnaires. The research Sister also oversaw the administration of the private patients questionnaires. Patients who did not attend were contacted by mail or telephone and requested to return a postal questionnaire.

Interventions

The diagnosis and treatment intervention in this trial was laparoscopy on an intention to treat basis. These were carried out in either the Day Surgery Unit or Main Theatres at the RSCH or Guildford Nuffield Hospital. Three surgeons were involved in the interventions; one Consultant, and two experienced senior gynaecological laparoscopic surgery Fellows, who were trained in the operative technique by the same Consultant mentioned above. All cases were undertaken with the intention of being day cases.

Laparoscopic entry was by the recognised Middlesbrough technique (1999). At laparoscopy patients were visually assessed for the presence of endometriosis by diagnostic laparoscopy. An assistant by the bedside completed the rASRM scoring sheet (Appendix H) with information supplied by the operating surgeon. All types of endometriosis were included including red, vesicular, blue, black and white lesions. The score was added up, the stage derived, and reported back to the surgeon. Disease was judged to be deep if subjectively on palpation it appeared to infiltrate >5mm below the peritoneal surface. Women who were found to have stage 1-3 endometriosis, according to the rASRM score were then randomised to complete destruction of all visible endometriotic lesions either by vaporisation or excision (see randomisation paragraph).

Sharplan carbon dioxide laser at 300mm focal length, 30w power with a 2.5mm Swiftlase spot, down a Stortz 10mm operating endoscope until the entire lesion was destroyed and normal underlying tissue was visible, carried out vaporisation. Excision was by Ethicon Endo-Surgery LCS-C5 or ACE Harmonic Scalpel staying in normal tissue at the edges to ensure total removal of lesions. Histology was not routinely collected from the beginning of the trial. This was changed and routine collection began in June 2005 with case number 46 when it was recognised that was desirable. On completion of the treatment the procedure was concluded by our standard closure technique.

The rASRM scoring sheet was reassessed post-operatively for depth score since actual excision or vaporisation of the lesion gives a more accurate subjective view of depth compared with the original assessment by palpation. This did not result in any score adjustments leading to trial exclusion. The procedures were carried out or directly supervised by the three surgeons in the trial. Patients were generally discharged home the same day in most cases. Patients were unable to tell from the appearance of wounds after surgery which treatment they had received and were effectively blinded.

Objectives

The hypothesis of this trial was that there is no difference between excision and vaporisation in the treatment of rASRM stage 1-3 minimal to moderate endometriosis using the CO2 laser for vaporisation and Harmonic Scalpel for excision where pain is the primary outcome measure.

Outcomes

Primary outcome measure

The primary outcome measure with respect to improvement in endometriosis was pain as recorded by Endometriosis Health Profile-30 Core Pain domain (Jones et al., 2001). This gave a score between 0-100 where 0 is the best possible state and 100 the worst (Appendix E).

Secondary outcome measures

Pain

- Visual Analogue Scales (VAS)

  10 cm ungraded line for dysmenorrhoea, dyspareunia, chronic pelvic pain (CPP, pain not associated with menstruation persisting for greater than 6 months), and dyschezia. Patients marked off a point on the line, which was measured and recorded as a score out of 10 to one decimal place (Appendix D).

Health-related quality of life (HRQoL)

- Endometriosis Health Profile Questionnaire (EHP-30)

  Core domains for control and powerlessness, emotional wellbeing, social support, self-image, and the intercourse module each resulting in a score out of 100 for each, where 0 is the best and 100 is the worst possible case (Appendix E).

- Hospital Anxiety & Depression Scale (HADS) (Appendix F).

  Separate scores are derived for Anxiety and Depression with a maximum of 21 where 0 is the best state and 21 the worst. Scores are then classified into 0-7 normal, 8-10 mild, 11-14 moderate and 15-21 severe.

Demographic

At 12 months a demographic questionnaire was given to all patients to collect data on whether or not they went onto hormonal treatment for endometriosis or had subsequent surgery or became pregnant in the 12 month follow up period (Appendix G).

Rationale for choosing outcome measures

A single VAS pain score may be subject to significant large day-to-day variation and so a more sensitive, responsive measure of pain incorporating the quality of life concerns of patients would be a more powerful tool. This resulted in the choice of EHP30 Core pain domain as the primary outcome measure. Mr Barton-Smith spent a day with the author of the Endometriosis Health Profile to learn its strengths and limitations to be sure that we applied it effectively. Also permission was granted to use EHP-30. EHP-30 is likely to be a more sensitive means of measuring endometriosis pain than a VAS because it has a validated bell shaped probability distribution, showing good construct validity, enabling a moderate shift in mean score to be easily detected with two moderately sized treatment groups. The pain domain was developed to “evaluate the outcomes of conservative surgical treatment for women with endometriosis” and has the following attributes (Jones et al., 2001):

1. Good construct validity against SF36 with a bell shaped probability distribution, showing good construct validity, enabling a moderate shift in mean score to be easily detected with two moderately sized treatment groups

2. Good internal reliability reflected by high alpha co-efficient values of >0.7 as required in standardised tools based upon established psychometric test theory (Nunnally 78).

3. Good test-test reliability with intra class correlations exceeding 0.8.

4. Good content validity as items are generated from the concerns of patients rather than medical signs and symptoms and give a more powerful indicator of patient benefit.

5. Good responsiveness showing that the test is sensitive to subtle changes. It shows greater responsiveness than the SF36 bodily pain scale.

The 11 questions in the EHP-30 Core pain domain give a total score of 44. The subjects' score is calculated by dividing their score into 44 and multiplying by 100 to give a score where 0 is the best health state and 100 is the worst. Any missing variable results in the whole score for that subject being discounted. Therefore there is a risk in choosing EHP-30 Core pain domain as the primary outcome, as it could have resulted in a large number of missing data. Consequently, the VAS scores were included for two reasons:

1. As a back up for the risk of losing large amounts of EHP-30 Core pain score data.
2. As a means of being able to directly compare with previous trials that used VAS scores (see sample size below).

In addition to pain data, it was considered important to collect HRQoL information that was relevant to patients' ability to function on a day-to-day

basis. The remainder of EHP-30 Core questions and the sexual intercourse module fulfilled this criteria. HADS was added in order to evaluate levels of anxiety and depression in patients, as endometriosis is known to have a significant psychological effect in sufferers (Jones et al., 2004b). The HADS shows internal consistency of 0.93 and 0.90 for the subscales of anxiety and depression, as well as good face, concurrent and construct validity (Zigmond, 1983). It is short, acceptable, easy to administer and also splits subjects into definable clinical groups.

Outcome collection during the trial

The following data was collected at the indicated time points during the trial. The primary time point of interest was 12 months.

- Pre-operative

  Age

  EHP-30 Core and Intercourse Module

  VAS scores for Dysmenorrhoea, Dyspareunia, CPP, and Dyschezia

  HADS

- Intra-operative

  rASRM score and stage

  Depth and location of disease

  Surgeon

  Instrument

  Histology from case 46 onwards

- 3, 6 and 12 months post-operative

  EHP-30 Core and Intercourse Module

  VAS scores for Dysmenorrhoea, Dyspareunia, CPP, and Dyschezia

  HADS

- 12 months post-operative

  Pregnancy data

  Adjuvant medical therapy

  Subsequent surgical intervention

Sample size

The power calculation for this trial was based upon two requirements:

1. To compare against previous trials.
2. To use a validated primary outcome measure for pain that is most pertinent to patients' quality of life.

To calculate a sample size against previous trials, there was only one RCT to use at the time in 2002. In the 1994 landmark Sutton vaporisation study (Sutton et al., 1994), 62.5% of patients showed an improvement in pain symptoms at 6 months, based on a visual analogue scale of 0-10 asking patients to score according to their worst symptom, which was dysmenorrhoea in all cases. Of the case studies that existed for excision of endometriosis, David Redwine's report of 400 consecutive women who had excision, showed a 75% complete relief, and 20% improvement in pain (Redwine, 1996). This suggested a potential difference of up to 32.5% in pain outcome. However, it was decided to

be more conservative with the difference, especially as the hypothesis was that there would be no difference. Being more conservative would result in an increase in the numbers required for the trial, but being able to show up to a 20% difference gave a sample size that was manageable for a single centre as shown below.

The hypothesis of this study was that there is no difference between excision and vaporisation, and so the power calculation to show that neither treatment was worse than the other was as follows. The Food and Drug Administration 80/20 rule for bioequivalence was used to calculate the sample size required to achieve 80% power. Thus ε=0.20, $\propto$=0.2 (as equivalence trial), 1-β=0.8. This will need to be a 2-sided test as it is possible the harmonic scalpel is better than the laser. If we are assuming equivalence, then $\pi_1=\pi_2$=0.625 (original study was 62.5%). On this basis we would require 53 patients in each arm if we were to have an 80% chance of showing a 20% difference in treatment outcomes (Statistical procedures for bioequivalence using a standard two treatment cross over design. US Dept of Health and Human Services, Public Health Service. Food and Drug Administration 1992).

As it turned out, the subsequent 2004 Abbott excision RCT (Abbott et al., 2004) used a 0-100 “no change in pain to complete relief of pain” visual analogue scale as the primary outcome measure, showing an improvement in 80% of patients at 6 months, and also VAS scores for all four pain modalities. This suggested a potential difference between excision and vaporisation in the order of around 20%, and endorsed the selection of 20% difference chosen for the power calculations.

The two primary outcome measures in the Sutton and Abbott RCTs are different and not easily directly comparable with each other. By using VAS scores in this study for dysmenorrhoea, dyspareunia, CPP and dyschezia, it will be possible to correlate the data directly to the dysmenorrhoea score in the Sutton trial and to all 4 modalities in the Abbott trial. There is no valid basis to combine the individual 4 pain modalities used for the VAS to create a global score, especially since some of the components are often not relevant to the patient (i.e. dyspareunia).

The primary outcome measure in this study is EHP-30 Core pain score, derived and recorded on a continuous scale, and has a previously reported maximum SD for change in pain score of 26.0 (Jones et al., 2004a). In order to detect an underlying difference of 20 points out of 100, 28 subjects are needed in each treatment group (2-sided test with size = 5% and power = 80%). The number in the bioequivalence power calculation above comfortably satisfies this requirement.

Randomisation

Sequence generation

Restricted randomisation was used to generate blocks of 10 random treatments where odd numbers 1,3,5,7,9 defined allocation to excision and even numbers 2,4,6,8,10 defined allocation to vaporisation. This improved the chances of a balanced outcome at the cost of reducing the unpredictability of the sequence. The block size was not randomly varied. No stratification was used.

Allocation concealment

Sealed opaque envelopes containing a number from 1-10, in blocks of ten, were then randomly sorted and added to the trial folders, one per folder. The sequence was therefore concealed until the intervention was assigned.

Implementation

The trial folders and envelopes containing the concealed treatment were produced by Mr Carpenter and Mr Barton-Smith and kept locked in a separate filing cupboard to the active and completed trial folders. The operating surgeons administered the pre-op questionnaires. Once in theatre, if the patient fulfilled the entry criteria by rASRM score, then the envelope was opened during the surgery. The surgeon was told the allocated treatment and carried this out immediately. Mr Carpenter and Mr Barton-Smith took part in both the generation and implementation of the random sequence of treatments.

Blinding

Both the patients and the research nurse who performed the post-operative assessments were blinded from the treatment received. The surgeons were blinded to the post-operative questionnaire replies. The success of the blinding was not evaluated to assess for performance or detection bias.

Statistical Methods

The study analysis was designed on an intention to treat basis. Descriptive analysis was generally presented as proportional numerator/denominator comparisons with percentages. Chi-square analyses were performed to analyse proportional differences. Primary and secondary outcome measures were

analysed, in terms of proportional improvements, with Chi-square tests. The extent of improvement for each technique at 12 months against baseline was analysed by paired t tests. Comparative analysis between treatment techniques of the extent of improvement was analysed with unpaired t tests. Standard deviations and 95% confidence intervals were quoted where appropriate. Pearson's Correlation Test was used to examine association between continuous variables. The Mann-Whitney U Test was used to compare two groups for ordinal variable scores. Exploratory analysis of major findings, to identify demographic and other factors influencing results, was performed with backward stepwise linear regression. All statistical analysis was performed using SPSS v17 (SPSS inc Chicago IL, USA; 2008).

Ethical approval

Ethical approval for this trial was obtained from the Surrey Local Research Ethics Committee, and Research Governance was obtained from the Royal Surrey County Hospital Research and Development Committee.

Cost of Study

There were no additional costs over and above that entailed in current treatment schedules. The laser and harmonic scalpel are routinely used in the operating theatre. The author's salary was 50% funded by the Minimal Access Therapy Training Unit with funds provided by Ethicon Endo-Surgery from October 2004 until April 2008.

Chapter 4 - Results

Results of an International Survey of Surgical Techniques used in the Treatment of Endometriosis

Introduction

The survey was developed to gain a snapshot of what equipment and techniques gynaecological surgeons were using and why, as many devices and energy forms are available. From this a picture would hopefully emerge of the current views of gynaecological laparoscopists in relation to the evidence, or lack of it. Implementing this trial was difficult in so far that obtaining agreement from the three societies proved to be very challenging. It took over a year to resolve data protection and distribution issues, and even then the plan for the AAGL was suboptimal, and the Australian Gynaecological Endoscopy Society had refused to participate. That being said, the survey was eventually sent out with optimism that it would achieve its aim.

Pilot Study Results

A Pilot Study of the Panorama© based survey took place between 10 January and 8 February 2006. The survey was sent to 12 laparoscopic gynaecologists who act as Faculty members at the Minimal Access Therapy Training Unit at the University of Surrey. There were 7 completed responses received between 10-31 January and one further response at the second attempt on 8 February 2006.

Total response after 2 emails was 8/12 (66.7%). The response rate was two thirds and so the length and feasibility of the survey seemed reasonable.

Certain changes were made to the questionnaire resulting from the pilot. Some of these were triggered from our own observations and some from the responders who had an extra question in their surveys asking about their views on the survey structure. The following adjustments were made:

1. A question was added asking about whether responders try to treat their patients surgically at the time of laparoscopic diagnosis.
2. A question about 2 stage procedures for endometriomas was included.
3. More text boxes after possibly ambiguous questions were added to allow greater ability for responders to explain their practice.
4. Minor wording changes were made to avoid ambiguity in some questions.

Main Survey Results

The main survey was initiated on 18 April 2008 and the last response before the survey was closed was recorded on 23 September 2008.

Data cleaning

The database was checked for errors by carrying out simple descriptive statistics and looking for potentially erroneous outliers. 17 responders were excluded because they failed to answer any questions once they had passed beyond the introduction page. 13 responders at question 4 said that they did not treat endometriosis surgically and so were automatically taken to the end of the survey and excluded from the analysis. 18 responders partially completed the

survey but were kept in the dataset. Therefore a total of 30 cases were excluded leaving a data set of 339 of which 321 were correctly completed and 18 were partially completed. There were a number of correct partial responses with 5 who did not treat endometriomas, and 134 not treating recto-vaginal nodules, which meant that they were automatically filtered to the end of the survey at questions 15 and 21 respectively. Zoomerang had electronically coded some answers as “no” after partial responders had ceased to answer further questions. These were recoded as missing data.

The wide variety of countries from which responses originated, coupled with the low response rate, meant that it was sensible to recode these as geographical regions of UK, mainland Europe, USA and the rest of the World. In addition to this, the free text responses were coded into either already existing codes or into new codes. New codes were created for the following:

Q9: Argon beam coagulator, Bipolar-sealing systems.

Q10: Argon beam coagulator.

Q17: May observe endometriomas <3cm.

Q22: Intravenous Urogram

Response Rate

Table 2. Survey response rates by specialist society.

	No on database	Successfully sent	No of Replies (%)
BSGE	489	390	92 (23.6)
ESGE	1623	1481	175 (10.8)
AAGL	3259	3007	102 (3.1)
Overall	5371	4878	369 (7.5)

There were 489 total visits to the survey, although as table 2 shows, 369 actually started it which means that 120 people did not get beyond the introduction page. Once started, only 35 responders of those 369 (9.5%) failed to complete the questionnaire.

General characteristics of responders

General demographic data questions were asked for age, region of principal practice, number of years performing laparoscopic surgery independently, main form of training in laparoscopic surgery, years qualified as a doctor and whether they were a specialist or trainee.

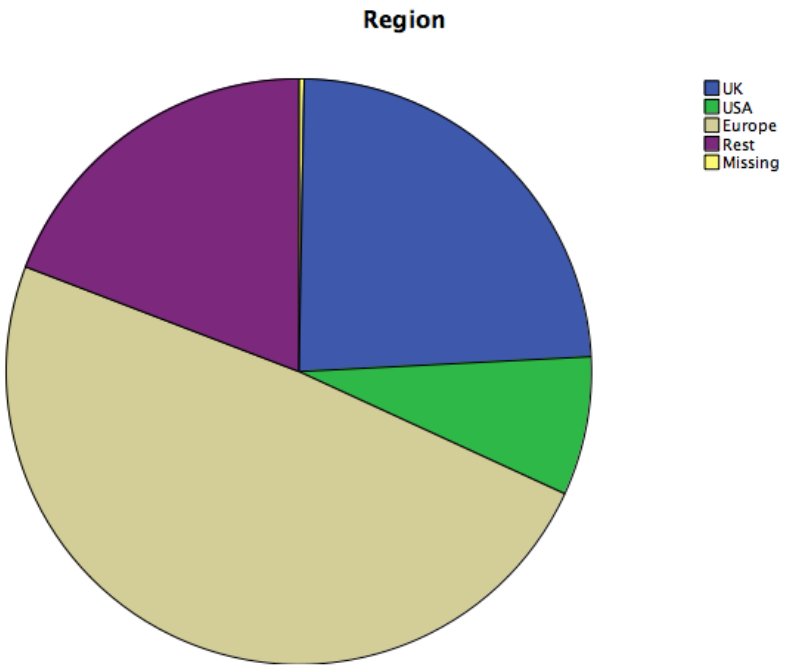
Specialist versus trainee

267 (88%) responders were specialists whilst 37 (12%) were trainees with 35 missing data. BSGE response was 23.6% of total membership but 194 (45%) are trainees and 237 (55%) specialists. When excluding trainee responses there were 54 responses from specialists, which is 54/237 = 22.8% of the consultant population.

Region

The majority of responses came from mainland Europe and the UK as is seen in Fig 1 below.

Fig 1. Distribution of responders by geographical region.

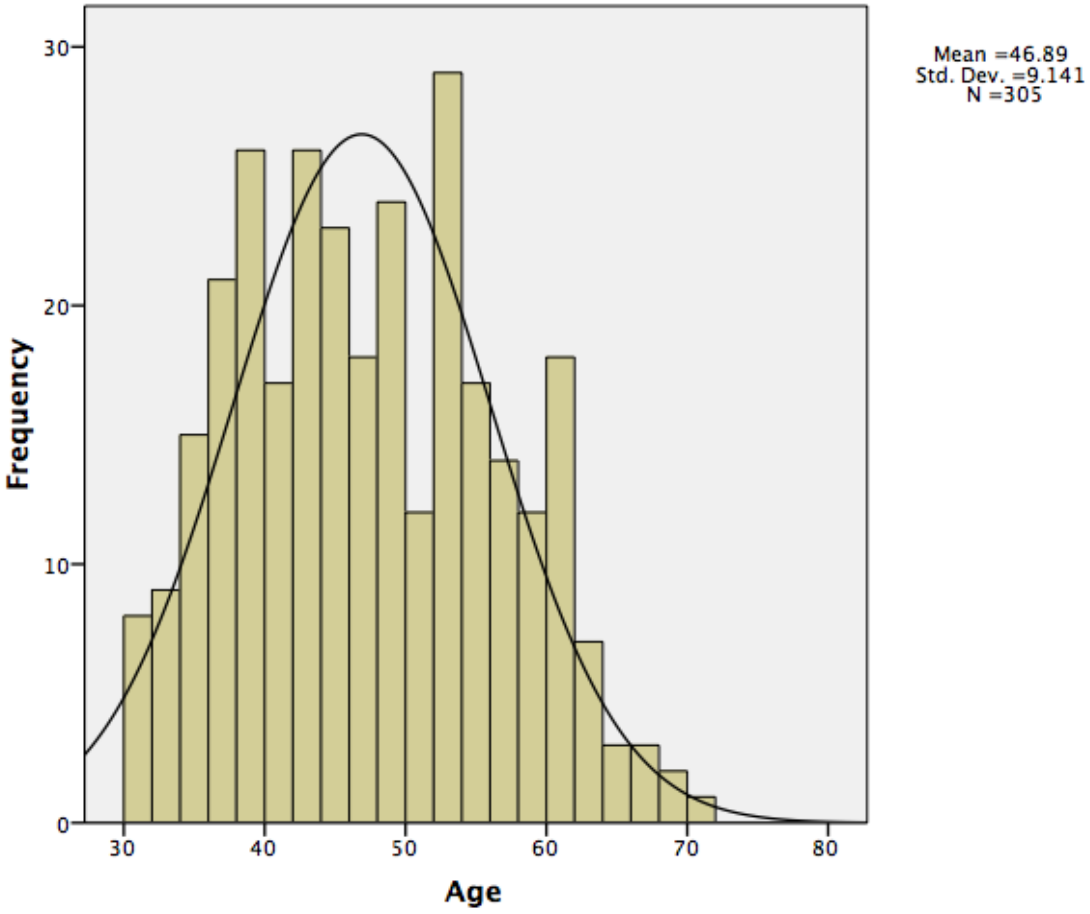


Mainland Europe	49%
UK	23.9%
Rest of World	19.2%
USA	7.7%

Experience

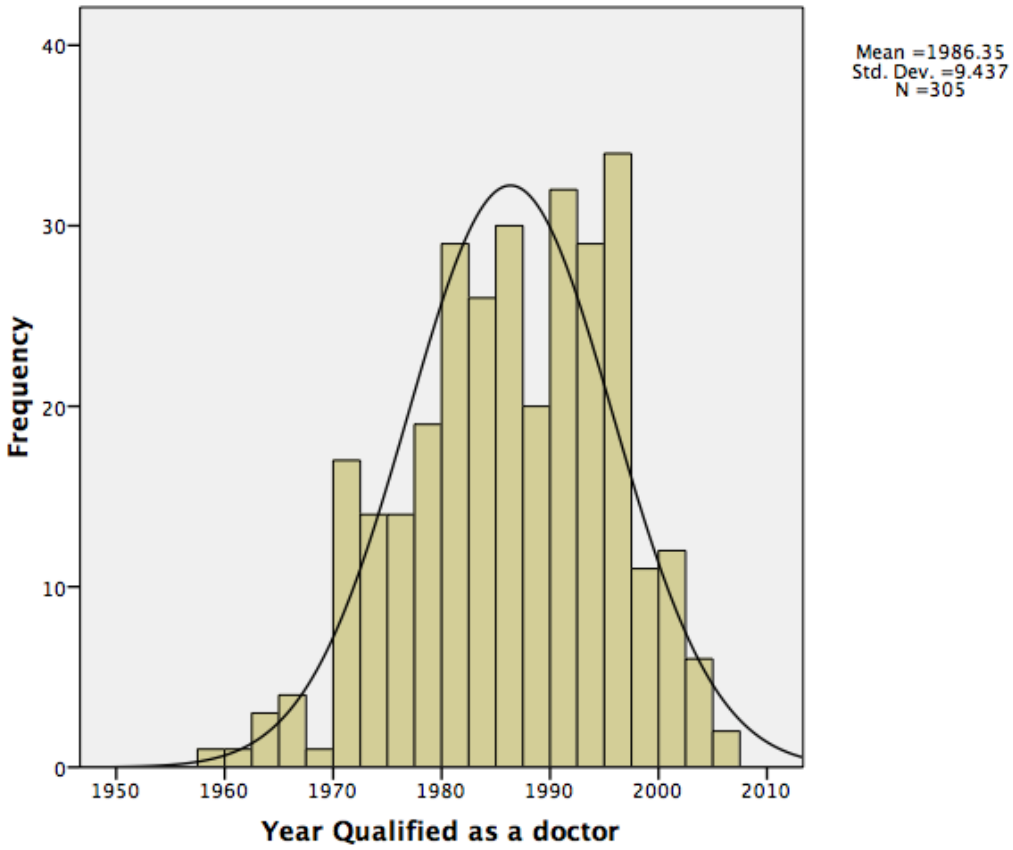
As fig 2 below shows, the average age of responders is 46.9 years (+/-9.14). Although the age data are slightly skewed, the skewness is within acceptable limits and therefore parametric statistics could be used (skewness = 0.214, SE 0.140).

Fig 2. Age distribution of survey responders.



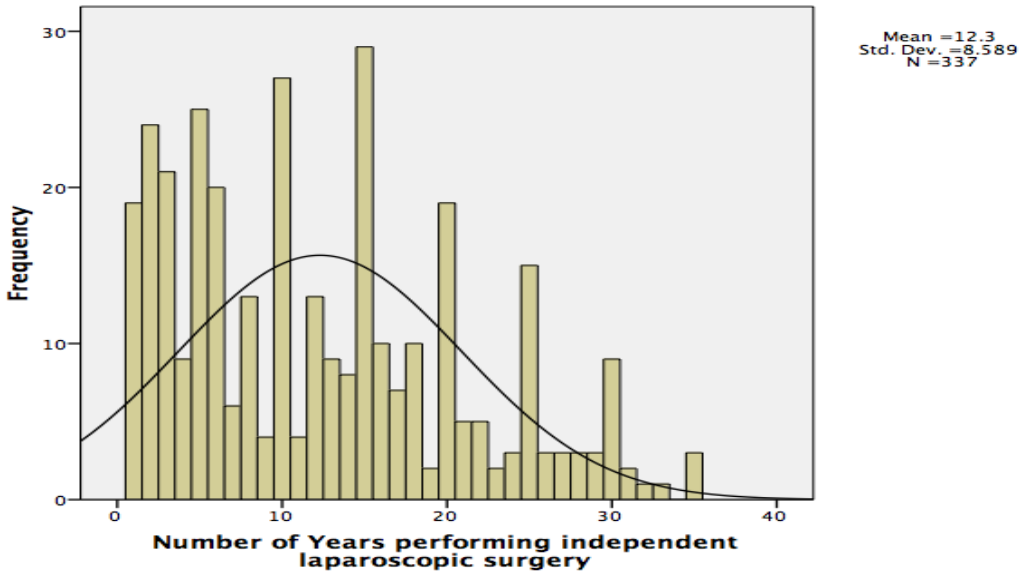
As can be seen from fig 3 below, the time qualified as a doctor is normally distributed (skewness = -0.330 SE 0.140) with an average of 37.4 years (+/-9.44) since qualification.

Fig 3. Year survey responder qualified as a doctor.



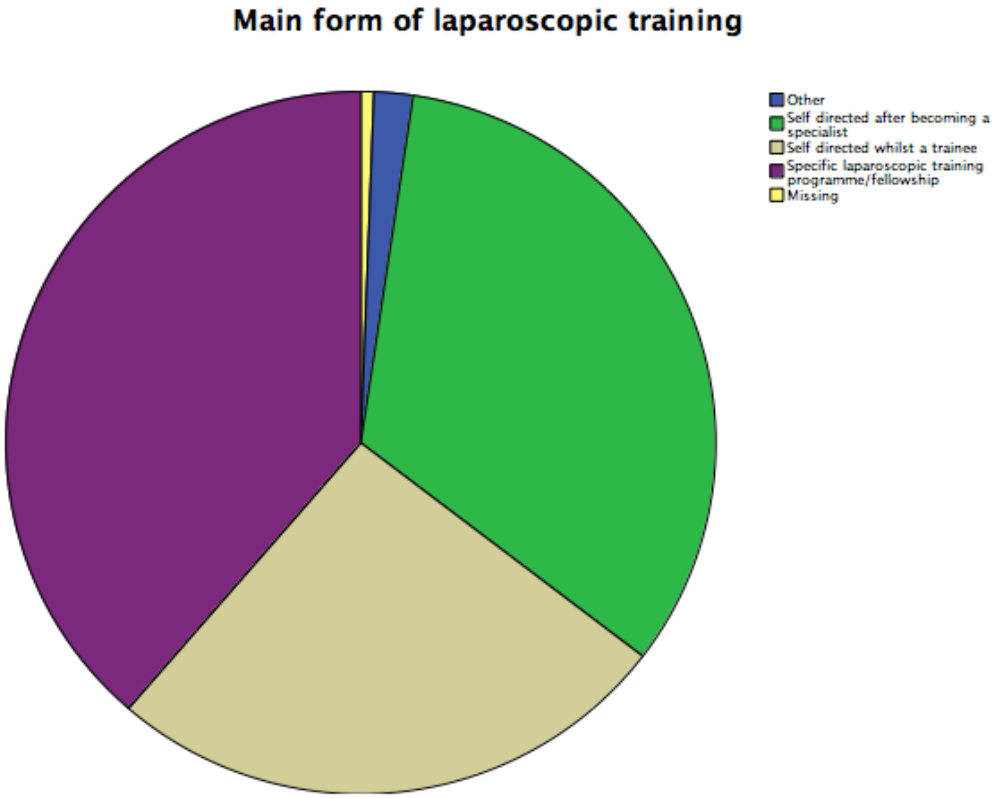
The data for the number of years that responders have been performing independent laparoscopic surgery is skewed (skewness 0.584 SE 0.133) and shows a median value of 11 years (range 1-35). The skewness seen in fig 4 below, illustrates more gynaecologists joining the specialty from about 20 years ago. As this skewness is minimal, it will be treated as normally distributed. This variable was used as the best indicator of experience in subsequent analysis.

Fig 4. Number of years survey responder has performed independent laparoscopic surgery.



Training

Fig 5. Pie chart of the distribution of training methods in survey responders.



As seen in fig 5 above, 39% of responders had trained through a specific laparoscopic training programme or fellowship. This was more likely if you were less experienced in terms of number of years independently performing laparoscopic surgery. Responders who had had formal training had a mean of 9.2 years experience versus 14.0 years for those who were self-taught, giving a mean difference of 4.6 years ($p<0.0005$, 95%CI 2.9 to 6.4). Those who had undergone a specific training program and fellowships also had a trend towards doing more complex surgery in terms of their likelihood to be doing surgery for recto-vaginal nodules (61% compared to 54%, although this difference was not statistically significantly different, $p=0.251$).

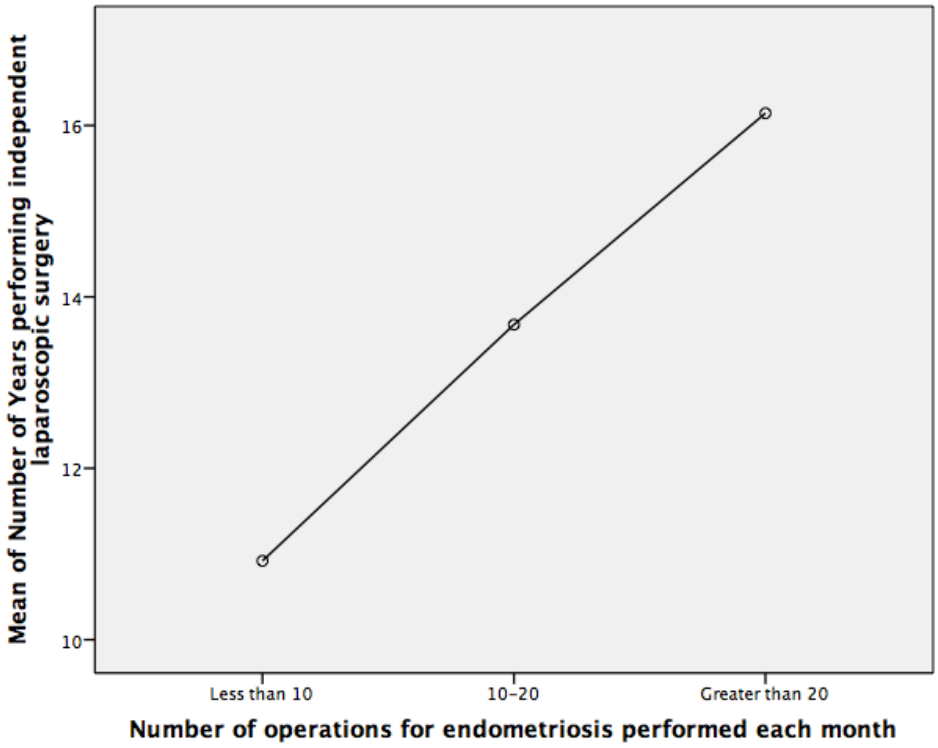
Number of operations performed per month for endometriosis

Table 3. Number of operations performed for endometriosis by survey responders per month.

Operations	<10 per month	10-20 per month	>20 per month
	n (%)		
Responders	202 (59.6)	102 (30.1)	35 (10.3)

In table 3 above, the majority of responders are performing <10 procedures for endometriosis per month. A sub-analysis of these results showed that training method does not influence the number of procedures carried out per month is ($p=0.227$). However, gynaecologists with more experience in independent laparoscopic surgery undertook more surgical cases per month than those with less experience (Anova Test $F=7.69$, $p=<0.001$). This is well illustrated in fig 6 below:

Fig 6. Means plot comparing the mean number of years performing laparoscopic surgery with the number of endometriosis operations performed per month.



Types of endometriosis operated on

Table 4. Percentages of survey responders that operate on various types of endometriosis.

Type of endometriosis	Responders n (%)
Minimal to moderate	275 (81.1)
Endometriomas	300 (88.5)
Severe	176 (51.9)
Recto vaginal nodules	141 (41.6)

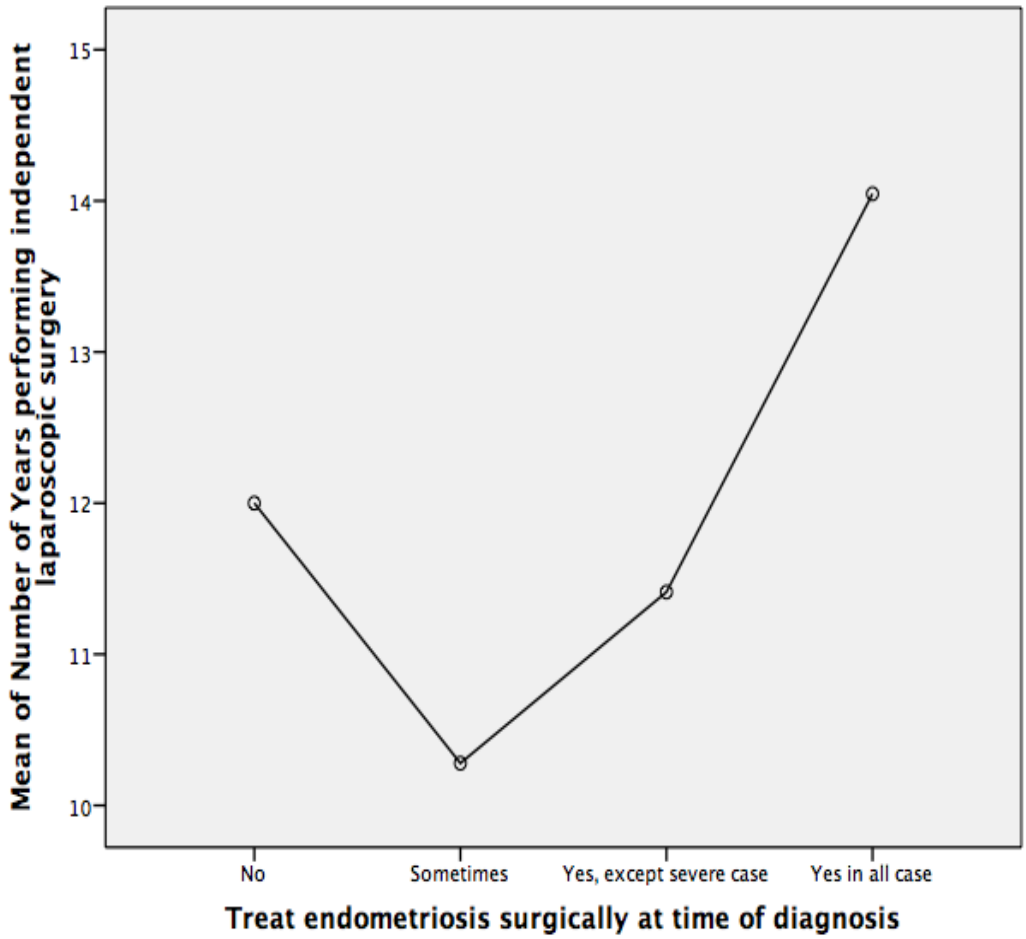
Do responders treat at the time of laparoscopic diagnosis?

Table 5. Proportion of surgeons who see and treat patients at the same time for endometriosis.

Treat at Diagnosis	n (%)
No	13 (3.8)
Sometimes	44 (13.0)
Yes, except severe	153 (45.1)
Yes, always	129 (38.1)

The data in table 5 above shows that the majority of patients are seen and treated at the same time. The means plot below in fig. 7 shows that more experienced surgeons treated patients at the same time as the diagnostic procedure, when compared to less experienced surgeons (Anova Test $F=3.18$, $p = 0.024$).

Fig 7. Means plot comparing the mean number of years performing independent laparoscopic surgery with “see and treat” management.



Changes in surgical instruments used to treat endometriosis

Responders replied by ticking all instruments that they may currently use and have previously used to treat endometriosis as seen in table 6 below.

Table 6. Previous and current use of surgical instruments for endometriosis.

Type of instrument	previous use	current use	P value
	n (%)		
Cold scissors	207 (61.1)	198 (58.4)	*0.481
Monopolar diathermy	231 (68.1)	193 (56.9)	*0.006
Bipolar diathermy	260 (76.7)	293 (86.4)	*0.001
Ultrasound technology	87 (25.8)	139 (41.1)	*<0.001
CO2/YAG/KTP laser	101 (29.8)	73 (21.5)	*0.014
Helica	24 (7.1)	19 (5.6)	*0.431
Argon beam coagulator	4 (1.2)	10 (2.9)	**0.105
Bipolar sealing devices	0 (0.0)	16 (4.7)	NA

* Pearson's Chi-square Test **Fisher's Exact Test

Electro-surgery is still the most frequently used energy source in the surgical treatment of endometriosis though the use of no energy with cold scissors only is still very common. Bipolar and ultrasound energy use have significantly increased from 77% to 86% and from 26 to 41% respectively.

Management of minimal to moderate endometriosis

Table 7. Number and percentages of responders who use various techniques as their main method for surgically treating minimal to moderate endometriosis.

	Superficial n (%)	Deep n (%)	*P value
Excision	90 (27.4)	158 (49.2)	P<0.0005
Vaporization	15 (4.6)	8 (2.5)	P=0.137
Combination	161 (48.9)	123 (38.3)	P=0.002
Coagulation	62 (18.8)	20 (6.2)	P<0.0005

*Pearson Chi-Square Test

In table 7 above, there is a significantly larger proportion of surgeons using excision as the main technique for excising deep minimal to moderate endometriosis compared with superficial.

There is a regional trend towards greater use of coagulation (22.7% v 11.7) and vaporisation (6.7% v 3.9%) in mainland Europe versus the UK (p=0.169). This seems to be reflected in the instrument use in Europe where a significantly greater use of bipolar diathermy exists (p<0.001). Interestingly, experience in terms of number of years performing independent laparoscopic surgery does not affect choice of technique (Anova test p=0.496).

Why do responders choose their preferred technique for treating superficial and deep minimal to moderate endometriosis.

Responders filled in a Likert scale question prompting them to reply to a set of statements as shown in the full survey (appendix M), along a spectrum where 1= strongly disagree, 2= disagree, 3= neutral, 4= agree, 5= strongly agree. The results are shown in tables 8 and 9 below.

Table 8. Reasons for choosing main technique for treating superficial minimal to moderate endometriosis.

	Excision	Vaporization	Combination	Coagulation	*P value
	Median (IQR)				
Trained	4 (3-4)	4 (3-4.25)	4 (3-4)	4 (3-4)	0.299
Self-taught	3 (2-4)	3.5 (2.75-4.25)	3 (2-4)	4 (3-4)	0.752
Best way	4.5 (4-5)	4 (3-4.25)	4 (4-5)	4 (3-4)	<0.0005
Easier	3 (2-4)	3.5 (2.75-4)	3 (2-4)	4 (3-4)	<0.0005
Tried other	4 (3-4)	3.5 (3-4.25)	3 (2-4)	3 (2-4)	0.003
No preference	2 (1-3)	2 (1-3.25)	2 (2-3.5)	3 (2-4)	<0.0005
Lack of equip	2 (1-4)	3 (2-4)	3 (1.5-4)	4 (3-5)	<0.0005
Lack of skill	2 (1-3)	2.5 (1.75-4)	3 (2-4)	4 (3-4)	<0.0005
Cost effective	3 (2.25-4)	3 (2.75-4.25)	3 (3-4)	4 (3-4)	0.194

*Kruskal –Wallis Test

As table 8 above illustrates, techniques for treating superficial endometriosis were used because the surgeon was trained in the particular procedure. Similarly, surgeons agreed that the technique they used was the best and disagreed that they had no preference over technique.

Table 9. Reasons for choosing main technique for treating deep minimal to moderate endometriosis.

	Excision	Vaporization	Combination	Coagulation	*P value
	Median (IQR)				
Trained	4 (3-4)	4 (3-4)	4 (3-4)	4 (4-4)	0.782
Self-taught	3 (2-4)	3 (2-4)	4 (3-4)	4 (3-4)	0.436
Best way	5 (4-5)	3 (3-4)	4 (3-4.5)	3 (3-4)	<0.0005
Easier	2.5 (2-3)	3 (3-4)	3 (3-4)	4 (3-4)	<0.0005
Tried other	3 (2-4)	3 (3-4)	3 (2-4)	3 (2-4)	0.939
No preference	2 (1-3)	3 (2-3)	3 (2-3)	3 (2-3)	<0.0005
Lack of equip	2 (1-4)	4 (3-4)	4 (2-4)	4 (3-4)	<0.0005
Lack of skill	2 (1-3)	3 (3-4)	4 (2-4)	4 (3-4)	<0.0005
Cost effective	3 (2-4)	4 (3-4)	3 (3-4)	4 (3-4)	0.210

*Kruskal-Wallis Test

In table 9 for deep disease, the users of all techniques agreed that they used their preferred technique because that is how they were trained or taught themselves to do it, though the feeling was stronger in favour of how they were trained and more coagulators appear to use their technique because they were self-taught. The feeling for all technique users was somewhere between neutral and agreement over concern over cost effectiveness. A further cross-tabulation of region against concern over cost effectiveness revealed no significant difference (p=0.292).

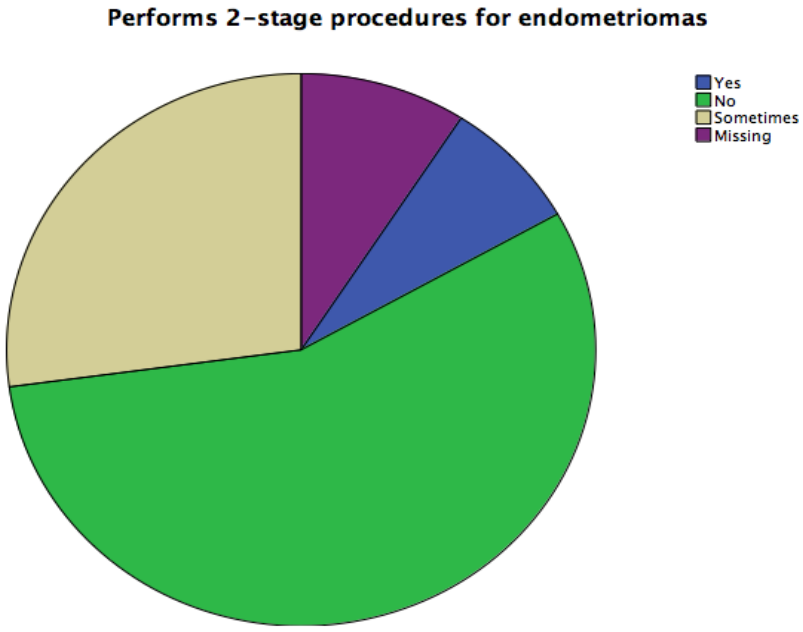
The excisers agreed more strongly than other technique users that they used their technique because they thought it was the best and feel this more strongly when treating deep disease. They also seemed to have tried more techniques

than the others for treating superficial endometriosis. The coagulators felt more strongly that they used their technique because they thought it was easier. However they also felt that they lacked the skill or equipment to use another technique (there are however only 19 responders in the deep disease response group). Despite this they still believed that their technique was the best. The vaporizers and combined exciser/vaporizers seem to fall somewhere in the middle between the excisers and coagulators in their views.

Management of Endometriomas

98.4% of responders said that they surgically treated endometriomas. Initially they were asked to say whether or not they used a 2-stage technique of drainage, hormonal down regulation and subsequent definitive procedure. The results of this are shown in the pie chart in fig 8 below.

Fig 8. Pie Chart showing the use of 2-stage procedures for endometriomas.



Yes=26 (8%) Sometimes=92 (29.9%) No=190 (61.7%)

Table 10. Responders use of techniques for surgically treating endometriomas.

	<3cm	>3cm	*P value
Excision	206 (66.2)	223 (72.2)	P=0.110
Ablation	24 (7.7)	19 (6.1)	P=0.580
Combination	69 (22.2)	61 (19.7)	P=0.455

*Pearson Chi-square Test

There is no significant difference in technique whether endometriomas are either less or greater than 3cm diameter however excision is clearly the commonest technique overall. 5 (1.5%) respondents commented that they observe endometriomas that are less than 3cm diameter and do not surgically treat them.

Why do responders choose their preferred technique for treating endometriomas of different size?

The results for this are divided into the techniques used for endometriomas of <3cm and >3cm diameter.

Table 11. Reasons for choosing technique for treating endometriomas of <3cm diameter.

	Excision	Ablation	Combination	*P value
	Median		(25-75%)	
Trained	4 (3-4)	4 (3-4)	4 (3-4)	0.862
Self-taught	4 (3-4)	4 (3-4)	4 (3-4)	0.500
Best	4 (4-5)	4 (3-4)	4 (4-5)	<0.0005
Easier	3 (2-4)	3 (3-4)	3 (3-4)	0.002
Tried other	3 (2-4)	4 (2-4)	3 (2-4)	0.939
No preference	2 (2-3)	3 (2-4)	3 (2-4)	0.001
Lack of equipment	2 (1-3)	4 (2-5)	3 (2-4)	<0.0005
Lack of skill	2 (1-3)	4 (2-5)	3 (2-4)	0.001
Cost effective	3 (3-4)	3 (3-4)	3 (3-4)	0.945

*Kruskal-Wallis Test

In table 11 above, for <3cm diameter endometriomas the technique groups do not vary in their view in that they agree that they carry out their technique because they were either trained or taught to do it. They are all neutral in their concern over cost effectiveness and whether they have tried other techniques or not. The excisers do not feel like they lack equipment or skill where as the ablators seem to, and the combined group are neutral on the issue.

Table 12. Reasons for choosing technique for treating endometriomas of >3cm diameter.

	Excision	Ablation	Combination	*P value
		Median	(25-75%)	
Trained	4 (3-4)	4 (3.25-4)	4 (3-4)	0.351
Self-taught	4 (3-4)	3 (2.25-4)	4 (3-4)	0.078
Best	4 (4-5)	3.5 (3-4)	4 (4-5)	<0.0005
Easier	3 (2-3)	3 (3-3.75)	3 (2-4)	0.021
Tried other	3 (2-4)	3 (2-4)	3.5 (2.75-4)	0.352
No preference	2 (1-3)	3 (2.25-3)	3 (2-4)	<0.0005
Lack of equip	2 (1-3)	4 (3-4)	3 (2-4)	<0.0005
Lack of skill	2 (1-3)	3.5 (3-4)	3 (2-4)	<0.0005
Cost effective	3 (3-4)	4 (3-4)	3 (2-4)	0.245

*Kruskal-Wallis Test

In table 12 above, similar trends are apparent in the reasons for choosing treatment technique for >3cm endometriomas, suggesting that the approach to endometriomas does not seem to differ much no matter what the size.

Management of recto-vaginal nodules

175 responders said that they surgically treat recto-vaginal nodules. Responders were more likely to do this if they were more experienced in terms of number of years performing independent laparoscopic surgery (mean of 13.9 v 10.1 years p<0.0005, mean diff 3.848, 95%CI 1.976-5.721). 78.6% of responders surgically treat recto-vaginal nodules more often by laparoscopy

compared with 10.7% who more often use laparotomy. A further 10.7% use laparoscopy and laparotomy equally.

Preoperative investigations

As table 13 below illustrates, trans-vaginal ultrasound scan (TVS) is the most common pre operative test for recto vaginal nodules followed by MRI.

Table 13. Use of pre-operative tests for recto-vaginal nodules.

	n (%)
TVS	142 (81.1)
TRS	55 (31.4)
CT	15 (8.6)
MRI	105 (60)
Colon/sig	80 (45.7)
Ba enema	25 (14.3)
IVU	7 (4.0)
None	4 (2.3)

Operating with a colorectal surgeon

Table 14. Number of responders who operate on recto-vaginal nodules with a colorectal surgeon.

	n (%)
Never	9 (5.4)
Rarely	66 (39.3)
Mostly	62 (36.9)
Always	31 (18.5)

In table 14 above, only 5.4% of responders never operate with a colorectal surgeon and 18.5% always operate with a colorectal surgeon. The remaining responders are split between rarely or mostly. There are no significant differences when comparing training method (p=0.512) or experience (p=0.360) against likelihood of operating with a colorectal surgeon.

Surgical technique for removing recto-vaginal nodules

Table 15 below, shows surgeons' surgical technique for removing recto-vaginal nodules in terms of whether an attempt is made to initially shave recto-vaginal nodules off the bowel to avoid opening it, those who try to use disc resection rather than segmental resection if shaving fails, those who are ever prepared to do a segmental resection, and those who always aim to do a segmental resection for all cases.

Table 15. Surgical technique for treating recto-vaginal nodules.

	Shave	Disc	Ever segment	Always segment
	n (%)			
No	22 (13.2)	57 (33.7)	48 (28.7)	124 (73.8)
Yes, by myself	56 (33.5)	28 (16.6)	4 (2.4)	3 (1.8)
Yes, with surgeon	27 (16.2)	56 (33.1)	103 (61.7)	32 (19.0)
Yes, either/or	61 (36.5)	27 (16.0)	12 (7.2)	9 (5.4)

144 (86.2%) responders were in favour of attempting an approach that tried to avoid opening the bowel in the first instance. 111 (65.7%) responders were prepared to carry out disc resections to avoid segmental resection if shaving

failed. 119 (71.3%) responders were prepared to use segmental resections. 44 (26.2%) responders will always aim to carry out a segmental resection.

Discussion

The validity of the data is immediately called into question by the low response rate achieved, despite efforts to follow recognised methods of questionnaire construction in the methodology (Nakash R, 2006, Boynton, 2004).

In an attempt to explain this, one can consider the strengths and limitations of the methodology. This study had certain strengths when considering survey administration. The questionnaire was salient to its population and should have generated an interest. An efficient means of completing the questionnaire was provided with an electronic link directly to it. A clear covering invitation letter confirming confidentiality was given. An incentive was provided in the form of a prize for one responder. A reminder was included, a researcher was available by email to answer questions, and a pilot study was performed.

However, there were some limitations in administration also. There is a possibility that some of the responders in mainland Europe or non-English speaking countries may have been put off from completing the questionnaire in English. There was no pre-notification of the survey to the population. It would have been nice to have an advert in each society a month or so before sending out the survey to warn people that it was coming and generate some interest. However, bearing in mind the complexities involved in getting societies to agree to even sending out the survey, this would likely have been difficult. In addition,

the incentive was probably not strong enough. However this was developed within the economic restraints of the study. The lack of personal invitation email to AAGL members, and the refusal to send a reminder, undoubtedly limited the response from the AAGL. Many AAGL members would have missed the invitation in the newsletter or perhaps never read the newsletter at all. There also remains the possibility of over exposure in the population and a feeling of "oh no….not another questionnaire!".

From the questionnaire design perspective, the study was strong in that it did produce a clear design and layout that was visually appealing. At 34 questions long it was short according to Nakash's meta-analysis, which defined shorter questionnaires as 7 to 47 questions (Nakash R, 2006). As has been described in the methodology section, a significant amount of effort went into question form, wording and ordering, that was refined following the pilot study. The main failure appeared to be getting people to start the survey as 90.5% did complete it if they went beyond the invitation page.

Despite the low response rate, the characteristics of those returning the questionnaire appear to reflect those expected in the general population of laparoscopic gynaecologists.

The age of responders is normally distributed and the number of years practising independently as a laparoscopic surgeon is only mildly negatively skewed. Assuming the historical growth of laparoscopic surgery over the last 20 years, then it is not unreasonable to expect this skewness in the population, as

gynaecological laparoscopic surgeons join the sub-specialty each year in increasing numbers.

Although only 10% of responders were trainees, they were analysed within the whole group together with qualified specialists. This was because they were considered as legitimate members of the specialist societies in their own right and there were not enough of them to excessively duplicate the answers of the specialist they worked with.

The regional divide of responses was not equally representative as has been explained above by the poor response rate especially from the AAGL (3.1%). Consequently comparative regional analysis was not able to be carried out.

41.6% of responders said that they operated on recto-vaginal endometriosis and this appears higher that one might expect. It seems unlikely that nearly half of gynaecological laparoscopic surgeons are genuinely tackling the most complex endometriosis. This suggests that, whilst we seem to be looking at a sample that is fairly normally distributed by age and experience, the sample population contains a greater proportion of surgeons undertaking complex endometriosis surgery than would be expected in the general population of gynaecological laparoscopic surgeons. It is perhaps not surprising that those who do tackle recto-vaginal endometriosis will have a greater vested interest in the disease, and therefore are more likely to respond to a survey such as this.

Within the limits of the sample population described above, the analysis revealed that formal training appears to be frequent, and a surprisingly high

percentage (39%) of responders had undergone some form of specialist laparoscopic training. The finding that more experienced surgeons carried out a greater number of endometriosis cases per month, suggests that they are becoming more specialised with a greater proportion of endometriosis cases in their referrals. It is also possible that they are operating more quickly and efficiently.

It is interesting that 19% of responders do not operate on minimal to moderate endometriosis. 78% of these 19% however do operate on endometriomas. Therefore, it is likely that this group consists mainly of infertility specialists who may be only dealing with endometriomas prior to IVF, and not dealing with any coexisting disease despite it existing in pretty much all cases (Banerjee et al., 2008). Also 31% of the 19% stated that they do operate on recto-vaginal disease, and so this may represent a super specialised group who are dealing with only more complex cases.

It is recommended that if a laparoscopy is performed and endometriosis diagnosed, then a see and treat approach be taken provided that adequate consent has been obtained (Kennedy et al., 2005). It is reassuring to see that the majority of surgeons take this approach. It perhaps is not surprising that if a patient sees a more experienced surgeon then they are more likely to get a see and treat approach.

In terms of instruments used to treat endometriosis, a substantial number of surgeons will avoid energy use altogether, and just use cold scissors for removing presumably more straightforward lesions in the peritoneum that may

lie over sensitive structures like the ureters. This reduces the risk of thermal damage to these structures and the amount of bleeding from the peritoneum whilst using cold scissors is small, negating the need for a haemostatic instrument.

When energy is used, electro-surgery remains the most frequently used energy source for treating endometriosis. This probably reflects its great flexibility as either an excision or vaporative tool in monopolar form, despite which surprisingly monopolar use has fallen significantly. The increase in bipolar use is potentially concerning as coagulating lesions not only fails to remove all disease and has been shown to result in a worse outcome for endometriomas (Hart et al., 2008), but also fails to allow full assessment and treatment of the full depth of lesions. However some bipolar use may be for haemostasis following excision by cold scissors or another energy source.

Ultrasound devices have significantly increased in popularity possibly as a result of successful marketing claiming advantages of increased safety and user friendliness. Despite laser technology being supported by the RCT evidence for surgically treating endometriosis behind it (Sutton et al., 1994), its use seems to have significantly fallen away which may be due to the specific training or substantial initial financial outlay required.

Minimal to moderate endometriosis

In terms of technique used for minimal to moderate endometriosis, the significant increase in excision use for deep versus superficial disease is logical. In deep disease, excision alone is more popular than a combined approach of

excision/vaporization, which was the most popular approach for superficial disease. That the “excisers only” are a group who “strongly agreed” in their approach over others, was not a surprise. At conference, the excisers appear to defend their technique with more fervour than others. The majority view that a combination of true vaporization, resulting in the same visual effect as excision, or excision alone for superficial endometriosis is reassuringly correlative with existing randomized data (Jacobson et al., 2009, Wright et al., 2005).

Coagulation by itself is a minority option compared with excision, vaporization or a combined excision/vaporization approach. This again seems to fit the hypothesis that ablation/coagulation is suboptimal in assessment and treatment. As argued above, the data may be biased in favour of experts as shown by the high percentage of responders that treat recto-vaginal endometriosis. This may mean that there is possibly an even higher percentage in the true population who use a superficial coagulation/ablation technique who lack the skills or instruments to carry out full excision or vaporization. This statement is supported by the fact that surgeons who are self-taught or feel they lack skills and equipment, were more likely to use coagulation. Despite admitting to a lack of equipment and skill, the coagulators had a tendency to agree that their technique was still the best, which may be influenced by a difficulty to admit that what you are doing is not the best option for the patient.

Endometriomas

The treatment of endometriomas is currently done by excision by the majority of responders whether or not they are > or < 3cm diameter. It is currently recommended in ESHRE guidelines that excision is the preferred technique in

endometriomas of >3cm to obtain the cyst wall for histology to exclude malignancy. If this fails then a two-stage procedure, with hormonal down regulation between operations, may be tried to improve the chances of ablation being successful at the second procedure. Only 30% of the responders in this study said that they sometimes use this technique, suggesting that they feel they are, more often than not, successful with a one-stage procedure, most likely using excision for this. It may also imply that the concern over potential ovarian damage from excision (Loh 99) is generally less important than the perceived improved pain, fertility and recurrence outcomes shown in several studies of endometrioma treatment (Beretta et al., 1998, Alborzi et al., 2004b). There is no randomised evidence commenting on the best treatment for endometriomas measuring <3cm diameter.

Recto-vaginal endometriosis

Laparoscopy is the predominant method to tackle recto-vaginal endometriosis amongst the responders. However, the finding that 10.7% mainly took a laparotomy approach may be erroneously low when considering the whole gynaecological surgical population. The question here remains whether or not women are being referred to this expert group for laparoscopic treatment and potentially fertility sparing surgery, or whether “non-experts” are still operating on a significant number with laparotomy and pelvic clearance.

For advocates of a “conservative” approach to surgically removing recto-vaginal endometriosis, the ideal aim of preoperative testing would be to accurately predict that a lesion could be shaved off or removed by disc resection of the bowel without segmental resection. This would require accurate measurement

of the depth of invasion into the bowel wall and being able to correlate this information to correctly identify the surgical procedure required to remove the disease. However, the accuracy of such a pre-operative test remains unproven. For those surgeons who advocate segmental resection in all cases of bowel involvement, the logic of this approach relates to the finding of macroscopic and microscopic satellite lesions of endometriosis in the rectum and sigmoid colon in 68% of cases (Keckstein, 1999). Thereby, removing the segment of bowel may reduce the risk of recurrence. This is however at the expense of significant chronic bowel morbidity in young patients (Dubernard et al., 2006).

Preoperative tests like TVS, MRI and TRS have been effective at predicting bowel involvement in recto-vaginal endometriosis (Dessole et al., 2003, Hudelist et al., 2009, Fedele et al., 1998, Chapron et al., 2004, Bazot et al., 2009) and so their common use in modern practice seen in the survey results is understandable if only to alert the surgeon to potential bowel involvement and consequently to be able to adequately inform and consent the patient prior to surgery. In Hudelist's report, involvement of the serosal and smooth muscle layers of the bowel was positively predicted in 98% of cases, and the PPV for mucosal involvement was 53%. These results are perhaps not immediately or easily reproducible in most units.

Barium enema or sigmoidoscopy/colonoscopy are still used as adjuncts to the more effective imaging modalities outlined above. Double contrast barium enema alone has been shown in two recent studies to have close to 90% sensitivity, and specificity ranging from 54 to 88% (Ribeiro et al., 2008, Faccioli et al., 2008).

In modern practice where litigation is becoming increasingly predominant it is not surprising to find that only 5.4% of gynaecological laparoscopists never operate with a colorectal surgeon for recto-vaginal endometriosis.

The argument of whether to shave, disc resect or segmental resect for recto-vaginal endometriosis is one that has been a main focus in conferences over the last few years with surgeons offering their strong opposing opinions based on large case series (see table 1). There is no high quality evidence to support one procedure over the other and due to the methodological difficulties of designing an RCT, it is unlikely that evidence will emerge in the near future. Prior to this survey little was known about the extent to which opinion is divided in this contentious area. The majority of responders (86.2%) in the survey are in favour of a conservative shaving approach if possible in the first instance, with no significant regional variation in this opinion (p=0.291). Whilst 144 surgeons stated that they would attempt a shave first, there are only 111 and 119 in favour of ever performing discs resections or segmental resections respectively. This suggests a group of responders who either believe that one should avoid opening the bowel at all costs, or will refer the patient onto someone who can.

At the other end of the spectrum lie the 26.2% of responders who will always aim to do a segmental resection. Nevertheless, the results show that the majority of responders take a pragmatic conservative approach to the problem of opening the bowel or performing segmental resections where they have to.

Conclusion

Taking into account the poor response rate, though seemingly fairly representative sample nevertheless, this study reveals for the first time the attitudes and practice of gynaecological laparoscopists dealing with endometriosis who belong to specialist societies. In the main the findings support previous study results, but we must be guarded in this statement as the responders may well be a biased group of experts, and these results represent practice within the specialist societies, not what is likely to be happening amongst the general population of gynaecologists.

It is reassuring to see that formal training is becoming commonplace especially as responders generally agreed that they carried out particular procedures because that is “how they had been taught to do it” implying that training is a major influence on practice. Practice was not dictated generally by concerns over cost, but some felt they lacked the skill or equipment to perform their optimal technique and this is something that is likely to improve over time. It is encouraging that the majority of responders favour a see and treat approach.

For minimal to moderate endometriosis treatment, the majority of laparoscopic gynaecologists are electro-surgery users with a tendency to excise, or take a combined excision/vaporization approach, in line with current evidence, with a greater tendency to excise deep disease. Questions remain over endometrioma treatment where laparoscopic gynaecologists are generally excisers for all sizes of cyst, and possibly influenced by the current evidence, believing that on balance they are doing more good than harm. By and large, laparoscopic

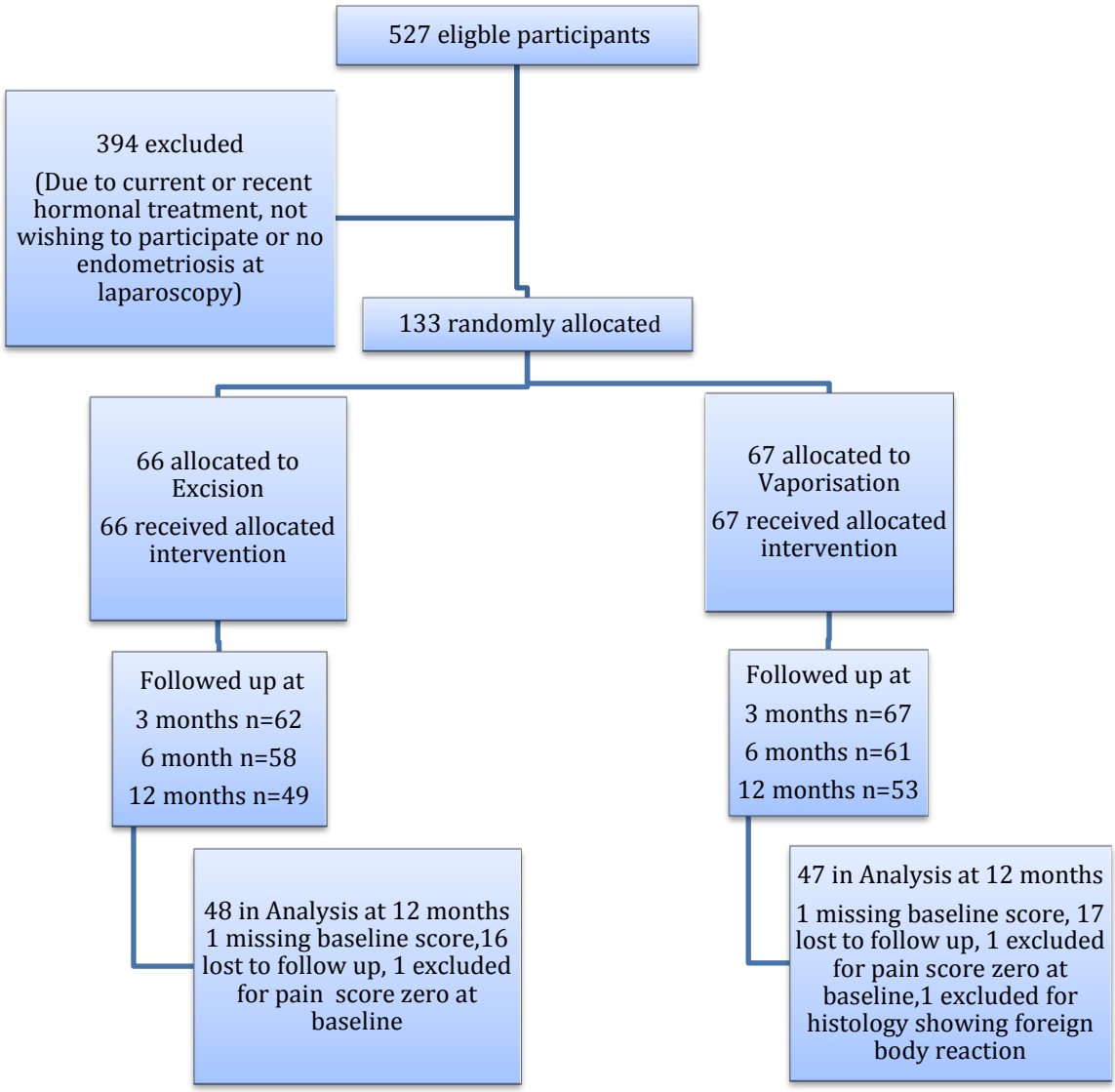
gynaecologists are taking a conservative approach to recto-vaginal disease where possible, to avoid the potential complications of bowel surgery. However, when required, the study shows an acceptance of a multi-disciplinary approach involving colorectal colleagues in the surgical management.

Chapter 5 - Results

Results of a randomised blinded trial of carbon dioxide laser vaporisation versus harmonic scalpel excision of rASRM stage 1-3 endometriosis in women with pelvic pain

Participant Flow

Fig 9. Flow diagram of participants through the trial.



The study analysis was designed on an “intention to treat basis” but in the event, all of the patients received the surgical procedure that they were allocated to. Data for the reasons why eligible patients were excluded from entering the trial prior to surgery was not collected. However, subjectively, the majority of patients were not eligible because they had either received hormonal therapy in the previous 3 months, or were currently receiving it for pain control or contraception. Additional, though less common reasons, were because they did not wish to participate or because they were found to not have endometriosis on visual inspection at laparoscopy.

Interim analysis of recruiting and follow up

Protocol deviations were identified in April 2006 when it was discovered that some patients were not actively being followed up because they had become pregnant. An interim analysis of recruiting and follow-up was therefore undertaken to analyse the effect of this. Dr Haider Jan independently reviewed the patient folders so that none of the researchers were unblinded. The completeness of the data and the reasons for failure to follow-up were reviewed. The findings were as follows:

Overall Result

79 women were in the database, 70 women were at 6 months or more post treatment. 56 of those women had completed 0,3 and 6 months questionnaires. Of the 14 who had not completed all questionnaires, 6 had not done so because they had become pregnant and 8 had not done so because they had failed to attend follow-up appointments.

Drop out rate

This reflected an overall drop out rate of 14/70 = 20%. Drop out rate due to reasons other than pregnancy was 8/70 = 11%. This was generally due to women not coming to appointments that had been sent to them through the post.

Trial state

106 women were required in total from the original power calculation. At the audit point, the trial was 56/106 = 53% complete.

9 women had not completed all questionnaires. Given the drop out rate of 20%, then 7 of those should complete the trial.

Therefore the current estimated number of trial completions was 63/106 (56+7) or was 59% complete.

Therefore 106-63 more women were needed = 43. Accounting for the estimated 20% projected drop out seen so far, then 9 patients out of 43 would be expected to drop out.

Therefore the total number required to complete the trial was 52 (43+ 9) in April 2006. With 79 already recruited, this implied that the total sample would now need to be 131 (79+52).

Recommendations of interim analysis:

1. The follow-up protocol needed to be enhanced to improve the drop out rate of patients (see clarification letter at Appendix).

2. Complete questionnaires for all those that missed their follow-up at 6 or 12 months for a snapshot of how they are now, no matter the time post procedure. This should be attempted by telephone if other means fail as described in the clarification letter.

3. Begin to transfer data from paper questionnaires onto an SPSS database so an electronic copy is formed.

4. Repeat mail-shot to GPs to improve recruitment.

5. OASIS training for the Nurse Researcher to improve her ability to independently contact women by telephone or mail.

6. Adjustment of the originally intended sample size to compensate for the drop out rate from 106 to 132.

7. Re-audit in 9 months.

Final Audit of Database

A 10% audit check of the entire SPSS database was carried out on 17/4/09 to confirm its accuracy. Incorrect data was found in the HADS 3 month and VAS 6 month files. Instead they contained EHP-30 intercourse module data. Therefore a previously backed up version of the files was recovered and re-entered into HADS 3 month and VAS 6 month fields. Following this 10% of cases were randomly selected by random number generation for assessment on 6/5/09. The SPSS data for each case was completely checked against the original paper questionnaires.

The selected cases were 11,17,33,37,48,53,64,67,77,88,102,121,127.

The following errors were discovered:

Case 11 – 1 error in HADS 3, 3 missing boxes in EHP-30 12 month.

Case 17 – 1 error EHP-30 6 month, 2 errors HADS 6 month.

Case 102 – 1 error in EHP-30 intercourse module 12 month.

The total number of data boxes per case is 220: (EHP-30=120, Intercourse=20, VAS=44, HADS=56). Therefore the total number of data boxes in the SPSS database is 220x133 patients = 29260. The total number of data box errors in the audit was 8 in 10% of the total dataset. Therefore 80 data box errors were estimated overall. As a percentage, the overall estimated data box error was 80/29260 = 0.27%. This was judged to be acceptable.

The final SPSS database was then analysed simply to look for outlying results suggestive of possible data entry errors. Two errors were found from this: Case 62 had missing data for 3, 6, and 12 month EHP-30 Core questions as she had failed to attend follow up due to pregnancy. This had been entered erroneously as -9 (not relevant) instead of 99 (missing). A similar problem was found for case 85 who had missing data that had been entered erroneously as -9 instead of 99.

Numbers analysed

Recruitment

133 Patients were recruited into the trial between 15 November 2002 and 30 May 2008. Case number 59 was excluded from the trial at the end of her follow-up period because her histology showed a foreign body reaction (she had had a

previous laparoscopy in 1990), suggesting that she did not have endometriosis. The follow-up period was completed in June 2009. The recruitment rate over 66.5 months was 2.03 patients per month.

Patients who did not attend for follow up

The patients who did not attend for follow-up at each time point were analysed to ensure that they were not a common subgroup that could bias the results of the overall study. There were 4 patients who did not attend follow-up at 3 months (2.3%), 14 at 6 months (10.5%) and 31 at 12 months (23.3%). Therefore 102 (76.7%) were followed up at 12 months.

However, to establish whether there was a bias created by missing variables as a whole, the total number of missing scores for EHP-30 Core pain domain was calculated for each time point. This included those with a missing or zero pain score at baseline, as well as those who completely failure to attend follow-up. This is displayed in table 16 below:

Table 16. Number of participants missing from EHP-30 Core pain score analysis.

Technique	Pre-op n/n	3 months n/n	6 months n/n	12 months n/n (%)	Missed >/= 1 follow up
Excision	2/66	5/66	11/66	18/66 (27.3)	19/66
Vaporisation	3/67	8/67	13/67	20/67 (29.9)	24/67

At 12 months there is no difference, in terms of group balance, between the 18/66 (27.3%) for excision and the 20/67 (29.9%) for vaporisation (p=0.742, chi-squared test). Therefore the number of patients in the main analysis for the primary outcome was well balanced between the two groups with 95 patients

analysed: 48 in the excision arm and 47 in the vaporisation arm. The characteristics of the 38 patients who had missing or excluded scores at 12 months were analysed to see if they were not representative of the whole population in any way. As seen in fig 17 below, there were no findings suggestive that the group of missing or excluded results for EHP-30 Core pain domain were greatly different from the analysed results.

Table 17. Comparison of baseline variables between patients included in the main analysis, and missing or excluded patients.

Characteristic	Analysed (n=95)	Missing/Excluded (n=38)
Mean age +/- SD	33.69+/-7.57	31.18+/-7.90
Median rASRM score (IQ Range)	6 (4-11)	5 (3-8)
Positive Histology n/n (%)	44/55 (80%)	10/12 (83.3%)
Deep disease n/n (%)	52/93 (55.9%)	20/37 (54.1%)

Other factors that were considered when deciding on numbers analysed

1. Pregnancy, adjuvant hormonal therapy and subsequent surgery.
2. Patients who scored zero for the variable at outset.

1. Pregnancy, adjuvant hormonal therapy and subsequent surgery.

There were 22 pregnancies in 19 patients (3 patients had 2 pregnancies each), 5 patients who underwent further surgery (including one hysterectomy and bilateral salpingo-oophorectomy, and four laparoscopies), and 16 patients who had adjuvant hormonal therapy at some point during the 12 month follow-up

period. These can be considered to be protocol deviations during the follow-up period. None of these patients were excluded from the main analysis in order to produce a result reflecting the natural evolution of the disease following surgery on an intention to treat basis. However, a “per protocol” sub-analysis of the main group without these patients was also carried out.

2. Zero scores for outcome modalities pre-op

Some patients had scores of zero for pain or QOL outcomes at the pre-op visit showing that they did not suffer from that particular symptom as a result of their endometriosis. These were excluded from the analysis of improvement for that particular modality as it was felt that they were unable to improve and only able to stay the same or get worse. The stay the same or get worse patients for each modality were subsequently analysed separately to ensure that we were not missing an effect of treatment causing symptoms to deteriorate. Similarly the same was applied to this group in that the patients who had the worst possible score at baseline were excluded as they were unable to get any worse.

Summary of numbers analysed at each time point

For the primary outcome measure EHP-30 Core pain score, the follow-up rates at 3, 6, and 12 months were 129/133 (97.0%), 119/133 (89.5%) and 102/133 (76.7%). Taking further into account missing data and exclusions, the analysis rates were 122/133 (91.7%), 111/133 (83.5%) and 96/133 (72.2%). Table 18 below summarises the numbers analysed for each outcome measure at the main analysis points in the trial:

Table 18. Numbers analysed at each point of the trial for each outcome measure.

Analysis point:	0 months		3 months		6 months		12 months	
Technique:	Exc	Vap	Exc	Vap	Exc	Vap	Exc	Vap
Outcome	n=66	n=67	n=66	n=67	n=66	n=67	n=66	n=67
EHP30								
Pain	65	65	62	60	56	55	48	48
Control & powerlessness	64	64	62	61	57	55	47	48
Emotional wellbeing	66	64	62	61	57	56	50	48
Social support	64	65	62	60	56	56	49	49
Self image	66	65	62	62	57	56	50	50
Intercourse	61	54	57	51	53	47	45	44
VAS								
Dysmenorrhoea	61	64	62	56	56	51	40	47
Dyspareunia	59	59	57	47	52	45	40	44
CPP	60	58	62	58	55	51	44	45
Dyschezia	62	60	56	57	56	47	45	45
HADS								
Anxiety	66	65	62	61	48	50	48	50
Depression	66	63	60	60	49	50	49	50

Baseline Data

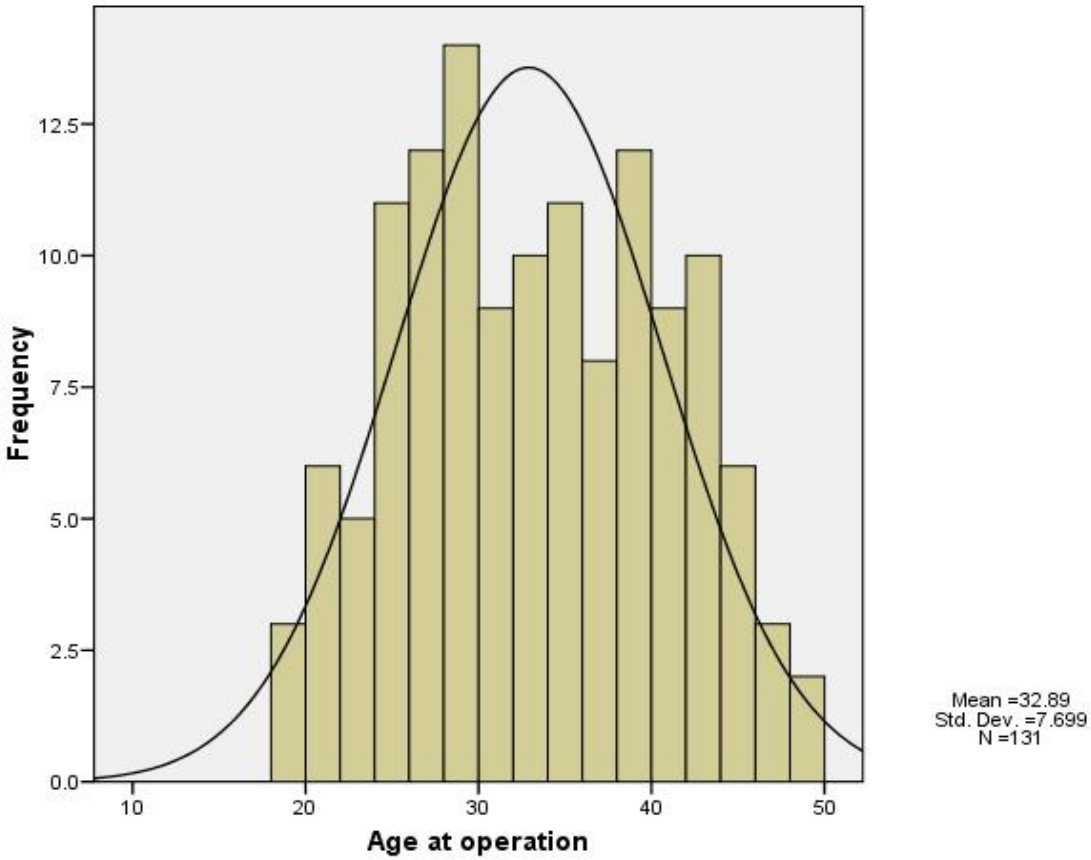
Baseline data for the 132 patients included in the analysis was calculated for Age, rASRM score and stage, histology, location and depth of disease.

Overall baseline statistics for continuous variables

Age

As fig 10 below shows, the mean age of patients was 32.9 years (+/-7.7 range 19-50) and was normally distributed.

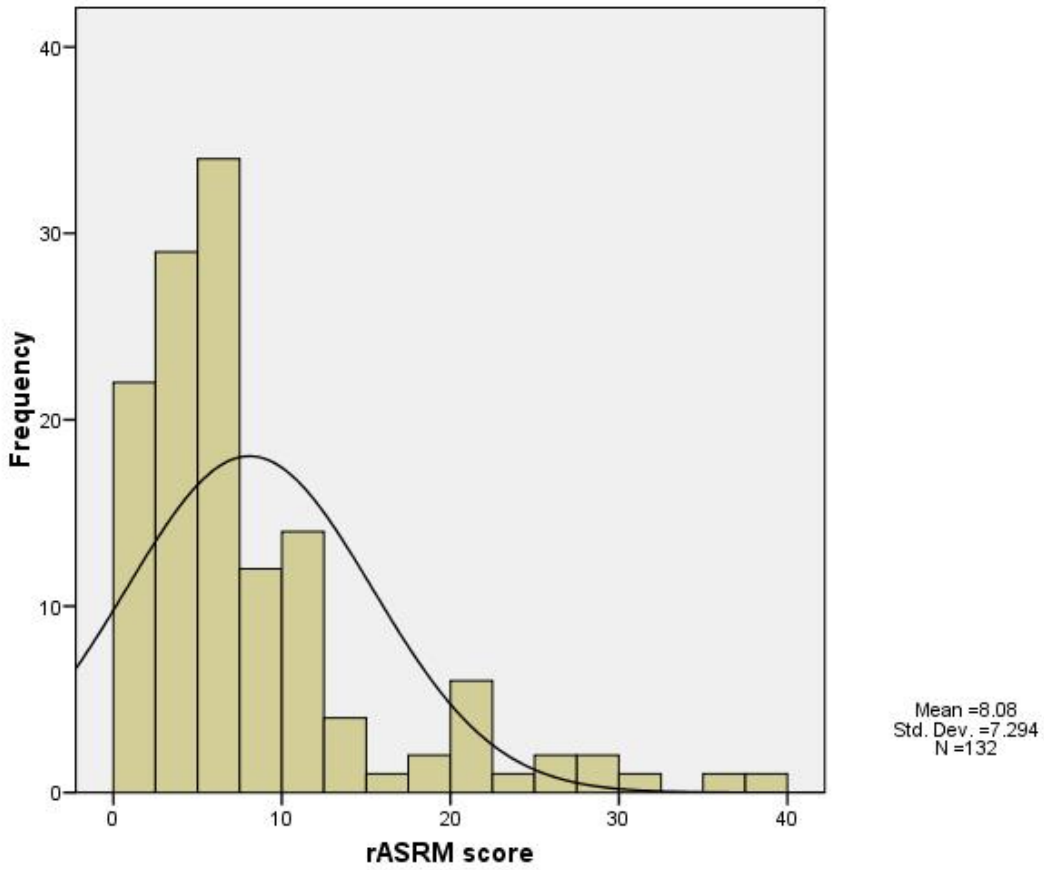
Fig 10. Age distribution of participants.



rASRM Score

In fig 11 below, the distribution has a long tail showing that patients in the study are more frequently found in the lower stages of the disease and confirms the finding that endometriosis is not normally distributed according to rASRM score. Therefore, the descriptive analysis for rASRM score was calculated by median and interquartile range. Median rASRM score was 6 (interquartile range 3-10).

Fig 11. Distribution of participants by rASRM score.

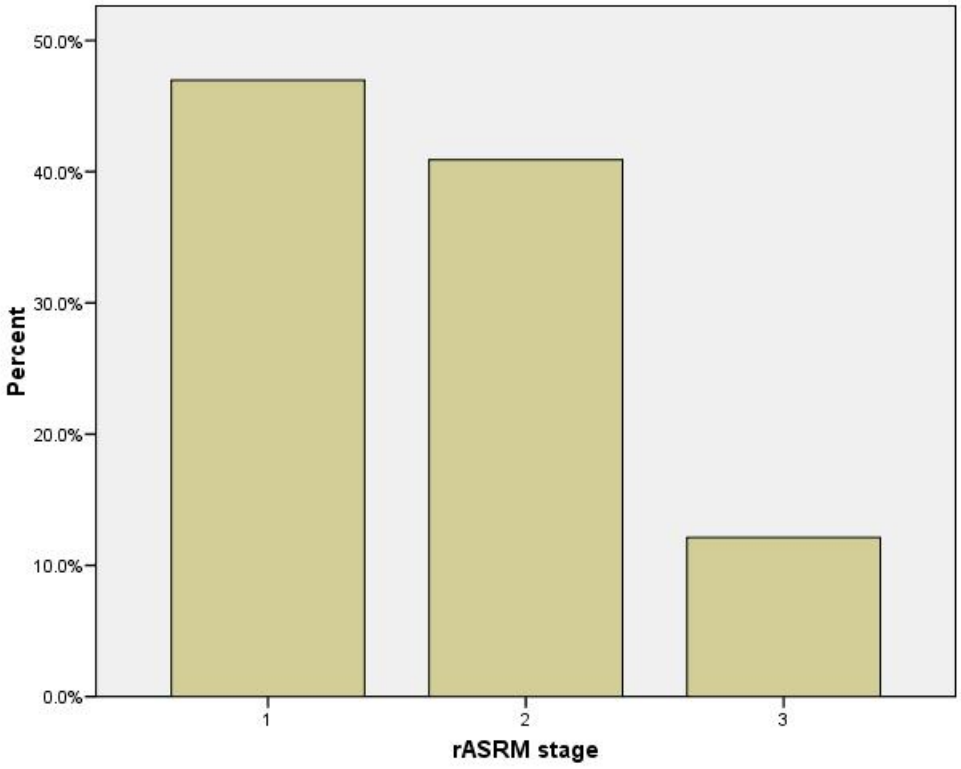


Overall baseline statistics for discrete variables

rASRM Stage

Fig 12 below shows that 87.9% patients are equally distributed between rASRM Stages 1 and 2. The remaining 12.1% fall into stage 3. This reflects the natural distribution of the disease between stages (Redwine, 1990a, 1994).

Fig 12. Distribution of participants by rASRM stage.



Histology

Histology was taken in 65 of 133 cases (48.9%), 49 from the excision group and 16 from the vaporisation group. It was not always possible to get histology from the vaporisation group as biopsy may have resulted in excision of all or most of some lesions. Taking histology was not started till case 46 in June 2005. Overall 54 of the 65 cases had histology positive for endometriosis, showing a successful correlation between visual inspection and histological analysis in 83.1% of cases.

Predominance of left sided disease

The number of times that left sided and right sided disease was recorded in any location was analysed. There were three possible locations on each side of the pelvis where disease could be recorded for the rASRM score; ovary, side-wall and uterosacral ligament. It was found that there was more left sided disease overall in the trial population in that there were 175 areas of left sided disease v 125 areas of right sided disease ($p=0.0005$ paired t-test) as one would expect from previous observers (Vercellini et al., 2004).

Did the patients with deep disease have a higher starting score

The baseline statistics were analysed to see whether or not deep disease had a higher mean baseline score (table 19 below), suggesting they suffer from greater levels of pain compared with superficial disease:

Table 19. Comparison of mean starting scores for pain outcomes for superficial and deep disease.

Outcome Mean +/-SD	Superficial (n=66)	Deep (n=66)	*p value
EHP30 pain	40.47+/-33.49	41.10 +/-22.28	p=0.899
Dysmenorrhoea	6.53 +/-2.69	6.65 +/- 2.71	p=0.809
Dyspareunia	4.15 +/-3.35	4.71 +/-3.20	p=0.36
CPP	4.77 +/-3.31	4.93 +/-3.17	p=0.785
Dyschezia	2.88 +/-3.44	3.29 +/-3.22	p=0.500

*unpaired t test

Comparative baseline statistics for patient characteristics

Table 20 below summarises the comparative statistics between the two treatment groups for general baseline characteristics:

Table 20. Comparison of mean baseline variables for excision and vaporisation.

Characteristic	Excision (n=66)	Vaporisation (n=66)
Mean age +/- SD	33.05+/-6.69	32.74+/-8.65
Median rASRM score (IQ Range)	6(4-10)	6(3-9)
Positive Histology n/n (%)	41/49 (83.7)	13/17 (76.5%)
Deep disease n (%)	44 (66.7%)	28 (43.8%)

The CONSORT Statement warns against using statistical tests to adjust for baseline variable differences as this can bias the estimated treatment effect (Altman et al., 2001). Deep disease has been claimed to show a greater extent of improvement after surgical treatment than superficial disease (Banerjee et al., 2008) and so imbalanced groups for depth of disease may bias the results. By chance there were 44 (66.7%) deep cases in the excision group compared with 28 (43.8%) in the vaporisation group (p=0.009, Chi-sq test).

However, no attempt was made to adjust for this difference in depth as this may have resulted in a bias in the estimated treatment effect. It has already been shown above that women with deep disease do not start on a significantly higher baseline pain score (table 20) and therefore uneven distribution in disease depth between the groups does not affect the baseline primary outcome measure of pain. To decide whether imbalanced depth of disease between the groups has biased outcomes, depth was sub analysed later in this chapter.

Comparative baseline statistics for outcome measures

Firstly, the data were analysed to see whether a higher baseline pain score resulted in a greater probability of a larger fall in score for the primary outcome measure EHP-30 Core pain domain if the patient improved. The implication of this is that if the groups are not balanced in baseline scores then the one with the significantly higher score has a greater chance of showing more improvement. There is a highly significant positive correlation between baseline pain score and amount of improvement in pain for EHP30 Core pain score (Pearson's Correlation test r=+0.535, p<0.0005). However in the table 21

below, the groups are well balanced for mean starting scores so this effect is not likely to affect the results in this study:

Table 21. Comparison of mean baseline outcome scores for excision and vaporisation.

Outcome	Excision	Vaporisation
Mean +/-SD	(n=66)	(n=66)
EHP30		
Pain	42.3 +/-21.6	43.3 +/-21.7
Control & powerlessness	51.0 +/-27.3	53.9 +/-21.3
Emotional wellbeing	48.6 +/-21.4	47.3 +/-19.6
Social support	40.4 +/-30.9	41.4 +/-24.8
Self image	33.7 +/-28.2	38.1 +/-26.8
Intercourse	48.9 +/-29.2	55.7 +/-28.6
VAS		
Dysmenorrhoea	6.8 +/-2.8	6.5 +/-2.6
Dyspareunia	4.2 +/-3.3	4.8 +/-3.3
CPP	4.8 +/-3.3	4.9 +/-3.1
Dyschezia	3.4 +/-3.5	2.8 +/-3.1
HADS		
Anxiety	9.6 +/-4.2	9.6 +/-4.0
Depression	4.1 +/-3.3	4.5 +/-3.7

Outcomes and Estimation

Primary outcome measure: EHP30 Core Pain

In the whole study group 76 (80%) patients improved and 19 (20%) patients stayed the same or got worse at 12 months.

Comparative pain was analysed using two outcomes:

1. The proportion of patients who improved or “stayed the same or got worse”, to see if one technique was managing to improve a greater number of people.
2. The extent of improvement for each technique to see if one technique gave a greater amount of improvement.

Proportional improvement in primary outcome measure

Table 22 below shows the proportion of patients showing improvement for the primary outcome variable EHP-30 Core pain score at all the analysis time points:

Table 22. Proportion of patients showing improvement for EHP-30 Core pain score.

Analysis point	Excision n/N (%)	Vaporisation n/N (%)	Difference %	p value*
Improved				
3 months	46/62 (74.2)	44/60 (73.3)	0.9	0.954
6 months	41/56 (73.2)	40/55 (72.7)	0.5	0.954
12 months	41/48 (85.4)	35/48 (72.9)	12.5	0.132

*Chi-square test

Both forms of surgical treatment are effective in reducing endometriosis-associated pain to any degree at 12 months (85.4% for excision against 72.9% for vaporisation). Comparing the two treatment arms against each other does not produce statistical significance (p=0.132) showing that both treatment modalities result in improvement in line with that found by previous observers (Sutton et al., 1994, Abbott et al., 2004).

Extent of improvement in primary outcome measure

Table 23 below shows that both treatment modalities alone result in significant improvement in absolute pain score at 12 months compared with baseline:

Table 23. Extent of improvement in EHP-30 Core pain score against baseline for excision and vaporisation alone at 12 months.

	Mean change 0 v 12 months +/- SD	*p value (95%CI)
Excision	-23.9 +/-26.2	p<0.0005 (-31.5 to -16.3)
Vaporisation	-10.7 +/-20.8	p=0.001 (-16.7 to -4.7)

*paired t test

Comparative extent of score improvement in primary outcome measure

Table 24 below summarises the changes in EHP-30 Core pain score (score at x months – score at baseline) for each of the analysis points. Since a higher score on the EHP-30 Core pain scale represents a higher level of pain, a negative change indicates an improvement (nb: this rule applies to score results for all questionnaires in the analysis):

Table 24. Comparative extent of improvement in EHP-30 Core pain score against baseline for excision and vaporisation at all follow-up points.

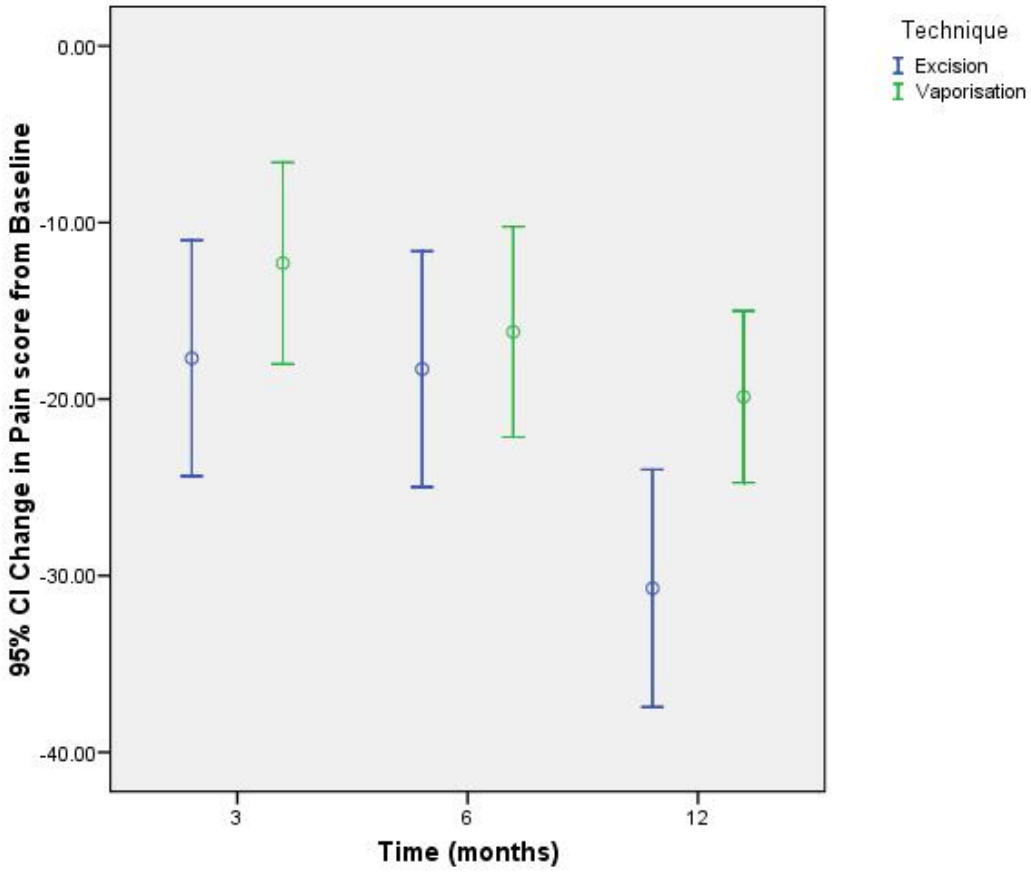
Analysis point	Excision	Vaporisation	Difference	p value*
	mean score improvement +/-SD		mean (95% CI)	
3 months	-15.8 +/-21.1	-11.0 +/-15.8	-4.7(-11.5 to 2.0)	0.168
6 months	-14.4 +/-23.3	-12.0 +/-17.9	-2.4(-10.3 to 5.5)	0.544
12 months	-23.9 +/-26.2	-10.7 +/-20.8	-13.2 (-22.8 to -3.5)	0.008

*unpaired t test

Excision exhibits a greater improvement in pain score than vaporisation at 3, 6 and 12 months and reaches statistical significance at 12 months with a greater improvement by -13.2 points (p=0.008, 95%CI -22.8 to -3.5, unpaired t-test).

As can be seen in the graph in fig 13 below, over time the two treatment modalities appear to be fairly equal up to 6 months. The significant difference between excision and vaporisation appears to develop between 6 and 12 months.

Fig 13. Graph of mean improvement in EHP-30 Core pain score against time for excision and vaporisation.



Overall 14.6% of the excision group and 27.2% of the vaporisation group were “the same or worse” at 12 months, however there is not a statistically significant difference between the two groups (p=0.132, Chi-square test).

Secondary outcome measures

Extent of score improvement in VAS

VAS pain scores were analysed independently for each of the 4 symptoms of dysmenorrhoea, dyspareunia, CPP and dyschezia. As both treatment arms, and superficial and deep disease, started with similar pre-op scores, the results are given as absolute changes in pain score out of 10.

Individual improvement in VAS pain modalities, by treatment arm, comparing baseline against 12 month follow up results (score at 12 months – score at baseline), are shown in tables 25 and 26 below.

Excision

Table 25. Mean improvement in VAS symptom scores for excision at 12 months against baseline.

	Mean change 0 v 12 months +/- SD	*p value (95%CI)
Dysmenorrhoea	-2.94 +/-3.65	<0.0005 (-4.22 to -1.67)
Dyspareunia	-1.98 +/-3.34	0.006 (-3.33 to -0.63)
CPP	-3.50 +/-3.62	<0.0005 (-4.91 to -2.10)
Dyschezia	-2.73 +/-4.18	0.007 (-4.64 to -0.83)

*paired t test

Vaporisation

Table 26. Mean improvement in VAS symptom scores for vaporisation at 12 months against baseline.

	Mean change 0 v 12 months +/- SD	*p value (95%CI)
Dysmenorrhoea	-1.50 +/-2.82	0.001 (-2.40 to -0.61)
Dyspareunia	-1.27 +/-3.42	0.040 (-2.49 to -0.06)
CPP	-0.93 +/-2.78	0.060 (-1.90 to 0.04)
Dyschezia	-1.11 +/-3.42	0.143 (-2.62 to 0.41)

*paired t test

There are statistically significant improvements in all VAS pain score symptoms in the excision arm at 12 months compared with baseline. For vaporisation, there are statistically significant improvements in dysmenorrhoea and dyspareunia.

Comparative improvement for VAS pain modalities

Table 27 below summarises the extent of comparative improvement by treatment arm in VAS for dysmenorrhoea, dyspareunia, CPP and dyschezia for each of the trial follow up points:

Table 27. Extent of comparative improvement for VAS symptom scores for excision and vaporisation at all follow up points.

Analysis point	Excision	Vaporisation	Difference	p value*
	mean score improvement +/-SD mean		(95%CI)	
Dysmenorrhoea				
3 months	-1.26 +/-2.85	-1.33 +/-2.68	0.07(-1.02 to 1.15)	0.904
6 months	-1.48 +/-2.80	-1.60 +/-3.01	0.12(-1.08 to 1.32)	0.841
12 months	-2.94 +/-3.65	-1.50 +/-2.82	-1.44(-2.93 to 0.05)	0.059
CPP				
3 months	-1.64 +/-3.05	-1.31 +/-2.83	-0.33(-1.61 to 0.95)	0.612
6 months	-2.38 +/-3.10	-0.99 +/-2.37	-1.38(-2.67 to -0.10)	0.035
12 months	-3.50 +/-3.62	-0.93 +/-2.78	-2.57(-4.20 to -0.95)	0.002
Dyspareunia				
3 months	-2.42 +/-3.29	-1.97 +/-3.53	-0.45(-2.00 to 1.10)	0.564
6 months	-1.91 +/-3.07	-2.36 +/-3.64	0.44(-1.17 to 2.05)	0.584
12 months	-1.98 +/-3.34	-1.27 +/-3.42	-0.71(-2.49 to 1.07)	0.429
Dyschezia				
3 months	-1.58 +/-3.09	-2.32 +/-3.54	0.73(-0.96 to 2.43)	0.391
6 months	-1.87 +/-2.99	-1.74 +/-3.10	-0.14(-1.78 to 1.50)	0.866
12 months	-2.73 +/-4.18	-1.11 +/-3.42	-1.62(-3.97 to 0.72)	0.170

*unpaired t test

In terms of the extent of score improvement, there was no significant difference between excision and vaporisation for dyspareunia and dyschezia. For dysmenorrhoea, there was an indication of excision being better than

vaporisation at 12 months but this did not reach statistical significance (p=0.059). However, there was a significantly greater improvement in CPP in the excision group at 6 and 12 months compared with vaporisation (p=0.035 and p=0.002).

Proportion of improvers for VAS pain scores

Table 28 below shows the comparative proportion between treatment arms of patients showing improvement for the 4 modalities of pain measured by VAS at all the analysis time points:

Table 28. Comparative proportion of improvement for VAS symptom scores for excision and vaporisation at all follow up points.

Analysis point	Excision n/n (%)	Vaporisation n/n (%)	Difference %	p value*
Dysmenorrhoea				
3 months	31/52(59.6)	32/51(62.7)	-2.9	0.745
6 months	27/47(57.4)	27/46(58.7)	-1.3	0.903
12 months	26/34(76.5)	26/41(63.4)	13.1	0.222
Dyspareunia				
3 months	27/39(69.2)	25/38(65.8)	3.4	0.747
6 months	24/34(70.6)	23/36(63.9)	6.7	0.551
12 months	18/26(69.2)	19/33(57.6)	11.6	0.358
CPP				
3 months	27/43(62.8)	26/41(63.4)	-0.6	0.953
6 months	27/38(71.1)	18/35(51.4)	19.7	0.085
12 months	22/28(78.6)	20/34(58.8)	19.8	0.098
Dyschezia				
3 months	22/32(68.8)	23/29(79.3)	-10.5	0.349
6 months	21/31(67.7)	19/25(76.0)	-8.3	0.496
12 months	14/21(66.7)	14/22(63.6)	3.1	0.835

*Chi-square test

There was no significant difference between excision and vaporisation in terms of the proportion of patients who improved at each follow up point.

Individual extent of score improvement in EHP-30 HRQoL measures

EHP-30 HRQoL scores were analysed independently for each of the domains. As both treatment arms, and superficial and deep disease, started with similar pre-op scores, the results are given as absolute changes in score out of 100.

Individual improvement in EHP-30 HRQoL domains, by treatment arm, comparing baseline against 12 month follow up results (score at 12 months – score at baseline), are shown in tables 29 and 30 below.

Excision

Table 29. Extent of improvement in EHP-30 HRQoL outcome measures for excision alone at baseline against 12 months.

	Mean change 0 v 12 months +/- SD	*p value (95%CI)
Control & Powerlessness	-30.56 +/-29.56	<0.0005 (-39.77 to -21.34)
Emotional wellbeing	-24.74 +/-20.65	<0.0005 (-30.68 to -18.81)
Social support	-31.25 +/-30.12	<0.0005 (-41.29 to -21.21)
Self image	-21.37 +/-25.13	<0.0005 (-29.51 to -13.22)
Intercourse	-21.11 +/-32.86	<0.0005 (-31.91 to -10.31)

*paired t test

Vaporisation

Table 30. Extent of improvement in EHP-30 HRQoL outcome measures for vaporisation alone at baseline against 12 months.

	Mean change 0 v 12 months +/- SD	*p value (95%CI)
Control & Powerlessness	-12.86 +/-28.74	0.004 (-21.40 to -4.33)
Emotional wellbeing	-13.95 +/-23.82	<0.0005 (-21.02 to -6.88)
Social support	-12.35 +/-28.91	0.008 (-21.36 to -3.34)
Self image	-5.75 +/-28.24	0.194 (-14.56 to 3.05)
Intercourse	-22.42 +/-30.18	<0.0005 (-32.07 to -12.76)

*paired t test

There were highly significant improvements in all domains at 12 months compared with baseline for excision patients. This was also the case with vaporisation other than for self-image.

Comparative extent of score improvement in EHP-30 HRQoL measures

Table 31 below summarises the extent of comparative improvement by treatment arm in EHP-30 HRQoL domains for each of the trial follow up points:

Table 31. Comparative extent of score improvement in EHP-30 HRQoL outcome measures for excision and vaporisation at all follow up points.

Analysis point	Excision	Vaporisation	Difference	p value*
	mean score improvement (+/-SD)		mean(95%CI)	
Control & powerlessness				
3 months	-22.73(+/-23.87)	-11.94(+/-23.55)	-10.80(-19.52 to -2.08)	0.0166
6 months	-18.75(+/-25.86)	-11.48(+/-28.82)	-7.27(-17.88 to 3.33)	0.177
12 months	-30.56(+/-29.56)	-12.86(+/-28.74)	-17.69(-30.05 to -5.33)	0.006
Emotional wellbeing				
3 months	-16.53(+/-22.13)	-9.04(+/-20.03)	-7.49(-15.13 to 0.15)	0.055
6 months	-17.19(+/-20.58)	-10.11(+/-22.91)	-7.08(-15.31 to 1.15)	0.091
12 months	-24.74(+/-20.65)	-13.95(+/-23.82)	-10.80(-19.86 to -1.73)	0.020
Social support				
3 months	-16.41(+/-28.90)	-2.55 (+/-24.75)	-13.86(-24.40 to -3.32)	0.010
6 months	-16.62 (+/-31.87)	-2.17(+/-29.77)	-14.45(-27.15 to -1.75)	0.026
12 months	-31.25(+/-30.12)	-12.35(+/-28.91)	-18.90(-32.13 to -5.66)	0.006
Self image				
3 months	-4.83(+/-28.08)	-4.17(+/-25.07)	-0.67(-11.00 to 9.67)	0.898
6 months	-9.63(+/-29.46)	-5.27(+/-29.94)	-4.36(-16.12 to 7.40)	0.464
12 months	-21.37(+/-25.13)	-5.75(+/-28.24)	-15.61(-27.47 to -3.75)	0.011
Intercourse				
3 months	-20.44(+/-27.48)	-14.33(+/-29.83)	-6.11(-17.79 to 5.56)	0.301
6 months	-15.77(+/-26.52)	-14.41(+/-27.09)	-1.36(-12.72 to 10.01)	0.813
12 months	-21.11(+/-32.86)	-22.42(+/-30.18)	1.31(-12.91 to 15.53)	0.855

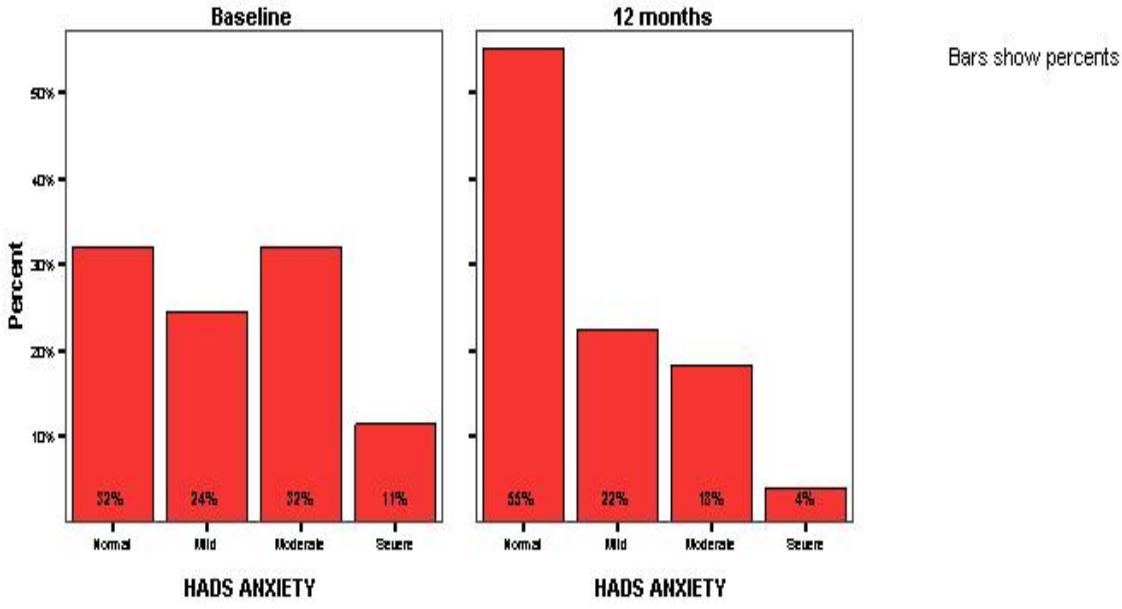
*Unpaired t test

At 12 months excision was statistically significantly better than vaporisation at improving scores in all of the EHP-30 HRQoL domains other than for sexual intercourse where no difference was found.

Change in Anxiety & Depression Categories between baseline and 12 months

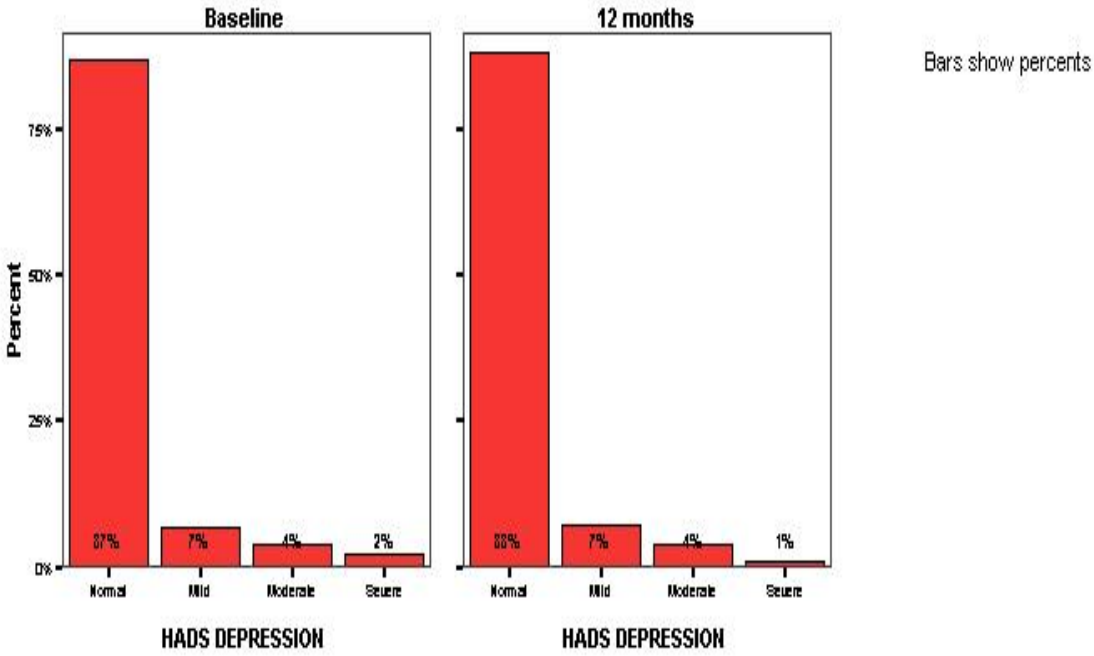
Fig 14 below shows the number of patients falling into the different categories of normal (0-7 points), mild (8-10 points), moderate (11-14 points) or severe (15-21 points) for anxiety and depression at baseline compared with 12 months for all patients not differentiating by treatment arm.

Fig 14. Distribution of participants for different grades of anxiety at baseline and 12 months.



In the anxiety graphs comparing baseline and 12 months for anxiety, visually there appears to be a shift of patients to the left, or more normal side of the graph at 12 months.

Fig 15. Distribution of participants for different grades of depression at baseline and 12 months.



This shift is not apparent in the depression graph as the majority of people were not depressed at the beginning and the two graphs remain very similar.

Individual extent of score improvement in HADS for treatment arms

HADS scores for anxiety and depression were analysed independently for changes. As both treatment arms, and superficial and deep disease, started with similar pre-op scores, the results are given as absolute changes in score out of 21.

Individual improvement in EHP-30 HRQoL domains, by treatment arm, comparing baseline against 12 month follow up results (score at 12 months – score at baseline), are shown in tables 32 and 33 below.

Excision

Table 32. Extent of improvement in anxiety and depression for excision alone at 12 months versus baseline.

	Mean change 0 v 12 months +/- SD	*p value (95%CI)
Anxiety	-2.88 +/-4.84	<0.0005 (-4.28 to -1.47)
Depression	-0.96 +/-3.46	0.068 (-1.99 to 0.07)

*paired t test

Vaporisation

Table 33. Extent of improvement in anxiety and depression for vaporisation alone at 12 months versus baseline.

	Mean change 0 v 12 months +/- SD	*p value (95%CI)
Anxiety	-1.64 +/-3.27	0.001 (-2.57 to -0.71)
Depression	-0.66 +/-3.21	0.165 (-1.60 to 0.28)

*paired t test

There was a significant improvement in anxiety levels for both excision and vaporisation at 12 months compared with baseline, but not for depression.

Comparative extent of score improvement in HADS for treatment arms

Table 34 below summarises the comparative extent of improvement for excision and vaporisation in scores for anxiety and depression:

Table 34. Comparative extent of improvement in anxiety and depression for excision and vaporisation at all follow up points.

Analysis point	Excision	Vaporisation	Difference	p value*
	mean score improvement +/-SD		mean(95%CI)	
Anxiety				
3 months	-1.94(+/-3.68)	-0.80(+/-3.35)	-1.13(-2.39 to 0.13)	0.077
6 months	-2.96(+/-4.89)	-1.64(+/-3.27)	-1.32(-2.98 to 0.34)	0.119
12 months	-2.88(+/-4.84)	-1.64(+/-3.27)	-1.24(-2.89 to 0.42)	0.141
Depression				
3 months	-0.74(+/-3.46)	-0.61(+/-3.07)	-0.13(-1.35 to 1.09)	0.833
6 months	-1.02(+/-3.52)	-0.66(+/-3.21)	-0.36(-1.75 to 1.02)	0.605
12 months	-0.96(+/-3.46)	-0.66(+/-3.21)	-0.30(-1.67 to 1.08)	0.669

*unpaired t test

Comparatively, there was no difference between excision and vaporisation for improvement of anxiety.

Exploratory Sub analysis

Linear regression analysis to investigate possible predictors of improvement in primary outcome measure EHP-30 Core pain score

Backward stepwise linear regression analysis was performed to investigate whether any of the demographic factors (technique, age, surgeon, rASRM score, depth of disease, location of disease) influence change in EHP-30 Core pain score at 12 months over baseline. Three statistically significant factors were identified as reducing improvement in pain (r squared for final model = 0.154):

1. Vaporisation (p=0.012)

   estimated loss of pain reduction = 12.24/100 (95%CI 2.81 to 21.67)
2. Being operated on by Surgeon 1 (p=0.035)

   estimated loss of pain reduction = 10.19/100 (95%CI 0.76 to 19.62)
3. Patient being older (p=0.035)

   estimated loss of pain reduction = 0.68/100 per year (95%CI 0.047 to 1.306)

Linear regression analysis to investigate possible predictors of CPP improvement

CPP was found to have statistically significantly improved to a greater extent than excision in the main analysis (table 28). Therefore backward stepwise linear regression analysis was performed to investigate whether any of the demographic factors (technique, age, surgeon, rASRM score, depth of disease, location of disease) influence change in CPP at 12 months over baseline. There

were two statistically significant factors identified as influencing improvement in CPP (r squared for final model = 0.195):

1. Vaporisation (p=0.014)

   estimated loss of pain reduction = 0.27/10 (95%CI 0.06 to 0.48)

2. Disease in uterovesical fold (p=0.027)

   estimated gain in pain reduction for superficial disease compared with no disease in uterovesical fold = -0.31/10 (95%CI -0.58 to -0.04)

   estimated gain in pain reduction for deep disease compared with no disease in uterovesical fold = -0.62/10 (95%CI -1.16 to -0.08)

Depth and rASRM Stage of disease

Sub analysis of deep against superficial disease for each treatment modality at 12 months for the primary outcome measure, EHP Core pain score, was performed. Excision results in significant improvement in pain score for both deep (mean point reduction of -23.86 out of 100, +/-26.59, p<0.0005, paired t test) and superficial disease (mean point reduction of -23.99, +/-26.36, p=0.001, paired t test). Whilst vaporisation shows significant pain score improvement for superficial disease (mean point reduction of -17.89 out of 100, +/-19.78, p<0.0005, paired t test), it fails to result in significant improvement for deep disease (mean point reduction of -4.44, +/-18.07, p=0.262, paired t test).

On direct comparison between the two treatment arms, as seen in table 35 below, there is no significant difference in outcome for the treatment of superficial disease. However, excision performs equally well for deep disease as it does for superficial, whereas vaporisation performs significantly worse than excision for the treatment of deep disease.

Table 35. Comparison of the extent of improvement in EHP-30 Core pain score for excision and vaporisation with deep and superficial disease at 12 months against baseline.

	Excision	Vaporisation	Difference	p value*
	mean score improvement +/-SD		mean (95%CI)	
Deep disease	-23.86+/-26.59	-4.44+/-18.07	-19.42(-32.61 to -6.23)	0.005
Superficial disease	-23.99+/-26.36	-17.89 +/-19.78	-6.10(-20.67 to 8.46)	0.402

*unpaired t test

Is deep disease or more severe disease (by rASRM stage) more likely to improve EHP-30 Core pain score at 12 months versus baseline?

The results in tables 36 and 37 below show a trend towards a greater chance of improvement at 6 and 12 months if endometriosis at baseline was superficial rather than deep, and a statistically significant chance of greater improvement for patients with a lower rASRM stage.

Table 36. Comparative proportional improvement of patients with deep disease against those with superficial disease at 6 and 12 months.

	6 months n/n (%)	12 months n/n (%)
Excision		
Deep	25/38 (65.8)	25/30 (83.3)
Superficial	16/18 (88.9)	16/18 (88.9)
*p value	0.106	0.696
Vaporisation		
Deep	19/27 (70.4)	15/23 (65.2)
Superficial	20/26 (76.9)	19/23 (82.6)
*p value	0.589	0.179
Overall		
Deep	44/65 (67.7)	40/53 (75.5)
Superficial	36/44 (81.8)	35/41 (85.4)
*p value	0.102	0.236

*Chi-square test

Table 37. Comparative proportional improvement of patients with different rASRM stages at 6 and 12 months.

	6 months n/n (%)	12 months n/n (%)
Excision		
rASRM 1	19/25 (76)	20/22 (90.9)
rASRM 2	18/25 (72)	18/21 (85.7)
rASRM 3	4/6 (66.7)	3/5 (60)
*p value	0.631	0.170
Vaporisation		
rASRM 1	21/27 (77.8)	18/21 (85.7)
rASRM 2	17/21 (81.0)	15/21 (71.4)
rASRM 3	2/7 (28.6)	2/6 (33.3)
*p value	0.114	0.024
Overall		
rASRM 1	40/52 (76.9)	38/43 (88.4)
rASRM 2	35/46 (76.1)	33/42 (78.6)
rASRM 3	6/13 (46.2)	5/11 (45.5)
*p value	0.137	0.008

*Mann-Whitney U test

Per protocol analysis for primary outcome measure EHP-30 Core pain score

Analysis was carried out on the sub sample whose benefits appear to be solely related to surgery, excluding the patients who became pregnant during follow up, took hormonal medication for pain or contraception in the follow up period, or had subsequent surgery within the follow up period. There were still 35 patients in each group at 12 months, and still a difference was found of -21.04

(+/-23.97) for excision against -9.42 (+/-19.36) for vaporisation (p=0.029, 95%CI -22.02 to -1.23). The results are shown in table 38 below.

Table 38. Extent of improvement in EHP-30 Core pain score for “per protocol” patients for excision and vaporisation at all follow up points.

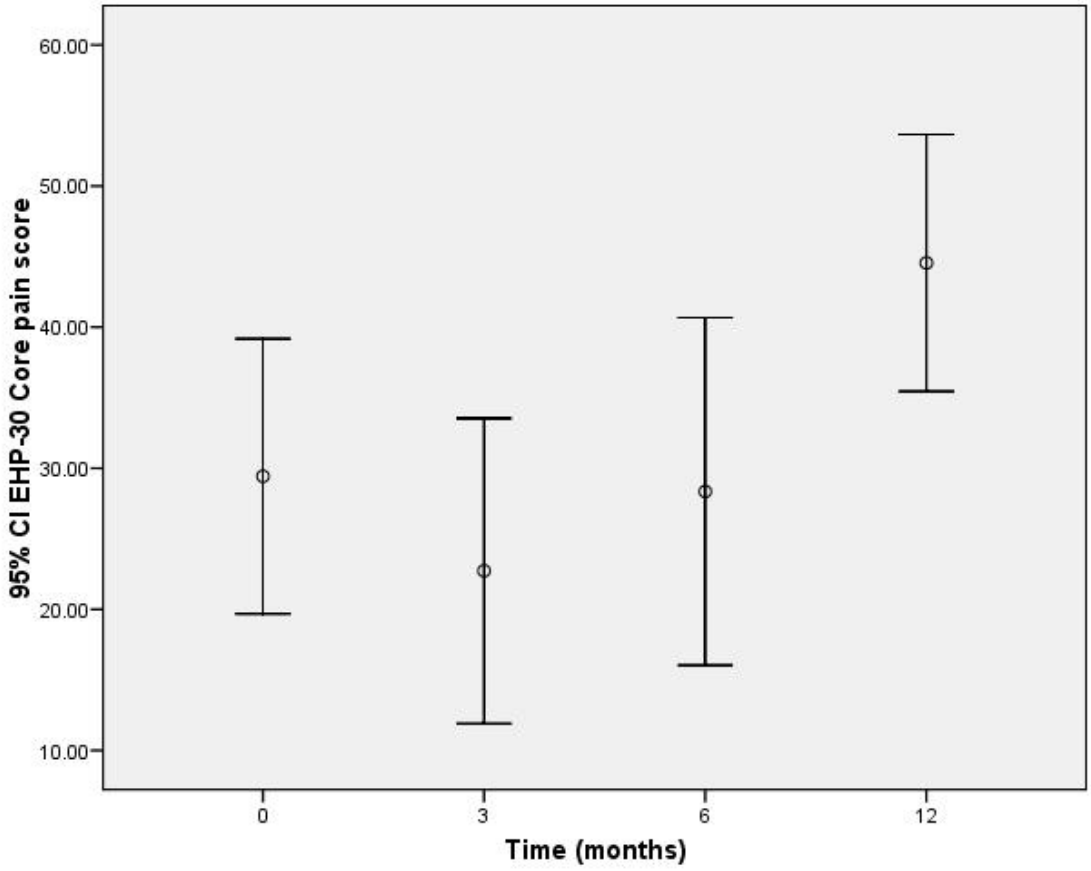
Analysis point	Excision	Vaporisation	Difference	p value*
	mean score improvement +/-SD		mean (95% CI)	
3 months	-14.64(+/-21.12)	-10.96(+/-16.06)	-3.68 (-10.64 to 3.28)	0.297
6 months	-12.75(+/-22.20)	-11.50(+/-17.41)	-1.25 (-9.08 to 6.59)	0.753
12 months	-21.04(+/-23.97)	-9.42(+/-19.36)	-11.62 (-22.02 to -1.23)	0.029

*unpaired t test

Was there a placebo effect in the “same or got worse” subgroup

Fig 16 below shows a graph for patients who at 12 months “stayed the same or got worse” for EHP-30 Core pain score over time. Interestingly these patients appear to improve initially at 3 months and recover to baseline at 6 months before then deteriorating. This may result from an initial placebo effect following treatment rather than a positive effect of the treatment itself. However, in this small sub group of patients (n=20), the only statistically significant difference was observed between 3 months and 12 months. In order to identify a statistically significant difference over the shorter time span of 3 months, from 0-3 months and 3-6 months, given the level of variation shown by the confidence limit intervals in the graph below accompanying this small sub group sample size, the underlying improvement at 3 months would have had to be extremely dramatic.

Fig 16. Extent of improvement in EHP-30 Core pain score for “same or worse” pateints at 12 months over time.



Adverse events

There were no major surgical complications reported in any of the trial patients in either group.

Discussion

Synopsis of the key findings

At the outset of this trial it was a firmly held belief that there would be no difference between excision and vaporisation for the treatment of minimal to moderate endometriosis. The major concern was that the sample size would be too small to show up the suspected small difference that might be found between the two treatment arms, and the bioequivalence power calculation allowed for this in that, with sufficient patients recruited, it would be possible to claim that one treatment was no worse than the other. The unexpected result, that excision performed better than vaporisation in this trial, was consequently a surprise that prompted an analysis that was often directed towards finding statistical evidence that the outcome was incorrect.

Primary outcome measure – EHP-30 Core pain score

For the primary outcome measure, EHP-30 Core pain score, there was a significant improvement in score at 12 months versus baseline whether excision or vaporisation was used as the treatment, where excision showed a mean -23.9 drop ($p<0.0005$), and vaporisation a mean -10.7 drop on the 100 point scale ($p=0.001$). Also, there was no significant difference in the proportion of patients who improved in each treatment arm (85.4% for excision and 72.9% for vaporisation, $p=0.132$). However, at 12 months, the extent of score improvement above was statistically significantly greater in the excision versus the vaporisation group ($p=0.008$, 95%CI -22.8 to -3.5). In addition, the excision

group appear to be still improving at 12 months, whereas the vaporisation group improvement did not continue after 6 months.

In terms of the treatment of deep and superficial disease, excision resulted in statistically significant improvement in pain score at 12 months versus baseline in both superficial (mean -23.99 +/-26.36, p<0.001) and deep disease (mean -23.86 +/-26.59, p<0.0005). However, vaporisation only showed statistically significant improvement for superficial disease (mean -17.89 +/-19.78, p<0.0005) and not for deep (mean -4.44 +/-18.07, p=0.262). Comparatively, there was no difference in the extent of improvement between excision and vaporisation for treating superficial disease (mean difference -6.10, p=0.402). However, the improvement in pain score for excision was highly statistically significantly better than vaporisation for the treatment of deep disease (mean difference -19.42, p=0.005).

Of interest is that 14.6% of the excision group and 27.2% of the vaporisation group were either the same or worse at 12 months compared with baseline. The comparative difference between excision and vaporisation does not reach statistical significance (p=0.132). Those patients who stayed the same or got worse appear to initially improve possibly showing a placebo effect, though it is not statistically possible to show this in this study.

VAS scores for Dysmenorrhoea, Dyspareunia, CPP and Dyschezia

Excision resulted in a statistically significant score improvement in all four pain modalities at 12 months versus baseline scores. This was true for vaporisation for dysmenorrhoea (p=0.001) and dyspareunia (p=0.040), but not for CPP

(p=0.060) and dyschezia (0.143). However, the proportion of improvers was not statistically different for the treatment arms at any time point in the trial. The extent of improvement in CPP in the excision group versus vaporisation was statistically significant at 6 (p=0.035) and 12 months (p=0.002). As this trial included only stage 1-3 rASRM scores one would expect dyschezia to be a less significant symptom in this group of patients and even question whether it is an appropriate question to include. In support of this Table 21 shows that dyschezia is the lowest scored symptom at baseline and appears less of a problem than dysmenorrhoea (the most significant symptom), CPP and dyspareunia. However patients still scored dyschezia between 2.8-3.4 out of 10 at baseline and it is interesting to note that excision still resulted in a statistically significant improvement in dyschezia in these stage 1-3 patients (p=0.007). The conclusion is that it was correct to include it as a symptom in the VAS pain scores.

EHP-30 HRQoL outcomes

Excision resulted in highly statistically significant improvements in all EHP-30 HRQoL domains at 12 months versus baseline (all p values <0.0005). Results for vaporisation were also statistically significant other than for self-image (0.194). However, when considering the extent of improvement, excision resulted in statistically significantly greater improvement than vaporisation at 12 months for all domains other than the intercourse module, for which there was no significant difference (p=0.855). For the social support domain, excision was significantly better at all follow up points in the trial. At no follow-up point, for any domain, was vaporisation significantly better than excision.

HADS Anxiety and Depression

For the sample as a whole, patients did not generally appear to be depressed at baseline, with the majority of patients falling into the normal category. For anxiety though, there was a spread of patients throughout the categories with most falling into the normal to moderate categories. At 12 months less patients appear to be anxious, with a shift into the normal and less severe groups. The lack of depression remains similar. The extent of improvement in anxiety was statistically significant for both excision ($p=<0.0005$) and for vaporisation ($p=0.001$). However, there was no difference in the extent of change in anxiety ($p=0.141$) or depressive scores ($p=0.669$) comparing between excision and vaporisation.

Summary

Contrary to expectation, for the primary outcome, VAS scores and HRQoL outcomes, whilst both techniques resulted in significant improvement in scores at 12 months, excision outperformed vaporisation statistically at 12 months in the extent of improvement for all outcome measures, suggesting that it is the best technique for the surgical treatment of minimal to moderate endometriosis. However it should be noted that the absolute improvement was no better than a mean -23.9 point drop on the 100 point EHP-30 Core pain scale at 12 months (from a baseline mean of 42.3 to 18.4, or a 56.5% drop in pain score), and a concerning number of patients reported being either the same or worse.

Possible mechanisms and explanations

The primary outcome for this study was pain as measured by EHP-30 Core pain score. This was selected as it was judged to be the most sensitive measure and

the one that would relate most directly to the impact of pain on women's quality of life. Based on this outcome measure the data show that excision is better than vaporisation at reducing pain at 12 months post treatment. It has been argued that ablation/vaporisation does not remove all of the disease particularly with superficial ablation (Wright et al., 2005). Wright theorised in his randomised trial of excision versus ablation that ablative techniques have the potential disadvantage of leaving a greater area of necrotic tissue behind, with increased inflammatory action and a higher propensity to develop adhesive disease.

In our study laser vaporisation was used to destroy all visible lesions down to normal tissue until it looked like an excision has been carried out. This can be done quickly and efficiently for widespread superficial disease and appears to be a useful technique. However our study shows that even this technique of vaporisation performs statistically significantly worse than excision. The reasons are not clear although several possible mechanisms can be suggested.

The implication of the results is that in some way the operative field is not the same for each treatment at the end of the operation despite it visually appearing so. It may be that there is more residual disease in the vaporisation cases than the excision ones. There are several possible ways to explain this. It may be that by vaporising a lesion, margins may be left that are not easily visible and are missed by the surgeon. In contrast, excision aims to remain in the normal tissue margin from the beginning of the dissection and so may be better at clearing marginal disease. Alternatively, possibly the power of the laser beam is driving off active endometriotic tissue particles into adjacent areas that then implant and recur. Full vaporisation of deep lesions is technically more difficult

as an eschar tends to build up on the lesion surface that has to be washed away to continue the vaporisation of the lesion. It is easier to imagine incomplete vaporisation with these deep lesions.

Our study also shows that excision is significantly better for treating deep disease than vaporisation. Vaporisation is not only significantly comparatively worse than excision, but also gave insignificant improvement in EHP-30 Core pain score at 12 months versus baseline for deep disease. This could have been explained by the fact that there were more deep cases in the excision group, if it had also been found that patients with deep disease had a higher mean starting score, and that a higher mean starting score resulted in a greater chance of having a larger score reduction. Both of these possibilities were tested for. It was indeed found that having a higher starting score resulted in a greater probability of a larger fall in score at 12 months for EHP-30 Core pain score (Pearson's Correlation test r=+0.535, p=<0.0005). However, mean scores at baseline were the same for superficial and deep disease for EHP-30 Core pain score and VAS scores, and also for excision and vaporisation arms for all outcome measures at baseline. This also fits with the finding that the extent or depth of the disease does not correlate with pain (Crosignani et al., 1996, Garry et al., 2000) Therefore the possible bias resulting from unbalanced baseline scores did not occur in favour of the excision group. Furthermore, the superficial group had an advantage by having less deep disease for two reasons. Firstly it performed significantly worse for deep disease and secondly, superficial disease was more likely to improve overall in our study.

Backward stepwise linear regression analysis was also carried out on the EHP-30 Core pain score results to see whether technique, age, surgeon, rASRM score and depth or location of disease influenced the change in EHP-30 Core pain score at 12 months over baseline. This confirmed the finding of vaporisation as a significant factor in reducing pain improvement (p=0.012, 95%CI 2.81 to 21.67). It has already been shown above that a sample with a lower mean baseline score has less capacity to improve. Mean baseline scores for instrument and technique use were similar and so the finding that vaporisation is genuinely performing worse was reinforced.

However, it was hypothesised that a significantly lower mean baseline score for the less successful surgeon and older patients could explain the finding that they appear to have resulted in a significantly lower improvement. Indeed, this was found to be the probable cause, as the surgeon identified had less capacity for his patients to improve. His 68 cases had a significantly lower mean baseline score of 34.79 (+/-31.47). This is compared with the mean baseline score for the other surgeons of 46.84 (+/-21.23) (difference of 12.05, p=0.012, unpaired t-test). At 12 months his patients mean improvement in score was -12.64 against the other surgeons mean improvement of -21.78 (difference of -9.14, p=0.066, unpaired t-test). Neither did the surgeon have significantly more vaporisation cases than the other surgeons, which would have biased his performance in favour of less improvement (he performed 34 cases with each technique). Older patients also had less capacity to improve, as there was a statistically significant negative correlation between age and pre-op pain score (Pearson's correlation test: r=-0.320, p<0.0005).

VAS scores for dysmenorrhoea, dyspareunia, CPP and dyschezia mirrored the findings in EHP-30 Core pain score in that there was no difference in the proportion of patients who improved at any follow-up point for excision and vaporisation. Vaporisation analysed alone did not result in a statistically significant improvement at 12 months versus baseline for CPP and dyschezia, though significance was almost reached for CPP. There seems to be no obvious explanation for this other than the general trend in this study that vaporisation performs less well at 12 months. Comparative scores of the extent of improvement show up a significant difference for excision performing better than vaporisation in reducing CPP at 6 and 12 months. Significance is almost reached for dysmenorrhoea too, and the remaining two symptoms of dyspareunia and dyschezia show a trend towards excision performing better.

Thus, as with EHP-30 Core pain score, the results illustrate that the proportion of patients improving after surgery is similar for vaporisation and excision, but the extent to which they improve is greater for excision compared with vaporisation. It may be that the failure to show significance in all symptoms is related to limitations in the performance of visual analogue scales as Abbott found and commented on in his trial (Abbott et al., 2004). Alternatively, it may be that women are able to relate better to some questions than others. Perhaps the notion of CPP is more meaningful than the notion of dyschezia. There appears to be no clear trend of one symptom improving to a greater extent than another from the results.

The backward stepwise linear regression analysis that was performed to see if any factors influenced the change in CPP score at 12 months versus baseline

again confirmed that vaporisation was predictive of a lesser improvement in the EHP-30 Core pain score, although this was only by 0.27 points on the 10 point scale. The finding that disease in the uterovesical fold results in a greater likelihood of score improvement cannot be explained, and is more likely to be due to chance.

The trend of excision outperforming vaporisation continued into the EHP-30 HRQoL parameters. Alone, though generally resulting in improvement, vaporisation did not produce results that were as significant. In comparative terms, the significantly better improvement in quality of life domains for excision, mirroring the reduction in pain, presumably reflects the profound effect that chronic pain has on quality of life. It stands to reason that, as the quality of life questions in EHP-30 are ones specifically identified by endometriosis sufferers, then they will improve if the treatment is effective. Again, there appeared to be no trend of any one domain improving more than any other, and it is not clear why sexual intercourse was the only domain that did not show up a comparatively statistically significant difference between excision and vaporisation. It is possible that women don't like responding to questions about sexual intercourse and are therefore less likely to provide responses that reflect reality. It is also possible that a considerable proportion of women feel that sexual intercourse is not such a prominent aspect of their lives as being able to go to work or socialise for example.

Study reports of medical therapy for endometriosis have commented that starting scores for HRQoL scores are less than population norms and do not return to normal levels following treatment (Miller, 2000, Zhao et al., 1999,

Bergqvist and Theorell, 2001), and only recently have HRQoL measures like SF-12 and EQ-5D been used in surgical studies (Garry et al., 2000, Abbott et al., 2003, Abbott et al., 2004). However, it is not possible to comment on whether scores started below or returned to that found in general population norms in our study, as EHP-30 is a disease specific measure and there are no data relating to the general population. Nonetheless, the EHP-30 has been externally validated against SF-36 and been shown to be more sensitive to changes (Jones et al., 2004a).

The HADS questionnaire attempts to find anxiety and depression in subjects, not in the sense of the extent of their predisposition to these stresses, but in the transient amount of stress they actually have. In contrast to the EHP-30 HRQoL domains, it does not deal with factors that moderate the impact of these stresses like coping or social support. The results show that depression is not a component of psychological stress in patients with minimal to moderate endometriosis. Most probably, those that lie outside of the normal range are depressed for reasons other than their endometriosis. Anxiety ratings did improve significantly for both treatments between baseline and 12 months. As a result, it appears to compare with the EHP-30 Core pain, HRQoL and VAS score outcomes. Contrary to the EHP-30 data, the HADS anxiety scale is judged against general population norms, suggesting that anxiety returns to normal levels in many cases.

Comparison with other studies

In the report of the trial by Sutton et al (Sutton et al., 1994), it is not clear in the original paper whether the linear analogue scale for pain as a primary outcome

measure related to overall pain, or for each of the symptoms of dysmenorrhoea, dyspareunia or pelvic pain. In their follow up paper in 1997, they comment that:

> "in the original study, no attempt was made to separately assess the symptoms….in all cases, the most severe symptom was dysmenorrhoea, which was therefore the symptom assessed when the patients were asked to quantify their worst symptom by visual analogue score…" (Sutton et al., 1997b).

In the original study by Sutton and colleagues (2004) there was a 62.5% improvement in pain for laser vaporisation at 6 months. Our trial shows a 72.7% improvement in EHP-30 Core pain, and a 58.7% improvement in dysmenorrhoea at 6 months, and consequently appears to have a similar outcome at 6 months, particularly when comparing dysmenorrhoea.

The Sutton trial reported a greater proportion of pain improvement of 73.7% for the mild and moderate patients analysed alone compared with the overall improvement of 62.5%, suggesting that more severe disease results in a greater chance of improvement. The statistical robustness of this finding is open to criticism as the data were broken down into stage 1-3 versus stage 2-3, and this kind of sub-analysis is likely to create bias in treatment outcomes. However, a view appears to have developed since this paper was published that superficial disease is more difficult to treat than deep disease. In contrast, in our study we found a definite trend that patients were more likely to have improved EHP-30 Core pain scores if they had superficial disease at baseline, and a statistically higher chance of improvement for patients with lower rASRM stage at baseline. Also this study did not support the finding by Banerjee that better

relief of pain was found in women who had deep disease rather than superficial (Banerjee et al., 2008). Their study had a poor follow-up rate of near 50% and it may be that the non-responders were those patients with deep disease who did not improve. Also their study includes those with stage 4 disease that are a sub-group not included in our study.

In our study we showed that having a higher baseline score results in a greater likelihood of a greater drop in pain score. It may be that these other studies had higher baseline scores in their more severe and deep disease biasing the outcome. In our study the baseline scores were not significantly different between superficial and deep disease, and it seems logical that less severe disease should be easier to treat and clear. Abbott's findings support this to the extent that the higher the stage of disease, the greater likelihood of requiring re-operation (Abbott et al., 2003).

The Abbott trial reports an 80% improvement for the immediate surgery group that underwent excision at 6 months, though it is not clear how the change in the overall level of pain was calculated (Abbott et al., 2004). Baseline demographic parameters could not be compared, as they are not detailed in the Abbott paper. In our study, the proportion of improvers for excision by EHP-30 Core pain score at 6 months was 73.2 %. This again appears comparable, although as previously mentioned, the sample in the Abbott trial differs in that it included severe disease, and had a median rASRM score of 16 in the group that underwent immediate excision, compared with a median score of 6 in our study. For HRQoL outcomes, our trial is unable to shed light on Abbott's finding of a return to statistically insignificant differences compared with population

norms, found in contrast to their previous investigations (Garry et al., 2000, Abbott et al., 2003).

In the Abbott 2003 prospective observational cohort study of excision treatment, there appears to be an improvement in pain sustained out to 2-5 years for 67% of patients. Our study confirms that there is no drop off in effect at 12 months for improvers who underwent excision, and in fact, for EHP-30 Core pain score, both the proportion and extent of improvement still appears to be increasing at 12 months post surgery for excision and not for vaporisation, in keeping with a trend that adds some weight to Abbott's 2-5 year findings.

In contrast, Sutton et al followed up on their 1994 trial and reported that 90% of those patients who had shown pain improvement at 6 months had reported continued benefit at 12 months, suggesting a small drop off in the effect of vaporisation, though this was no longer part of the blinded trial (Sutton et al., 1997b). In this study, the proportion of patients with improved dysmenorrhoea score (the best direct comparison with the Sutton results) increased from 58.7 at 6 months to 63.4% at 12 months, but stayed the same for EHP-30 Core pain score (72.7% versus 72.9%). This does not confirm this possible drop off effect. However, whilst the extent of score improvement in EHP-30 and dysmenorrhoea continued to improve in the excision group from 6 months to 12 months, this did not occur in the vaporisation group, again suggesting that vaporisation is struggling to maintain its effect at 12 months compared with excision.

In our study it is not the proportion of patients showing any improvement that shows the difference between excision and vaporisation, but the extent of improvement at 12 months. In Sutton's trial the median VAS score for vaporisation dropped by 2.85/10 points from a baseline median score of 8.5 (based mainly on dysmenorrhoea) between baseline and 6 months. This is comparable with the 30/100 (range 0-95 on a 100 point linear scale) noted for excision in Abbot's trial for the immediate surgery group. In our study, VAS dysmenorrhoea score for vaporisation reduced by a more conservative 1.60/10, from a mean baseline score of 6.5, at 6 months. For excision this improved to 2.94/10 at 12 months versus baseline. Alarmingly, what the data from all these results suggests is that at best on average, pain is improved by only somewhere between a quarter and a half.

Added to this seemingly moderate improvement in pain scores, that are similar for EHP-30 HRQoL outcomes, is the concerning finding that 20% of patients in this study stayed the same or got worse. Abbott also found 20% of the patients in his study stayed the same or got worse (Abbott et al., 2004) all of whom had positive histology for endometriosis. It is probable in these cases that it is not the surgery per se that is causing symptoms to worsen. Recurrence of new, or progression of residual lesions are both possible culprits. However, Sutton found that only 2 of the 5 women with continued pain, who had laser treatment initially and then had a second look laparoscopy, were found to have visually confirmed endometriosis (Sutton et al., 1994). The other possibility is that pelvic pain in these women is not related to endometriosis at all, and is caused by other pathologies with very similar symptoms like adenomyosis, irritable bowel syndrome or interstitial cystitis.

If the range of improvement in pain scores was narrow then the moderate extent of pain improvement achieved would call into question whether subjecting patients to surgery is indeed worth it. However, the ranges of improvement are wide, with some patients showing extensive improvement and others showing very little, none, or becoming worse; this implies that we need to have better prognostic indicators to select out those who will truly benefit from surgical treatment of endometriosis.

There remains one other possibility suggested by the findings of Abbott's prospective cohort (Abbott et al., 2003) looking at follow-up at 2-5 years after excision. It may be that the benefits of surgery are in fact much more gradual than we believe, as the level of pain improvement in this study measured by drop in median VAS pain score appears greater than that seen at 6-12 months (dysmenorrhoea 9 to 3, non-menstrual pain 8 to 3, dyspareunia 7 to 0, and dyschezia 7 to 2). However, at such follow-up periods, many confounding variables are likely to be introduced including recurrent surgery or hysterectomy, hormonal therapy and intervening pregnancies, all of which are present in these results.

Limitations of the study

Methodological limitations

As with all surgical trials, there are many pitfalls that can cast doubts upon the validity of results. In this trial every attempt was made to be a rigorous as

possible over methodology. However, retrospectively it is always possible to find limitations, and that was no different with this trial.

Patient selection

One must first consider the type of patients that were entered into this trial. Surrey is a relatively wealthy area, with a significant proportion of educated, “middle class” patients that have a keen interest in their own health care. Therefore they may be, to some extent, a biased set of patients in comparison to the general population. However, they will of course be a similar set of patients to the Sutton trial that was performed in the same unit 10 years previously (Sutton et al., 1994). All geographical locations are likely to have their own climates, economics, physical geography, social and cultural peculiarities, all of which can affect a studies external validity. However, none of the factors in this trial area or population are so extreme that they are likely to be having a major influence on external validity.

Eligibility criteria

The other factors influencing the type of patients in the trial, and consequently the external validity, are the eligibility criteria. In this trial, as in the other major trials reported by Jacobson in his Cochrane review (Jacobson et al., 2009), we excluded patients aged under 18, pregnancy, pelvic inflammatory disease and inflammatory bowel conditions of the pelvis, and patients not willing to comply with the trial protocol. However, there were several other exclusions mentioned in these other trials that we did not use:

Sub-fertility patients were not excluded, as in this trial they all received treatment and so had the possible benefit of improved fertility as a result (Jacobson et al., 2004b). Those women who were included with sub-fertility were not assessed for normal ovulatory cycles, partner's semen sample, recent infertility treatment or previous fertility surgery. Therefore, we were not able to assess whether or not surgical treatment for endometriosis resulted in an improvement in spontaneous conception.

Suspected gynaecological malignancy was not stated as an exclusion in the protocol. No patients had suspected gynaecological malignancy, although one turned out to have a borderline tumour of the ovary following ovarian cystectomy, which was managed conservatively for fertility reasons.

Urgent patients were not included in the exclusion criteria, but no emergency patients were included in the trial. All patients were admitted for elective surgery.

Severe adhesions were not included in the list of exclusion criteria. If patients fell within the rASRM score for stages 1-3 then they were included in the trial no matter what the distribution of disease was.

Previous abdominal surgery was not listed as a reason for exclusion. There is a possible limitation with this trial as a result of this. Some patients may have had multiple unsuccessful laparoscopies for pelvic pain previously, with perhaps little improvement. This may have biased the result against the positive effect of surgical treatment. Conversely it may have biased the result in favour of

treatment, where “expert patients” had received repeated benefit from previous surgeries. The other problem arising from previous surgery is that of creating lesions containing psammoma bodies that mimic endometriosis leading to false positive assessment of the pelvis (Martin and Vander Zwagg, 1987). In fact, the sole exclusion from this trial before analysis was due to this.

This potential limitation of including patients who had undergone previous abdominal surgery could have been prevented by taking histology in all cases, and only including those with positive histology in the analysis as Abbott rigorously did in his studies (Abbott et al., 2003, Abbott et al., 2004). However, in those trials, excision was the only treatment modality, and so the problem of biopsying small lesions without excising them before vaporisation did not exist. Further to this, inflammation in lesions and traumatic biopsy can affect the architecture of endometrial glands and stroma, making histological examination difficult, resulting in false negative results (Shafik A, 2000), meaning that patients are erroneously excluded. As has already been described, in this study histology was taken in 65 of 133 cases (48.9%), partly because taking histology was not begun until case 46 and partly because it was not always possible to get a biopsy with vaporisation, as it may have resulted in excision of all or most of the lesion. Overall 54 of the 65 cases had histology positive for endometriosis, showing a successful correlation between visual inspection and histological analysis in 83.1% of cases. A similar correlation of 88% was found by Ballard between visual inspection and positive histology (Ballard et al., 2009).

Randomisation

Proper randomisation should be able to eliminate selection bias from a sample and is very important to achieve a high quality result (Altman, 1991). In this trial the generation of the randomisation sequence was not computer generated. However, the generated sequence was truly random in blocks of ten and there was no way of telling which treatment was contained in the sealed opaque envelope in each unallocated folder. There is a potential argument that, as the generation of the sequence was done by two of the surgeons, this could have affected the randomisation concealment at allocation at the time of surgery. However, neither surgeon felt that this was a problem in this trial, especially as the recruitment rate was about 2 patients per month, and each block of ten folders took, on average, 5 months to allocate. This meant that mentally keeping track of randomisation generation and allocations was unfeasible.

Recruitment

The slow recruitment rate of two patients per month mainly arose from the exclusion of potentially eligible patients because they were on hormonal medication for contraception rather than patients not wishing to participate. Those who were on hormonal therapy for symptomatic relief only were asked if they would stop it 3 months prior to surgery so as to fit the inclusion criteria. However, by no means all patients agreed to do this. Additionally, there was also an increased risk that such patients may have been more likely to restart hormonal medication within the follow up period. Recruitment and follow up management of patients in surgical trials is particularly difficult as strong eligibility criteria are required to reduce the risk of confounding variables, resulting in long recruitment periods that subsequently require long term follow-

up. It is not surprising, therefore, that it took nearly 66 months to recruit for this trial, followed by another 1 year for the follow-up of the final patient, to complete the trial in a total of six and a half years, during which time the trial standards need to be maintained.

Blinding

Strict double blinding was not possible as this is a surgical trial and so there was no way of blinding the surgeon from the procedure he was performing. However, the surgeon was blinded from the outcomes, the patient was blinded from the procedure, and the evaluator was also blinded from the procedure. Although there was no evaluation carried out of the success of blinding, the importance of blinding was strongly appreciated, particularly as this trial had the subjective measure of pain as its primary outcome measure. An additional question in the 12 month demographic questionnaire asking whether patients were able to guess the treatment they received would have been useful. Theoretically, they should have been no more likely to guess correctly than chance. That being said, the fact that all patients were treated with what had been hypothesised as equally good treatments, and there was no placebo group, reduced the risk of performance bias also. There were no specific adverse effects from treatment that could lead the patient or evaluator to ascertain the treatment group. Equally, a positive outcome at evaluation did not suggest one treatment or other as both treatments were thought to be equally efficacious.

Protocol deviations

The protocol deviations discovered in April 2006, whereby pregnant women were not being followed up, resulted in a mid term audit that proved to be very useful in assessing the recruitment and drop out rate into the trial as well as tightening any areas of the protocol that had become loose. This seems particularly important in trials that take a long time to recruit.

Lack of control group

Both Sutton and Abbott reported placebo effects at 3 months (Sutton et al., 1994, Abbott et al., 2004), and possibly up to 6 months in Abbott's trial. The follow up in this study was continued up to 12 months for this reason. Since there is no control group, there was potential placebo interference that would result in criticism of 6 months results. It seems more likely that the placebo effect has worn off at 12 months and the results show the benefits of surgical treatment.

Outcome limitations

Follow up rates and missing data

The loss of 27.8% of patients at 12 months for the analysis of the primary outcome measure is a potential limitation of this trial. However, the lost sub group was analysed in two ways to see if their absence from the main analysis may have had a significant effect on the result. Firstly, it was determined whether or not this had created imbalanced groups. This was not found to be the case as the excision arm lost 27.3% of cases and the vaporisation arm lost 29.9% (p=0.742). Secondly, the lost sub group was analysed against the

remaining patients in the main analysis to see whether they differed in age, median rASRM score, histology finding and depth of disease. No difference was found here either; suggesting that the lost sub group did not differ significantly from the main analysis group, and consequently had not biased the result.

Balanced arms in the main analysis group

From the descriptive statistics, that otherwise showed well balanced groups for age, rASRM score and positive histology, there was a potential limitation found in that there were more deep cases in the excision group (44/66, 66.7%) compared with the vaporisation group (28/66, 43.8%). As the results show that vaporisation performed significantly less well for deep disease, both independently and in comparison with excision, then less deep cases in the vaporisation group gave it an advantage. Consequently, vaporisation appeared to be performing better than it would have done had the number of deep cases been evenly distributed. The comparative advantages of excision over vaporisation may well be underestimated by this study as a result.

A further limitation relating to depth of disease exists here, as its assessment was by palpation the visual appearance of the lesions, and so was a subjective decision by the surgeon that it appeared to be infiltrating >5mm below the surface of the peritoneum. This may have resulted in assignment errors to the wrong depth classification, casting doubt on the results relating to depth of disease. However, all the surgeons were experienced at diagnosing endometriosis and the depth adjusted on the rASRM score sheet at the end of the case once a better assessment of depth was available following treatment of the lesions. If any bias resulted, it is likely that there would have been an over

diagnosis of deep disease, rather than an under diagnosis. This would have diluted the deep category with more superficial cases, again allowing the vaporisation group an advantage.

Protocol deviations and “per protocol” analysis

The patients with protocol deviations during the follow up period were included in the main analysis and result in a possible trial limitation. There were 19 patients who became pregnant, 5 who underwent further surgery, and 16 who had some form of adjuvant hormonal therapy. A “per protocol” analysis for the primary outcome measure EHP-30 Core pain was carried out on those patients who had not deviated from the protocol. The improvements found in these patients are more likely to be related to surgical treatment. There were still 35 patients in each arm at 12 months (more than the 28 patients required in the power calculation for EHP-30 Core pain to have an 80% chance of showing a 20% difference). Excision (-21.04 +/- 23.97) still outperformed vaporisation (-9.42 +/-19.36) at 12 months (p=0.029, 95%CI -22.02 to -1.23).

Chapter 6 - Conclusions

This thesis set out to improve our understanding of the surgical treatment of endometriosis. Much of the early evidence in the literature was related to fertility outcomes rather than pelvic pain and clinical practice thus emphasised this component of the problem. Larger case series and randomised trials have subsequently begun to focus on the more subjective issue of pelvic pain. Two clear technique categories developed, vaporisation/ablation and excision, both with randomised data supporting their use. However, there has been no clear data about who is really using which techniques, and whether any one is really any better than the other. In addition, the hypothesis of this thesis was that there would be no difference between the two techniques in terms of pain outcome if the lesions were truly vaporised by CO2 laser down to normal tissue.

The lack of information regarding the extent to which gynaecological laparoscopic surgeons are using varying techniques for treating pelvic endometriosis of all types, was investigated with an international web-based survey to address this. This survey has some definite limitations in terms of its sample size, however it does suggest that surgeons who belong to the specialist laparoscopic societies appear to be aware of the evidence currently available and are trying to practise in an evidence-based manner. Some surgeons would change their practice if they had the access to training and equipment to allow them to do so. In general, there exists a view that endometriomas should be excised and that bowel resection should be avoided if possible for recto-vaginal disease. For minimal to moderate disease,

superficial disease can be treated with a combination of excision or vaporisation depending on the case, but that deep disease should be excised.

This very question for minimal to moderate disease was addressed in the randomised blinded trial reported in this thesis. It was clearly found that, contrary to expectation, although the proportion of patients who improve is no different for either vaporisation or excision, the extent of improvement in both pain and quality of life is significantly better for excision than vaporisation at 12 months post operation. In addition to this, for deep disease vaporisation does not convey significant improvement at 12 months. The statistical analysis very much set out to try and disprove this finding as it was contrary to the hypothesis at the outset. However, it became apparent that the finding was genuine and the limitations were sufficiently small to accept the result. Since diagnosing deep endometriosis is essentially an intra-operative one, and since excision will give the best results in all forms of minimal to moderate disease, it makes logical sense to approach treatment intending to excise in every case in the light of these findings.

The implications of this view must be considered in the context of clinical practice. There is little doubt that training doctors to laparoscopically excise endometriosis is not a straightforward one. A sound knowledge of the anatomy of the pelvic side-wall and the skill to avoid damage in this location is integral. Not all gynaecologists are likely to be able to achieve the skills required or have the training opportunity to achieve this safely, in order to stop the culture of not surgically excising at the time of diagnosis or dusting the surface with bipolar diathermy. The implication of this is that most patients with endometriosis may

need referral to a specialist gynaecologist, which is probably currently unattainable. This does however seem to present more evidence that we should be moving towards a culture of greater subspecialisation, and away from the old fashioned “jack of all trades” Obstetrician and Gynaecologist.

Furthermore it must be added that a significant proportion of patients will deteriorate even with surgery and that the extent of improvement is disappointing on average and widely variable in practice. To this end, much more work is required to ascertain the symptoms or signs that will allow us to direct our surgical treatment towards those patients who are most likely to benefit, and avoid operating unnecessarily on those who will not.

The current randomised data only tells of improvement for a year, which brings into question the cost-benefit of endometriosis surgery, especially when there is at least a third risk of recurrent surgery within five years. The extent of improvement resulting from excision beyond 12 months still remains unclear as no randomised data exists, and is likely to be confounded by other variables introduced over time following the index surgery.

The use of EHP-30 as a validated tool to evaluate pain and quality of life in endometriosis appears to have been successful in this study as it attempts to address issues directly related to the patient and their quality of life. The data gained here will be pooled with existing data to further improve its use as a tool for endometriosis, though ideally population norm data is required for EHP-30.

In conclusion, whilst it is recognised that all studies have their limitations, and that is no different in this case, it appears that for the surgical treatment of endometriosis, excision is the way forward and that training and referral strategies need to be put in place to ensure that women have access to the optimal treatment.

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Appendices

Appendix B – Endometriosis Trial Patient Information Leaflet

Patient information

A study comparing:

Laser surgery with the harmonic scalpel

In the treatment of pelvic pain due to endometriosis.

THANK YOU FOR READING THIS.

Introduction

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Consumers for Ethics in Research (CERES) publish a leaflet entitled ‘ Medical Research and You ‘. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 OBW.

Purpose of Study

Endometriosis is a common and debilitating disorder that diminishes the quality of women’s lives in their reproductive years. It is associated with pelvic pain, infertility and menstrual disorders. It remains a difficult condition to treat. Drugs are ineffective in the long term and have unacceptable side effects. However, laparoscopic (key hole) surgery has been shown to be an effective form of treatment.

Keyhole laser surgery was first performed in this country at St. Luke's Hospital in Guildford in l982, so we have 20 years experience of this technique and an excellent safety record on more than 4,500 patients. We conducted the world’s first scientific study of laser surgery, which clearly showed that laser treatment is an effective treatment in the majority of patients and has considerable advantages over medical therapy with anti-endometriosis drugs.

It is now our normal practice is to use a carbon dioxide laser to vaporise the endometriotic deposits.

Recently, the UltraCision Harmonic Scalpel has been developed. It was introduced commercially in 1993, and since then it has been increasingly used in surgery. We would like to lead the way in developing the use of the UltraCision Harmonic Scalpel in the treatment of endometriosis.

The UltraCision Harmonic Scalpel converts electrical energy, to mechanical motion at the instrument's titanium tip, which vibrates at a speed of 55,500 cycles per second. This mechanical energy allows both cutting of tissue and coagulation (the prevention of bleeding) at the precise point of impact. For this reason, we feel that the UltraCision Harmonic Scalpel offers a safe alternative to the carbon dioxide laser. Further more, keyhole laser surgery is not widely available in this country. The UltraCision Harmonic Scalpel is easier to use than a laser, and considerable cheaper to purchase. It is potentially much more widely available in other hospitals, and it also has multiple applications in gynaecological surgery, whereas the lasers have much more limited range of uses.

Why have I been chosen?

Patients with pelvic pain and a known or possible diagnosis of endometriosis are being asked to take part in the study. We plan to recruit around 100 patients over the space of one year.

Do I have to take part?

It is up you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive. If you do not wish to take part in the study, then you will receive keyhole laser surgery as per our usual practice.

What will happen to me if I take part?

Your symptoms will be recorded before surgery in the usual way. Standard questionnaires will be used to assess the effect your symptoms have on the quality of your life and on your psychological state.

The comparison of laser and the UltraCision Harmonic Scalpel has never been subjected to a scientific study. Because we do not know which way of treating patients is best, we need to make such a comparison. People will be put into two groups. The groups will be selected by a computer, which has no information about the individual (i.e. by chance). Patients in each group will then have a different treatment and these treatments are then compared. Because this is a double blind trial neither you nor the research nurse who will follow you up in the clinic will know in which treatment group you are (although, if your doctor needs to find out he / she can do so).
The operation (keyhole surgery) is performed under general anaesthesia through a telescope called a laparoscope, which is introduced inside the abdomen via a tiny cut within the umbilicus. You will also have 2 or 3 small cuts just above the hairline for additional instruments to be inserted into your abdomen. The remaining endometriotic

deposits will then be destroyed by means of the UltraCision Harmonic Scalpel or the laser.

The research nurse will also record any changes in your symptoms at 3, and 6 months following surgery. The need for any medical therapy or further surgical treatment for pelvic pain will also be recorded.

What do I have to do?

You will not have to restrict or change your life style in any way. This study will not affect your fertility intentions at all. Those women who want to get pregnant will be encouraged to do so. Those women who do not will be asked to use a barrier contraceptive (cap, condom or coil) or be sterilised as they wish. We will ask you to avoid using an oral or an injectable hormonal contraceptive for the 6 months following surgery. This is because hormonal contraceptives affect the degree of pain and the amount of bleeding during a period.

What are the additional risks of taking part?

There are no additional risks beyond that of routine laparoscopic (keyhole) surgery. The risks include injury to the bowel, bladder, or blood vessels, which occurs in about 1 in 1000 cases and may need a laparotomy (a surgical procedure to open the abdomen and repair the injuries). These issues are routinely discussed with the patients at the time of informed consent.

What are the possible benefits of taking part?

We hope that both the treatments will help you. However, this cannot be guaranteed. The information we get from this study may help us to treat future patients endometriosis better.

What if new information becomes available?

If new information about the treatment being studied becomes available during the course of a research project, you will be told about it. If this happens, your research doctor will discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

What if something goes wrong?

If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have

grounds for legal action. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. Your GP or the doctor who referred you to Mr Kent for treatment will be kept informed of your treatment and your participation in the study by hospital discharge summary in the usual way.

What will happen to the results of the study?

After your 6 months follow up appointment the research doctor will tell you which arm of the study you were in. The results of this study will be published in a medical journal, and they will be presented to other doctors at scientific meetings. You will not be identified in any report or publication.

Who is organising and funding the research?

The project is being organised by Mr Peter Barton-Smith and Mr Andrew Kent. We do not receive any specific funding for this project at the present time. Ethicon-endo Surgery, who make the UltraCision Harmonic Scalpel do however contribute to the research budget of the department.

Who has reviewed the study?

The South West Surrey LREC has reviewed and approved this study.

Contact for further information

The persons to contact in the event of an unexpected reaction or incident will be Mr Peter Barton-Smith, 01483 571122 page 4210 or Mrs Pat Haines 01483 571122 ext 4569.

Please keep this information sheet for your own records, together with the copy of the consent form.

Appendix C – Endometriosis Trial Consent Form

Study Number:
Patient Identification Number for this trial

CONSENT FORM

Title of Project: Carbon dioxide-laser versus UltraCision Harmonic Scalpel in the treatment of pelvic pain due to endometriosis.

Name of Researcher: Mr Peter Barton-Smith, Clinical Research Fellow in Gynaecological Endoscopy.

1. I confirm that I have read and understand the information sheet dated ……. (Version) for the above study and have had the opportunity to ask questions
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected
3. I agree to take part in the study

Name of Patient	Date	Signature
Name of Person Taking Consent (*If different from researcher*)	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept in hospital notes

Appendix D – Endometriosis Trial Visual Analogue Scale

Visual Analogue Score for Pelvic Pain due to Endometriosis

Hospital No:

Dysmenorrhoea Yes / No / Not Sure
(painful periods)

No pain _____ Worst pain

Chronic Pelvic Pain Yes / No / Not Sure
(pain not linked to periods going on for >6 months)

No pain _____ Worst pain

Dyspareunia Yes / No / Not Sure
(painful sexual intercourse)

No pain _____ Worst pain

Dyschezia Yes / No / Not Sure
(pain on bowel opening)

No pain _____ Worst pain

Additional information:

Appendix E – Endometriosis Trial EHP 30 Questionnaire

University of Oxford National Endometriosis Society

The Endometriosis Health Profile Questionnaire (EHP 30)

In collaboration with The National Endometriosis Society U.K.

- *This questionnaire has been developed to measure the effect endometriosis has upon a woman's quality of life*
- *To complete the questionnaire please would you answer;*

  ***Part 1**: All 30 questions*

  ***Part 2**: All sections that apply to you*
- *We are aware that you may have had endometriosis for a long time. We also understand that how you feel now may be different to how you have felt in the past. However, please would you answer the questions only in relation to the effect that endometriosis has had on your life* ***during the last 4 weeks***
- *There are no right or wrong answers, so please tick the answers which best represent your feelings and experiences.*
- *Due to the personal nature of some of the questions please understand that you do not have to answer any questions if you would prefer not to.*
- *The information and answers you give will be treated with the utmost confidentiality.*
- *If you have any problems or would like any help or assistance with the completion of this questionnaire please contact Pat Haines on 01483 406797 who will be happy to help you.*
- *Once you have completed the questionnaire please could you return it in the pre-paid envelope provided.*

- *We would like to thank you very much in anticipation for taking the time to help us with this important research and we look forward to receiving your answers.*
- *This research was funded with an educational grant from Pharmacia Corporation, USA*

PART 1: CORE QUESTIONNAIRE

DURING THE LAST 4 WEEKS, HOW OFTEN BECAUSE OF YOUR ENDOMETRIOSIS HAVE YOU…..

	Never	Rarely	Sometimes	Often	Always
1. Been unable to go to social events because of the pain?	☐	☐	☐	☐	☐
2. Been unable to do jobs around the home because of the pain?	☐	☐	☐	☐	☐
3. Found it difficult to stand because of the pain?	☐	☐	☐	☐	☐
4. Found it difficult to sit because of the pain?	☐	☐	☐	☐	☐
5. Found it difficult to walk because of the pain?	☐	☐	☐	☐	☐
6. Found it difficult to exercise or do the leisure activities you would like to do because of the pain?	☐	☐	☐	☐	☐
7. Lost your appetite and/or been unable	☐	☐	☐	☐	☐

to eat because of the pain?

Please check that you have ticked ***one box for each question***
before moving onto the next page

DURING THE LAST 4 WEEKS, HOW OFTEN BECAUSE OF YOUR ENDOMETRIOSIS HAVE YOU…..

	Never	Rarely	Sometimes	Often	Always
8. Been unable to sleep properly because of the pain?	☐	☐	☐	☐	☐
9. Had to go to bed/lie down because of the pain?	☐	☐	☐	☐	☐
10. Been unable to do the things you want to do because of the pain?	☐	☐	☐	☐	☐
11. Felt unable to cope with the pain?	☐	☐	☐	☐	☐
12. Generally felt unwell?	☐	☐	☐	☐	☐
13. Felt frustrated because your symptoms are not getting better?	☐	☐	☐	☐	☐
14. Felt frustrated because you are not able to control your symptoms?	☐	☐	☐	☐	☐

Please check that you have ticked ***one box for each question***
before moving onto the next page

DURING THE LAST 4 WEEKS, HOW OFTEN BECAUSE OF YOUR ENDOMETRIOSIS HAVE YOU…..

	Never	Rarely	Sometimes	Often	Always
15. Felt unable to forget your symptoms?	☐	☐	☐	☐	☐
16. Felt as though your symptoms are ruling your life?	☐	☐	☐	☐	☐
17. Felt your symptoms are taking away your life?	☐	☐	☐	☐	☐
18. Felt depressed?	☐	☐	☐	☐	☐
19. Felt weepy/tearful?	☐	☐	☐	☐	☐
20. Felt miserable?	☐	☐	☐	☐	☐
21. Had mood swings?	☐	☐	☐	☐	☐

22. Felt bad tempered or short tempered? ☐ ☐ ☐ ☐ ☐

Please check that you have ticked ***one box for each question***
before moving onto the next page

DURING THE LAST 4 WEEKS, HOW OFTEN
BECAUSE OF YOUR ENDOMETRIOSIS HAVE YOU…..

	Never	Rarely	Sometimes	Often	Always
23. Felt violent or aggressive?	☐	☐	☐	☐	☐
24. Felt unable to tell people how you feel?	☐	☐	☐	☐	☐
25. Felt others do not understand what you are going through?	☐	☐	☐	☐	☐
26. Felt as though others think you are moaning?	☐	☐	☐	☐	☐
27. Felt alone?	☐	☐	☐	☐	☐
28. Felt frustrated as you cannot always wear the clothes you would choose?	☐	☐	☐	☐	☐
29. Felt your appearance has been affected?	☐	☐	☐	☐	☐

30. Lacked confidence? ☐ ☐ ☐ ☐ ☐

Please check that you have ticked ***one box for each question***
before moving onto Part 2

Part 2: Modular Questionnaire

Section C: These questions concern the effect endometriosis has had on your sexual relationships **during the last 4 weeks**

How often during the last 4 weeks
BECAUSE OF YOUR ENDOMETRIOSIS HAVE YOU…..

	Never	Rarely	Sometimes	Often	Always
1. Experienced pain during or after intercourse? ***If not relevant please tick here*** ☐	☐	☐	☐	☐	☐
2. Felt worried about having intercourse because of the pain? ***If not relevant please tick here*** ☐	☐	☐	☐	☐	☐
3. Avoided intercourse because of the pain? ***If not relevant please tick here*** ☐	☐	☐	☐	☐	☐
4. Felt guilty about not wanting to have intercourse? ***If not relevant please tick here*** ☐	☐	☐	☐	☐	☐
5. Felt frustrated because you cannot enjoy intercourse? ***If not relevant please tick here*** ☐	☐	☐	☐	☐	☐

Appendix F – Endometriosis Trial HADS Questionnaire

Hospital Anxiety and Depression Scale (HADS)

Patients are asked to choose one response from the four given for each interview. They should give an immediate response and be dissuaded from thinking too long about their answers. The questions relating to anxiety are marked "A", and to depression "D". The score for each answer is given in the right column. Instruct the patient to answer how it currently describes their feelings.

A	**I feel tense or 'wound up':**	
	Most of the time	3
	A lot of the time	2
	From time to time, occasionally	1
	Not at all	0

D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite so much	1
	Only a little	2
	Hardly at all	3

A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3

	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0

D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3

A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not too often	1
	Only occasionally	0

D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0

A	**I can sit at ease and feel relaxed:**	
	Definitely	0
	Usually	1
	Not Often	2

	Not at all	3

D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0

A	**I get a sort of frightened feeling like 'butterflies' in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite Often	2
	Very Often	3

D	**I have lost interest in my appearance:**	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care as ever	0

A	**I feel restless as I have to be**	

	on the move:	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0

D	**I look forward with enjoyment to things:**	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3

A	**I get sudden feelings of panic:**	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0

D	**I can enjoy a good book or radio or TV program:**	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

	Scoring (add the As = Anxiety. Add the Ds = Depression). The norms below will give you an idea of	

	the level of Anxiety and Depression.	
	0-7 = Normal	
	8-10 = Borderline abnormal	
	11-21 = Abnormal	

Reference: *Zigmond and Snaith (1983)*

Appendix G – Endometriosis Trial 12 month Demographic Questionnaire

Endometriosis Trial Demographic Questionnaire **12 months**

……Months since initial operation

You were recruited into our trial comparing the surgical treatment of endometriosis by vaporisation with a carbon dioxide laser or excision with harmonic scalpel on:

……....

We would now like to ask you to answer these questions about what has happened to you since your operation.

Further surgery

Have you undergone any of the following procedures since your initial operation?

1. Repeat laparoscopy and treatment of endometriosis WITHOUT removal of the uterus or ovaries

YES NO

2. Hysterectomy

YES NO

3. Removal of one or both ovaries

YES NO

Details

……..

……..

Medical treatment for endometriosis

Have you received any of the following treatments FOR ENDOMETRIOSIS since your initial operation?

Combined oral contraceptive pill	YES	NO
Progesterone pill	YES	NO
Mirena coil	YES	NO
GnRH analogues	YES	NO
Other…….....	YES	NO

Details (e.g.: how soon after operation/dates/ongoing?):

……..

……..

……..

……..

……..

……..

……..

……..

……..

Fertility

1. How many times had you been pregnant BEFORE your initial operation?

……times

Details of dates and outcome (live births/top/miscarriage/IVF etc)…..……

……

2. Were you actively trying to become pregnant BEFORE your initial operation?

YES NO

If YES, how long had you been actively trying for?

……..Months

3. Have you had difficulty in becoming pregnant AFTER your initial operation?

YES NO

If YES, how long have you been actively trying for?

……Months

4. How many times have you been pregnant AFTER you had your initial operation?

……..times

Details of dates and outcome (live births/TOP/miscarriage etc)…..……

……

……

5. Have you had infertility treatment since your initial operation?

YES NO

If YES, give details (IVF/IUI, outcome etc)

……..

……..

……..

……..

Overall

If you had pain from your endometriosis, the pain has changed in the following way:

Pain free much improved improved same worse much worse

Overall my operation resulted in my quality of life being:

much improved improved same worse much worse

Appendix H – rASRM Scoring Sheet

Harmonic / Laser Study
Randomisation No:

Hospital ID no:

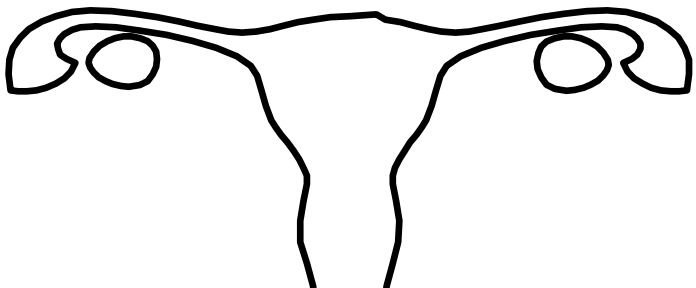
Laparoscopic staging of endometriosis

Revised American Fertility Society Classification

Endometriosis		**< 1 cm**	**1 – 3 cm**	**>3 cm**
Pelvic Peritoneum	Superficial	1	2	4
	Deep	2	4	6
Right Ovary	Superficial	1	2	4
	Deep	4	16	20
Left Ovary	Superficial	1	2	4
	Deep	4	16	20
Posterior cul-de-sac obliteration		**Partial**		**Complete**
		4		40
Adhesions		**< 1/3**	**1/3 – 2/3**	**> 2/3**
Right Ovary	Flimsy	1	2	4
	Dense	4	8	16
Left Ovary	Flimsy	1	2	4
	Dense	4	8	16
Right Tube	Flimsy	1	2	4
	Dense	4*	8*	16
Left Tube	Flimsy	1	2	4
	Dense	4*	8*	16

*If the fimbrial end of the fallopian tube is completely enclosed, change the point to 16

Additional endometriosis……..**.....**
……



Stage 1: 1 - 5 Stage II : 6 - 15 Stage III : 16 - 40 Stage IV : > 40

Appendix I – Trial Follow up Clarification letter

Clarification on follow-up protocol for women taking part in the carbon dioxide laser vs. harmonic scalpel endometriosis study. March 2006

1. ALL women who are entered into the study must be followed up according to the protocol at 3, 6 and 12 months post-surgical treatment. This includes women who have become pregnant and women who have started on other treatments for endometriosis since being entered into the trial. These women may form interesting subgroups at later analysis.
2. Should the woman be unavailable at exactly 3,6,or 12 months then every attempt should be made to ensure that the questionnaires are completed as close to the correct time as possible.
3. Every attempt within reason should be made to locate women for follow up if they do not attend for their follow up appointment. Normally this would entail a polite telephone call to the patient if they have not responded to contact by letter.
4. They must complete ALL of the questionnaires as normal.
5. In cases where the woman is not menstruating due to pregnancy, or medical treatment inducing a "pseudo menopausal" or "pseudo pregnancy" state, then they should be directed by the person conducting the questionnaires to omit answering questions relating to menstruation. The person conducting the questionnaires should record the reason why these answers have been omitted. This will include what medication is taken, why, its duration and who started it. In the case of pregnancy, the LMP and EDD must be recorded. These subgroups will be analysed at the end of the trial.
6. Initially, ALL women should be invited to the hospital to fill in the questionnaires to ensure that as many as possible are completed in the same environment. This will reduce the risk of bias especially in the anxiety questionnaire, as patients are less likely to be anxious in their home environments. If they are unwilling and this is not possible, then responses by telephone or postal questionnaire may be carried out and the method used must be recorded. This must be first discussed with the research fellow, or if he is unavailable then AK.

7. Once the patient has completed the questionnaires then the responses should be also entered onto the SPSS database as soon as possible so that an electronic record is also held. At present there is only one copy of the results and a duplicate is required in case of loss of data for any reason. This database is currently being produced.

Mr Andrew Kent
Investigator

Mr Peter Barton-Smith
Investigator

13 March 2006

Appendix J – Invitation email for Pilot Survey

An International Survey of Surgical Techniques in the Treatment of Endometriosis – Pilot Study

Compiled by the Minimal Access Therapy Training unit, Guildford, UK.
Approved by the British Society of Gynaecological Endoscopy.

Dear MATTU Faculty,

We are conducting a web survey of the surgical techniques used worldwide by laparoscopists in the treatment of endometriosis. We would like to invite you to take part in the pilot study of this survey. It should only take between 5 and 10 minute to fill in!

The results of this pilot study will be used to improve the survey for general release in 2006. We hope to collate UK data first and then expand the survey to other countries including the USA, European countries and Australia.

Please now click on the following link to start the survey or come back to this email later when you have a few moments free to fill it in:

http://surveys.som.surrey.ac.uk/survey?code=32425470

Many thanks for sparing a few minutes to help out

Peter Barton-Smith
Research Fellow

Andrew Kent
Gynaecology Director

Karen Ballard
Lecturer

Appendix K – Invitation email for Main Web Survey

mattu
international centre of excellence for telesurgery

An International Survey of Surgical Techniques in the Treatment of Endometriosis

Compiled by the Minimal Access Therapy Training unit, Guildford, UK.

In Affiliation with the

American Association of Gynecologic Laparoscopists

European Society of Gynaecological Endoscopy

British Society of Gynaecological Endoscopy

Dear Colleague,

We are conducting a web-survey of the surgical techniques used worldwide by laparoscopists in the treatment of endometriosis. This email has been sent to members of gynaecological endoscopy societies around the world. We are interested in how you trained in laparoscopic surgery, how you treat endometriosis and which instruments you use.

We would like to invite you to take part in this survey. It consists of 34 mainly multiple choice type questions. It should only take between 5 and 10 minutes to fill in!

Clicking on the link to the survey below will constitute your consent to participate in the study. However you may withdraw at any time by contacting us (p.barton-smith@surrey.ac.uk). Your responses will then be removed from the database if you so wish. The anonymous responses you give are confidential and held on a secure database.

If you complete the survey and enter your email address (for prize draw purpose only) then you will be automatically entered into a prize draw and one lucky respondent will win an Apple iPod nano!

YOU MAY RECEIVE THIS EMAIL MORE THAN ONCE BY VIRTUE OF BEING ON THE MAILING LIST OF MORE THAN ONE SOCIETY. HOWEVER PLEASE ONLY COMPLETE IT ONCE.

Many thanks for sparing a few minutes to help out.

Peter Barton-Smith	Andrew Kent	Karen Ballard
Research Fellow	Director of Gynaecological Surgery	Senior Lecturer

Please now click on the following link to start the survey or come back to this email later when you have a few moments free to fill it in.

http://www.zoomerang.com/survey.zgi?p=WEB227E6KPU7AD

Appendix L – Pilot Web Survey

Appendix M – Main Web Survey