HYSTEROSCOPIC SURGERY AS AN ALTERNATIVE TO HYSTERECTOMY IN THE TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING

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DECLARATION

I declare that this thesis has been written by myself.

The work described was undertaken by me during my appointment as clinical research fellow at Aberdeen Royal Infirmary. The grant application was submitted by Drs Kitchener, Parkin, Abramovich, Alexander and Professor Russell, and they each played a part in the original design of the trial. I was responsible for the finalised design, I recruited the women and carried out all the clinical follow-up, and performed at least half of the hysteroscopic operations, attending the majority of the remainder, and some of the hysterectomies. Audrey Naji, psychology research assistant, helped design and administer the psychology questionnaires, and computerised them ready for analysis. All the computerisation and analysis was otherwise carried out by myself. Oestradiol estimations were performed by Ivan Reid of the Biochemistry Department of Aberdeen Royal Infirmary.

This work has not been submitted for any other degree, diploma or professional qualification.

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Dr Sheena Pinion

PUBLICATIONS

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Pinion SB, Kitchener HC, Abramovich DR, Parkin DE, Russell IT, Alexander DA. Patient selection for hysteroscopic endometrial resection (letter). Br J Obstet Gynaecol 1991;98:839.

Related publications

Pinion SB, Kitchener HC. Conservative alternatives to hysterectomy (mini-symposium). Current Obstetrics and Gynaecology 1992;2:141-5.

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Presentations

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ABSTRACT

The basis of this thesis is a prospective randomised trial comparing hysterectomy (n=99) with two methods of hysteroscopic surgery, endometrial laser ablation (n=53) and transcervical resection of the endometrium (n=52), in the treatment of dysfunctional uterine bleeding. Two women in each group refused the allocated treatment, but analysis was by intention to treat. The main outcome measures were efficacy in the relief of menstrual and related symptoms, operative complication rates, postoperative recovery, the effect of treatment on other symptoms, and on psychosocial morbidity, and patient satisfaction.

In the hysterectomy group, all women (except one treated hysteroscopically) were amenorrhoeic at 12 months; in the hysteroscopy group, 93 (97%) were either amenorrhoeic or had light menstrual loss, although 32 women required a second procedure to achieve this status. The remainder had loss similar to that before treatment. At 12 months 13 (15%) of the hysterectomy group and 46 (58%) of the hysteroscopy group had continuing cyclical abdominal pain, although dysmenorrhoea improved in the majority.

Major operative complications were rare in all groups, but minor morbidity, principally infection, was significantly more common following hysterectomy (difference 32%, 95% CI 20-44%, $P<.001$). There were major differences in postoperative recovery rates, with median time to self-reported recovery being two to three months in the hysterectomy group compared with two to four weeks in the hysteroscopy group ($P<.0.001$).

Premenstrual symptoms improved in both groups and, although significantly less common in the hysterectomy group at six months, differences were no longer present at 12 months. Similarly there were no differences between the groups in the incidence of urinary or bowel symptoms, dyspareunia or menopausal symptoms.

Anxiety and depression were common preoperatively, but improved significantly postoperatively, with a significant difference in favour of hysterectomy at six months, but no difference between the groups at 12 months. Other aspects of psychosocial functioning were studied and found to be no different between the two groups.

Using self-reporting questionnaires, 89% of the hysterectomy group and 78% of the hysteroscopy group were very satisfied with treatment (difference 11%, 95% CI 8-13%, $P < .05$) and 95% and 90% respectively felt there had been an acceptable improvement in symptoms ($P < .001$). The same operation was recommended by 72% and 71% respectively (not significant).

In conclusion, all but five women were satisfied with their outcome at 12 months, although, in the hysteroscopy group, 22 (21%) had required a second operation for continuing symptoms. Those in the hysteroscopy group enjoyed a greatly reduced recovery time and significantly less postoperative morbidity. The data suggest that hysteroscopic surgery is a valuable alternative to hysterectomy for the treatment of dysfunctional uterine bleeding.

INTRODUCTION

The rise in hysterectomy rates in the developed world has reached epidemic proportions (Easterday et al, 1983, Teo, 1987, Coulter et al, 1988). Many people have questioned the need for this, especially for dysfunctional uterine bleeding (Grant and Hussein, 1984, Teo, 1987, Coulter et al, 1988). Concern about the rising hysterectomy rate has led to a search for a satisfactory but less invasive alternative treatment for dysfunctional uterine bleeding (DUB).

Such an approach is hysteroscopic endometrial ablation, first reported by Goldrath et al (1981). Since the original description of the operation, there have been a number of uncontrolled reports of ablation procedures. At the time that this trial was planned, there was no reported randomised study, and there was a clear need for this.

An application for funding was made to the Chief Scientist Office of the Scottish Office Home and Health Department and resources were allocated for a randomised trial comparing hysterectomy with two methods of endometrial ablation to be undertaken in Aberdeen. I was appointed under the terms of the grant and the work reported in this thesis was undertaken while in this post. Ethical approval for this study was obtained from the Grampian Health Board and Aberdeen University Joint Ethical Committee.

CONSERVATIVE ALTERNATIVES TO HYSTERECTOMY STUDY

A pragmatic prospective randomised trial comparing hysterectomy, laser ablation, and endometrial resection in women with dysfunctional uterine bleeding has been carried out. The main aims of the study were:

1) **to compare the complication rates of hysterectomy, endometrial laser ablation and transcervical resection of the endometrium**

2) **to compare postoperative recovery after hysteroscopic surgery with that following hysterectomy**

3) **to compare the efficacy of hysteroscopic surgery with hysterectomy in the relief of dysfunctional uterine bleeding and other related symptoms**

4) **to compare the effect of hysteroscopic surgery and hysterectomy on other symptoms**

5) **to compare the effects of the two types of operation on psychosocial factors**

6) **to compare patient satisfaction with the two types of operation**

7) **to identify, if possible, predictive factors, in the history, examination, operative findings or psychosocial characteristics of women, for a good or poor outcome after hysteroscopic surgery**

The first part of the thesis is a detailed review of the relevant literature in three sections, namely hysterectomy (Chapter 1), dysfunctional uterine bleeding (Chapter 2), and hysteroscopic surgery (Chapter3).

The next section gives details of the patients recruited to and the methods used in the randomised trial (Chapter4).

The results section is set out as follows - firstly, a report of women treated during the learning curve of the introduction of hysteroscopic surgery and women treated outwith the randomised trial (Chapter 5), and preoperative characteristics of women recruited to the randomised trial (Chapter 6); secondly, according to the main aims of the trial detailed above, namely a comparison of operative details and complications (Chapter 7), postoperative recovery (Chapter 8), the effect of the treatment on menstrual symptoms (Chapter 9), the effect on other symptoms (Chapter 10), psychosocial effects (Chapter 11), satisfaction with treatment (Chapter 12), and predictive factors for outcome after hysteroscopic surgery (Chapter 13). A full cost benefit analysis of the three procedures has also been undertaken, but will not be included in this thesis, as it is not wholly the work of the author.

The results of each part of the study will be discussed in turn (Chapter 14), followed by a discussion of the overall conclusions and implications of the findings (Chapter 15).

CHAPTER 1. HYSTERECTOMY

TRENDS IN HYSTERECTOMY RATES.

In 1853 Burnham performed the first successful hysterectomy. However, only three of 15 patients operated on survived. From this inauspicious beginning, hysterectomy has become one of the most commonly performed surgical procedures. In 1985, 66,470 hysterectomies were performed in England and Wales (Hospital Inpatient Enquiry, 1987) and in 1986, 6,592 were performed in Scotland (Scottish Health Statistics, 1988). In Scotland the rate doubled between 1961 and 1984, mainly because of an increase in operations for menstrual disorders in women aged 35 to 44 (Teo, 1987). Hysterectomy is the most frequently performed major operation in the United States,where the rate increased until 1975, to 670 per 100,000 women, after which it declined slightly (Easterday et al, 1983). Most were performed during the reproductive years.

There is, however, considerable variation in hysterectomy rates between different countries, and between different regions of the same country. The rate in 1975 varied between 181 and 287 per 100,000 female population in England and Wales, 419 to 731 in Canada, and 528 to 792 per 100,000 in the United States (McPherson et al, 1981). In England and Wales in 1985, the NHS rate varied from 122 to 175 per 100,000 population. However, figures are artificially low, as at least 21% of hysterectomies in England and Wales are carried out outside the NHS (Coulter et al, 1988). The lifetime risk of a woman undergoing hysterectomy varies from 20% in the UK (Teo, 1987, Coulter et al, 1988) to 40% in Australia (Selwood and Wood, 1978) to 50%+ in the USA.

Media information can affect the hysterectomy rate. A campaign in one area of Switzerland, publicising the recent 57% increase in hysterectomies, decreased the hysterectomy rate by 25.8% overall and by 33.2% in women aged 35-49 (Domenighetti et al, 1988). This variation has stimulated much debate about the necessity of the operation.

In 1946 Miller stated "hysterectomy in the absence of pelvic disease cannot be justified any more than can removal of the normal breast or gall bladder". Of 246 hysterectomies reviewed (two-thirds of which were subtotal) 41.4% were performed for bleeding, and 30.8% had no abnormality on pathological examination. D'Esopo (1962) also attacked the "seemingly irrational practice of removing an organ which is anatomically sound". He identified 450 cases with no disease apart from small fibroids, in half of whom the indication for operation was dysfunctional uterine bleeding. This comprised about 15% of all hysterectomies, but he concluded that this was justifiable on the basis of symptom relief.

In contrast, Wright (1969), declared "after the last planned pregnancy, the uterus becomes a useless, bleeding, symptom-producing, potentially cancer-bearing organ and therefore should be removed." He also favoured the removal of the cervix for cancer prophylaxis. Parrott (1972) said the uterus was "frequently removed for good cause without histological aberration" and called for the establishment of a "solid data background" to prevent accusations about unnecessary operations.

In Scotland, Grant and Hussein (1984) looked at abdominal hysterectomies in a district general hospital during two years a decade apart. The rate had doubled in that time,

and the mean age of women had fallen. There had been an increase in operations for pelvic pain (two-thirds of whom had no organic disease) and in patients with normal histology (from 21% to 47%). In Scotland in 1984, 34.9% of hysterectomies were performed for menstrual disorders, 20.2% for fibroids (Teo, 1987). In the Oxford region, 30% were for disorders of menstruation, and in women under 45, 38% were for DUB and 37% for fibroids (Coulter et al, 1988).

In a study of 1,851 patients in America (Lee et al, 1984), 31% of whom had a vaginal hysterectomy, 69% an abdominal hysterectomy, 22% had no detectable abnormality at pathological examination. 48% were carried out for bleeding disorders, pelvic pain or prolapse, and 38% of these had no abnormality.

Before deciding whether other countries are carrying out unnecessary operations, or the UK is depriving patients of the operation, quality of life after various different management policies still needs to be evaluated (Coulter et al, 1988).

COMPLICATIONS OF HYSTERECTOMY

Mortality and early morbidity.

In a study comparing 300 vaginal with 300 abdominal hysterectomies (White et al, 1971), the mortality rate for abdominal hysterectomy was 0.7% (there were three deaths in the abdominal, one in the vaginal group). The reoperation rate was 5%, and readmission rate 3%. Only 19% had no morbidity or complications, which included urinary retention, bladder laceration, ureteral damage, vaginal vault infection or haematoma, abdominal wound infection, haemorrhage (2.7%), deep venous thrombosis

and pulmonary embolism, intestinal obstruction, and febrile morbidity. The vaginal group had 50% more post-operative pyrexia and 40% more urinary tract infections (65% compared to 44%) than the abdominal group.

Ledger and Child (1973) analysed 12,026 hysterectomies, a one in seven sample from the American Professional Activity Study, of which 30% were carried out vaginally, 70% abdominally. Patients undergoing vaginal operation had more postoperative fevers (38% versus 31%) and antibiotic treatment; those having the abdominal procedure required blood transfusion (17% versus 13%), intermittent positive pressure ventilation, and anticoagulants more frequently. The mortality rate was 0.1% for vaginal, 0.2% for abdominal hysterectomy, giving an overall rate of 16.4 per 10,000. This was less than half the mortality for appendisectomy, and less than one-eighth that for cholecystectomy, during the same period.

Amirikia and Evans (1979) reviewed 6,435 hysterectomies, one third carried out vaginally. There were 17 deaths, 19% had febrile morbidity, 12% were transfused, 1.4% had postoperative haemorrhage, and less than 1% urinary tract injury. They concluded "Probably there are few operations today that contribute more to improving the quality of life of women than an indicated hysterectomy. However, the associated morbidity and mortality rates warrant critical consideration of the indications and contraindications to surgery."

In a prospective study, the risks of hysterectomy in women of reproductive age were assessed (Dicker et al, 1982). Vaginal hysterectomy (performed in 30%) had fewer complications than abdominal - 24.5% versus 42.8% had one or more complications. Febrile morbidity was the most common (15.3 and 32.3%); haemorrhage occurred in

8.3 and 15.4% respectively. The mortality was 0.2 and 0.1%. However more patients in the vaginal group (5.1%) had an unscheduled major operation. The conclusion was that there was appreciable morbidity with either operation.

In a study of approximately 40% of patients in the USA in 1979 and 1980 (Wingo et al, 1985), the mortality rate was 477/317,389 abdominal and 46/119,972 vaginal hysterectomies. It was increased in association with pregnancy or cancer (8% of procedures). If these were excluded, the mortality was 6/10,000. In 1984 in Scotland, mortality was 0.06%, but all the deaths were in patients with malignancy (Teo, 1987).

A recent study of complications of hysterectomy (vaginal and abdominal) showed an infection rate of 25.2%, a transfusion rate of 13.3%, a reoperation rate of 5.9% and a readmission rate of 5.2% (Gambone et al, 1990). A population based study in Denmark revealed a mortality of 16.1 per 10,000 within 30 days of admission for non-cancer hysterectomy (Loft et al, 1991), cardiovascular disease accounting for 60% of the deaths.

It can be seen therefore that although early morbidity is common after hysterectomy, this is rarely due to life-threatening complications, and mortality is almost negligible when the operation is carried out for dysfunctional uterine bleeding.

Late complications.

Failure to relieve symptoms.

There is no doubt that hysterectomy cures DUB, but its success in curing pelvic pain is questionable. Of 243 premenopausal hysterectomy patients, 16.5% had had a further operation within ten years (Riedel et al, 1986), usually for pain. In a study of patients six months after hysterectomy for pelvic pain, where there had been no extrauterine disease and the uterus had been of normal size (Stovall et al, 1990), 22.2% had persistent pain. This was not related to preoperative characteristics or the presence or absence of pathology.

Ovarian function.

Ovarian function after hysterectomy has been studied by a variety of methods. There is little correlation between menopausal symptoms and ovarian status (De Neef and Hollenbeck, 1966, Richards, 1974, Riedel et al, 1986, Menon et al, 1987).

In a study of the immediate effect of operation on ovarian function, serum gonadotrophins and ovarian steroids were measured in women undergoing hysterectomy and laparoscopy (Stone et al, 1975). The latter operation had no effect, but there was a decrease in oestradiol and progesterone after hysterectomy, with no change in gonadotrophins. This is probably explained by a decrease in blood flow (52-89% in premenopausal and 29% in postmenopausal patients, Janson and Jansson,

1977). Another study found no evidence of ovarian damage during operation (Coppen et al, 1981).

Zaczek (1963) observed functional ovaries (and a continuing pregnancy!) at a second laparotomy in 35 patients. Urinary oestrogens and pregnanediol were measured in women six months to 13 years after hysterectomy with ovarian conservation (Beavis et al, 1969), and 75% with both ovaries showed evidence of ovulation, 10% were functional but anovulatory, 15% were inactive (the expected figure). In those with only one ovary, 27% were ovulatory, the rest anovulatory or inactive. Riedel et al (1986) found most still had biphasic cycles, although oestrogen and progesterone levels were lower than normal.

The average age of the menopause has been found to be four years lower (45.5 years) in women undergoing hysterectomy with ovarian conservation (Siddle et al, 1987), and correlated with the age at hysterectomy. Further prospective work is, however, needed.

Ovarian pathology.

In a retrospective analysis of oophorectomies, 202 patients had had a previous hysterectomy (Christ and Lotze, 1975), 3% had ovarian cancer, 23.3% a benign neoplasm, 56.6% cystic ovaries. An incidence for the "residual ovary syndrome" was calculated at 1 to 3% and removal of ovaries in women over 40 was suggested. Of 1,557 patients with retained ovarian tissue, 14 required subsequent laparotomy and four developed ovarian cancer (Ranney and Abu-Ghazaleh, 1977). McGowan (1987) found 14% of 291 women with ovarian cancer had had a previous hysterectomy. A widely quoted risk for the development of ovarian cancer after hysterectomy is 0.2%, but as a

cohort of women has not been followed until death, the true figure is unknown (Studd, 1989).

Cardiovascular disease.

There is an increased risk of cardiovascular disease in women after the menopause. It would therefore be expected that removal of the ovaries at the time of hysterectomy would have the same effect (7.2 times the risk if the ovaries are removed before age 35 (Rosenberg et al, 1981)). However, evidence is emerging that hysterectomy with ovarian conservation may also have an effect. Centerwall (1981) found a threefold increase in coronary heart disease during the remaining premenopausal years in women after hysterectomy. During the 10 years after hysterectomy there was a 4% probability of developing ischaemic heart disease, and a 0.4% risk of dying from it. This was also found in the Framingham study (Gordon et al, 1978). Rosenberg et al (1981), however, found hysterectomy without the removal of ovaries was only weakly associated with an increased risk of myocardial infarction. Punnonen et al (1987) retrospectively compared women after hysterectomy and myomectomy, and found a threefold risk of cardiovascular disease in the former, unexplained by other risk factors or whether the ovaries were removed or not.

Urological problems.

An association has long been noted between hysterectomy and urinary problems; although many of these women have had similar problems in the past (Hanley, 1969), a significant number relate the onset of problems to the operation (Smith et al, 1970). The cause may be infection, obstruction, alteration in urethral support, denervation or

oestrogen deficiency, (Hanley, 1969, Smith et al, 1970). In the early postoperative period there is a decrease in bladder capacity, with increased residual volume and intravesical pressure, which resolves after one week (Wake, 1980).

A variety of symptoms (Hanley, 1969) and disorders (Farghaly et al, 1986) may be found. In retrospective studies of post-hysterectomy patients presenting with bladder dysfunction (Farghaly et al, 1986, Vervest et al, 1988), there are no specific patterns. One such study (Vervest et al, 1988) found significantly less nocturia, dysuria and stress and urge incontinence postoperatively; 26% of asymptomatic women developed symptoms, 23% had symptoms which resolved.

In a prospective study (Jequier, 1976), 62% of women had symptoms preoperatively, and 50% at six months postoperatively; 34% had symptoms which resolved, 25% developed symptoms. Hanley (1969) suggested problems could be avoided by performing subtotal hysterectomy. In a prospective comparison of subtotal and total hysterectomy (Kilkku, 1985), 36.2 and 47.7% respectively had preoperative incontinence. At one year, the figures were 28.8 and 22.6%, but it was felt the differences were probably explained by differences in the patient groups.

In urodynamic studies on 36 women before and after operation (Parys et al, 1989), the proportion with symptoms went from 58% to 78%, and with urodynamic abnormality from 39 to 58%. Eleven patients had altered or de novo abnormalities, the commonest of which was stress incontinence.

Bowel function.

In a retrospective case-control study (Taylor et al, 1989), more women consulted a doctor for bowel problems after hysterectomy, they were more likely to complain of infrequent bowel movement, and this was worse after the operation, possibly due to autonomic denervation.

Sexual function.

Sexual function may be altered by a change in interest, activity or satisfaction. Sexual problems after gynaecological surgery may be due to loss of ovarian function, alteration in the anatomy, or continuation of existing problems (Amias, 1975). In a prospective study (Utian, 1975), a high incidence of decreased libido (25-44%) occurred after hysterectomy. This was unaffected by HRT, and was not dependent on whether the ovaries were removed or whether the woman was pre- or postmenopausal. Another study (Richards, 1974) found no consistent effect of hysterectomy on libido. Dennerstein et al (1977) found sexual relations improved in 34%, deteriorated in 37% and stayed the same in 29%. Preoperative anxiety about the effect of the operation significantly correlated with problems afterwards, which were thought to be psychological in origin, rather than organic or hormonal. In a prospective study (Chynoweth and Abrahams, 1977), 18% had a deterioration in sexual relationships, but 19% felt the situation had improved. Zussman et al (1981) reviewed nine studies from 1944-1973 of sexual response after hysterectomy and oophorectomy, which were mainly retrospective, had variable findings and concluded that problems were psychogenic, and five studies from 1973-77, which showed a 33 to 46% decrease in

sexual response and concluded that hormonal (such as decreased androgens) or anatomical change (removal of the cervix) might be responsible. The conclusion was that further prospective studies were necessary. In two such studies, (Martin et al, 1980, Coppen et al, 1981) no significant alteration in sexual functioning was found.

PSYCHOLOGY OF MENSTRUAL DISORDERS.

It has long been recognised that there is an association between gynaecological problems and psychology. The prevalence of dysmenorrhoea and premenstrual symptoms and their relationship to personality were studied in a random sample of 500 women (Coppen and Kessel, 1963). Increased neuroticism on the Maudsley Personality Inventory was associated with irregular periods, and premenstrual tension was associated with neuroticism, although dysmenorrhoea was not.

Psychological morbidity is increased in women attending gynaecology clinics. In an entirely subjective study (Dutton, 1965), 82.6% of 155 patients with DUB attending a clinic had a psychological illness, which was cited as the probable cause of the DUB. 29% of 539 women age 40 to 55 in general practice, and 50% of 215 new patients at a gynaecology out-patient clinic (Ballinger, 1975), were 'cases' on the General Health Questionnaire (GHQ, Goldberg, 1972), and 49% of cases compared to 22.7% of non-cases complained of excessive menstruation. Worsley et al (1977) also found 48 of 97 patients attending a gynaecology clinic were cases on GHQ. There was an increase in menstrual dysfunction and "psychologically orientated illness" in those with high scores.

Of 50 patients with subjective menorrhagia, 62% were cases on GHQ (Greenberg, 1983), 85% of whom had clinical mild to moderate depression, and this was associated with an increase in the neuroticism score on the Eysenck Personality Questionnaire (EPQ, Eysenck and Eysenck, 1975). Of 211 patients attending a gynaecology clinic, 46% were cases on GHQ, and there was a significant association with pelvic pain (Byrne, 1984). 35 women were also interviewed using the Present State Examination (PSE, Wing, 1976), and compared to 140 controls - 29% versus 17% were 'cases'.

Salter (1985) studied 102 women referred to a gynaecology clinic for treatment of menstrual disorders, and found that depression on the Zung self-rating scale correlated with bleeding, flooding and clotting, anxiety correlated with dysmenorrhoea, and that anxiety and depression levels were considerably higher than the normal population. The lie scale from the EPQ did not correlate with any of the other indices used. Gath et al (1987) studied 521 women age 35-59 from general practice, and found that psychiatric morbidity, as measured by PSE (9.6% cases) and GHQ (21.2% cases) and the neuroticism scale of the EPQ, were significantly associated with gynaecological symptoms, especially PMT and dysmenorrhoea, but less so with heavy periods.

PSYCHOLOGICAL FACTORS AND HYSTERECTOMY.

Hysterectomy is often cited as causing psychological problems, especially depression. The majority of studies are retrospective and uncontrolled, but even in these, it is often doubtful whether the operation itself has had a significant effect.

In one study (Melody, 1962), 4% of 267 women undergoing hysterectomy became severely depressed during the first three months after operation, but this was usually precipitated by life situations, and a history of previous depression was of predictive significance. Patterson and Craig (1963) reviewed 100 patients admitted to psychiatric hospital after hysterectomy and found that only 15% were in the first year after the operation, 42% within five years. Except in one case they concluded there was no relationship between the operation and the illness. Bragg (1965) found no significant difference in the rate of admission to mental hospital after hysterectomy compared to cholecystectomy, although the observed admission rate in the hysterectomy group was 30% greater than the expected rate.

Using referral to a psychiatrist as the criterion of illness, 7% of 729 women were affected, but 57% of those with a previous psychiatric history were rereferred (Barker, 1968), reaching a peak by the second postoperative year. The rate was three times that expected, and two and a half times the rate after cholecystectomy. Richards (1973) compared 200 patients in general practice with 200 controls, defining depression as drug treatment with antidepressants. Ninety-nine of the hysterectomies versus 31 controls required treatment, but 32 had also been treated before operation. There was no obvious relation with social class, marital state, parity, or oophorectomy.

Hysterectomy patients were four times as likely to become depressed in the first three years (33% versus 7%), and the depression was longer lasting and more severe.

Richards (1974) also described a "post-hysterectomy syndrome" of depression, flushes, urinary symptoms, dizziness, headaches, insomnia and prolonged convalescence. The incidence of depression within three years (reported by the patient) was 70%. Kaltreider et al (1979) found 61% of 28 women after hysterectomy to be suffering from the "stress response syndrome" (a symptomatic response to traumatic life events). 29% were still experiencing neurotic symptoms at one year. They found increasing severity of response to be associated with persisting child-wish, deterioration in sexual functioning, and change in self-concept.

More recent prospective studies are more likely to show a beneficial effect of hysterectomy on psychological status. Using the Profile of Mood Status (POMS)(Meikle et al, 1977), there was no increase in psychological trauma in hysterectomy patients postoperatively compared to cholecystectomy and sterilisation. In a prospective study of 49 patients (Martin et al, 1977) 57% were found to be psychiatrically ill, 27% with hysteria, 18% with depression, at interview before hysterectomy. Younger women (under 40) were more likely to have had previous surgery and more psychiatric symptoms. At one year (Martin et al, 1980), there were fewer psychiatric symptoms, and those affected had usually had similar problems preoperatively. In a study of 60 patients with DUB or fibroids (Coppen et al, 1981), using the General Health Questionnaire, no depression related to hysterectomy was found and there was less depression and an improvement in mood postoperatively. In 20 Chinese patients (Tsoi et al, 1984) GHQ status improved, and correlated with preoperative status. There was no correlation with the sex role inventory, contrary to

expectations. Another study, however, found evidence of impaired mental health in 30% after hysterectomy, 1% of whom required hospital admission (Chynoweth and Abrahams, 1977).

Using the PSE in 156 women, Gath et al (1982) found 58% before and 29% 18 months after hysterectomy for benign disease to be psychiatric cases, mainly neurotic disorders. There was also a large fall in POMS score. Levels were high both before and after, compared to women in the general population. Most cases after operation could not be attributed to the hysterectomy itself. If recovery had not occurred by six months, there was a significant association with PSE score. Ryan et al (1989) found preoperative psychological morbidity in 55%, decreasing to 31.7% after operation. The main risk factor was a previous poor score, but there was again no relationship with the sex role inventory.

General health status and patient satisfaction.

Chynoweth and Abrahams (1977) found 26% of women had regrets about the operation, and felt their physical health had deteriorated, but only 2% wished they had not had it. However, a large proportion felt their physical and mental health had improved. 75% of 44 patients in a prospective study said hysterectomy was a "good thing" for them, and 89% had relief or improvement in symptoms (Martin, 1980). Gath et al (1982) found 86% to be satisfied with the operation. Marital relations were mostly unchanged, and by three months over 75% were back to normal social and occupational level. Ryan et al (1989) found a "clear reduction in the disabling symptoms that led to operation" and that recovery had usually taken place by four months. A recent study of 236 women two to ten years after hysterectomy, 50% for

bleeding or pain, showed that symptoms improved in most, 96% were glad they had had the operation, 88% would recommend it, and 55% wished they had had it sooner (Schofield et al, 1991). However, 22% had visited their GP with symptoms related to the operation and 7% had been referred to a gynaecologist.

Summary.

Hysterectomy is therefore one of the most commonly performed major operations, with low mortality when carried out for DUB, although there is considerable early postoperative morbidity, and a high rate of patient satisfaction. Despite this, there is still much to be learned about the long-term sequelae, as many studies are retrospective, and even when prospective, often fail to include an adequate control group for comparison. Questions therefore remain about the effect of hysterectomy on urinary, bowel, ovarian, cardiovascular and sexual function. There have been no randomised trials comparing hysterectomy with alternative therapies for dysfunctional uterine bleeding, the commonest indication in women in the reproductive years, and the main reason for the recent increase in the hysterectomy rate.

CHAPTER 2. DYSFUNCTIONAL UTERINE BLEEDING.

NORMAL MENSTRUATION

Menstruation occurs only in women and certain primates. It involves the partial shedding of the endometrium, accompanied by vaginal bleeding, in response to abrupt hormonal changes caused by involution of the corpus luteum. Modern woman experiences more menstrual cycles in a lifetime than her historical counterpart, as there is less interruption for pregnancy and lactation, earlier menarche and later menopause, and greater life expectancy. There is therefore more opportunity for disturbed menstrual function. In addition, the changed role of women in society means menstrual dysfunction is possibly more disruptive than before.

Vascular and structural changes in the endometrium.

Each uterine artery supplies lateral branches which enter the uterus dividing into anterior and posterior arcuate divisions. Each arcuate artery gives off branches that run outwards towards the serosa and inwards to the endometrium. The inner branches are tortuous and terminate in a capillary network surrounding groups of muscle fibres. During the secretory phase, the arterioles become more prominent and run a spiral course towards the surface, where they form a subepithelial capillary plexus (Farrer-Brown et al, 1970).

The spiral arteries are end-arterioles and are sensitive to hormonal change, unlike the other uterine arteries. Stasis and vasodilatation occurs 1-5 days before menstruation. Vasoconstriction occurs 4-24 hours before bleeding and persists throughout the

menstrual period, interrupted by brief periods of relaxation allowing haemorrhage. Most of the bleeding is from arterioles, but 35% is from venules and capillaries (Markee, 1940).

Endometrium consists of the epithelium of the surface and glands, and stromal cells of mesenchymal origin. Most of the tissue, down to the basal layer, is shed during the first day of menstruation. Endometrial repair is initiated when the zona basalis is exposed before the end of menstruation, and lasts around 48 hours. There is a complete surface epithelium by Day 5. Regeneration occurs from the ends of basal glands and from the cornual regions (Ferenczy, 1976 (a), (b)).

Recently, binding sites for epidermal growth factor have been found in the endometrium (Hofman et al, 1984), and this, as well as the increasing use of endometrial ablation, has stimulated interest in endometrial repair as a research subject (Smith, 1990).

Prostaglandins.

There is evidence that the vessel changes resulting in menstruation are controlled by prostaglandins, 20-carbon polyunsaturated fatty acids which are not stored in tissues, but rapidly synthesised from arachidonic acid.

Arachidonic acid is released from cell membrane phospholipids by phospholipase A2, or in platelets by phospholipase C. It is metabolised in two ways. One is the production of leukotrienes by the lipoxygenase system present in platelets and leukocytes. The second is the conversion by cyclooxygenase, present in the membranes of all cells, to

the unstable PGG2 and PGH2, which are converted to thromboxane A2 (TXA2), to PGD2, PGE2 and PGF2a, or to prostacyclin (PGI2). PGE2 and PGI2 cause vasodilation, whereas PGF2a and TXA2 produce vasoconstriction. TXA2 causes platelet aggregation, PGI2 inhibits it. PGE2 inhibits while PGF2a and TXA2 stimulate smooth muscle contractility. Cyclooxygenase is inhibited by aspirin, indomethacin and the fenamates, such as mefenamic acid (Christiaens et al, 1982).

Concentrations of prostaglandins in tissue or a tissue's capacity for synthesising prostaglandin may be measured, but these vary under different experimental conditions (Christiaens et al, 1982). Pickles et al (1965) first identified high concentrations of PGF2a and lesser amounts of PGE2 in endometrium and menstrual fluid.

Most prostaglandins are produced by glandular rather than stromal cells, and the capacity is decreased after ovulation in glandular cells, whereas stromal production is non-cyclical (Smith and Kelly, 1988). Endometrium produces mainly PGF2a (Pickles et al, 1965), which alters with the menstrual cycle, whereas the myometrium produces mainly 6-keto PGF2a (a PGI2 metabolite) with no cyclical changes (Abel, 1979, Rees et al, 1984(a)). PGE2 and PGF2a concentrations are increased in endometrium in the menstrual and late secretory phases of the cycle compared to follicular phase endometrium in normal women (Willman et al, 1976). Leukotriene release also alters throughout the menstrual cycle, and increases at the time of menstruation (Rees et al, 1987).

Oestradiol causes secretory but not proliferative endometrium in culture to increase output of PGF2a (Smith and Kelly, 1987), and addition of progesterone reduces the output of PGF2a and PGE by both proliferative and secretory endometrium, also

preventing the oestradiol stimulated rise in PGF2a (Abel, 1979, Schatz et al, 1985). Abel (1979) suggests that following progesterone withdrawal the increased production of PGF2a causes the premenstrual and menstrual vasoconstriction, regulating the amount of haemorrhage during menstruation.

The precise relationships between specific prostaglandins and menstrual haemostasis remain to be clarified, but these observations suggest that prostaglandins have a role in menstrual physiology (Christiaens et al, 1982).

Fibrinolysis.

A number of haemostatic disorders can present as menstrual dysfunction (Bonnar and Sheppard, 1983), providing evidence for a role for the haemostatic system in menstruation. Platelet function and activation of the coagulation system are essential to the control of uterine bleeding.

Fibrinolytic activity is high in the endometrium and myometrium, increases towards the end of the cycle, and is maximal on the first day of bleeding (Christiaens et al, 1982). This may be to aid emptying of the uterus by liquefaction of the tissue shed, or to promote wound healing. There is no detectable fibrinogen and a large quantity of fibrin degradation products in menstrual blood (Bonnar and Sheppard, 1983, Dockeray et al, 1987).

Fibrinolytic activity is similar in menstrual and peripheral blood, but plasminogen levels are much lower in menstrual blood. Antiplasmin and antithrombin III levels are similar in menstrual and peripheral blood (Bonnar and Sheppard, 1983). Rees et al

(1985) collected menstrual fluid for 2 hours during the first 2 days of menstruation and found absent thrombin generating activity and exhaustion of fibrinolytic proteins, with no difference between the 2 days.

The means whereby platelets and the coagulation and fibrinolytic systems interact within the endometrium to regulate menstruation are, however, poorly understood (Bonnar and Sheppard, 1983).

Normal menstrual blood loss.

Hallberg and Nilsson (1964) devised the alkaline haematin method of measuring menstrual blood loss. All sanitary protection used is collected, and soaked in sodium hydroxide, transforming haemoglobin into alkaline haematin, which is then estimated spectrophotometrically. Using this method, a population study of menstrual blood loss was carried out to determine the 'normal' range (Hallberg et al, 1966). The mean blood loss per period was 43.4 mls (SD 2.3 mls). The upper limit of normal was defined as the 95th percentile in women with normal haemoglobin and iron levels - 76.4 mls. Women losing 61-80 mls were likely to have a lower haemoglobin, and this was more evident in those losing over 80 mls. Women's perceptions of blood loss were unrelated to the measured loss.

In a similar study in Northumbria (Cole et al, 1971) a wide range of menstrual loss was found, with a positive skew. Loss increased with parity and varied with use of the oral contraceptive pill and the intra-uterine contraceptive device. The mean blood loss per period was 37.5 mls (SD 34.2 mls).

DYSFUNCTIONAL UTERINE BLEEDING

Menorrhagia means excessive menstrual bleeding. Dysfunctional uterine bleeding (DUB) is defined as abnormal bleeding from the genital tract in the absence of pelvic pathology. It may be primary, secondary to disease outside the genital tract, such as thyroid disorders or coagulation problems, or iatrogenic, due to hormonal therapy or the intra-uterine contraceptive device for example (Davey, 1986). The incidence of DUB among women with menstrual disorders will therefore depend in part on the investigations carried out. Most gynaecologists in the UK would carry out a pelvic examination and some assessment of endometrial histology, with coagulation studies, hormone levels, hysteroscopy or laparoscopy only where indicated. Pathology such as small fibroids or endometriosis may therefore be missed. However, the management in these cases is often the same as in women with no identifiable cause. No cause is found in approximately 50% of women undergoing hysterectomy for menorrhagia. The majority have ovulatory cycles and normal hormone levels (Haynes et al, 1977).

Prevalence of menstrual disorders.

The prevalence of menstrual symptoms is very high, with over one in nine women having severe symptoms (Coppen and Kessel, 1963). A community study in Oxford (Coulter et al, 1988) found that 50% of women had one or more menstrual problems, of whom only 20% had attended their general practitioner. Gath et al (1987) found 57% of 265 premenopausal women complained of dysmenorrhoea, 95% had premenstrual symptoms, 30% complained of heavy periods, 14% of flooding, 32% of passing clots, and 7% had consulted their doctor in the past six months for excessive menstruation. In 1981/82 30.7 per 1000 consultations by women were for heavy,

frequent or irregular periods, and only 9.8% were referred to a specialist (OPCS, 1986). However, GP referrals for DUB rose by 73% between 1971 and 1981, suggesting that women are becoming less tolerant of menstrual problems.

The most common cause of iron deficiency anaemia is excessive menstrual blood loss (Cohen and Gibar, 1980). In European countries, the incidence of anaemia among women of childbearing age varies from 10 to 25%.

Measured menstrual blood loss in menorrhagia.

In a study of 92 women with regular heavy periods for which no cause was identified (Chimbira et al, 1980(b)), no correlation was found between the measured blood loss and the patient's subjective assessment, the number of pads used, the number of days of bleeding, the surface area or weight of the uterus. Of those periods described as heavy 47% were less than 80 mls. Of those described as light 34% were greater than 80 mls. A similar study on 69 women (Fraser et al, 1984) found only 38% had a loss greater than 80mls, 59% greater than 60mls, and 20% less than 35mls per period. Younger women were more likely to regard moderate loss as heavy. Again there was no correlation with the number of pads or tampons used, and all the women described flooding or clots. Haynes et al (1977) studied 50 women with blood loss over 80mls and found no relationship between the duration of the period and blood loss; 92% of the loss occurred in the first three days, as normal.

During recruitment to trials of medical treatment (Cameron et al, 1987(b), Dockeray et al, 1989, Cameron et al, 1990), consistently only around 50% of women with regular heavy periods are found to have a loss over 80mls.

Many women relate the onset of heavy periods to sterilisation. However, Kasonde and Bonnar (1976) measured blood loss in 25 women before and after sterilisation and found no significant change, although women complaining of heavy periods were excluded.

The discrepancy in perception might be due to loss of fluid other than blood, as the percentage of blood varies considerably, from 1.6 to 81.7% (Fraser et al, 1985). This fluid is thought to be endometrial tissue fluid. There is, however, a significant correlation between total fluid and blood loss

Aetiology of menorrhagia and dysmenorrhoea.

Prostaglandins.

PGE2 and PGF2a have been found to be increased in women with subjective DUB, endometriosis, dysmenorrhoea and carcinoma (Willman et al, 1976). Increased PGF2a has been found in the endometrium of dysmenorrhoeic women (Lundstrom and Green, 1978), as has an increased PGF2a/PGE ratio (Pickles et al, 1965). In menorrhagia, however, Smith et al (1981)(a) found no significant difference in PGE2, PGF2a or PGF2a/PGE2 ratio, although the ratio was significantly lower in a subgroup of women with loss greater than 90ml. In a further study (Smith et al, 1983), patients with ovulatory DUB synthesised more PGE2 and D2 at the expense of PGF2a, and in anovulatory DUB the endometrium lacked the capacity to synthesise PGF2a. Kelly et al (1984) found the PGF2a/PGE2 ratio was decreased in the endometrium of women with increased menstrual loss. Rees et al (1984) found no correlation between

blood loss and endometrial or myometrial PGE2 or PGF2a levels, but PGF2a and PGE2 levels in menstrual fluid were increased in women with dysmenorrhoea or menorrhagia, although this did not correlate with blood loss (Rees et al, 1984(b)). There was an increase in the PGF2a/PGE2 ratio in both conditions. Cameron et al (1987)(a) found endometrial PGE and "total" PG to be increased in women with increased menstrual blood loss. PGE receptors have been found to be increased in myometrium from women with menorrhagia and correlated to blood loss (Adelanto et al, 1988).

Smith et al (1981)(b) found an increase in PGI2 metabolites in myometrium cultured with endometrium from menorrhagic women, suggesting that this was the reason for the decreased fibrin deposition and platelet aggregation observed in endometrium as compared to other tissues. Another study (Makarainen and Ylikorkala, 1986) found no difference in PGI2 and TXA2 metabolites in menorrhagic women, but the ratio was inversely related to blood loss in women losing over 70 mls per cycle.

Rees et al (1987) found endometrial but not myometrial leukotriene release was higher in women with dysmenorrhoea, but there was no correlation with blood loss. Bonney et al (1991) found no difference between normal women and those with ovulatory menorrhagia in phospholipase A2 type 1 activity, but phospholipase A type 2 was decreased in the proliferative phase, and phospholipase C was increased in women with menorrhagia.

Fibrinolysis.

In a study of menstrual blood from women with normal loss and with regular heavy cycles, fibrin and aggregating platelets were found in nearly all, with no difference

between the two groups (Sheppard et al, 1983). Fibrinolytic activity has been found to be higher in menstrual blood of patients with DUB (Hahn et al, 1976, Bonnar and Sheppard, 1983, Dockeray et al, 1987). Increased fibrinogen, FDPs, factor 5 and 8 activity, antithrombin 3 and a-antitrypsin have been found in menorrhagic women (Hahn et al, 1976), but another study showed no significant difference in FDPs or plasminogen level, with antiplasmin levels significantly lower (Bonnar and Sheppard, 1983). Dockeray et al (1987) found an increase in plasminogen activator and plasmin activity, a decrease in antiplasmin, and no difference in antithrombin 3. However Rees et al (1985) found no alteration in coagulation and fibrinolytic proteins in menstrual fluid from women with menorrhagia.

In conclusion, although abnormalities have been found in the prostaglandin and fibrinolytic systems in menorrhagia, the findings are not consistent, and the precise aetiology of the condition remains unclear.

MEDICAL TREATMENT OF DUB AND MENORRHAGIA

Reassurance that there is no serious pathology may be all that is required, and the condition may remit spontaneously. Rees (1991) told 17 patients with regular "heavy" blood loss that their loss was normal (15-60 mls) and that they did not need treatment. Three years later, one had had a hysterectomy, two were taking mefenamic acid and 14 had had no further treatment. Otherwise, medical treatment is usually the first line management. This may be in the form of hormonal therapy, such as the oral contraceptive pill in younger women or progestagen in older women, prostaglandin synthetase inhibitors, antifibrinolytics, ethamsylate or danazol (Noble, 1985).

The majority of studies of medical management include only women with regular heavy periods, with no other gynaecological symptoms, and increasingly, only women with blood loss of over 80 mls per period. As indicated already, this represents only a proportion of women attending for help with menstrual problems. Coulter et al (1988) concluded, however, that "those women who perceive their blood loss to be excessive require some form of help even if it does not reach the 80ml level which clinically constitutes menorrhagia."

The various classes of drugs used in menstrual disorders will be described, with information from therapeutic trials. Particular attention will be paid to danazol and the LHRH agonist analogues because of their use not only in the treatment of menorrhagia and fibroids, but in preparing the uterus for hysteroscopic surgery.

Prostaglandin synthetase inhibitors.

These are non-steroidal antiinflammatory agents which act mainly by inhibiting the cyclooxygenase enzyme system. They are taken only during the days of bleeding, and have few side-effects, apart from dyspepsia. Mefenamic acid has been shown to decrease blood loss in women with proven menorrhagia by an average of 20 to 50% (Anderson et al, 1976, Fraser et al, 1983, Hall et al, 1987, Dockeray et al, 1989, Cameron et al, 1990, Chamberlain et al, 1991) and flufenamic acid, naproxen, diclofenac and ibuprofen have similar effects (Anderson et al, 1976, Hall et al, 1987, Ylikorkala and Viinikka, 1983, Makarainen and Ylikorkala, 1986). Although many women remain menorrhagic on treatment (Cameron et al, 1990), the decreased

incidence of side-effects compared with other drugs (Dockeray et al, 1989) make the non-steroidals preferred first-line treatment.

Progestagens

The rationale behind the use of progestagens is that they inhibit the proliferative effect of oestrogen, and produce a thinner endometrium, especially if given early in the cycle. Side effects of progestagens include weight gain, nausea, bloating, ankle swelling, headaches, depression, acne and hirsutism. Norethisterone, a 19-nortestosterone compound, is commonly used in menstrual disorders. There is surprisingly little published information about its effect, and in the trials that have been carried out it is often given late in the cycle.

Norethisterone can induce regular withdrawal bleeds in women with metropathia haemorrhagica, and subjectively decrease bleeding in women with ovulatory menorrhagia (Bishop and Almeida, 1960). Norethisterone 5mg bd for 10 days each cycle did not reduce blood loss in women losing over 50 mls per cycle (Cameron et al, 1987(b)), but in women losing over 80 mls, reduced loss by 20% (Cameron et al, 1990), although 67% remained menorrhagic on treatment.

Bergqvist and Rybo (1983) found that a progesterone releasing contraceptive device reduced blood loss to 35% of the preinsertion level, at the expense of prolonged bleeding. This is not yet available for general use.

However, one very effective way to treat menorrhagia is the combined oral contraceptive pill, which can decrease blood loss by 53% (Nilsson and Rybo, 1971).

Danazol

Danazol is a 2,3 isoxazole derivative of 17a-ethinyl testosterone. It is metabolised to around 60 different products, one of the main ones being 17a-ethinyl testosterone, which is progestational and mildly androgenic. Basal gonadotrophin levels are not altered, but ovulation is inhibited by elimination of the midcycle LH and FSH surge, and plasma oestradiol levels fall. There may also be a direct androgenic and antiprogestational effect on endometrium producing atrophy. Danazol binds to many classes of steroid receptors - androgenic, progestagenic - with mixed agonist-antagonist activity, but not oestrogenic. There is no change in serum cortisol, but a significant increase in progesterone, dehydroepiandrosterone and androstenedione concentrations. Side effects include weight gain, oedema, acne, hirsutism, voice deepening, headache, hot flushes, decreased libido and muscle cramp (Barbieri and Ryan, 1981).

Danazol is of proven benefit in menorrhagia, reducing blood loss, increasing the interval between periods, and producing amenorrhoea, with an effect that can last for several months after discontinuing treatment (Chimbira et al, 1979, Fraser et al, 1985, Dockeray et al, 1989). The effects and side-effects are dose dependent (Chimbira et al, 1980(a), Fraser et al, 1985). At a dose of 400mg daily there is a mean weight gain of 4.5 kg and skin problems are common (Chimbira et al, 1979). Even on 200mg per day, 75% experience side effects, and 40% find these unacceptable (Dockeray et al, 1989).

Antifibrinolytics

These have been used to try and correct the observed abnormalities of the coagulation system found in women with menorrhagia (Bonnar and Sheppard, 1983, Dockeray et al, 1987). They again have the advantage that they are only taken during bleeding, and have few side-effects. Epsilon aminocaproic acid (EACA) and tranexamic acid (AMCA) inhibit the activation of plasminogen. In women with proven menorrhagia, they have been shown to decrease blood loss by an average of 36 to 59% (Nilsson and Rybo, 1965, Nilsson and Rybo, 1967, Callender et al, 1970, Nilsson and Rybo, 1971, Ylikorkala and Viinikka, 1983). However, around a third of women remain menorrhagic (Nilsson and Rybo, 1971).

Ethamsylate is a synthetic cyclohexadine compound which increases capillary resistance and reduces the bleeding time. The mode of action appears to be associated with antihyaluronidase activity preventing breakdown of mucopolysaccharides in the capillary wall. Blood loss decreases by 20 to50% in primary menorrhagia and 19% in IUCD users (Harrison and Campbell, 1976, Chamberlain et al, 1991).

LHRH agonist analogues

Luteinising hormone-releasing hormone (LHRH), a decapeptide, is a local hormone which circulates between the hypothalamus and the pituitary, with very little in the peripheral circulation. Pulsatile release of LHRH from the hypothalamus causes LH and FSH release from the pituitary. The incorporation of large D-amino acids in position 6 gives synthetic analogues of greatly increased potency (50 to 200 times).

Those with antagonist activity suppress LH release immediately, but need to be used in large doses. Agonists give an initial stimulatory effect, followed by reversible suppression of pituitary function, and subsequent decrease in ovarian steroid production - "down-regulation". LHRH analogues are inactivated orally, and therefore need to be given by nasal spray or injection. The dose, route and phase of the menstrual cycle influence the effect, and there are also significant individual differences in response (McLachlan et al, 1986).

The stimulatory effect is greatest in the late follicular phase (Jaramillo et al, 1978, Casper et al, 1980). Commencement of therapy in the early follicular phase leads to oestrogen secretion without progesterone release, followed by a withdrawal bleed at 10 to 14 days, whereas if started in the luteal phase both oestrogen and progesterone are stimulated, but only until the onset of menstruation, which occurs at the normal time (McLachlan et al, 1986).

Slow-release implants have been developed, making long-term therapy more consistent and convenient. Zoladex (D-Ser tBu6 Aza Gly10 LHRH, goserelin, ICI) consists of a 50:50 lactide-glycolide polymer, containing 3.6 mg of the agonist, which is degraded on exposure to body fluids, resulting in a continuous release of 120 ug per day for 30 days, achieving gonadal suppression with a lower dose than with intermittent therapy.

The effect of a single depot injection of goserelin given on day one of the cycle was studied in women with normal periods (Thomas et al, 1986). Some women had slight spotting, but otherwise amenorrhoea developed for 61 to 71 days. LH increased within three days, then decreased for five weeks, followed by a rise to normal. Oestradiol

increased, fell to postmenopausal levels within one week, and increased to normal again at six to eight weeks. All the women experienced hot flushes. In women treated with monthly depot injections of goserelin for six months, commencing in the luteal phase (West and Baird, 1987), LH increased in the first 24 hours, with a rapid return to basal levels followed by suppression. Oestradiol fell to early follicular levels within 14 days. After the initial cycle, when bleeding occurred at the normal time but was more prolonged, amenorrhoea was induced, until 68 to 78 days after the last depot. All women developed hot flushes, one withdrew because of depression, but there were no other side-effects. They concluded there was less risk of endometrial hyperplasia than with intermittent therapy, as ovarian function was abolished.

If goserelin depot is given in the luteal phase, menstruation occurs at the expected time, but is lighter and prolonged; if given in the follicular phase, the response is less predictable, but corresponds to the fall in oestradiol, and the period is less prolonged (West et al, 1987).

LHRH agonist therapy is remarkably free of side-effects, apart from those of hypo-oestrogenism - hot flushes, vaginal dryness, headaches and decreased libido. Antibodies and urticarial reactions have developed after intermittent subcutaneous therapy, but with doubtful clinical significance (Meakin et al, 1985), although there has been a report of anaphylaxis after intravenous therapy (MacLeod et al, 1987). Transient skin rashes occasionally occur (West et al, 1987).

Four women with regular cycles losing over 80 mls per period were treated with intranasal buserelin for 12 weeks (Shaw and Fraser, 1984). Blood loss decreased to four to 30 ml in two to three months, with one becoming amenorrhoeic. On stopping

therapy, blood loss returned to pretreatment levels. There are concerns about osteoporosis on long-term LHRH agonist treatment, and a decrease in bone density has been noted (Matta et al, 1987). However, addition of combined oestrogen/progestagen hormone replacement therapy may prevent this complication while still relieving symptoms of menorrhagia (Thomas et al, 1991). This form of treatment should probably be reserved for those unsuitable for other methods and who are nearing the menopause.

In 13 women with fibroids treated with monthly depot injections of goserelin (West et al, 1987), fibroid volume decreased by 38 to 84% (average 55%), with maximal shrinkage in the first treatment cycle and little further decrease in size after three months. The effect did not depend on the phase of the cycle that treatment was initiated. It is not clear whether the effect on fibroids is due to changes in blood flow, hormone receptors or growth factors (Baird and West, 1988).

In a randomised double-blind trial comparing the LHRH analogue leuprolide with and without medroxyprogesterone acetate, there was no decrease in fibroid size while on progesterone, although oestradiol levels were not significantly different (Friedman et al, 1988). Hot flushes occurred in 86% without and only 11% with progesterone. In a further study, women were treated with leuprolide alone for three months, followed by 24 months leuprolide with cyclical oestrogen and progesterone supplementation. After three months the uterine volume decreased to 51% of pretreatment size, and this remained unchanged on subsequent therapy. Cyclical bleeding resumed, and flushes resolved within two months of HRT. There was no change in bone density.

After stopping long-term LHRH treatment fibroids have been found to increase to pretreatment size within six months (Letterie et al, 1989, Matta et al, 1989).

LHRH analogue treatment has been used prior to conventional myomectomy or laser ablation of fibroids. Although uterine volume decreased after three months on buserelin, blood loss and operative morbidity at open myomectomy were unchanged (Fedele et al, 1990(b)). On eight weeks treatment with a buserelin implant given in the luteal phase (Donnez et al, 1989), oestradiol levels fell to postmenopausal levels in two weeks, the uterine cavity assessed by hysterography decreased by an average 35%, although there was no significant effect if the initial cavity was less than 10 cm^2, and the effect was not increased by continuing treatment for a further month.

When LHRH analogues and danazol are compared, the effect is similar, but side-effects other than flushes occur more often with danazol (Henzl et al, 1988). Endometrial biopsy shows danazol to have a progestational and atrophic effect, whereas endometrium is weakly proliferative or atrophic on buserelin. Oestradiol concentrations are significantly lower on buserelin (Fedele et al, 1990(b)).

Danazol, medroxyprogesterone acetate and leuprolide were each given to five women four to six weeks before endometrial resection (Brooks et al, 1991). Leuprolide was the most and progestagen the least "successful" in preparing the endometrium, although the effect was not quantified, and the clinical outcomes of surgery were not reported.

In summary it can be seen that, whatever the preparation used for the medical treatment of menorrhagia, although menstrual blood loss is decreased by 30 to 60%, a

significant number of women remain menorrhagic on medical treatment, and the effect is reversed on stopping therapy. The most effective treatment, danazol, unfortunately has an unacceptably high level of side-effects.

OVERALL PROGNOSIS OF DUB

Two hundred patients over 40 diagnosed as having DUB were followed up six years later (Ngu and Quirin, 1984). Ninety-three had had a hysterectomy, 63 were on progestagen therapy, 12 were on the oral contraceptive pill. Of the hysterectomy specimens, 64% had pathological abnormalities. Patients with painful or heavy, irregular periods were more likely to have undergone hysterectomy, as were patients who had been sterilised. Of 286 patients who had had curettage for DUB aged 40-49 10 years previously (Carr, 1966), 102 had had a hysterectomy or radiation menopause. Over 70% of the hysterectomies were within 2 years of the D&C. Older women with a shorter duration of symptoms were more likely to have a spontaneous 'cure'.

Two hundred and five women referred to a gynaecology clinic five years previously, of whom 71% had menorrhagia, were traced (Coulter et al, 1991). Overall 44% had had a hysterectomy, and of the menorrhagic patients, 60% had had a hysterectomy.

It can be seen therefore that the operation of hysterectomy plays a very significant role in the treatment of menstrual disorders, as, unlike medical treatment, it guarantees amenorrhoea, and therefore cannot be lightly dismissed (Noble, 1985).

CHAPTER 3. HYSTEROSCOPY AND HYSTEROSCOPIC SURGERY

DIAGNOSTIC HYSTEROSCOPY

Dilatation and curettage

Dilatation and curettage (D&C) has been one of the most commonly performed gynaecological procedures, the main indication being abnormal genital tract bleeding, to make a diagnosis and specifically to exclude intra-uterine malignancy. It was also used for many years as a treatment for menstrual disorders, but although menstrual loss decreases in the first period after D&C, there is no lasting effect (Haynes et al, 1977). If carried out before Day 2, endometrial regeneration occurs normally, but after this, especially if carried out during the secretory phase, endometrium is thinner or defective (McLennan, 1969), which would account for the perceived decrease in menstrual loss.

The efficacy of D&C even for diagnosis is now in question. Stock and Kanbour (1975) evaluated the extent of curettage in patients prior to hysterectomy, and found that in 60% less than half of the uterine cavity had been curetted. Ten years of D&Cs were reviewed retrospectively (Smith and Shulman, 1985) - no pathology was found in 52-70%, and only two cases out of 500 in women under 40 years of age had endometrial cancer. There were 29 complications in 1383 procedures. Nickelsen (1986) found D&C made a diagnosis in only 50% of patients, no pathology was found in women under 35, and no carcinoma was found in women under 45. The complication rate was 2.8%. Mackenzie and Bibby (1978) found 38% of D&Cs were for menstrual disorder, more than half were in women under 40, and in both these groups the yield of intra-uterine disease was low. All the carcinomas were in women with postmenopausal bleeding.

A review of 33 reports of 13,598 D&Cs and 5,851 Vabra aspirations (Grimes, 1982) found that although both were relatively safe, D&C had a higher complication rate (of haemorrhage, perforation or infection). The adequacy of the specimen for diagnostic purposes was similar, and it was concluded that for most benign conditions of the endometrium, vabra aspiration was sufficient.

Hysteroscopy

Since the 19th century (Pantaleoni, 1869), attempts have been made to visualise the uterine cavity directly. Initially a simple tube was inserted through the cervix, with no lens and an external light source. With the introduction in 1952 of cold light and fibreoptics, with lenses to improve the image and field of vision, endoscopy was revolutionised, and developments continue to be made (Valle and Sciarra, 1979).

The walls of the uterine cavity must be separated for adequate examination. Initially water and saline were used as the distending medium, and in the 1970's 10% dextrose and low molecular weight dextran solutions were tried. However, dextran may be associated with anaphylactic reactions, and the hysteroscope requires immediate cleansing (Levine and Neuwirth, 1972). Lindemann and Mohr (1976) used CO2 gas via a Hysterosufflator, which was designed especially for hysteroscopy, so that if the intra-uterine pressure increased, gas flow stopped to avoid the possibility of gas intravasation and hypercarbia resulting in cardiac arrest.

The technique may be used to investigate abnormal uterine bleeding, postmenopausal bleeding, infertility, IUCD localisation, habitual abortion or amenorrhoea (LaSala et al,

1987). Hysteroscopy is contraindicated in pelvic infection, pregnancy, profuse bleeding and cervical malignancy (Valle and Sciarra, 1979, LaSala et al, 1987). Recognised complications are those of anaesthesia, uterine perforation and trauma, infection (0 to 0.3% LaSala et al, 1987), bleeding, and distention medium-related problems (Valle and Sciarra, 1979).

There have been many studies of diagnostic hysteroscopy, and the percentages with abnormal findings are summarised in Table 3.1. Outpatient examination is possible in over 90% of cases (LaSala et al, 1987, Mencaglia et al, 1987, De Jong et al, 1990). It may be difficult to distinguish between secretory endometrium and hyperplasia (Valle, 1981, LaSala et al, 1987, Mencaglia et al, 1987). There is otherwise good correlation with the findings at D&C (Gimpelson, 1988(b)) and Vabra aspiration (LaSala et al, 1987). Loffer (1989) found that only in one case of endometritis was hysteroscopy less accurate than sampling. In 9.1%, hysteroscopy and selective sampling were more accurate than blind curettage - fibroids and polyps were the conditions missed.

Table 3.1. Studies of diagnostic hysteroscopy.

Author	No & type of patients	% abnormal
Lindemann,1976	1100 mixed	29%
Sciarra,1977	320 mixed	72%
Valle,1981	419 (premenopausal)	66%
LaSala,1987	889 (369 DUB)	50% (50%)
Mencaglia,1987	618 mixed	46%
Loffer,1989	187 mixed	41%
De Jong,1990	152 mixed	50%
Fraser,1990	182 (menorrhagia)	51%

In the United Kingdom, diagnostic hysteroscopy has only really become popular since the advent of operative hysteroscopy for menorrhagia. It is true that many more abnormalities are being detected, but findings are still negative in a large proportion of women with DUB, and before recommending that hysteroscopy replace endometrial sampling, it must be shown that these findings change the eventual management of patients.

ENDOMETRIAL DESTRUCTION

Many attempts in the past have been made to destroy the endometrium and create an artificial "Asherman's syndrome" (Asherman, 1948) as treatment for DUB. Various chemical agents, such as ethanol and formalin (Zipper et al, 1969), have been instilled into the uterus. However, menstrual patterns are not significantly altered as the basal endometrium is unaffected. Of a variety of chemical agents - ethanol, formalin, copper sulphate, talc, quinacrine - only 10% formalin prevented endometrial regeneration in rabbits, and none produced uterine adhesions (Schenker and Polishuk, 1973). In a small series of women, fibroblast impregnated sponges produced amenorrhoea or hypomenorrhoea (Polishuk, 1975).

Cryosurgery produced variable areas and depths of destruction (Cahan, 1964), but controlled bleeding in five of six women (Cahan and Brockunier, 1967). One developed a pelvic abscess. Hysterectomy performed six to eight weeks later (Droegemuller et al, 1971) rarely showed complete endometrial ablation, most had isolated fragments of endometrium at the fundus and cornua. Burke et al (1973) reported a further uterine abscess developing in a patient treated with cryosurgery and concluded that there was inadequate control of the depth of tissue destruction with this method.

Patients at poor operative risk were in the past often treated by radiotherapy, primarily to ablate the ovaries ("radium menopause"). However, the use of radiotherapy for benign disease has declined with the realisation that there is an excess of malignant tumours in the irradiated site (Doll and Smith, 1968), and bone marrow (Alderson and Jackson, 1971). It has recently been recognised that even radiotherapy to the uterus itself is not effective in producing total endometrial ablation (Habeshaw and Pinion, 1992), presumably due to the varying dose reaching the endometrial surface.

With the advent of hysteroscopy, renewed attempts have made to destroy the endometrium, this time under direct visual control.

HYSTEROSCOPIC SURGERY

Simple procedures, such as the removal of endometrial polyps or retrieval of IUCDs, can be performed through the hysteroscope. There are at least two conditions, Asherman's syndrome (Sugimoto, 1978, Friedman et al, 1986, Valle and Sciarra, 1988) and intrauterine septae (Hassiakos and Zourlas, 1990), where hysteroscopic surgery is now the treatment method of choice. Hysteroscopic endometrial ablation and removal of fibroids are rapidly gaining in popularity, but still need to be properly assessed, and hysteroscopic sterilisation, although possible, is still under development (Cooper, 1992).

The current literature on endometrial ablation will now be reviewed.

ENDOMETRIAL LASER ABLATION

Properties of medical lasers.

LASER stands for "light amplification by stimulated emission of radiation". Two parallel mirrors enclose the laser medium, which is excited by a power supply. Spontaneous emission of electromagnetic energy occurs when atoms of the medium move from high to low energy states. Most is lost as heat, but a small fraction travels perpendicular to the mirrors, providing a source for stimulated emission. This is the process whereby an atom releases a photon sooner than normal, after being struck by a photon of exactly the same energy. These photons travel in the same direction and in phase with each other. On reflection by the mirrors, the light is rapidly amplified. The mirror at the front of the laser cavity is only partially reflecting, resulting in an intense beam of coherent radiation (Fuller, 1980).

In medicine, the laser is used as a source of energy which is directed and focused onto tissue, where it is reflected, transmitted, scattered or absorbed. The last two cause tissue destruction (Goldrath, 1986(b)). Absorption of energy causes a localised temperature increase, resulting in vaporisation or photocoagulation. Above 60 degrees coagulation begins, caused by the denaturation of proteins, mainly collagen. Above 100 degrees, cell water boils, is converted to steam, and the cell walls are disrupted. Above 300 degrees tissue becomes carbonised, and at over 500 degrees tissue burns and evaporates (McKenzie and Carruth, 1984).

The wavelength and spectral absorption characteristics of the laser determine the percentage of the incident beam that will be absorbed. The power density (energy in

watts per unit area), irradiation time, beam geometry and parameters of the tissue itself determine the amount of tissue vaporisation or coagulation (Frank et al, 1982). The characteristics of lasers which make them attractive to surgeons are that they are accurate, intrinsically sterile, haemostatic, and because of lack of damage to surrounding tissue, lead to fast postoperative recovery (McKenzie and Carruth, 1984).

The carbon dioxide laser emits light of wavelength 10.6 um, in the mid infra-red spectrum. Absorption by water is very high so 90% of the energy is absorbed within 100 um, only a few cell widths, and scatter is negligible. It can be used for incising or vaporising tissue, but haemostasis is poor (Frank et al, 1982, McKenzie and Carruth, 1984).

The active medium of the Nd-YAG laser is a rod of a single crystal of Yttrium-Aluminium-Garnet doped with 1-3% neodymium ions (Fuller, 1980). The wavelength is 1.06 um, in the near infra-red spectrum. It penetrates water more deeply than the CO2 laser, absorption is slight, but increased in a blood-rich environment, and it is absorbed by a few millimetres of tissue (McKenzie and Carruth, 1984). The reason for this is the degree of scattering of the beam, which increases as tissue coagulates. As it is therefore more diffuse, it is useful where bulky volumes of tissue need to be coagulated, and is also very effective at haemostasis. It produces sharply delineated coagulation necrosis with only slight tissue removal (Frank et al, 1982).

The argon laser emits radiation of wavelength 488-515 nm. Transmission through water is even better than the Nd-YAG laser, and it is strongly absorbed by haemoglobin. There is a shallow thermal effect with some tissue removal (Frank et al, 1982).

The Helium-Neon laser, wavelength 633 nm, does not develop sufficient power for use, but produces a visible red spot and is used in conjunction with other (invisible) lasers to show where energy is being directed.

There are hazards to patients and staff in the use of medical lasers, with the risk of injury, especially to the eye, resulting from a lack of protective measures, faulty equipment, misdirected beams or inappropriate settings. Laser safety guidelines must be set out and adhered to. CO2 lasers affect the cornea, and Nd-YAG lasers affect the retinal pigment epithelium, so appropriate protective eye-wear must be used.

Experimental studies.

Ophthalmologists were the first to use lasers surgically, followed by dermatologists, gastroenterologists and urologists. Experimental animal studies demonstrated the useful properties of the Nd-YAG laser, including haemostasis and depth of tissue penetration (Dixon et al, 1979). The effect on tissue is greater than the visual effect, as higher power settings produce a combination of coagulation and vaporisation. Backscatter of 30-40% and forward scatter of 25-30% of the power occurs (Halldorsson et al, 1981, Staehler et al, 1981), and with advancing necrosis, backscatter increases and forward scatter decreases, minimising absorption and slowing down tissue damage (Stein, 1986).

For a laser to be effective in treating menorrhagia, it must destroy the basal endometrium and superficial myometrium. The Nd-YAG laser was deemed more

suitable than the argon and CO2 lasers because of the greater power output, tissue penetrance and scatter - giving less precision but more haemostasis (Goldrath, 1986(b)), as well as its ability to be transmitted through a fluid medium and down an optical fibre.

In tests on hysterectomy specimens, the maximum depth of penetration was 3mm. At 1 cm from the endometrium, the "worst case" temperature rise was still less than that needed for tissue denaturisation (Goldrath et al, 1981). The maximum temperature rise on the peritoneal surface of the uterus during ablation with 70 watts in vivo was 2 degrees centigrade (Moseley et al, 1987). Heat conduction was deemed insufficient to cause damage to adjoining organs.

Contact artificial sapphire tips were tested in in vitro endometrial ablation experiments (Zumwalt et al, 1986). Duration was prolonged and effectiveness was limited - increased precision was a disadvantage for this application.

CLINICAL EXPERIENCE.

Methods and results.

Goldrath, in the United States, pioneered laser ablation of the endometrium (ELA), and Davis, in Glasgow, introduced laser ablation to the United Kingdom (Davis, 1989). The first patient was treated in 1979, and the first report, of 22 patients, was published in 1981 (Goldrath et al, 1981). A three week course of danazol was given preoperatively to try and recreate the hormonal conditions for producing Asherman's syndrome. This was found incidentally to greatly facilitate the operation, by thinning the endometrium, and it is now standard practice to prepare the endometrium prior

to ELA. The Nd-YAG laser energy, at a power of 55 to 60 Watts, was directed via a 0.6mm fibreoptic inserted through the operating channel of a hysteroscope, and the procedure was performed under direct vision with a protective filter covering the eyepiece. The endometrium was destroyed by moving the fibre tip over the whole cavity while firing the laser, which took 30 to 40 minutes. Dextrose in saline was the uterine distention medium, injected manually by two assistants, and the cervix was widely dilated to allow egress of fluid. The patients had tubal occlusion performed to prevent fluid entering the peritoneal cavity, as well as for contraception. The women were all discharged within two days, and experienced a sero-sanguinous discharge for up to three weeks.

Twenty-one had "excellent results", defined as amenorrhoea or hypomenorrhoea. At hysterography (HSG) three to six months later, there was marked scarring and deformity of the contracted cavity. Biopsies showed necrotic myometrium until four months, with foreign body giant cells but otherwise little inflammatory reaction. Little or no endometrium was obtained. In a woman who had a hysterectomy for another reason, the endometrial surface was lined by simple cuboidal epithelium.

Of 335 procedures in 324 women treated over 11 years (Goldrath, 1990), over 50% of whom had fibroids, the results were "excellent" in 292, of whom 50% were amenorrhoeic, seven had a "good" result, and 22 a poor result. Eleven of these were retreated; 10 became amenorrhoeic, and one eventually had a hysterectomy; 10 others underwent hysterectomy. The histology of the uterus showed fibroids in two, adenomyosis in five, and it has been suggested that this is a common cause of endometrial regeneration and treatment failure. Eight "successes" also had hysterectomies, but the reasons were not stated. He has started giving

medroxyprogesterone acetate 150mg on the day of operation, and claims that this increases the amenorrhoea rate from 37% to 69%, but the follow-up period is not stated.

Most of the subsequent reports have been on small numbers of patients with limited follow-up. The results are summarised in Table 3.2. The majority use the contact or "dragging" technique employed by Goldrath, but others use a "blanching" or non-contact technique. The latter method is thought to be technically easier, but more likely to leave patches of endometrium (Lomano, 1986).

Table 3.2. Results of endometrial laser ablation in published series.

Author	Number of patients	Follow up intervals	No periods	Lighter periods	Failure
Daniell, 1986	18	3-6m	7 (39%)	4 (22%)	2 (11%)
Lomano, 1986	61	6m	14 (23%)	47 (77%)	
Loffer, 1987	33	>3m	11 (33%)	13 (39%)	2 (6%)
Baggish, 1988	14	>4m	10 (71%)	3 (21%)	1 (7%)
Gimpelson, 1988	20	3-18m	9 (45%)	6 (30%)	1 (.5%)
Davis, 1989	25	6m	3 (12%)	10 (40%)	12 (48%)
Goldfarb, 1990	35	>1y	21 (60%)	11 (31%)	2 (6%)
Goldrath, 1990	324	-11y	181(56%)	181(56%)	22 (7%)
Bent, 1990	42	3m-2y	14 (33%)	13 (31%)	8 (19%)
Garry, 1991	479	6m-3y	288(60%)	162(34%)	39 (8%)

Later developments have been operating with the aid of a video camera and television monitor (Baggish and Boltoyannis, 1988), and a dual channel hysteroscope (Baggish, 1988) to allow simultaneous aspiration of debris. The cervix was therefore minimally dilated. Leuprolide, an LHRH analogue, was used to prepare the endometrium and was reported as subjectively giving "more complete atrophy" (Goldfarb, 1990).

Bent and Ostergard (1990) found success of treatment did not correlate with uterine size, endometrial hyperplasia, fibroids, polyps or obesity. Lomano (1991) compared results in 63 women with a normal sized uterus, 65 with an enlarged (> 10 cm) uterus, and 33 with fibroids. Amenorrhoea rates were 54%, 42% and 49% respectively, 14%, 42% and 39% had light periods, normal periods occurred in 24%, 7% and 12%.

The largest series reported so far is of 859 women treated over three years in three centres (Garry et al, 1991), 479 of whom had been followed up for over six months. The mean operating time was 24 minutes (range 11-90), and 99% were home in 24 hours. Of these women, 288 (60%) became amenorrhoeic, 162 (34%) hypomenorrhoeic, and 39 (8%) were not helped; 23 had a second laser; 16 were successful. Overall, 97% had a satisfactory result.

A significant decrease in premenstrual symptoms, and a correlation with improvement in menstrual flow, has been reported in 18 women after laser ablation of the endometrium (Lefler, 1989).

A total of 956 patients were treated by the contact and 157 by the non-contact method in the above papers (Table 2). The overall amenorrhoea rate was 55% (12-71%) for the contact, 39% (23-65%) for the non-contact technique, given that in at least one series, monthly spotting or discharge was counted as amenorrhoea (Garry - personal communication). Forty percent and 47% respectively became hypomenorrhoeic (21-77%), and 4% and 8% had "normal" periods. The failure rate was 9% and 3% (0-48%), but some counted failure as subsequent hysterectomy, whereas some counted patient dissatisfaction with the outcome.

Transurethral resection.

Since 1935 urologists have been carrying out transurethral resection of bladder tumours and prostates. Some of the lessons learned are applicable to gynaecology, now that similar techniques have been adopted.

The introduction of non-haemolytic irrigating solutions was a major advance, reducing mortality to less than 0.5%, but markedly reducing the "TUR syndrome" caused by absorption of irrigating fluid (Emmett et al, 1969). The introduction of a dual channel hysteroscope (Iglesias et al, 1975), allowing simultaneous suction, continuous irrigation, and low intravesical pressure, was an advance that made fluid balance easier to calculate, as well as improving vision and decreasing operating time and fluid absorption. Fluid absorption can, however, occur in a very short time (Hurlbert and Wingford, 1979, Thomas and Hales, 1984)) if venous sinuses are opened. A relationship has been found between the intravesical pressure and fluid absorption (Rao et al, 1983).

Fluid dynamics during urological endoscopy had been reviewed by Rao (1987). Fluid enters the systemic circulation by extravasation or through the prostatic veins producing significant hyponatraemia in 11-41% of cases. There is a good correlation between the decrease in serum sodium and the increased level of irrigating fluid solute. Glycine does not cause haemolysis as it is isotonic, but can cause water intoxication, leading to hyponatraemia, bradycardia and hypotension, confusion and coma. Signs and symptoms usually occur during the operation, but may be delayed for several hours.

Glycine can be metabolised to ammonia, which may delay recovery from general anaesthesia. The treatment is to give a diuretic, treat serum sodium of less than 120 mmol/l, and stop the operation.

Transurethral prostatectomy replaced open prostatectomy as the surgical treatment of choice for benign hyperplasia of the prostate without systematic assessment of its efficacy and safety. A retrospective study of 12,090 patients operated on in three centres followed for up to eight years showed a significant increase in second operations and mortality after TURP, in both low and high risk patients (Roos et al, 1989). The records of485 patients were studied in detail, and the relative risk of dying was increased in all categories of patients after TUR, with an increase in reoperation (Malenka et al, 1990). The belated conclusion was that a prospective trial was needed.

Transcervical resection of the endometrium.

DeCherney and Polan (1983) first used hysteroscopic electro-surgery for menorrhagia, cauterising the endometrium with the wire loop of the resectoscope in 11 women. In a subsequent report, 21 women in whom hysterectomy was contraindicated were treated by excision of endometrium using the urological resectoscope (DeCherney et al, 1987). The procedure took 15 to 30 minutes. Of 19 women followed up for six months to five years, 18 had no bleeding. Another method of ablating the endometrium is to use the "rollerball" attachment to coagulate the surface (Vancaillie, 1989, Townsend et al, 1990, Fraser et al, 1993). This method may be associated with less fluid absorption.

There have been fewer scientific in vitro and in vivo studies of the depth of tissue destruction with electro-surgery than laser ablation. Biopsies taken after rollerball

ablation to see if the basal layer had been coagulated (Townsend et al, 1990) found the depth of destruction to be 3 to 4 mm. The effects of different cutting and coagulating currents used four days prior to hysterectomy were studied, and it was found that low power coagulating current produced deepest destruction (Indman and Soderstrom, 1990). Duffy et al (1992)(a) studied effects of power and duration of cutting and coagulating current in vivo prior to hysterectomy, and discovered a consistent 0.73mm zone of thermal necrosis adjacent to the cutting loop, and 3.3 mm zone of tissue damage with the rollerball, which did not vary with power or duration. This was less than in in vitro experiments, due to the cooling effect of blood. The electrosurgical loop and rollerball are less effective in a blood filled environment, so irrigation is important (Duffy et al, 1992(b)).

TCRE has, however, been proven objectively to decrease blood loss. Menstrual blood loss measured before and after TCRE (Cooper et al, 1992) decreased by 90% from 159 to 17 mls per period, with 34% becoming amenorrhoeic. The mean loss of those continuing to bleed was 26 ml. Proven menorrhagia persisted in six women. Menstrual blood loss estimations in 18 women before and after rollerball ablation (Fraser et al, 1993) showed loss decreased from a mean 104 mls to 1.7 mls at six months.

Magos et al (1989)(b) reported the first series of women treated by TCRE in the UK. Sixteen women underwent endometrial resection with an unmodified resectoscope and no uterine preparation, using glycine as the distention medium. Four had a "partial" resection, to try to reduce rather than abolish menstruation. Fifteen procedures were completed, in 20 to 100 minutes. Of 11 "total" resections, six became amenorrhoeic, five hypomenorrhoeic. Of the "partial", all had lighter shorter periods. Thirteen were hysteroscoped at three months, showing pale fibrous tissue, without obliteration of the

cavity. There was no relationship between biopsy findings and the pattern of bleeding - microscopic deposits of endometrium were found even in amenorrhoeic women. There was a progressive decrease in menses over the first six months. Two women subsequently required hysterectomy, the rest were satisfied with the outcome.

The operation was then carried out under local anaesthesia, (Magos et al, 1989(a)), after preoperative danazol. Temazepam, ponstan, midazolam, fentanyl, and 1% lignocaine were administered. The first 250 resections in 234 women, of whom 22% had fibroids, were reported (Magos et al, 1991). Follow-up in 203 women was from three months to two and a half years; 16 (7%) were repeat treatments; 95% were completed (11 could not be because of perforation or fibroids); 12% had "adenomyosis" on the histology specimen. Amenorrhoea developed in 27 to 42%, but this was less common in women under 35 years of age. There was over 80% satisfaction with the procedure; 4% (10) underwent hysterectomy, at which the findings were adenomyosis, endometriosis, haematometra, or persistent menorrhagia or pain for which no cause could be identified. Postoperative hysteroscopy findings were shortening or obliteration of the cavity, and fundal fibrosis.

In contrast, in 10 months follow-up of 220 women, including some of the same patients as above (Slade et al, 1991), only 19.5% were amenorrhoeic, 32.7% were disappointed with the result, and 52.7% had persistent dysmenorrhoea.

Many other reports have appeared in the literature and these are summarised in Table 3.3. It can be seen that it is difficult to determine the true success rate for TCRE, because of the small numbers in the reports published, variable follow-up periods, and different definitions of "success". There is also no concensus about the need for

endometrial preparation prior to surgery (Pyper and Haeri, 1991, Rankin and Steinberg, 1992). Dysmenorrhoea and premenstrual symptoms have been shown to improve in the majority of cases (Fraser et al, 1993), although there are anecdotal reports of increased dysmenorrhoea occurring in some women.

Table 3.3. Results of electrosurgical endometrial ablation (resection and rollerball) in published series.

Author	Number of patients	Follow up intervals	No periods	Lighter periods	Failure
DeCherney, 1987	19	6m-5y	18(95%)	1 (5%)	
Vancaillie, 1989	15	>6m	10(67%)	4 (27%)	1 (6%)
Boto, 1989	17		11(65%)	1 (6%)	2(12%)
Brooks, 1989	19	>3m	15(79%)	2 (10%)	2 (11%)
McLucas, 1990	12	4m	8 (67%)	4 (33%)	
Townsend, 1990	25	6-22m	10(40%)	15(60%)	0
Magos, 1991	203	3-30m	27-42%		<10%
Slade, 1991	220	10-30m	19.5%		35(16%)
Rankin, 1992	400	4m	85% satisfied		27(7%)
Gannon, 1991	25	9-16m	64%	16%	16%
Dwyer, 1993	99	4m	13(13%)	76(77%)	13(13%)
Fraser, 1993	77	12-18m	25%	59%	16%

Myomectomy

Fibroids may be removed hysteroscopically with or without simultaneous endometrial ablation. Resection of pedunculated and submucous fibroids were the first gynaecological procedures performed with the urological resectoscope (Neuwirth, 1978, DeCherney and Polan, 1983). The myomata were shaved to the level of the uterine cavity, and follow-up hysteroscopy showed regeneration of normal endometrium. 28 women were treated and followed up for one to seven years (Neuwirth, 1983). Seven women had a hysterectomy for bleeding or recurrent fibroids, two within three months of treatment, and two had repeat resections. Seventeen women remained symptom-free, and five subsequently became pregnant.

Hallez et al (1987) used the resectoscope to treat 61 women with fibroids. The surface vessels were coagulated, then the whole myoma was resected, and the base coagulated. Menorrhagia was cured in 30 of 32 women, metrorrhagia was relieved in 38 of 41, seven of 11 with infertility became pregnant.

The Nd-YAG laser can also be used to remove submucous fibroids, with or without endometrial ablation, in a one or two-stage operation (Donnez et al, 1990). After preparation with an LHRH analogue, all of the protruding myoma is ablated at the first operation, devascularising the remaining intramural portion, and after a further eight weeks, the rest of the fibroid, which by this time has extruded into the cavity as a polyp, is removed.

Of 53 women with large intra-uterine fibroids (Loffer, 1990), pretreated with danazol or leuprolide, 45 were followed for over a year, 93% had control of excessive bleeding, seven of 12 with infertility became pregnant, and 13 had further surgery.

COMPLICATIONS OF HYSTEROSCOPIC SURGERY

Trauma and perforation.

During insertion of the rigid hysteroscope the cervix may be torn or bleed, and the uterus may be perforated. Perforation during hysteroscopic treatment carries the additional danger of injury outside the uterus, with bowel, bladder, ureteric and blood vessel damage.

Five uncomplicated uterine perforations occurring in relation to ELA have been reported (Goldrath, 1990, Lomano, 1986, Garry et al 1991). It seems that although perforation of the uterus does occur, this is not usually a serious complication, as it happens during hysteroscopy and not while lasering. In 1440 procedures reported above (Table 2), the incidence of perforation was 0.3%. Three cases of bowel injury have however been reported (Perry et al, 1990). One occurred after treatment of a congenitally abnormal uterus, one after treatment by an inexperienced surgeon with no monitored supervision, and one with very high power non-contact treatment. A similar case has occurred after rollerball (Kivnik and Kanter, 1992).

There has been a higher incidence of uterine perforation with the resectoscope. Three authors have each reported one perforation (Hallez et al, 1987, Brooks et al, 1989, Sturdee and Hoggart, 1991). Magos et al (1991) reported four perforations, three followed by minilaparotomy. Pyper and Haeri (1991) reported three perforations. Rankin and Steinberg (1992) had two perforations requiring laparotomy and hysterectomy.

Many of the serious complications that have occurred with this procedure do not appear in the literature. In a survey of members of the British Society for Gynaecological Endoscopy in August 1990 (MacDonald et al, 1992), perforation accounted for 37% of complications, and 91% were associated with TCRE. In three cases bladder was involved, in three ureteric damage occurred, and there were three blood vessel injuries in 2796 cases. Of all complications, 30%, and 53% of perforations, occurred in the first five cases performed by a surgeon. Six major complications occurred in the first

50 cases reported by Sturdee and Hoggart (1991), who stressed that the potential hazards of this operation must be appreciated and training was essential.

Distending medium-related problems.

Absorption of the distending medium is more likely during operative hysteroscopy because of the longer time taken, and the opening of blood vessel channels during the procedure. Use of artificial gas-cooled sapphire tips or a gaseous distension medium for endometrial ablation can lead to fatal gas embolism, so a fluid medium is essential (Baggish and Daniell, 1989).

There is a wide variation in fluid absorption in reported series, but in general amounts are greater during ELA than TCRE. This problem may be overcome by controlling intra-uterine pressure (Hasham et al, 1992). Fluid deficit is not influenced by prior sterilisation (Morrison et al, 1989, Bent and Ostergard, 1990, Molnar et al, 1992).

More important is the number of women experiencing significant fluid overload. MacDonald et al (1992) found the incidence of clinical fluid overload to be 0.9% for ELA and 0.3% for TCRE. Pulmonary oedema occurred in 15 cases in the following series (Lomano, 1986, Baggish, 1988, Gimpelson, 1988(a), Davis, 1989, Goldfarb, 1990, Goldrath, 1990, Garry et al, 1990, Bent and Ostergard, 1990, Sturdee and Hoggart, 1991, Kirwan et al, 1993).

Morrison et al (1989) reported fluid effects in 12 women undergoing laser ablation compared to five control hysterectomy patients, and several reports of electrolyte disturbance in excessive absorption have appeared (Van Boven et al, 1989, Feinberg et

al, 1989). In two studies (West and Robinson, 1989, Boto et al, 1990) no significant biochemical change was observed. In another, two patients developed asymptomatic hyponatraemia within 10 to 20 minutes - both absorbed over 900 mls (Baumann et al, 1990). There was a correlation between fluid deficit and plasma sodium, although severe hyponatraemia was only seen if over two litres were absorbed. All returned to normal in 24 hours. Peak glycine levels also occur immediately postoperative and decrease within 24 hours (Kirwan et al, 1993). Resultant hyperammonaemia may lead to delayed recovery.

Ethanol labelling of the irrigating fluid and intraoperative breath ethanol analysis has been proposed as a clinically useful method for estimating fluid absorption (Duffy et al, 1992(c)).

Molnar et al (1992) assessed fluid absorption in 300 patients in order to identify important factors and devise a risk score for excessive absorption. Factors which affected absorption included parity, preparation, uterine size and cavity length, myomectomy and duration of surgery. The score was tested on 56 women prospectively, but was ineffective at identifying women at high risk.

Infection.

Post-operative intra-uterine infection does occur, but seems to be uncommon. However, 31 cases were identified by MacDonald et al (1990), which suggests underreporting in the literature. Although some operators use antibiotic prophylaxis, there have been no controlled studies of their efficacy. However, there have been at least three deaths in the United Kingdom due to septicaemia (personal communications).

Haemorrhage.

Bleeding at the time of operation is rare and usually easily controlled by the insertion of an intra-uterine Foley catheter with balloon inflated. Operative blood loss has been measured and found to be only 20 to 30 mls (West and Robinson, 1989, Fraser et al, 1993). Secondary haemorrhage requiring hysterectomy occasionally occurs (Goldrath et al, 1981, Rankin and Steinberg, 1992).

Haematometra.

Postoperative sounding of the cavity (Goldrath et al, 1981, Baggish, 1988) or suction curettage (Goldfarb, 1990) have been recommended to try and prevent the development of postoperative haematometra, but neither seems to be effective. Persistent cyclical pain may be due to this complication (Magos et al, 1991). It may also develop after starting hormone replacement therapy (Dwyer et al, 1991).

Pregnancy.

The majority of women undergoing these procedures have completed their family. However, in those who have not been sterilised, the risk of pregnancy remains. Several pregnancies have already occurred after both ELA and TCRE (Hill and Maher, 1992, Whitelaw et al, 1992), and although most women have opted for termination, a few have continued with the pregnancy. The two main concerns are that the pregnancy will be compromised by the altered uterine vasculature, and that the placenta will be morbidly adherent (Whitelaw et al, 1992).

Long term complications.

There have been no other longterm complications reported so far, but one worry is the possibility that should endometrial cancer develop, it might present late due to obliteration of the uterine cavity. It is unlikely that the risk of uterine cancer will be abolished, as endometrium persists even in amenorrhoeic women.

Unsuspected pathology at the time of the procedure can be recognised by histology of the endometrial strips after TCRE, although not after ELA or rollerball. Emanuel et al (1992) found two cases of leiomyosarcoma in 140 transcervical myomectomies. Dwyer and Stirrat (1991) have reported an endometrial cancer, which was missed at hysteroscopy and biopsy. In one series (Rankin et al, 1992) four had endometrial cancer.

It may be some time before unsuspected longterm complications surface, as was the case with TURP. There is also no reliable information about mortality rates of these procedures, as deaths are known to have occurred, but have not been reported in the literature.

RADIOFREQUENCY ENDOMETRIAL ABLATION

A third method of ablating the endometrium has been developed recently and is under investigation (Phipps et al, 1990(a)). This differs from the other two methods in that it is not carried out under direct hysteroscopic vision. This may be a disadvantage, or an advantage - a fluid distending medium is not required and there are no fluid overload problems. A probe which heats the endometrium by radiofrequency electromagnetic

energy is inserted into the uterus for around 20 minutes. Direct contact is not required, but the original probe was modified, as endometrium at the cornua was spared. Penetration beyond 7mm is negligible. The serious complication of vesico-vaginal fistula has apparently been eliminated by development of a special guard for obese women.

Of the first 33 patients treated, at four to 10 months follow-up 30% were amenorrhoeic, 55% had decreased menstrual flow, two underwent hysterectomy for continued bleeding (and were found to have adenomyosis) and two developed vesico-vaginal fistulae (Phipps et al, 1990(b)). In a further report of four to six month follow-up of 42 women treated using this method (Phipps et al, 1990(a)), those treated with 660 kJ (N=22) had an amenorrhoea rate of 87%, but at two lower doses there was no amenorrhoea, 30 and 60% improved, and 70 and 40% did not improve. Unlike the previously described treatments, women with submucous fibroids were excluded. A further report of 63 women (Oates and Hamer, 1992) with at least 18 months follow up, revealed 16 (25%) had had a hysterectomy at two to 16 months.

This procedure has run into difficulties because of failure of monitoring equipment in the UK to comply with EEC standards, which can result in earthing and burns, for example at the point of contact of ECG leads.

THE PLACE OF HYSTEROSCOPIC SURGERY FOR DUB.

Hysteroscopic surgery undoubtedly has a place in gynaecology. It is now the preferred method of treatment of Asherman's syndrome and intra-uterine septae. However, the place of hysteroscopic operations for menorrhagia still needs to be defined. Are they a

true replacement for hysterectomy for all women with DUB, an alternative to hysterectomy for some women, a treatment only for patients who at present are not fit for hysterectomy, or an alternative to medical treatment in women with less severe symptoms than those warranting hysterectomy?

Many unsubstantiated claims have so far been made. "Laser photoevaporation of the endometrium appears to have no advantages over hysterectomy" (Noble, 1985). "Hysteroscopic techniques of endometrial destruction will probably replace most hysterectomies for menorrhagia" with "considerable savings in cost" (Magos, 1990). "Results are similar for all the endoscopic methods" (Magos, 1990). "The best results will be achieved when endometrial resection is restricted to women who have a regular menstrual cycle, with genuine menorrhagia, very little dysmenorrhoea, and no expectation of amenorrhoea" (Slade et al, 1991).

Hysteroscopic surgery is extremely attractive to many women, principally because of the rapid recovery time, and once readily available, many more women may come forward for treatment. The complication rates and long term efficacy of this form of therapy must be assessed before this occurs. It is also attractive to managers because of the decreased cost associated with shorter hospital stay, but the reoperation rate must be taken into consideration when costs are calculated. Despite its drawbacks, hysterectomy is a very effective treatment for DUB, with high rates of patient satisfaction, and treatment designed to replace it must be rigorously evaluated.

It is now realised that new surgical techniques should be assessed in the same way as new medical treatments. They should be proven to be effective, and free from serious side-effects or complications, and should be compared to standard treatment with

regard to efficacy and acceptability. This can only be achieved by carrying out prospective randomised controlled trials - the method of choice for evaluating alternative therapies, as it avoids selection bias and also provides a sound mathematical basis for subsequent analysis.

As Garry has said (1990) "there is increasing consumer, administrative and commercial pressure to become involved" in hysteroscopic surgery, but "the relative effectiveness, safety, and true costs of each of these procedures are not yet established....we must... be certain that what we introduce is indeed an improvement on current practice and we can only ensure this by carefully evaluating both the old and the new procedures with correctly structured, collaborative, prospective studies". Magos (1990) agreed that the value of endometrial resection needed to be compared to that of hysterectomy in a randomised prospective trial. Stirrat et al (1990) said "hysterectomy is the only proven method to deal effectively with excessive menstrual loss: any new method must therefore be compared against it".

The relative merits of the different types of conservative operation need to be established, as there may "be a different incidence of major complications associated with the procedures, and these potentially important differences need to be investigated in prospective trials before either procedure is widely adopted" (Davis, 1991).

These operations need to be assessed now, at their introduction into practice, rather than in the future, should problems occur, as has happened with transurethral prostatectomy (Roos et al, 1989, Malenka et al 1990, McDonald and Singer, 1989).

A retrospective case-note study (Rutherford et al, 1991) tried to define the possible role of TCRE in replacing hysterectomy. Of 375 hysterectomies, 186 were for excessive menstruation, of which 85 (45.7%) had no pathological abnormality. They deemed that overall 108 (29% of all hysterectomies) were "suitable" for resection - others were excluded because of pain, fibroids, endometriosis, urinary symptoms or a previous Manchester repair.

Two randomised trials of TCRE and hysterectomy have been reported during the time of the study reported in this thesis. In a small study of 51 women taken from a hysterectomy waiting list (Gannon et al, 1991) randomised between TCRE and hysterectomy, 16% required repeat resection but none hysterectomy at a mean follow up of 12 months. There was a decrease in operative time and hospital stay and an estimated cost of £407 for TCRE compared with £1270 for hysterectomy. There were 12 complications in the hysterectomy group, and one pregnancy in the TCRE group.

Four months follow-up of the Bristol randomised trial of TCRE and hysterectomy, carried out at the same time as the Aberdeen study, has recently been reported (Dwyer et al, 1993). Two hundred women were recruited, four of whom were withdrawn. There were three major complications in the hysterectomy group. The complications in the TCRE group were four perforations, three requiring laparoscopy and one developing peritonitis, and one fluid deficit over 1.5 litres. Operating time was significantly reduced in the TCRE group, and postoperative infection was significantly less, as was hospital stay. Eleven had had further surgery - seven repeat TCRE and four hysterectomy, 13 women were amenorrhoeic, 76 hypomenorrhoeic. After hysterectomy, 94% were satisfied compared with 85% after TCRE. The cost to the

health service was £1060 for hysterectomy and £500 for TCRE (Sculpher et al, 1993). Reports of longer term follow-up are awaited.

It was because of the concern about the possible serious complications and uncertain effectiveness of hysteroscopic surgery, and its rapid introduction in an uncontrolled fashion into clinical practice, that the Aberdeen randomised trial was set up, with the aims detailed on page 15.

The design of the trial and methods used will next be described.

CHAPTER 4. PATIENTS AND METHODS

STUDY DESIGN

The main study is a randomised prospective controlled trial comparing two methods of hysteroscopic surgery with hysterectomy for the treatment of women with dysfunctional uterine bleeding. The study was intended to be pragmatic, to assess the effect of introducing the new methods into routine clinical practice, rather than under tightly controlled experimental conditions.

It was calculated that around 160 hysterectomies had been carried out for dysfunctional uterine bleeding by the three consultants participating in the study during the previous two year period. Recruitment of 160 women to the trial would give 80% power of detecting at the 5% significance level a difference of the order of 20% between hysterectomy and hysteroscopic surgery. It would however give only 50% power of detecting a similar difference between laser and resection. The randomisation was therefore primarily between hysterectomy and conservative surgery, with the latter randomised between laser ablation and endometrial resection. A second phase study is currently underway, randomising only between the conservative treatments, as with a similar recruitment rate, this would increase the power of detecting a significant difference between the two.

THE LEARNING CURVE

It is recognised that any new technical procedure has a "learning curve" of success as experience is gained. If assessment is carried out at the introduction of a new technique, it will therefore be at a disadvantage compared to an established technique. If, however, assessment is delayed, the new technique may become established in

practice, and randomised studies may prove impossible. To achieve a balance between these two extremes, this trial commenced six months after the simultaneous introduction of laser ablation of the endometrium and endometrial resection into Aberdeen Royal Infirmary. Owing to illness of one of the participating consultants, fewer lasers than resections were carried out during this time. One operator learned each technique, and the surgeons were essentially self-taught, as these operations were at that time being performed by very few others in Scotland.

For comparison with later results, these initial operations were reviewed. The case records of all women undergoing ELA and TCRE at Aberdeen Royal Infirmary before the randomised trial commenced were retrieved. Operative complications were noted, as was any subsequent treatment for dysfunctional uterine bleeding. The menstrual status of the patient at the last hospital review was noted.

Women who had not had an intervening hysterectomy were invited to attend for out-patient hysteroscopy (vide infra). At this time, the menstrual status (amenorrhoea, hypomenorrhoea, normal menstruation or continuing menorrhagia) was documented, and the women were questioned as to dysmenorrhoea and satisfaction with the effect of treatment. Twelve months later, a five item self-completion postal questionnaire was sent to women who had not had a hysterectomy performed, asking about menstrual status, dysmenorrhoea, any subsequent treatment, and satisfaction with symptomatic outcome.

Although the introduction of another operator (myself) at the start of the trial meant that a "learning curve" was involved, both procedures were learned simultaneously, so this does not favour one hysteroscopic method over the other. It also mimics the normal

clinical situation where operations are carried out under supervision by surgeons in training.

PREOPERATIVE DETAILS

Patient recruitment

Women were recruited from all the general gynaecology clinics at Aberdeen Royal Infirmary and the surrounding referral area of Grampian Region, although the majority were recruited from clinics of the three consultants participating in the trial.

Eligibility:

Women were eligible to enter the study if they

1) were under 50 years of age,

2) were under 100 kg in weight,

3) had a clinical diagnosis of dysfunctional uterine bleeding and

4) would normally have been undergoing hysterectomy for their symptoms.

Exclusion criteria:

1) Women with a uterus greater than 10 weeks size or

2) abnormal endometrial histology. Patients with small fibroids were not excluded.

3) Women over 50 - as subsequent amenorrhoea might be due to the menopause rather than successful surgery.

4) Women over 100 kg - as they would not normally be considered for hysterectomy without significant weight loss.

5) Women with medical problems which might complicate anaesthesia, and especially in whom large fluid infusions would be hazardous.

All women were seen by myself, either at the clinic visit or by special appointment, and written informed consent to the trial was obtained. Sterilisation was discussed with those randomised to hysteroscopic surgery, where appropriate. Preoperative hysteroscopy or laparoscopy were not routinely performed, as this would have been a deviation from normal clinical practice at Aberdeen Royal Infirmary, and might have biased entry to the trial.

Randomisation

After giving written informed consent to enter the trial, women were randomised between hysterectomy and conservative surgery, and within the conservative group between endometrial laser ablation and transcervical endometrial resection. This was achieved by an overall randomisation between the three treatments in a ratio of 2:1:1. A series of numbered opaque envelopes contained the treatment options in a random order (unknown to me).

Preoperative symptom review

At the first interview a symptom questionnaire was completed. Details of the patient's age, marital status, duration of symptoms, menstrual history, dysmenorrhoea, premenstrual symptoms, dyspareunia, urinary and bowel symptoms, parity and obstetric history, previous medical therapy for menstrual problems, and previous

gynaecological surgery were obtained. No objective measurement of menstrual blood loss was carried out, as this is not normal clinical practice and would not have influenced our decision to treat, which is based on the severity of the patient's symptoms. Instead, each woman was asked to subjectively grade the heaviness of each day of her period on a five point scale.

OPERATIONS

Hysterectomy

Women randomised to hysterectomy were treated by the referring team according to their normal practice. Usually total abdominal hysterectomy was carried out, but occasionally the vaginal route was chosen.

Hysteroscopic surgery

Uterine preparation.

Women randomised to conservative surgery had a vaginal ultrasound scan performed by myself to exclude gross pelvic pathology, such as large fibroids or ovarian pathology, which would be a contraindication to this form of treatment, and to measure the uterine size. This was calculated according to the formula for an ellipsoid,

$$\text{volume} = 4/3 \text{ pi } r3 \text{ or}$$

$$= 0.523 * a * b * c$$

where a is the uterine length, b the anteroposterior diameter and c the transverse diameter. An endometrial biopsy was also carried out, if endometrial histology had not previously been assessed.

It was decided to use the gonadotrophin releasing hormone agonist analogue goserelin (Zoladex) to prepare the endometrium prior to surgery. The reason for this was that the alternative, danazol, had proved unpopular because of the high incidence of side-effects, and indeed some women stopped taking it prior to surgery. Zoladex was supplied by ICI for patients in the trial, and given as a single 3.6mg deep subcutaneous depot injection into the anterior abdominal wall.

Endometrial laser ablation

Patients undergoing laser ablation of the endometrium were treated either by the supervising consultant or myself. General anaesthesia was induced. Vaginal examination was carried out, the cervix grasped with a volsellum forcep, the uterine cavity sounded and the cervix dilated to number 7 or 8 Hegar. The uterine cavity was inspected using a Wolff operating hysteroscope specially modified for use with the laser. A video camera attached to the hysteroscope eyepiece enabled the procedure to be carried out watching a television monitor. The irrigating fluid, 0.9% sodium chloride, was infused under gravity from a three litre bag and pumped out via a separate channel using a simple rotary pump. The fluid used and recovered was carefully measured to calculate the amount of fluid absorbed. A 600 or 800um quartz fibre transmitted the laser beam from a 100 Watt Sharplan Neodymium Yttrium Aluminium Garnet (Nd YAG) laser. Throughout the procedure strict laser safety precautions were taken, including the wearing of protective eye-wear by everyone in the operating theatre.

Commencing at the tubal ostia, moving across the uterine fundus, treating first the anterior wall and then the rest of the cavity, the laser fibre was dragged in contact with

the endometrium while firing at a power setting of 80 Watts, in continuous mode. The total energy used in joules was recorded.

Transcervical resection of the endometrium

Patients randomised to transcervical endometrial resection were treated by either the supervising consultant or myself. Again general anaesthesia was employed. As for laser ablation, a vaginal examination was carried out, the cavity sounded and cervix dilated prior to hysteroscopy using a Wolff diathermy resectoscope, with 1.5% glycine as the irrigating medium, a video camera and television monitor. The cornua were first coagulated with the rollerball attachment, a strip of endometrium was resected from the fundus using a straight loop, and the remainder of the endometrium resected using a 90 degree loop attachment. The diameter of both loops is 7mm, giving a depth of resection around 3.5mm. For coagulation, 60 watts of current were used, blended with 160 to 175 watts of cutting diathermy for resection. After completion of the procedure, the fluid inflow was turned off, and bleeding points were identified and coagulated. The endometrial chips obtained were evacuated and sent for histological examination. If there was still significant bleeding, a Foley catheter with balloon inflated was left in the uterine cavity overnight and removed the next morning.

Uterine score.

To document the findings at operation, a clinical uterine score was developed. The aim was to assess the efficacy of Zoladex in preparing the uterus for surgery, and to correlate findings with postoperative outcome. The score is similar to the Bishop score for assessing the cervix prior to labour, in that criteria are graded from 0 to 2, and added to give an overall score. The criteria chosen were cavity length, endometrial

colour, endometrial thickness, the amount of bleeding on instrumentation, and the presence of fibroids or polyps (figure 1).

Figure 4.1. Endometrial scoring system.

ENDOMETRIAL SCORE				
Score	**0**	**1**	**2**	**3**
APPEARANCE	white	pink	red/velvet	polyps
THICKNESS	thin	moderate	thick	
BLEEDING on instrumentation	little	moderate	large	
CAVITY LENGTH	< =7cm	8cm	9cm	10cm+
REGULARITY	regular	irregular	fibroids	

TOTAL _____

Hormonal assessment.

To assess the effect of Zoladex and to identify any correlation with clinical uterine preparation for surgery or clinical outcome, serum oestradiol levels were measured at the time of operation in a subgroup of patients undergoing conservative surgery. This was carried out by the biochemistry department of Aberdeen Royal Infirmary, using a no-extraction solid-phase radioimmunoassay (Diagnostic Products Corporation, Abingdon, Oxford).

Cervical resistance.

Within a short time of introducing Zoladex for uterine preparation for hysteroscopic surgery, it was felt that the cervix was clinically much more difficult to dilate, probably due to the hypooestrogenic effect. To objectively measure cervical resistance, an instrument designed for assessment of patients with cervical incompetence leading to

second trimester pregnancy loss was used (Fisher et al, 1981). This consists of a series of graduated dilators attached to a cylindrical stainless steel casing containing a stainless steel piston, a compression spring and a linear displacement transducer, which converts axial force into a voltage output signal. The result is displayed as peak force used in Newtons and is recorded using each dilator, and summed to give a total force. Cervical resistance was measured in a subgroup of patients after Zoladex and in patients undergoing hysterectomy as controls.

Operative details

A questionnaire was placed in the case records at the time of admission for surgery. This was partly completed at the time of surgery, and partly on the patient's discharge from hospital. Details of hospital stay, duration of the operation, blood loss, operative complications, fluid absorption, operative findings, postoperative complications, pain relief required and histological findings were recorded.

FOLLOW UP

One month visit

All patients were reviewed at one month, when a questionnaire about postoperative symptoms and recovery was completed. This time was selected to compare the speed of recovery of the two types of procedure and pick up any early postoperative problems. The information gained in the early days of the study was used to inform other women what to expect after hysteroscopic surgery. Details of vaginal discharge and bleeding, wound problems, urinary or gastrointestinal symptoms, time of return to work and resuming sexual intercourse, and acceptability of the operation were obtained. A 10cm linear analogue pain score was used to compare perception of operative pain. It could be argued that this should have been used during admission, but it would have been

difficult to choose which day to use it, as most of the women undergoing hysteroscopic surgery went home on the first postoperative day, and the pain could have been maximal after discharge. Although with time the woman's recollection of pain might have altered, this should apply equally to both groups, and therefore a valid comparison can be made.

Six month visit

At six months, all women were sent a symptom questionnaire to complete. This asked for details of time to complete recovery and return to work, menstrual status, abdominal pain and dysmenorrhoea, premenstrual symptoms, urinary and gastrointestinal symptoms and flushing attacks, how well they felt their problems had been relieved and which operation they would recommend to a friend. Hysterectomy patients returned the questionnaires in a reply paid envelope, and those who had undergone conservative surgery were asked to attend for out-patient hysteroscopy, bringing the questionnaires with them.

Out-patient hysteroscopy.

At six months out-patient hysteroscopy was carried out

a) to assess and compare healing of the uterine cavity after laser ablation and endometrial resection

b) to see if the findings correlated with symptomatic outcome

c) to see if the findings correlated with the findings at the time of operation.

d) to assess the possibility of repeating hysteroscopic surgery, should it prove necessary.

The patient was placed in the lithotomy position, the cervix visualised with a speculum, and grasped with a tenaculum, and 1% prilocaine with octapressin injected directly into the cervix to provide local anaesthesia. Hysteroscopy was carried out using the Hamou microcolpohysteroscope (Karl Storz, Tuttlingen, Germany), which is 4mm in diameter with a 30 degree foroblique lens, in a 5 mm sheath. A 150 watt cold light source was used. The hysteroscope was inserted into the external os, and carbon dioxide gas insufflation begun, creating a microcavity in front of the instrument. The scope was then focused and advanced under direct vision, according to the method of Taylor and Hamou (1983). Carbon dioxide was delivered from a Wolff CO2 Metromat 2129 at a rate of 70 mls per minute. If the procedure was difficult or uncomfortable, it was abandoned.

Twelve month follow up

At one year postoperatively, all patients were sent a symptom questionnaire to complete. This again asked about recovery, menstrual history, abdominal pain and dysmenorrhoea, premenstrual symptoms, urinary and gastrointestinal symptoms and flushing attacks. They were asked whether their symptoms had been fully relieved, how satisfied they were with the outcome, and which operation they would recommend to a friend requiring treatment.

PSYCHOLOGY STUDY

A variety of psychological measures were used to assess the women preoperatively and at intervals postoperatively. The aims were to identify the characteristics of patients undergoing surgery for DUB, to assess the change at various stages after treatment, and to compare the two treatment groups at each stage.

Anxiety and depression.

The Hospital Anxiety and Depression Scale (HAD, Zigmond and Snaith, 1983) was administered at each visit. This is a self assessment scale designed for detecting states of depression and anxiety in a hospital out-patient clinic. It was chosen over the General Health Questionnaire (Goldberg, 1972), which was tried in the first few patients, as it is considerably shorter, and also gives an indication of the nature and severity of the psychiatric disorder. It does not contain items which might be affected by physical illness. It has a 1% false positive and 1% false negative rate for depression and a 5% false positive and 1% false negative rate for anxiety. Either the upper (10/11) or lower (8/9) end of the borderline range in each subscale may be taken as the cut-off point for a 'case'. It has been shown to be a valid instrument for use in hospital out-patient clinics (Aylard et al, 1987, Barczak et al, 1988, Thapar and Thapar, 1992).

Eysenck Personality Questionnaire.

This is a 90 item questionnaire for measuring personality traits. It contains four scales for measuring introversion-extraversion (E), neuroticism (N), psychoticism (P) and a lie scale (L), which measures the tendency to give the "right" answer. The "normal" values for women age 20-29, 30-39, and 40-49 are 2.79 (2.41), 2.28 (2.20), 2.35 (2.11) for P; 12.89 (4.70), 11.97 (4.95), 12.24(4.92), for E; 12.87 (4.99), 12.57 (5.28), 12.63 (5.38) for N; and 7.17 (3.85), 8.84 (4.05),8.86 (3.87) for L. The questionnaire was administered at the first visit only. It is designed to give information about permanent characteristics and therefore need not be repeated.

Menstrual Distress Questionnaire.

The Moos Menstrual Distress Questionnaire (Moos, 1968) was developed to evaluate cyclical menstrual and premenstrual symptoms. It is, however, long (47 items), and complicated (each item is rated on a 6 point scale for 3 different phases of the menstrual cycle). As many of our patients had irregular cycles or continuous bleeding preoperatively and at least half would be amenorrhoeic after treatment, and would therefore be unable to complete the Moos, we developed a modified questionnaire, based on the Moos, to assess premenstrual-type symptoms. 28 items were selected, ensuring that several were taken from each of the eight categories - pain, concentration, behavioural change, autonomic reactions, water retention, negative affect, arousal and control. (The control symptoms had been taken from the Blatt Menopausal Index to measure how likely the woman was to complain of a variety of different symptoms). Each item was rated from 0 to 5 for the previous 30 days. A score was obtained for each category of symptoms and a total score for the whole questionnaire. This questionnaire was administered at the preoperative, six and twelve month visits.

Marital State Questionnaire.

The Golumbuk Rust Inventory of Marital State (Rust et al, 1986) is a 28 item questionnaire for assessing the quality of a relationship, designed for use in a marriage guidance setting. It consists of a series of statements, half positive and half negative, which patients have to agree or disagree with, and allows strength of feeling to be assessed. In combination with the other questionnaires, we felt this was too long, and therefore shortened it to 14 items, keeping half positive and half negative. This modified questionnaire was used, in patients with a steady partner, at the preoperative assessment, and at six and twelve months.

Psychosocial Adjustment to Illness.

The Psychosocial Adjustment to Illness Scale (PAIS) was developed by Derogatis (1986) to assess the psychological and social adjustment of medical patients to their illness, which may be as important as the physical aspects. It was modified from a semi-structured interview to a self-report scale (PAIS-SR). Seven principal areas are covered - health care orientation, vocational environment, domestic environment, sexual relationships, extended family relationships, social environment and psychological distress. It is comprised of 46 items and refers to the previous 30 days. A higher score means poorer adjustment.

The unaltered questionnaire was administered at the preoperative interview. However, as no allowance is made for improvement in status in the previous 30 days, the responses had to be altered for administration postoperatively, to include positive as well as negative change. Sections 2, 3 and 7 were used at one month, sections 4, 6 and 7 at six months and all 7 sections at 12 months.

Semi-structured interview.

At one and 12 months, a semi-structured interview was carried out by a psychology research assistant. The data obtained are not included in this thesis. A full cost-benefit analysis has also been carried out, but again the results are not included in the thesis.

STATISTICAL ANALYSIS

The sample size calculation (p 80) was based on reported levels of satisfaction of 86% following hysterectomy (Gath et al, 1982). The number of subjects needed to give 80% power of detecting a 20% difference between the two groups with 95% confidence was 160. Recruitment continued after this number was achieved for as long as possible to give the study greater power.

Analysis was by **"intention to treat"**, unless otherwise stated; that is, patients remained in the group to which they were allocated even if they were treated by another method. All information was computerised using a database created with EPI INFO. Analysis was carried out using the Statistical Package for the Social Sciences (SPSS-PC) with calculation of confidence intervals where appropriate.

The Student's T-test was used for continuous variables with a normal distribution, or after transformation to a normal distribution. The standard chi-squared test was used for unpaired categorical data and McNemar's chi-squared test for paired categorical data arising from comparisons of postoperative symptoms with the preoperative symptoms in the same woman. The Mann-Whitney U test was used for ordinal variables or continuous variables with a non-normal distribution.

Results were taken as statistically significant if $p < 0.05$, or if the confidence limits did not overlap.

RESULTS

CHAPTER 5. NON-TRIAL OPERATIONS FOR DUB

THE LEARNING CURVE

Treatments and complications.

Before the randomised trial began, 51 women had been treated by hysteroscopic surgery; 35 (69%) by TCRE, 16 (31%) by ELA. There were no complications in 43 women (84%). The operative complications which did occur were bleeding, controlled by Foley catheter, in two women treated by TCRE, fluid overload (defined as over 1000 mls deficit) in four women treated by ELA, one pelvic infection requiring antibiotic therapy, and urinary retention in a women with a past history of this complaint. No uterine perforation occurred and no emergency laparoscopy or laparotomy was required.

Results of surgery.

Of these 51 women, 36 (71%) attended the out-patient hysteroscopy clinic at a mean eight months (range four to 17 months) following treatment. The postal symptom questionnaire was sent to 33 women, of whom 28 replied (85% response rate). The "last follow-up" was taken as the last time the patient attended the hospital or responded to a questionnaire, or the date of hysterectomy. The mean time to last follow-up was 15 months (range nought to 24 months) overall, 12 months for ELA and 16 months for TCRE. At the last follow-up contact, whether hysterectomy, out-patient clinic, hysteroscopy or questionnaire, the menstrual status was as shown in Table 5.1, and the effect on dysmenorrhoea is shown in Table 5.2.

Table 5.1. Menstrual status at last follow up in women treated by hysteroscopic surgery during the learning curve.

Menstrual state	TCRE	ELA	Total	%	Cum %
	(n=35)	(n=16)	(n=51)		
Amenorrhoea	1	5	6	(12)	
Brown discharge	4	0	4	(8)	(20)
Periods much lighter	18	7	25	(49)	(69)
Periods a bit lighter	10	3	13	(25)	(94)
Periods the same	1	1	2	(4)	(98)
Unknown	1	0	1	(2)	(100)

Table 5.2. Effect of pretrial treatments on dysmenorrhoea.

Dysmenorrhoea	Total	%	Cum %
	(n=51)		
None	17	(33)	
Less than before	15	(29)	(63)
Unchanged	10	(20)	(82)
Worse than before	2	(4)	(86)
Not recorded	7	(14)	(100)

At this time, 14 women (27%), eight (23%) treated by TCRE and six (37%) treated by ELA, had had a hysterectomy performed for persistent symptoms at a mean 10 months after the initial operation (three before six months, seven between six and 12 months, and four between 12 and 23 months). At the time of hysterectomy, one woman was hypomenorrhoeic, four reported "normal" periods, and nine reported continuing menorrhagia. The pathological findings at the time of operation were - no abnormality in seven, small fibroids in six and endometriosis in one. Five women had had a repeat hysteroscopic operation (one ELA, four TCRE) at a mean 18 months (range 16 - 19 months) after the first operation.

If the first 10 women treated by each surgeon are compared with the later treatments, the hysterectomy rate decreased from eight of 21 (38%) to six of 30 (20%) (P = 0.15). The success rate, if amenorrhoea and hypomenorrhoea are taken as "success", increased from 12 of 21 (57%) to 23 of 30 (77%) (P = 0.14).

These findings are encouraging in that they demonstrate that hysteroscopic endometrial ablation can be a safe operation, even during the learning phase, and that, even if initially disappointing, results should improve as experience is gained.

OPERATIVE TREATMENTS FOR DUB OUTWITH THE RANDOMISED TRIAL

Hysterectomy.

During the period when the trial operations were carried out (1.10.1990 to 1.5.1992), 368 hysterectomies were performed for non-malignant conditions in women under 50 years of age admitted to the gynaecology ward at Aberdeen Royal Infirmary used by the three consultants involved in the trial and two others. The case records of these women were examined to determine how many would have been eligible to enter the trial but either were not considered or refused to enter (Table 5.3). In 60% the primary indication for surgery was DUB and the women were eligible for the trial. Of those who refused to enter the trial, 36 did so after discussion with myself, and the two main reasons given were that they wanted everything "all over and done with" or did not want to attend for follow up. Although not all eligible women were recruited to the trial, the majority were offered the opportunity, and this study should therefore give some indication of the potential for hysteroscopic surgery to replace hysterectomy in the operative treatment of DUB.

Table 5.3. Indications for non-cancer hysterectomy in women under 50, 1990-92.

Reason for hysterectomy	Number	%
DUB (not offered trial)	93	(25)
DUB (refused trial)	60	(16)
DUB (treated within trial)*	69*	(19)
DUB (previous ELA/TCRE)	9	(2)
Not eligible (pathology)	77	(21)
Not eligible (other reasons)	60	(16)

* the remainder of the trial hysterectomies were carried out by other consultants at Aberdeen Royal Infirmary.

Hysteroscopic surgery.

During the period of the trial treatments, 49 endometrial resections and 21 laser ablations were performed on the NHS outwith the trial. Forty-seven women (18 treated by ELA and 29 by TCRE) would have been eligible to enter the trial, but presumably refused, since all treatments were performed on the lists of the participating consultants. The remainder were in women over 50 years of age, over 100 kg, or with a fibroid uterus over 10 weeks size. Those women who refused to enter the trial after discussion with myself usually did so because they wanted to avoid hysterectomy principally because of the need to take time off work.

CHAPTER 6. RANDOMISED TRIAL - PATIENTS AND OPERATIONS

RECRUITMENT AND WITHDRAWALS.

Two hundred and five women gave written informed consent to the trial, and were randomised to be treated by hysterectomy (n=99), by TCRE (n=52),or by ELA (n=53). There were three withdrawals before treatment. The first woman to enter the trial should not have been entered, as she did not have dysfunctional uterine bleeding, but dysmenorrhoea alone. She was randomised to hysterectomy, refused it, was treated by TCRE, continued to have dysmenorrhoea, and requested hysterectomy. She has not been included in the analysis. Two women in the hysterectomy group did not receive any operative treatment; one moved away from the area, and one changed her mind about the need for an operation.

Two women in the hysterectomy group and two women in the conservative group (one TCRE and one ELA) refused the assigned treatment, and were treated by the alternative method (both the conservative treatments were ELA). One woman was withdrawn after hysterectomy, as histology showed early endometrial carcinoma, and follow up within the trial would not have been appropriate. (This patient is discussed further in Chapter.)

PATIENT CHARACTERISTICS.

Preoperative details of women recruited to the randomised trial are shown in Tables 6.1 and 6.2. In the social factors, an important point is that three-quarters were in paid employment, and of these 42 women (27%) regularly, and a further 35 (22%) occasionally, took time off work because of symptoms. The majority had a long-standing history of menstrual symptoms (Table 6.1), and had already received medical therapy, which had been unsatisfactory. Heavy menstrual loss was not the only

symptom, with irregular menstruation, dysmenorrhoea and premenstrual symptoms featuring prominently. Other symptoms, such as urinary and bowel symptoms, were common, as were flushing attacks. The latter were unrelated to age, being just as common in women under 35 years of age as in those over 45. In 83% of cases either the woman or her partner had been sterilised, so future fertility was not an important issue. Only four women were nulliparous.

Table 6.1. Randomised trial preoperative menstrual symptoms.

	No (n=204)	%	Cum %
Duration of symptoms			
6 months to 1 year	4	2	2
1 to 2 years	23	11	13
2 to 5 years	75	37	50
more than 5 years	102	50	100
Length of cycle			
4 to 6 weeks	67	33	33
3 to 4 weeks	89	44	76
less than 3 weeks	37	18	95
continuous bleeding	11	5	100
Length of period			
less than 5 days	8	4	4
5 to 7 days	77	38	42
7 to 10 days	66	32	74
10 to 14 days	32	16	90
14 to 21 days	7	3	93
continuous bleeding	14	7	100
Irregular cycle	104	51	
Menstrual clots	194	95	
Number of heavy days (mean)	4.9		
Bleeding score (mean)	27.1	(SD 9.0)	

Table 6.2. Preoperative characteristics of women recruited to the randomised trial (n=204).

Mean age (years)	40.2	(SD 5.1)	
Social status			
Married/steady relationship	186	(91%)	
Paid employment.	158	(77%)	
No of children (mean)	2.4		
Dysmenorrhoea	171	(84%)	
Mean duration of pain (days)	4.9		
Regular analgesia	142	(70%)	
Pain score (mean)	10.1	(SD 10.3).	
Medical treatment	200	(98%)	
Progestagens	187	(92%)	
Non-steroidal anti-inflammatories	113	(55%)	
Danazol	75	(37%)	
Antifibrinolytics	7	(3%)	
Oral contraceptive pill	44	(22%)	
Other drugs	14	(7%)	
Other symptoms			
Flushing attacks	96	(47%)	
Abdominal bloating	189	(93%)	mean 9.8 days
Breast discomfort	140	(69%)	mean 7.1 days
Headaches	110	(54%)	
Irritability	161	(79%)	mean 8.3 days
Depression	112	(55%)	mean 8.4 days
Dyspareunia	70	(38%)	
Bowel symptoms	55	(27%)	
Urinary symptoms	104	(51%)	
stress incontinence	81	(40%)	
urge incontinence	21	(10%)	
frequency	52	(25%)	
nocturia	31	(15%)	
urgency	42	(21%)	
hesitancy	6	(3%)	
Contraception			
sterilised	124	(61%)	
vasectomy	46	(22%)	
Previous gynaecological surgery	179	(88%)	
D&C	115	(56%)	
Caesarean section	18	(9%)	
diagnostic laparoscopy	22	(11%)	
treatment for CIN	10	(5%)	
other operations	24	(12%)	

RANDOMISATION.

The two arms of the study have been compared for all variables to ensure that randomisation has led to equivalent groups for further analysis. In addition, the two conservative treatment arms have been compared. The results are shown in Table 6.3. There were no significant differences between the two arms of the study, or between those treated by ELA and those treated by TCRE.

Table 6.3. A comparison of preoperative patient details in the three treatment groups.

	Hysterectomy (n=99)	**ELA** (n=53)	**TCRE** (n=52)
Age (years)	40.3 (5%)	39.6 (6%)	40.5 (4%)
Social status			
married/steady partner	92 (93%)	49(92%)	45(87%)
employed	79 (80%)	42(79%)	37(71%)
no of children (mean)	2.3	2.5	2.5
sterilised/vasectomy	80 (81%)	47 (89%)	43 (83%)
Menstrual symptoms			
irregular periods	52 (53%)	28 (53%)	24 (46%)
regular dysmenorrhoea	68 (69%)	40 (75%)	39 (75%)
duration more than 2 years	83 (84%)	48 (91%)	46 (88%)
cycle less than 4 weeks	70 (71%)	35 (66%)	32 (61%)
period more than 7 days	57 (58%)	26 (49%)	36 (69%)
Score - bleeding - mean(SD)	27.5 (9)	26.2 (8)	27.5 (9)
pain - mean(SD)	10.2 (11)	9.5 (8)	10.4 (11)
Premenstrual symptoms			
bloating	92 (93%)	47 (89%)	50 (96%)
breast discomfort	73 (74%)	33 (62%)	34 (65%)
irritability	75 (76%)	45 (85%)	41 (79%)
headaches	53 (53%)	27 (51%)	30 (58%)
depression	56(57%)	31 (58%)	25 (48%)
Other symptoms			
urological	53 (53%)	25 (47%)	26 (50%)
bowel	22 (22%)	13 (24%)	20 (38%)
flushes	46 (46%)	25 (47%)	25 (48%)
dyspareunia	52 (53%)	34 (64%)	21 (40%)

TREATMENTS PERFORMED.

Of the 204 eligible women entered into the trial, 202 women received treatment. As previously mentioned, four women, two in each group, refused the assigned treatment. On two occasions the laser was out of order - one woman was forewarned and TCRE was carried out instead. After induction of anaesthesia in the other case, the water coolant system failed, and rather than undergo a repeated attempt, the patient opted for hysterectomy. The actual treatments carried out were therefore 99 hysterectomies, 51 ELA and 52 TCRE. Unless otherwise stated, data is analysed by the treatment group to which the patient was randomised - **"intention to treat"**.

In nine women, conservative surgery (six ELA, three TCRE) had to be abandoned before completion of the operation - one of these was a patient randomised to hysterectomy who refused the allocated treatment. In one woman the cervix was incompetent and hence uterine distension was not possible; she underwent later hysterectomy. In another, a probable false passage was created during initial hysteroscopy; TCRE was successfully carried out at a later date. In two cases a two-stage procedure was carried out, because of the presence of a large submucous fibroid. In four cases, one TCRE and three ELA, vision was obscured by bleeding or the rate of fluid absorption was such that the operation could not safely be completed. Three of these women had fibroids. Of these, two women chose to undergo hysterectomy, and one had a repeat hysteroscopic procedure. Seven women (3.5%) were sterilised at the time of hysteroscopic surgery, one by mini-laparotomy as a pneumoperitoneum could not be achieved. There were no other immediate unplanned procedures (laparoscopy or laparotomy) in the conservative treatment arm of the trial.

Abdominal hysterectomy was performed in 87 women, six of whom had bilateral salpingo-oophorectomy and one a subtotal hysterectomy, because of adhesions. Vaginal hysterectomy was performed in 12 women (12.2%).

FOLLOW-UP.

At the time of writing, 12 months follow up is complete. There were six non attenders for the one month follow up visit (97% response rate), four after hysterectomy, one after ELA and one who moved away from the area after TCRE; 21 women failed to respond to the six month questionnaire (90% response rate), 11 post-hysterectomy and 10 post-hysteroscopic surgery, and 16 were lost to follow up at 12 months, eight in each group (92% response rate). The case records of all women participating in the trial were however reviewed to identify those who had had further surgery for gynaecological problems in Aberdeen Royal Infirmary.

CHAPTER 7. RANDOMISED TRIAL - COMPARISON OF OPERATIVE DETAILS AND COMPLICATIONS

OPERATIVE DETAILS.

The mean duration of operation, from beginning to end of anaesthesia, hospital stay and postoperative pain relief requirements are shown in Table 7.1. As expected there are significant differences between the two groups, with those treated by hysteroscopic surgery requiring less theatre time, less postoperative analgesia, and having a much reduced hospital stay.

Table 7.1. Operation details by group (mean and 95% CI or number and %).
H = Hysterectomy C = Conservative

	H(n=97)	C(n=105)	
Theatre time(mins)	61.4 (56.7-66.1)	44.8 (42.1-47.4)	p<.0001
Days in hospital	8.4 (7.9-8.9)	3.6 (3.0-4.2)	p<.0001
Analgesia required			
injection	86 (89%)	28 (27%)	p<.0001
number of injections	4.3	1.7	
oral	93 (96%)	68 (65%)	p<.0001
number of doses	9	2	
Pain score(cm)	5.2 (4.5-5.7)	2.6 (2.0-3.2)	p<.0001

Although the study was not primarily designed to compare TCRE and ELA, there were statistically significant differences in some of the operative details. These are shown in Table 7.2. The only difference which might be of clinical significance is the amount of fluid absorbed, which was greater during ELA.

Table 7.2. Operative details by intended hysteroscopic treatment.

	ELA (n=55)	TCRE (n=51)	
Operation not completed	6 (11%)	3 (6%)	NS
Theatre time Mean and 95% CI	50.3 (46.0-54.5)	39.9 (36.8-42.9)	p<.0001
Operating time Mean and 95% CI	33.7 (30.4-37.0)	28.9 (25.7-32.1)	p=.043
Fluid used Mean and 95% CI	4014 (3610-4418)	2395 (2168-2622)	p<.0001
Fluid absorbed	766	414	p=.02
Fluid deficit more than 1 litre	11 (20%)	2 (4%)	p=.011
more than 2 litres	6	1	

Pathology.

Pathological findings at the time of laparotomy or hysteroscopy are shown in Table 7.3. Two-thirds of women had no obvious pathological abnormality at laparotomy, although fibroids diagnosed histologically were common. The one case where serious unsuspected pathology was identified was a 38 year old woman with a long-standing history of regular heavy periods. When she was allocated hysterectomy, endometrial biopsy was not felt to be necessary. Histology of the uterus, however, showed a very early invasive adenocarcinoma of the endometrium. This emphasises the importance of excluding endometrial pathology in women undergoing hysteroscopic surgery. No significant ovarian pathology was identified in any of the removed ovaries. In women having a hysterectomy for "treatment failure", fibroids were found in 3, adenomyosis in 4, and no abnormality in 4. However, minor changes may have been missed, as not all of the specimen is examined histologically.

Table 7.3. Pathological findings at laparotomy or hysteroscopy, and on histology of uterine and endometrial specimens.

	Hysterectomy (n=97)		**Conservative** (n=104)	
Clinical				
None	62	(64%)	74	(71%)
Fibroids	11	(11%)	21	(20%)
Endometriosis	8	(8%)	1	(1%)
Adhesions	8	(8%)	1	(1%)
Ovarian cyst	7	(7%)	0	
Polyps	0		6	(6%)
Other	1	(1%)	1	(1%)
	Hysterectomy (n=93)		**Conservative** (n=55) *	
Histological				
None	31	(33%)	38	(69%)
Fibroids	36	(39%)	7	(13%)
Endometriosis	4	(4%)	0	
Adenomyosis	16	(17%)	8	(14%)
Ovarian cyst	2	(2%)	0	
Endometrial cancer	1	(1%)	0	
Other	3	(3%)	2	(4%)

* TCRE only

NB. Pathological findings at hysterectomy for treatment failure: none - 4, fibroids - 3, adenomyosis - 4.

Efficacy of Zoladex in uterine preparation for hysteroscopic surgery.

The goserelin (Zoladex) injection was initially given arbitrarily six weeks preoperatively, but as the effect appeared to be wearing off at this stage, the interval was changed to four weeks. Many women were still having a withdrawal bleed at this time, so a compromise interval of five weeks was reached, and this was found to be satisfactory in the majority of cases, 93% of women having a withdrawal bleed in the interval before operation. No attempt was made to time the injection to a specific stage of the menstrual cycle. Side-effects noted were flushing attacks in 87%, headaches in 11%, 3% experienced pain at the injection site, and 3% a transient rash. There were no other reported ill effects. However, 28 women (27%) said the flushes were the worst

thing about the whole operation, and two required hormone replacement in the immediate postoperative weeks.

Serum oestradiol was measured at the time of operation in a subgroup of 35 women, and in all cases was in the postmenopausal range for this hospital (< 0.10 umol/l). Four to five weeks preparation therefore seems to be adequate in inducing hypo-oestrogenism.

A preoperative vaginal ultrasound scan was performed by myself before the LHRH injection in 61 women. The mean uterine volume in 51 women was 85.0 mm3 (95% CI 71.9-98.0), with no significant difference between those treated by ELA and TCRE. In no case was any significant pathology identified. At the time of operative hysteroscopy, the uterine score was documented in 92 women and the results are shown in Table 7.4. The mean score was 2.1, and 73 women (79.3%) had a score less than 5 (good preparation).

Table 7.4. Uterine score at hysteroscopy after LHRH analogue.

Score	0	1	2	3
Regularity	67 (73%)	4 (4%)	21 (23%)	
Endometrial thickness	58 (63%)	24 (26%)	10 (11%)	
Bleeding	70 (76%)	16 (17%)	6 (6%)	
Cavity length	46 (50%)	39 (42%)	6 (6%)	1 (1%)
Endometrial colour	34 (37%)	45 (49%)	11 (12%)	2 (2%)

It was felt clinically that the cervix was more difficult to dilate after Zoladex, although this did not prevent completion of the operation in any case. Cervical resistance to dilatation was therefore measured in 60 women after Zoladex, and in 20 women in the hysterectomy arm as controls. The total resistance (the sum of the maximum force used with dilators 4, 5, 6 and 7) was significantly higher in women treated with Zoladex compared to controls (Table 7.5).

Table 7.5. Cervical resistance to dilatation after Zoladex (mean force in Newtons and 95% CI).

Dilator	LHRH(n=60)	Control(n=20)	
4	4.15	2.50	NS
5	7.73	4.30	p=.004
6	13.70	8.65	p=.010
7	21.78	16.60	p=.054
Total	47.37 (40.88-88.25)	32.05 (25.52-38.58)	p=.002

OPERATIVE COMPLICATIONS.

EARLY COMPLICATIONS.

Intraoperative and early postoperative complications are compared in Table 7.6. Serious complications were rare in all groups, but minor morbidity, especially infection, was common in the hysterectomy group compared with the hysteroscopic surgery group. This would appear to be another major advantage of hysteroscopic surgery over hysterectomy.

Table 7.6. Early complications of surgery.			
	Hysterectomy (n=97)	**Conservative (n=105)**	
Anaesthetic	2	0	
Haemorrhage	5 (5%)	6 (6%)	NS
blood transfusion	5 (5%)	1 (1%)	
vault haematoma	11 (11%)		
wound haematoma	14 (14%)		
Foley catheter		3 (3%)	
Infection (all)	46 (47%)	16 (15%)	p<.0001
chest infection	7 (7%)	2 (2%)	NS
pelvic infection	9 (9%)	9 (9%)	NS
urine infection	22 (23%)	6 (6%)	p=.0005
wound infection	13 (13%)		
Fluid overload (>1l)	1	12 (11%)	
Perforation		1	
GI obstruction/ileus	2	1	
Laparotomy	3 (3%)	1 (1%)	NS
Readmission	4 (4%)	3 (3%)	NS

Major complications.

In the hysterectomy group there were five major complications. Two women had major anaesthetic problems - one had a respiratory arrest, and one developed stridor and was admitted to the Intensive Care Unit, and three required laparotomy - one for early intra-abdominal bleeding, two for drainage of a pelvic abscess.

One serious complication occurred in the laser arm of the trial. This woman complained of abdominal pain following the procedure, but it settled and she was allowed home. She was readmitted, and diagnosed as having small bowel obstruction,

for which she underwent laparotomy on the 10th postoperative day. A loop of small bowel was found adherent to the uterine fundus, with generalised pelvic infection, the loop had to be resected and an anastomosis performed. This is the only woman in the conservative arm to have required laparotomy or blood transfusion.

Minor complications.

1. Haemorrhage.

Troublesome bleeding at the time of operation was noted in 11 women (Table 7.6). In the hysterectomy group the mean recorded blood loss was 264mls (range 35-2000mls) (in 26 cases this was unrecorded), and five women required blood transfusion. The mean drop in haemoglobin was 1.9g (range +1.0 to -6.7g). Postoperative haemoglobin was not routinely measured in the conservative group. Three women in this group had a Foley catheter inserted, which controlled the bleeding immediately in all cases.

2. Fluid absorption.

Thirteen women absorbed over 1000 mls of the distending medium, but only seven absorbed over 2000mls (Tables 7.2 and 7.6). None had symptomatic fluid overload, perhaps because prophylactic intravenous diuretic was given to eight women at the end of the operation, and several operations (mentioned earlier) were not completed partly because of rapid fluid absorption.

3. Uterine perforation.

One uncomplicated uterine perforation occurred, during cervical dilatation prior to TCRE. This was clearly seen at hysteroscopy and did not prevent successful completion of the operation, laparoscopy not being required.

4. Infection.

Infective complications are shown in Table 7.6. The difference between the two groups was highly significant (32%, 95% CI 20-44%). In addition, 11 women in the hysterectomy group had postoperative pyrexia, defined as a temperature greater than 38 degrees on two occasions, and 71 (55 hysterectomy, 16 conservative) had antibiotic treatment. In 26 cases (15 hysterectomy, 11 conservative) this was prescribed by the general practitioner after discharge from hospital.

5. Readmission to hospital.

The mean stay in hospital is shown in Table 7.1. Seven women were readmitted. The reasons were pelvic abscess in two, and infected vault haematoma in two, following hysterectomy, one small bowel obstruction after ELA, one pelvic infection following ELA, and one woman was admitted several times following TCRE for various spurious reasons, eventually requesting hysterectomy.

INTERMEDIATE COMPLICATIONS.

1. Haematometra.

Two women developed symptomatic haematometra requiring dilatation and curettage, both subsequently required further surgery for menstrual symptoms.

2. Pregnancy.

One woman was found to be 12 weeks pregnant when she attended for her six month follow up visit after TCRE (reported in Whitelaw et al, 1992). Her first two periods

had been heavy, and she reported continuous bleeding for the previous 10 weeks. She had known of the risk of pregnancy, but her then partner claimed to have had a vasectomy. She opted for termination of pregnancy, which was uneventful, after which she continued to have menorrhagia, and had a hysterectomy performed at 12 months.

3. Incisional hernia.

Two women in the hysterectomy group developed incisional herniae requiring repair.

4. Laparoscopy.

Four women in the conservative group have had a laparoscopy because of abdominal pain. In no case was a pathological cause found. Two had laser uterine nerve ablation, and became pain-free.

5. Laparotomy.

One woman in the hysterectomy group has since had a laparotomy for an ovarian cyst.

CHAPTER 8. RANDOMISED TRIAL - COMPARISON OF POSTOPERATIVE RECOVERY

The duration of postoperative vaginal bleeding, discharge and pain are compared in Table 8.1. After hysteroscopic surgery, the majority of women (56%) had a bleed like a period at four to six weeks, and this was not related to subsequent outcome.

Table 8.1. A comparison of postoperative symptoms at one month.

	Hysterectomy (n=92)	Conservative (n=103)	p
Discharge			
less than 2 weeks	56 (61%)	44 (43%)	
more than 2 weeks	36 (39%)	59 (57%)	
median	'1 week'	'2-3 weeks'	<0.001
Bleeding			
less than 2 weeks	74 (80%)	80 (78%)	
more than 2 weeks	18 (20%)	23 (22%)	
median	'none'	'< 1 week'	<0.001
Pain			
less than 2 weeks	60 (65%)	89 (86%)	
more than 2 weeks	32 (35)	14 (14)	
median	'1-2 weeks'	'< 1 week'	<0.001
Wind			
none	17 (19%)	86 (84%)	
mild	14 (16%)	6 (6%)	
moderate	22 (25%)	6 (6%)	
severe	36 (40%)	4 (4%)	<0.001
Recovery			
less than 1 week	0	22 (21%)	
1 to 2 weeks	7 (8%)	34 (33%)	
2 to 3 weeks	0	18 (17%)	
3 to 4 weeks	7 (8%)	9 (9%)	
more than 4 weeks	78 (85%)	21 (20%)	<0.001
Return to work			
less than 1 week	0	4 (4%)	
1 to 2 weeks	1 (1%)	30 (29%)	
2 to 3 weeks	0	11 (11%)	
3 to 4 weeks	2 (2%)	11 (11%)	
more than 4 weeks	72 (78%)	27 (26%)	<0.001
not applicable	17 (18%)	21 (20%)	

Bleeding and discharge were more of a problem after hysteroscopic surgery, but there was significantly less pain than following hysterectomy, as would be expected.

Women were asked what the worst part of treatment was, and their replies are shown in Table 8.2. Pain and gastrointestinal upset, especially "wind". were troublesome in the hysterectomy group; flushing attacks secondary to the premedication with an LHRH analogue were the most common complaint in the hysteroscopy group.

Table 8.2. Women's replies to the question "What was the worst part of treatment?".

Hysterectomy		Conservative	
Pain	27%	Flushes	27%
Wind	18%	Anaesthetic	18%
Tiredness	12%	Anxiety	17%
Anxiety	8%	Pain	15%
Gastrointestinal symptoms	5%	Tiredness	5%
Urinary symptoms	3%	Gastrointestinal symptoms	2%
Anaesthetic	2%	Miscellaneous	16%
Miscellaneous	25%		

The recovery interval and return to work reported at four weeks are shown in Table 8.1, and at six months are shown in Table 8.3. At the six month follow up contact, 162 women (90%) reported complete recovery. All but one of those who worked were back at work. However, seven women in the hysteroscopy group and 10 in the hysterectomy group said they had not yet recovered. The median time to complete recovery and return to work was significantly less in the hysteroscopic surgery group, although there was a wide variation. Only four women at six months and six at 12 months reported taking time off work because of symptoms, which is a marked improvement on preoperative findings (Chapter 6, page 99).

Of the 178 sexually active women, 71 (40%) had resumed intercourse by four weeks postoperatively, 11% of the hysterectomy group and 68% of the hysteroscopy group ($P<0.001$). Most women in the hysteroscopy group resumed intercourse between one and four weeks.

Table 8.3. Postoperative recovery reported at six months.

	Hysterectomy (n=84)	Conservative (n=96)	p
Recovery			
less than 4 weeks	8 (10%)	61 (63%)	
4 to 8 weeks	20 (24%)	13 (13%)	
2 to 3 months	15 (18%)	8 (8%)	
3 to 6 months	31 (37%)	6 (6%)	
more than 6 months	10 (12%)	7 (7%)	<0.001
median	'2-3 months'	'2-4 weeks'	
Return to work			
less than 4 weeks	3 (3%)	54 (56%)	
4 to 8 weeks	11 (13%)	14 (15%)	
2 to 3 months	25 (30%)	7 (7%)	
3 to 6 months	28 (33%)	3 (3%)	
more than 6 months	1 (1%)	0	
median	'2-3 months'	'2-4 weeks'	
doesn't apply	16 (19%)	17 (18%)	<0.001

It can be seen therefore that there are major differences between the hysterectomy group and the conservative group in the time taken to recover from the operation.

There were no significant differences for any of these variables between those in the laser and resection treatment arms of the trial.

HYSTEROSCOPY FOLLOWING TCRE AND ELA.

At six months, 83 women treated by hysteroscopic surgery within the trial attended for out-patient diagnostic CO_2 hysteroscopy. Hysteroscopy was successful in 63 (76%) and unsuccessful in 20 (24%). There was no difference between the success rates in thelaser and resection groups. The reasons for failure are shown in Table 8.4. The commonest, accounting for 70%, was stenosis at either the ecto- or endocervix. Endocervical stenosis was more common following TCRE. The treatment outcomes were no different in the hysteroscopy failures compared to the group as a whole.

Table 8.4. Reason for unsuccessful hysteroscopy.

	TCRE (n=10)	ELA (n=10)	Total (n=20)	(%)
Ectocervical stenosis	1	3	4	(20)
Endocervical stenosis	7	3	10	(50)
Pain	1	1	2	(10)
Equipment failure	1	0	1	(5)
Miscellaneous	0	3	3	(15)

The findings at hysteroscopy were - a completely white cavity, presumably due to fibrosis and simple epithelium replacing the endometrial surface, isolated patches of endometrium, a "normal" cavity, a visible intra-cavitary stenosis, and intra-uterine adhesions (Table 8.5). The last finding again more commonly occurred following TCRE.

Table 8.5. Hysteroscopy findings at six months.			
Appearance	**TCRE** (n=31)	**ELA** (n=32)	**Total** (n=63)
White cavity	16 (52%)	16 (50%)	32 (16%)
Patches of endometrium	8 (26%)	13 (41%)	21 (33%)
Normal cavity	0	1 (3%)	1 (2%)
Intrauterine stenosis	3 (10%)	1 (3%)	4 (6%)
Adhesions	4 (13%)	1 (3%)	5 (8%)

The symptomatic outcome at 12 months in relation to hysteroscopic findings is shown in Table 8.6. Amenorrhoea or hypomenorrhoea is taken as a "good outcome", normal or heavy menstruation or repeat surgery as "poor outcome". A white cavity was significantly associated with good outcome ($P<0.001$, Odds Ratio 9.9, 95% CI 2.0-46.8), and the finding of patches of endometrium was more common in those with poor outcome ($P<0.001$, Odds Ratio 12.2 (2.9-54.5)). It is, however, interesting to note that around a third of those with visible patches of endometrium reported a good outcome after surgery. Intra-uterine adhesions, although infrequent, were invariably associated with a good outcome. Eleven of the 14 women with endocervical or intra-uterine stenosis also had a good outcome after surgery.

Table 8.6. Hysteroscopy findings versus symptomatic outcome.			
	Good outcome (n=40)	**Poor outcome** (n=23)	**%**
White cavity	29	3	(51%)
Patches of endometrium	8	13	(33%)
Normal cavity	0	1	(2%)
Stenosis	3	1	(6%)
Adhesions	5	0	(8%)

CHAPTER 9. RANDOMISED TRIAL - EFFECT OF TREATMENT ON MENSTRUAL SYMPTOMS

EFFECT OF TREATMENT ON MENSTRUAL LOSS.

All the women in the hysterectomy arm (except one treated by hysteroscopic surgery who was hypomenorrhoeic) were of course amenorrhoeic at both six and 12 months. Six women (3%) randomised to conservative treatment had had a hysterectomy prior to the six month visit - two who refused the allocated treatment, one who opted for hysterectomy because the laser was not working, one who had an incompetent cervix, one who had an incomplete operation due to fibroids, and one who was readmitted on several occasions and demanded hysterectomy. One woman who refused hysterectomy and was treated by ELA also had had a hysterectomy because of incomplete treatment.

The menstrual status of the conservative group at six months is shown in Table 9.1. Of those women followed up, 82 (85%) were either amenorrhoeic or hypomenorrhoeic (light menstruation only), although five (5%) had had a hysterectomy and four (4%) had required a two-stage hysteroscopic operation to achieve this status. The menstrual status of the conservative group at 12 months is shown in Table 9.2. Of those followed up, 93 women (97%) were amenorrhoeic or hypomenorrhoeic, but 13 women (13%) had required a hysterectomy and 15 (16%) had had a repeat hysteroscopic procedure by this time. The menstrual status in the conservative group at six and 12 months is illustrated in Figure 9.1.

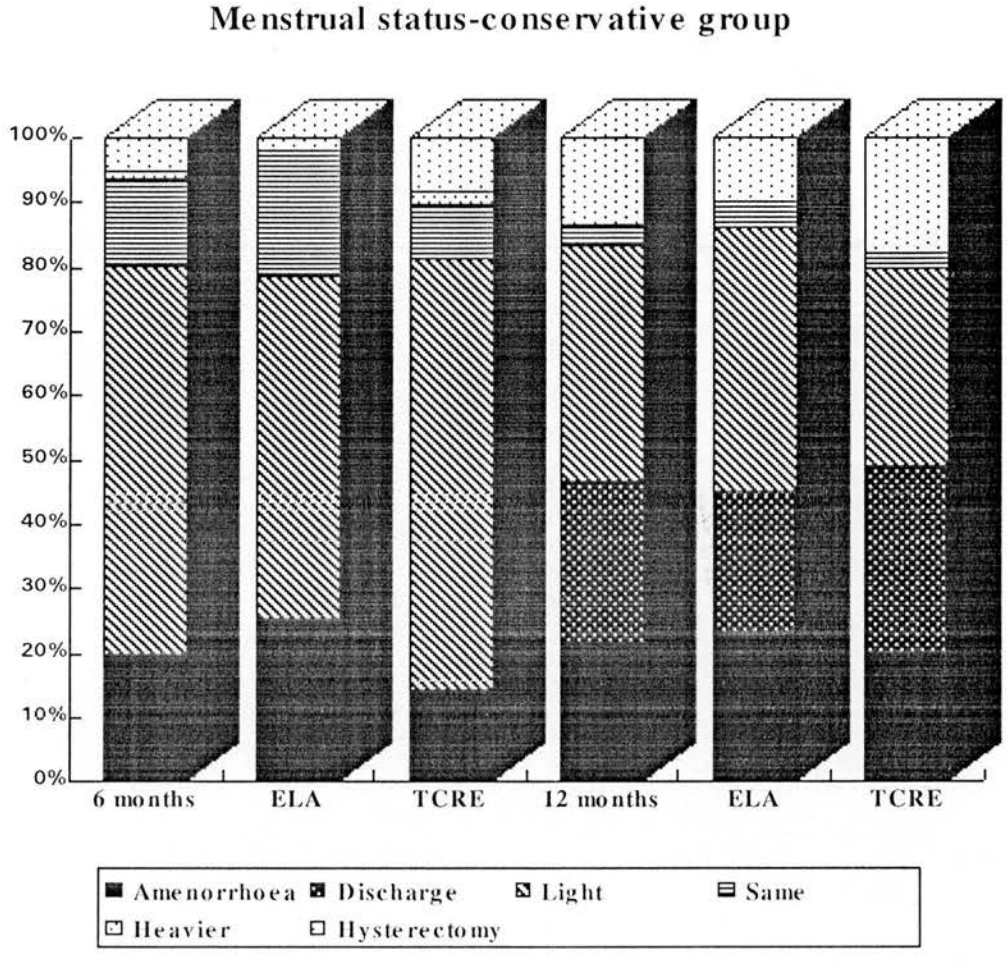
Table 9.1. Menstrual symptoms in the conservative group at six months.

	ELA n=47	TCRE n=49	Total n=96
Menstrual status			
Amenorrhoea	12 (26%)	7 (14%)	19 (20%)
Oligomenorrhoea	25 (53%)	33 (67%)	58 (60%)
Same	9 (19%)	4 (8%)	13 (14%)
Heavier	0	1 (2%)	1 (1%)
Hysterectomy	1 (2%)	4 (8%)	5 (5%)
		NS	
Cycle length			
more than 4 weeks	3 (9%)	8 (22%)	11 (16%)
3 to 4 weeks	25 (73%)	22 (59%)	47 (66%)
less than 3 weeks	6 (18%)	7 (19%)	13 (18%)
		NS	
Duration of bleeding			
less than 3 days	3 (9%)	9 (24%)	12 (17%)
3 to 5 days	12 (35%)	13 (34%)	25 (35%)
5 to 7 days	15 (44%)	12 (32%)	27 (37%)
more than 7 days	4 (12%)	4 (10%)	8 (11%)
		NS	
Dysmenorrhoea			
none	10 (26%)	11 (28%)	21 (27%)
less	16 (41%)	9 (23%)	25 (32%)
same	9 (23%)	10 (26%)	19 (24%)
worse	4 (10%)	9 (23%)	13 (17%)
		NS	
Bleeding score (mean and 95% CI)	9.68 (6.8-12.5)	8.47 (5.7-11.2)	9.06 (6.4-11.8)
Pain score (mean and 95% CI)	6.98 (4.5-9.4)	7.35 (4.8-9.9)	7.17 (4.7-9.7)
		NS	

Table 9.2. Menstrual symptoms in the conservative group at 12 months.

	ELA n=51	TCRE n=45	Total n=96
Menstrual status			
Amenorrhoea	12 (23%)	9 (20%)	21 (22%)
Brown discharge	11 (22%)	13 (29%)	24 (25%)
Oligomenorrhoea	21 (41%)	14 (31%)	35 (37%)
Same	2 (4%)	1 (2%)	3 (3%)
Heavier	0	0	0
Hysterectomy	5 (10%)	8 (18%)	13 (13%)
		NS	
Cycle length			
more than 4 weeks	11 (31%)	2 (7%)	13 (21%)
3 to 4 weeks	22 (63%)	25 (89%)	47 (74%)
less than 3 weeks	2 (6%)	1 (4%)	3 (5%)
		NS	
Duration of bleeding			
less than 3 days	10 (29%)	10 (37%)	20 (33%)
3 to 5 days	12 (35%)	12 (45%)	24 (39%)
5 to 7 days	10 (29%)	3 (11%)	13 (21%)
more than 7 days	2 (6%)	2 (7%)	4 (7%)
		NS	
Regularity			
regular	27 (71%)	25 (86%)	52 (78%)
irregular	11 (29%)	4 (14%)	15 (22%)
		NS	
Dysmenorrhoea			
none	21 (47%)	12 (35%)	33 (42%)
less	17 (38%)	17 (50%)	34 (43%)
same	3 (6%)	1 (3%)	4 (5%)
worse	4 (9%)	4 (12%)	8 (10%)
		NS	
Bleeding score	5.27	3.56	4.47
(mean and 95% CI)	(3.3-7.3)	(2.2-4.9)	(3.2-5.7)
Pain score	3.39	3.76	3.56
(mean and 95% CI)	(2.0-4.8)	(1.8-5.7)	(2.4-4.7)
		NS	

Figure 9.1. Menstrual status in the conservative group at six and 12 months.



On case note review of all women, 17 (16%) of the conservative group had had a hysterectomy by 12 months, giving 32 women in total (30%) who had required further surgery, 22 (21%) for continuing menstrual symptoms. Half of those requiring further treatment for menstrual symptoms had opted for hysterectomy, and half for repeat hysteroscopic surgery (six were treated by ELA, five by TCRE). Histology reports of the uterine specimens at hysterectomy for "treatment failure" showed no abnormality in four, fibroids in two, fibroids and simple endometrial hyperplasia in one, adenomyosis in three, adenomyosis and fibroids in one. The latter also had an ovary removed for a small cyst (less than five cm) which was reported as a serous tumour of low malignant potential.

The majority of women still menstruating had a regular cycle lasting more than three weeks, and less than five days bleeding. This is compared with preoperative menstrual symptoms in Table 9.3. The bleeding score was significantly lower than that preoperatively at both time intervals. and showed significant improvement between six and 12 months. There were no significant differences between ELA and TCRE, and the only difference between six and 12 months was that those with an unsatisfactory result had usually undergone hysterectomy.

After a second hysteroscopic procedure for continuing symptoms the outcome was success in all but one case, with eight women amenorrhoeic or with a brown discharge only, and two hypomenorrhoeic.

These findings suggest that it is worth waiting at least six months after hysteroscopic surgery before offering further treatment for menstrual symptoms, and that women opting for repeat hysteroscopic surgery can be reassured that there is a high chance of success.

Table 9.3. Menstrual symptoms preoperatively, and in the conservative group at six and 12 months.

	Preop n=204	6 months n=96	12 months n=96
Menstrual status			
Amenorrhoea		19 (20%)	21 (22%)
Oligomenorrhoea		58 (60%)	59 (62%)
Same		13 (14%)	3 (3%)
Heavier		1 (1%)	0
Hysterectomy		5 (5%)	13 (13%)
Cycle length			
more than 3 weeks	156(76%)	58 (82%)	60 (95%)
less than 3 weeks	48 (24%)	13 (18%)	3 (5%)
Duration of bleeding			
less than 5 days	8 (4%)	37 (51%)	44 (72%)
5 to 7 days	77 (38%)	27 (38%)	13 (21%)
more than 7 days	119(58%)	8 (11%)	4 (7%)
Regularity			
regular	100(49%)		52 (78%)
irregular	104(51%)		15 (22%)
Dysmenorrhoea			
none	33 (16%)	21 (27%)	33 (42%)
less		25 (32%)	34 (43%)
same		19 (24%)	4 (5%)
worse		13 (17%)	8 (10%)
Bleeding score	26.8	9.06	4.47
(mean and 95% CI)	(25.2-28.5)	(6.4-11.8)	(3.2-5.7)
Pain score	9.96	7.17	3.56
(mean and 95% CI)	(8.1-11.8)	(4.7-9.7)	(2.4-4.7)

EFFECT OF TREATMENT ON DYSMENORRHOEA.

Although dysmenorrhoea by definition can no longer be present after hysterectomy, at six months nine women (13%) regularly and a further 34 (40%) occasionally experienced abdominal pain, and at 12 months the figures were 13 (15%) and 30 (34%) respectively.

In the conservative group, dysmenorrhoea improved in the majority of cases, although 13 women (17%) at six months and eight women (10%) at 12 months reported increased dysmenorrhoea (Tables 9.1, 9.2, and 9.3). Four women in this group also continued to experience pain after hysterectomy. The pain score at six months was not significantly lower than preoperatively, but the score at 12 months was significantly lower than both preoperative and six month scores. There were no significant differences between ELA and TCRE. These findings are reassuring in that women with DUB can be reassured that the common associated symptom of dysmenorrhoea will probably improve following operative treatment.

CHAPTER 10. RANDOMISED TRIAL - EFFECT OF TREATMENT ON OTHER SYMPTOMS

URINARY SYMPTOMS.

Preoperatively, the incidence of urinary symptoms was very high, stress incontinence being the most common, as shown in Table 10.1. At one month 34 women (37%) in the hysterectomy group and 23 women (22%) in the conservative group had urinary symptoms (P=.025, Odds Ratio 2.04, 95% CI 1.04-4.01), but 28 women, 22 of whom were in the hysterectomy group, had had a urinary tract infection postoperatively.

Table 10.1. Urinary symptoms at 0, 6, and 12 months.

H = hysterectomy, C = conservative group.

	preop	6 months		12 months		Pooled difference between preop and 12 months[1]	
	All n=204	H n=84	C n=96	H n=89	C n=96	95% CI	P
Urinary symptoms	104 (51%)	57 (68%)	67 (70%)	70 (79%)	67 (70%)	+13-+32%	**0.001**
stress incontinence	81 (40%)	17 (20%)	31 (32%)	26 (29%)	31 (32%)	-18-+1%	**NS**
urge incontinence	21 (10%)	16 (19%)	14 (15%)	21 (24%)	11* (11%)	+4-+23%	**0.01 (H)**
frequency	52 (25%)	26 (31%)	30 (31%)	30 (34%)	29 (30%)	-1-+13%	**NS**
nocturia	31 (15%)	28 (33%)	41 (43%)	42 (47%)	42 (44%)	+21-+39%	**0.001**
urgency	42 (21%)	15 (18%)	21 (22%)	20 (22%)	18 (19%)	-8-+8%	**NS**
hesitancy	6 (3%)	6 (7%)	7 (7%)	4 (4%)	4 (4%)	-3-+5%	**NS**

1. With the exception of urge incontinence, none of these variables show a significant difference between hysterectomy and conservative surgery in the change from preoperative symptoms to those at 12 months. Hence the confidence limits for these changes are based on data pooled across both types of operation.

* $P < 0.05$ Odds Ratio 2.39 (95% CI 1.01-5.71)

At six and 12 months the incidence of urinary symptoms was as shown in Table 10.1. The only statistically significant difference between the two groups was the higher incidence of urge incontinence in the hysterectomy group at 12 months.

The overall incidence of symptoms at six and 12 months is significantly higher postoperatively in both groups, but this can mainly be accounted for by the almost certain over-reporting of nocturia by the women in the self-report questionnaires compared to the preoperative questionnaire, which was completed by a doctor. However, urge incontinence was significantly more common in the hysterectomy group at 12 months compared to preoperatively. Stress incontinence was less common than preoperatively in this group at six months ($p=0.002$), but this difference was no longer apparent at 12 months.

After hysterectomy, 28 women developed de novo urinary symptoms, whereas 11 women had symptoms which resolved. After conservative surgery, 35 women developed symptoms, five had symptoms which resolved.

From these results it would seem that, with the possible exception of the effect of hysterectomy on urge incontinence, neither operation has any long-term effect on urinary symptoms.

BOWEL SYMPTOMS.

Preoperatively, a quarter of women reported constipation or diarrhoea. At one month 49% in the hysterectomy group had symptoms, mainly constipation, versus 17% in the conservative group ($P<0.001$, Odds Ratio 4.52, 95% CI 2.25-9.17). At six and 12 months there were no statistical differences between the two groups (Table 10.2). The

incidence of symptoms at 12 months was increased compared to preoperative levels, but this only just reached significance, with wide confidence limits.

Table 10.2 Bowel symptoms at 0, 6 and 12 months.

H = hysterectomy, C = conservative group

	preop	6months		12months		Pooled difference between preop and 12 months	
	All n=204	H n=84	C n=96	H n=89	C n=96	95% CI	P
Bowel symptoms	55 (27%)	29 (34%)	25 (26%)	34 (38%)	35 (36%)	+1-+20%	**0.05**
constipation	42 (21%)	23 (27%)	22 (23%)	26 (29%)	28 (29%)	-1-+17%	**NS**
diarrhoea	13 (6%)	6 (7%)	3 (3%)	8 (9%)	6 (6%)	-4-+6%	**NS**

After hysterectomy, 21 women developed new bowel symptoms and 12 women with preoperative symptoms had none postoperatively. After hysteroscopic surgery, 17 had relief of symptoms, 25 developed symptoms.

Again, from these findings, although constipation is common in the immediate postoperative period following hysterectomy, neither type of operation has any effect on long-term bowel symptoms.

DYSPAREUNIA.

Preoperatively only 53% of sexually active women never had pain on intercourse. The incidence of this symptom at six and 12 months is shown in Table 10.3. There were no statistically significant differences between the groups or between pre- and postoperative levels.

Table 10.3 Dyspareunia at 0, 6 and 12 months.

H= hysterectomy, C = conservative group

	Preop	6 months		12 months		Pooled difference between preop and 12 months	
	All n=204	H n=84	C n=96	H n=89	C n=96	95% CI	P
Dyspareunia	85 (47%)	41 (53%)	54 (54%)	35 (44%)	36 (43%)	-14-+6%	**NS**
n/a	22	6	6	9	11		

After hysterectomy, 24 women developed dyspareunia, 27 had relief from this symptom; after conservative surgery, the numbers were 17 and 24 respectively. Again, neither operation appears to have a consistent effect on dyspareunia. Women can be reassured that operative treatment for DUB will not lead to pain on intercourse, but may be disappointed if they are expecting relief from this symptom.

PREMENSTRUAL AND MENOPAUSAL SYMPTOMS.

At six months, premenstrual breast discomfort, abdominal bloating and irritability were significantly less common in the hysterectomy group compared to the hysteroscopy group, but these differences were no longer apparent at 12 months, as shown in Table 10.4. Compared to preoperative levels, breast discomfort, bloating, irritability, headaches and depression were significantly less common in the hysterectomy group at six and 12 months ($p < .001$). In the conservative group, bloating, irritability and depression were significantly less common at six months ($p < .001$), and bloating, irritability, depression ($p < .001$) and headaches ($p = .02$) were significantly less common at 12 months compared to preoperative levels, but breast discomfort was not significantly different at six or 12 months, neither were headaches at six months.

The differences between the preoperative symptoms and postoperative symptoms at 12 months in the group as a whole are shown in Table 10.4.

Table 10.4. Premenstrual and menopausal symptoms at 0, 6 and 12 months.

H= hysterectomy, C = conservative group.

	All	6 months		12 months		Pooled difference between preop and 12 months	
	Preop n=204	H n=84	C n=96	H n=89	C n=96	95% CI	P
Breast discomfort	140 (69%)	37 (44%)	61* (63%)	46 (52%)	57 (59%)	-22- -3%	**0.01**
Bloating	189 (93%)	36 (43%)	66+ (69%)	45 (51%)	60 (62%)	-44- -28%	**0.001**
Irritability	161 (79%)	33 (39%)	59~ (61%)	40 (45%)	57** (59%)	-36- -17%	**0.001**
Headaches	110 (54%)	28 (33%)	45 (47%)	29 (33%)	38 (40%)	-27- -8%	**0.001**
Depression	112 (55%)	22 (26%)	32 (34%)	23 (26%)	28 (29%)	-37- -17%	**0.001**
Flushes	96 (47%)	47 (56%)	51 (54%)	49 (55%)	55 (57%)	-1-+19%	**NS**

*p<0.05 Odds Ratio 2.21 (95% CI 1.17-4.22)
+p<0.001 Odds Ratio 2.93 (1.52-5.67)
~p<0.01 Odds Ratio 2.46 (1.29-4.71)
**p<0.05 Odds Ratio 1.79 (0.96-3.35)

Both types of operative treatment for DUB therefore lead to a significant improvement in premenstrual symptoms, with a difference in favour of hysterectomy at six months, but no difference between the two treatments at 12 months.

There were no statistically significant differences between the groups in the incidence of flushes at six and 12 months, or between preoperative and postoperative levels (Table 10.4).

CHAPTER 11. RANDOMISED TRIAL - EFFECT OF TREATMENT ON PSYCHOSOCIAL FACTORS

PERSONALITY TRAITS.

The Eysenck Personality Questionnaire was returned by 190 women (93% response rate). Where an item had not been answered, the relevant subscale was discounted. Therefore 3 (2%) had a missing E score, 11 (6%) a missing P score, 6 (3%) a missing N score and 6 (3%) had a missing L score. The mean scores are shown in Table 11.1.

There were no significant differences between women in the two arms of the trial, or between the laser and resection groups.

Table 11.1. Mean EPQ scores by group.

	Hysterectomy n=91	Conservative n=99	Total n=190	P
E score (mean (SD))	11.03	10.84	10.93(5.10)	NS
N score	14.73	14.60	14.66(5.12)	NS
P score	2.04	2.20	2.12(1.84)	NS
L score	10.63	9.40	9.98(4.48)	NS

The E score and P score are lower than the "normal" range quoted earlier (see methods), the N score and the L score are higher.

ANXIETY AND DEPRESSION.

The Hospital Anxiety and Depression Scale was completed by 198 women (97%) preoperatively. If an item was missing, the total for that subscale was discounted. No anxiety scores and two depression scores (1%) were missing. The mean scores and the numbers of women in each group with low, borderline and high scores are shown in Table 11.2. A third of women had high anxiety scores, and a further third were borderline high scorers. Just under half of the women had borderline or high depression scores. There were no significant differences between the two arms of the study, or between the laser and resection groups.

Table 11.2. Preoperative anxiety and depression scores.

(Mean scores are followed by 95% confidence intervals)

	Hysterectomy n=96	**Conservative** n=102	**Total** n=198	
Anxiety	9.45 (8.60-10.30)	8.73 (8.00-9.46)	9.08 (8.52-9.64)	
Low (<8)	29	37	66	(33%)
Borderline (8-10)	28	34	62	(31%)
High (>10)	39	31	70	(35%)
Depression	7.07 (6.27-7.87)	6.31 (5.66-6.96)	6.68 (6.17-7.19)	
Low (<8)	52	59	111	(57%)
Borderline (8-10)	25	33	58	(30%)
High (>10)	18	9	27	(14%)

At one month 197 women (98%) completed the questionnaire. Two had incomplete depression scores. The results are shown in Table 11.3. There were again no significant differences between the two groups.

Table 11.3. One month anxiety and depression scores.

(Mean scores are followed by 95% confidence intervals)

	Hysterectomy n=93	Conservative n=104	Total n=197	
Anxiety	5.40 (4.73-6.07)	5.95 (5.20-6.70)	5.69 (5.18-6.20)	
Low (<8)	69	74	143	(73%)
Borderline (8-10)	19	19	38	(19%)
High (>10)	5	11	16	(8%)
		NS		
Depression	2.99 (2.38-3.60)	2.35 (1.86-2.84)	2.65 (2.26-3.04)	
Low (<8)	85	96	181	(93%)
Borderline (8-10)	4	7	11	(6%)
High (>10)	3	0	3	(1%)
		NS		

At six months 179 women completed the questionnaire (89% response rate). One had an incomplete anxiety subscale, and one an incomplete depression subscale. The results are shown in Table 11.4. There is significantly less morbidity in the hysterectomy group. The mean scores are lower than at one month in the hysterectomy group, but higher than one month in the conservative group, although these differences are not statistically significant.

Table 11.4. Six month anxiety and depression scores.

(Mean scores are followed by 95% confidence intervals)

	Hysterectomy n=83	Conservative n=96	Total n=179	
Anxiety	4.71 (3.92-5.50)	6.44 (5.60-7.28)	5.64 (5.04-6.24)	
Low (<8)	63	62	125	(70%)
Borderline (8-10)	13	15	28	(16%)
High (>10)	6	19	25	(14%)
		p=.006		
Depression	1.76 (1.31-2.21)	2.82 (2.23-3.41)	2.33 (1.94-2.72)	
Low (<8)	80	85	165	(93%)
Borderline (8-10)	2	8	10	(5%)
High (>10)	0	3	3	(2%)
		p=.015		

At 12 months 184 women (92%) completed the HAD scale. Two had an incomplete anxiety score, and one an incomplete depression score. There were no significant differences between the treatment groups at this stage (Table 11.5).

Table 11.5. Twelve month anxiety and depression scores.

	Hysterectomy n=86	Conservative n=98	Total n=184	
Anxiety (mean)	5.51	5.71	5.62	
(95%CI)	(4.69-6.34)	(4.87-6.56)	(5.03-6.21)	
Low (<8)	64	71	135	(74%)
Borderline (8-10)	10	16	26	(14%)
High (>10)	10	11	21	(12%)
		NS		
Depression (mean)	2.38	2.56	2.48	
(95%CI)	(1.74-3.01)	(1.97-3.15)	(2.04-2.91)	
Low (<8)	78	90	168	(92%)
Borderline (8-10)	6	6	12	(7%)
High (>10)	1	2	3	(2%)
		NS		

The mean (95% CI) scores for all patients preoperatively and at one, six and 12 months are compared in Table 11.6, and the number with high, low and borderline scores in Figures 11.1 and 11.2. For both anxiety and depression, the scores are significantly lower at one month, six months and 12 months ($p < .001$) compared to preoperative levels, but there were no significant differences between one, six and 12 months.

Table 11.6. Mean and 95% confidence intervals for anxiety and depression at 0, 1, 6 and 12 months.

	Anxiety	Depression
Preoperative	9.08	6.68
	(8.52-9.64)	(6.17-7.19)
1 month	5.69	2.65
	(5.18-6.20)	(2.26-3.04)
6 months	5.64	2.33
	(5.04-6.24)	(1.94-2.72)
12 months	5.62	2.48
	(5.03-6.21)	(2.04-2.91)

Figure 11.1. HAD Scale - anxiety scores at 0, 1, 6 and 12 months.

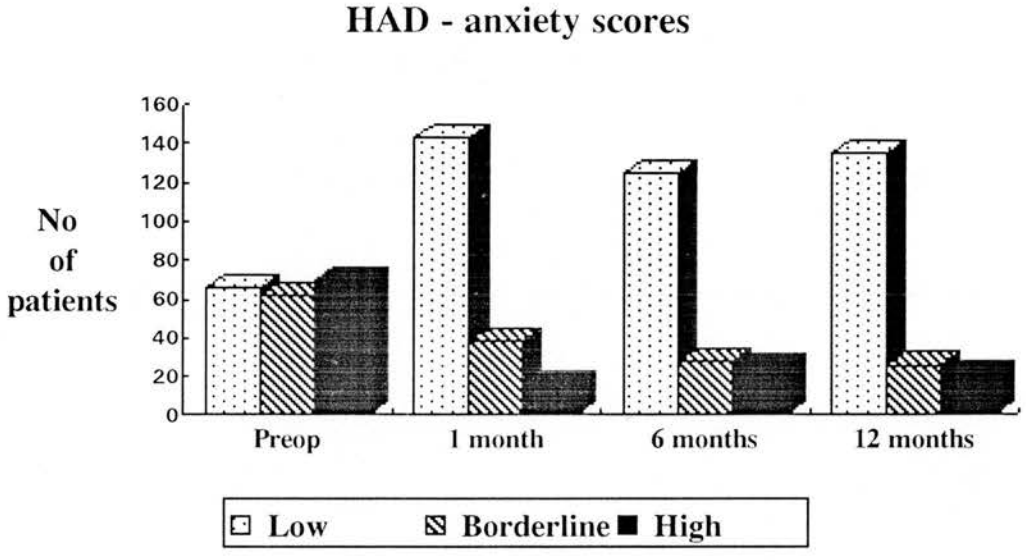
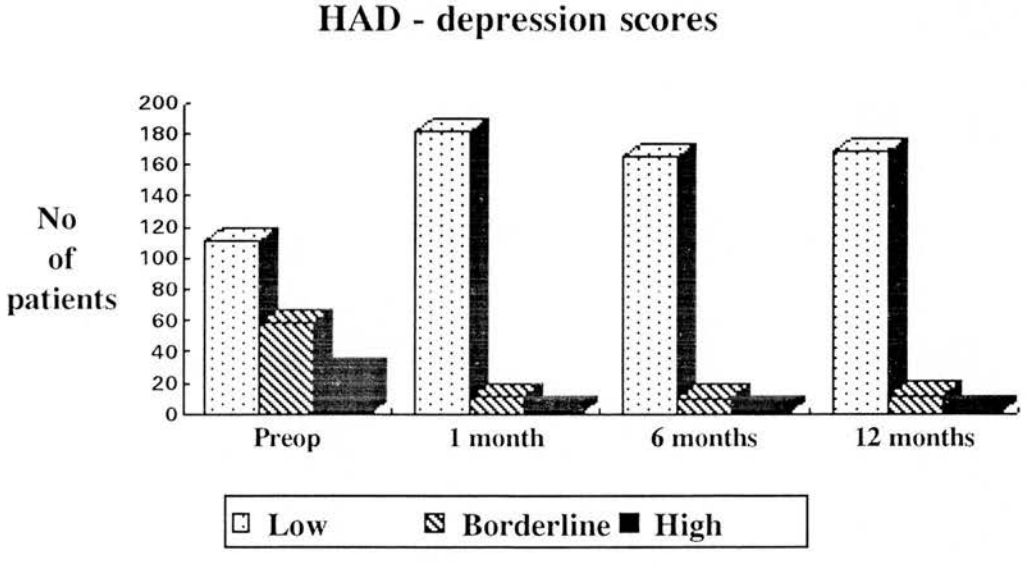


Figure 11.2. HAD Scale -depression scores at 0, 1, 6 and 12 months.



Those women with high postoperative scores ("cases") on the HAD scale nearly always had high preoperative scores, as shown in Tables 11.7 and 11.8. There were very few cases of depression postoperatively, and these came almost exclusively from the high scoring group preoperatively. From these results it must be concluded that neither operation causes psychological morbidity, and, on the contrary, treatment of DUB leads to resolution of anxiety and depression.

Table 11.7. Postoperative high HAD anxiety scores compared to preoperative scores.

Preoperative score	Low n=66	Borderline n=62	High n=70
One month	2	2	11
Six month	3	4	16
12 month	2	2	16

Table 11.8. Postoperative high HAD depression scores compared to preoperative scores.

Preoperative score	Low n=111	Borderline n=58	High n=27
One month	1	1	1
Six month	0	0	2
12 month	0	1	2

MENSTRUAL DISTRESS QUESTIONNAIRE.

The first 17 women in the study attempted to complete the original Moos menstrual distress questionnaire, and could not be included in the analysis. The modified questionnaire was completed by 185 women (99% of those administered). Subtotals with missing items were excluded. There were 7 (4%) missing pain totals, 5 (3%) missing concentration, 2 (1%) missing behavioural change, 4 (2%) missing autonomic

reactions, 1 (1%) missing fluid retention, 15 (8%) missing negative affect, 6 (3%) missing arousal, 11 (6%) missing control, and 37 (20%) missing total scores. The mean scores in each of the eight categories and total score for each group preoperatively are shown in Table 11.9. There were no significant differences between the two arms of the study.

Table 11.9. Mean preoperative menstrual distress scores by group.

	Hysterectomy n=91	Conservative n=94	Total n=185
Pain (out of 20)	9.1	9.5	9.3
Concentration (out of 10)	7.4	7.1	7.2
Behavioural change (out of 10)	3.9	3.4	3.6
Autonomic reactions (out of 10)	2.2	2.0	2.1
Water retention (out of 10)	5.6	5.6	5.6
Negative affect (out of 40)	18.2	18.2	18.2
Arousal (out of 10)	3.4	3.4	3.4
Control (out of 25)	4.5	3.7	4.1
Total score (out of 140)	54.9	52.4	53.6

The following items were reported as present with at least moderate severity in over 50% of women - cramps, backache, fatigue, breast pain, irritability, mood swings, feeling tense, and abdominal swelling. These all fell into the categories of pain, water retention and negative affect. This is consistent with the high incidence of premenstrual breast discomfort, bloating, depression and anxiety already reported in Chapter 6. The following symptoms were absent in over 50% of women - loneliness, nausea, buzzing in ears, palpitations, numbness, and fuzzy vision. These include all the control symptoms, and one from the negative affect category.

At six months 177 women (88%) completed the questionnaire. There were - one missing pain total, four missing concentration scores, one missing behaviour score, four missing autonomic scores, two missing fluid retention scores, eight missing affect and arousal scores, and 18 (10%) missing total scores. The mean scores in each group were as shown in Table 11.10. In the categories of pain, fluid retention and affect, as well as the total score, the results were significantly better in the hysterectomy group compared with the conservative group.

Table 11.10. Mean menstrual distress scores at six months.

	Hysterectomy n=83	**Conservative** n=94	**Total** n=177	**P**
Pain (out of 20)	4.4	6.4	5.5	**<0.001**
Concentration (out of 10)	4.7	5.3	5.0	**NS**
Behavioural change (out of 10)	1.6	1.8	1.7	**NS**
Autonomic reactions (out of 10)	0.9	1.2	1.1	**NS**
Water retention (out of 10)	3.2	4.5	3.8	**0.002**
Negative affect (out of 40)	9.0	11.8	10.5	**0.038**
Arousal (out of 10)	3.7	3.8	3.7	**NS**
Control (out of 25)	2.7	2.9	2.8	**NS**
Total score (out of 140)	29.6	37.5	33.9	**0.022**

At 12 months 183 women (91%) completed the menstrual distress questionnaire. The scores are shown in Table 11.11. At this time interval there were no significant differences between the two groups in any category.

Table 11.11. Mean menstrual distress scores at 12 months.				
	Hysterectomy n=86	**Conservative** n=97	**Total** n=183	**P**
Pain (out of 20)	4.4	4.9	4.6	**NS**
Concentration (out of 10)	5.1	5.1	5.1	**NS**
Behavioural change (out of 10)	1.5	1.3	1.4	**NS**
Autonomic reactions (out of 10)	1.4	0.9	1.1	**NS**
Water retention (out of 10)	3.4	3.5	3.4	**NS**
Negative affect (out of 40)	9.3	10.5	9.9	**NS**
Arousal (out of 10)	3.5	3.7	3.6	**NS**
Control (out of 25)	3.2	2.4	2.8	**NS**
Total score (out of 140)	31.9	32.6	32.3	**NS**

The overall scores at six and 12 months are compared with preoperative scores in Table 11.12. At six and 12 months, the scores had improved significantly from those preoperatively in all categories but arousal. No individual symptom was present in moderate severity or greater in more than 50% of women. Individual symptoms which were significantly less common at six months were - insomnia, crying, forgetfulness, cramps, dizziness, avoidance of activities, anxiety, backache, fatigue, nausea, restlessness, poor concentration, breast pain, well-being, irritability, mood swings, sadness, palpitations, clumsiness, numbness, change in eating habits, feeling tense, and ankle or abdominal swelling. Symptoms which were not significantly different were - loneliness, feeling suffocated, ringing in the ears, visual disturbance and energy. The only significant difference between six and 12 months was in the pain score ($p=.02$).

These results are very similar to the findings reported in Chapter 10, in that they show a marked improvement in premenstrual symptoms, with a difference in favour of hysterectomy at six months, but no difference between the two groups at 12 months.

Table 11.12. Comparison of mean (95% CI) menstrual distress scores at 0, 6 and 12 months.

	Preop n=185	6 month n=177	p	12 month n=183	p
Pain	9.3 (8.8-9.8)	5.5 (4.9-6.1)	**.001**	4.6 (4.1-5.1)	**.001**
Concentration	7.2 (6.4-7.8)	5.0 (4.4-5.6)	**.001**	5.1 (4.5-5.7)	**.001**
Behavioural change	3.6 (3.2-4.0)	1.7 (1.4-2.0)	**.001**	1.4 (1.1-1.7)	**.001**
Autonomic reactions	2.1 (1.8-2.4)	1.1 (0.8-1.4)	**.001**	1.1 (0.9-1.3)	**.001**
Water retention	5.6 (5.2-6.0)	3.8 (3.4-4.2)	**.001**	3.4 (3.0-3.8)	**.001**
Negative affect	18.2 (16.9-19.5)	10.5 (9.2-11.8)	**.001**	9.9 (8.7-11.1)	**.001**
Arousal	3.4 (3.0-3.8)	3.7 (3.3-4.1)	**NS**	3.6 (3.3-3.9)	**NS**
Control	4.1 (3.5-4.7)	2.8 (2.3-3.3)	**.001**	2.8 (2.3-3.3)	**.01**
Total score	53.6 (50.5-56.7)	33.9 (30.5-37.3)	**.001**	32.3 (29.2-35.4)	**.001**

MARITAL STATE.

The first 24 women in the trial completed the original Golombok Rust Inventory of Marital Status, and could not therefore be included in the analysis. Ten women stated they did not have a steady partner and did not complete the questionnaire. Of the remainder, 152 women (89%) completed the modified questionnaire preoperatively, and the results are shown in Table 11.13. Six (4%) had missing items and therefore a total score could not be assigned. There was no significant difference between the two arms of the study.

At six months postoperatively 177 women (88%) completed the questionnaire. Of these, 42 had missing items (a common mistake was not to turn the page and only to complete half the questions). At 12 months 169 women (84%) completed the questionnaire and 19 had missing items. The mean scores (and 95% CI) in each group at each administration are shown in Table 11.13. Again at six and 12 months, there were no differences between the two groups. There was no significant change between the preoperative and six month postoperative score, as the confidence intervals overlap, although the p value was 0.03, or between that and 12 months postoperatively.

Table 11.13. Marital status scores at 0, 6 and 12 months (mean and 95% CI).

	Preoperative n=152	**6 months** n=177	**12 months** n=169
Hysterectomy	54.7 (52.6-56.8) (n=70)	56.9 (54.8-59.0) (n=60)	54.8 (52.5-57.1) (n=70)
Conservative	54.5 (52.5-56.5) (n=76)	56.8 (54.8-58.8) (n=75)	55.7 (53.9-57.5) (n=80)
All patients	54.6 (53.1-56.1) (n=146)	56.8 (55.4-58.3) (n=135)	55.3 (53.9-56.7) (n=150)

PSYCHOSOCIAL ADJUSTMENT.

Preoperatively 184 women (90%) completed the Psychosocial Adjustment to Illness Scale. There were 11 (6%) missing scores in the health care orientation section, 17 (9%) in the work environment section, 17 (9%) in the domestic environment, 17 (9%) in the sexual relationships section, 20 (11%) in the extended family relationships section, 7 (4%) in the social environment section and 4 (2%) in the psychological distress section, giving 50 women (27%) for whom a total score could not be assigned.

The scores in each section for each group and overall are shown in Table 11.14. There were no significant differences between the two arms of the trial.

Table 11.14. Mean preoperative PAIS scores.

	Hysterectomy n=90	Conservative n=94	Total n=184
Health	5.4	5.5	5.4
Work	4.1	3.9	4.0
Domestic	6.0	5.9	5.9
Sexual	6.0	5.7	5.8
Family	2.4	2.8	2.6
Social	6.6	6.6	6.6
Psychological	9.1	8.4	8.7
Total score	40.8	39.0	39.8

At one month, 197 women (98%) completed the relevant sections. There were 17 incomplete vocation scores, 51 incomplete family scores, two incomplete psychological scores, and 58 (29%) incomplete totals. There were, as would be expected, significant differences in the areas of vocational environment and family relationships between the two types of treatment (Table 11.15). These scores cannot, with the exception of the psychological scores, be compared to preoperative values. As with the HAD scale, the scores for this section were lower postoperatively, with no difference between the two groups.

Table 11.15. Mean PAIS scores (95% CI) at one month.				
	Hysterectomy n=93	**Conservative** n=104	**Total** n=197	**P**
Work	6.3 (5.7-6.9)	3.7 (3.1-4.3)	4.9	**0.001**
Family	3.1 (2.6-3.6)	1.7 (1.3-2.1)	2.3	**0.001**
Psychological	4.6 (3.9-5.3)	4.4 (3.7-5.1)	4.5	**NS**
Total score	14.3 (12.7-15.9)	9.3 (7.9-10.7)	11.6	**0.001**

At six months, 178 women (89%) returned the PAIS questionnaire. 42 (24%) did not complete the sexual relationship section, 7 (4%) had missing items in the social environment section, and 3 (2%) had missing items in the psychological section. There were no significant differences between the two groups in any section (Table 11.16).

Table 11.16. Mean PAIS scores six months postoperatively.			
	Hysterectomy n=85	**Conservative** n=93	**Total** n=178
Sexual	9.1	9.1	9.1
Social	5.3	5.4	5.3
Psychological	4.6	4.9	4.8
Total score	18.7	19.4	19.1

At 12 months, 184 women (92%) completed the full but altered version of the PAIS. There were three (2%) incomplete health care orientation scores, 11 (6%) missing vocational environment, 22 (12%) domestic environment, 20 (11%) sexual relationship, three (2%) family relationship, two (1%) social environment and no missing psychological distress scores, giving 38 (21%) with incomplete total scores. There were no significant differences in the scores between the groups (Table 11.17) with the exception of domestic environment, where the scores were significantly lower in the conservative group ($p=0.03$).

Table 11.17. Mean PAIS scores 12 months postoperatively.

	Hysterectomy n=86	Conservative n=98	Total n=184
Health	3.95	3.33	3.62
Work	1.1	1.2	1.2
Domestic	1.7	1.2	1.4
Sexual	9.1	8.5	8.8
Family	2.2	1.8	2.0
Social	4.9	5.1	5.0
Psychological	4.7	4.3	4.5
Total score	27.9	24.8	26.2

Of particular interest is change in sexual function after operation. The areas investigated, and responses in each category, are shown in Table 11.18. It can be seen that the majority experience no change in any aspect of their sexual relationship, but more notice improvement than deterioration. There were no significant differences for

the responses to any of these items at six or 12 months between the two groups of women.

Table 11.18. Change in sexual function at six and 12 months.

	6 months	12 months
1. Problems in relationship		
Much better	27 (15%)	41 (22%)
Better	32 (18%)	17 (9%)
No change	90 (51%)	90 (49%)
Worse	9 (5%)	14 (8%)
Much worse	2 (1%)	5 (3%)
No response	18 (10%)	16 (9%)
2. Change in sexual interest		
Much better	17 (10%)	23 (12%)
Better	37 (21%)	28 (15%)
No change	66 (37%)	71 (39%)
Worse	35 (20%)	37 (20%)
Much worse	8 (4%)	9 (5%)
No response	15 (8%)	16 (9%)
3. Change in sexual activity		
Much better	20 (11%)	25 (14%)
Better	34 (19%)	33 (18%)
No change	69 (39%)	69 (37%)
Worse	36 (20%)	35 (19%)
Much worse	3 (2%)	5 (3%)
No response	16 (9%)	17 (9%)
4. Change in sexual pleasure		
Much better	18 (10%)	23 (12%)
Better	29 (16%)	33 (18%)
No change	64 (36%)	82 (45%)
Worse	25 (14%)	23 (12%)
Much worse	4 (2%)	5 (3%)
No response	38 (21%)	18 (10%)
5. Change in sexual performance		
Much better	9 (5%)	16 (9%)
Better	17 (10%)	19 (10%)
No change	89 (50%)	102 (55%)
Worse	22 (12%)	22 (12%)
Much worse	3 (2%)	6 (3%)
No response	38 (21%)	19 (10%)

CHAPTER 12. RANDOMISED TRIAL - EFFECT OF TREATMENT ON PATIENT SATISFACTION

There is no one way to assess patient satisfaction. Women were therefore asked about several different aspects - whether the operation was acceptable to them, whether their general health had improved, how effective the treatment had been at relieving their original symptoms, which type of operation they would recommend to a friend, and how satisfied they were with the treatment overall.

The majority of women said the operation was acceptable at both one and six months (Table 12.1), with a trend towards conservative surgery at one month, but a significant difference in favour of hysterectomy at six months. At 12 months, 169 women (91%) reported that they were in good, very good or excellent health, and 163 (88%) said they were better or much better than a year before (Table 12.2), with a significant difference in favour of hysterectomy.

Table 12.1. Acceptability of operation.

		1 month n=195	**6 months** n=179
Overall	yes	178(91%)	156(87%)
	no	17 (9%)	23 (13%)
Hysterectomy	yes	82 (89%)	80 (95%)
	no	10 (11%)	4 (5%)
Conservative	yes	96 (93%)	76 (80%)
	no	7 (7%)	19 (20%)
		NS	**p=0.002** OR 5.00(1.51-18.27)

Table 12.2. General health at 12 months.			
	Hysterectomy n=89	**Conservative** n=96	**Total** n=185
How would you describe your general health?			
Excellent	10 (11%)	7 (7%)	17 (9%)
Very good	42 (47%)	51 (53%)	93 (50%)
Good	29 (33%)	30 (31%)	59 (32%)
Fair	8 (9%)	7 (7%)	15 (8%)
Poor	0	1 (1%)	1 (1%)
		NS	
How does your general health compare to a year ago?			
Much better	65 (73%)	46 (48%)	111(60%)
Better	20 (23%)	32 (33%)	52 (28%)
Same	2 (2%)	16 (17%)	18 (10%)
Worse	1 (1%)	2 (2%)	3 (2%)
Much worse	1 (1%)	0	1 (1%)
		p<0.001	

At all time intervals the majority of women would recommend the same operation to someone else. The only significant difference between the two groups was at one month, as shown in Table 12.3, when, not surprisingly, more women would recommend hysteroscopic surgery.

At six months 142 women (79%) and at 12 months 171 women (92%) reported that the treatment had cured or significantly improved their symptoms, with significant differences in favour of hysterectomy (Table 12.3). It is interesting to note that some women in the hysterectomy group said the operation had had no effect, despite the primary reason for surgery being dysfunctional uterine bleeding. Only five women were dissatisfied with the effect of treatment at 12 months, but women were more likely to say they were very satisfied after hysterectomy (difference 11%, 95% CI 8-13%, Table 12.3).

Table 12.3. Patient satisfaction at one, six and 12 months.

H = hysterectomy, C = conservative.

	1 month		6 months		12 months	
	H	C	H	C	H	C
	n=92	n=103	n=84	n=96	n=89	n=96
Which operation would you recommend?						
Hysterectomy	54 (59%)	3 (3%)	66 (72%)	8 (8.6)	64 (72%)	15 (16%)
Conservative	14 (15%)	91 (88%)	8 (10%)	64 (69%)	13 (15%)	68 (71%)
Don't know	24 (26%)	9 (9%)	8 (10%)	21 (23%)	10 (11%)	12 (13%)
Neither					1 (1%)	1 (1%)
	p<0.001 OR 5.34 (2.44-11.87)		**NS**		**NS**	
What effect has the operation had on symptoms?						
No effect			2 (2%)	9 (9%)	0	4 (4%)
Insufficient improvement			4 (5%)	22 (23%)	4 (5%)	6 (6%)
Acceptable improvement			28 (34%)	41 (43%)	26 (29%)	53 (55%)
Cured			49 (59%)	24 (25%)	59 (66%)	33 (34%)
			p<0.001		**p<0.001**	
How satisfied are you with the effect of treatment?						
Very satisfied					79 (89%)	75 (78%)
Moderately satisfied					9 (10%)	17 (18%)
Dissatisfied					0	4 (4%)
Very dissatisfied					1 (1%)	0
					p=0.05	

It can be seen therefore that, in general, hysterectomy results in higher levels of satisfaction than conservative treatment. However, between 71 and 90% of women in this study were satisfied with the outcome of hysteroscopic surgery at 12 months.

CHAPTER 13. PREDICTIVE FACTORS FOR OUTCOME AFTER HYSTEROSCOPIC SURGERY

From the previous results, it can be seen that whatever method is taken for assessing success of hysteroscopic surgery, between 15 and 30% of this group of women do not have a successful outcome after one procedure, although those opting for a repeat hysteroscopic operation usually have a good outcome. As the success rate of hysterectomy is high, if there were a method for predicting the chance of success of hysteroscopic surgery, women with a lower chance of success might opt for hysterectomy in the first instance.

In the menstrual history, there was no difference in the duration of symptoms, length of the cycle, duration of bleeding, and regularity of the cycle between those with a successful outcome (defined as amenorrhoea or hypomenorrhoea after one hysteroscopic procedure) and treatment failures (defined as women who had a hysterectomy, or repeat hysteroscopic operation for symptoms, or continuing heavy periods at 12 months). The incidence of dysmenorrhoea, premenstrual symptoms, flushing attacks, dyspareunia, or prior sterilisation was also the same in both outcome groups. There was no correlation between the bleeding or pain score and success. Some of these factors are included in Table 13.1.

It has been suggested that hysteroscopic surgery is less successful in younger women. The outcome of treatment in women under 35 is shown in Table 13.1. There was no significant difference between the outcome in women under and over 35, although numbers were small. This was also the case if the cut-off point was taken as age 40. It may be that late treatment failure is more common in younger women, but the results of long term follow up must be awaited.

Table 13.1. Preoperative and operative details versus outcome of hysteroscopic surgery.

Outcome of initial procedure	Success n=73	Failure n=32	P
Age less than 35	8 (11%)	5 (16%)	NS
Irregular cycle	38 (52%)	17 (53%)	NS
Mean bleeding score	27.0	26.5	NS
Mean pain score	10.3	9.2	NS
HAD anxiety (cases)	20 (27%)	11 (34%)	NS
HAD depression (cases)	4 (5%)	5 (16%)	NS
Uterine volume (mean)	86.6	87.2	NS
Duration of operation (mean)	30.6 mins	32.5 mins	NS
Fluid deficit (mean)	451 ml	630 ml	NS
Uterine score (mean)	2.50	2.68	NS
Score < 5	52 (71%)	20 (63%)	NS

In the operative details, the presence or absence of submucous fibroids at hysteroscopy did not predict treatment success; of those in whom the operation was not completed, half were successful; of those with adenomyosis in the endometrial chips, half were successful; and the surgeon carrying out the procedure made no difference to the outcome. There was no correlation with uterine volume, duration of the operation, fluid deficit or the endometrial score (Table 13.1).

Preoperative psychological morbidity was also just as common in those with a successful outcome (Table 13.1).

Unfortunately, therefore, from this study no useful predictive factors for outcome following hysteroscopic surgery were identified.

CHAPTER 14. DISCUSSION

The results presented in this thesis are those of a pragmatic randomised trial comparing current practice with a new surgical technique in a relatively unselected group of women with menstrual problems. Although it is now recognised that this is the ideal way to assess new surgical treatments, this has not always been the case, and there have been few such trials in the past. The two trials of TCRE and hysterectomy which have been published recently were undertaken concurrently with this trial (Gannon et al, 1991, Dwyer et al, 1993).

The results will be discussed in the same order as the preceding chapters.

THE LEARNING CURVE.

One of the concerns about the introduction of hysteroscopic surgery is that the incidence of serious complications, particularly during endometrial resection, has been not insignificant, especially when carried out by an inexperienced surgeon (MacDonald et al, 1992). Many of the serious complications which have occurred do not appear in the literature. It is also recognised that results of hysteroscopic surgery improve as experience increases, until a 'plateau' is reached - this initial phase is commonly called the 'learning curve'.

Experience of diagnostic hysteroscopy is advisable before commencing operative hysteroscopy, and this condition was fulfilled in this unit. As the first operations were, however, performed unsupervised, the surgeons, aware of the possible complications, were probably more cautious initially, partly explaining the relatively high "failure

rate" in the first patients treated. Treatment failures were not initially offered repeat hysteroscopic surgery, hence the high hysterectomy rate. Although the complications of bleeding and fluid overload did occur in a few women, there were no serious ill-effects.

The overall success rate of these initial operations, defined as amenorrhoea or hypomenorrhoea, was 71%, but this improved from 57% for the first 10 women treated to 77% for women treated further along the learning curve. However, the follow-up interval in these women varied. The 12 month success rate for women in the randomised study was 83%, suggesting that results were continuing to improve. It is not possible to comment on the length of the learning curve from these results, as another operator (myself) was introduced at the beginning of the trial. However, there was no statistical difference between the success rates for individual surgeons within the trial. It may be therefore that learning under supervision shortens the learning curve.

Conclusion.

This series demonstrates that the operations of TCRE and ELA do have a "learning curve" of success. The disparity in numbers prevents direct comparison of the two procedures, or an estimation of the length of the curve. There were no life-threatening complications, and no emergency (unplanned) procedures carried out, during this phase of the introduction of hysteroscopic surgery in this unit, showing that ELA and TCRE are safe procedures as long as there is an awareness of possible complications.

OPERATIVE TREATMENTS OUTWITH THE RANDOMISED TRIAL.

It was anticipated that 160 women might be recruited to the randomised trial, and 205 women were actually recruited. It would obviously have been better if all eligible women had been entered, but some women were not offered entry into the trial, and some refused to be randomised. Women who refused randomisation usually did so because they wanted the standard treatment of hysterectomy, rather than the new procedures. The usual reason given was that they wanted an operation that would guarantee amenorrhoea. Women were not offered TCRE or ELA during this period except as part of the trial, but some had heard of the operations and refused to enter the trial, insisting on the hysteroscopic option. The usual reason given was the shorter time off work. Initially the same data were collected on women treated outwith the trial, but as women treated by hysterectomy were reluctant to attend for follow-up, this was discontinued. However, the limited data collected suggested that there were no major differences between these women and those entered into the trial.

There has been discussion recently about the need for informed consent in randomised trials (Tobias and Souhami, 1993), as it can reduce recruitment. Although obtaining informed consent was time-consuming, this study of two very different types of operation has shown that women understand the need for randomised trials of new treatments, and other procedures could and should be evaluated in this way.

A large proportion (63%) of women under 50 years of age undergoing hysterectomy for non-malignant conditions were deemed eligible for the trial. If hysteroscopic surgery were to replace hysterectomy, this would have a significant effect on hysterectomy rates in young women.

Conclusion.

Recruitment exceeded anticipated numbers, thereby increasing the power of the study. There were no significant differences in age, duration or severity of symptoms in women refusing randomisation compared to women in the trial, so it appears to be a true representation of women undergoing treatment for DUB in this hospital.

PREOPERATIVE DATA.

The majority of women (98%) had a long history of menstrual symptoms and had already unsuccessfully tried at least one form of medical therapy, so a "no treatment" or "medical treatment" arm of the trial would not have been possible (Coulter, 1993). The aim of the trial was to include only those women who would otherwise have been undergoing hysterectomy, to first assess the safety and efficacy of these operative methods before offering them to women outside this group.

Recent trials of medical therapy have included only women with regular periods losing over 80 mls per cycle (Callender et al, 1970, Nilsson and Rybo, 1971, Chimbira et al, 1979,80(a), Shaw and Fraser, 1984, Dockeray et al, 1989, Cameron et al, 1990) and this usually represents around 50% of those with subjective menorrhagia attending gynaecology clinics (Chimbira et al, 1980(b), Fraser et al, 1984, Cameron et al, 1987(b),90, Dockeray et al, 1989). It is not usual clinical practice to estimate blood loss, and the decision was made not to do so in this trial, which was designed to be pragmatic. Half of the women in the Bristol trial who had blood loss estimated had objective menorrhagia (Dwyer et al, 1993), so it could reasonably be assumed that our findings would have been similar. Although there is no relationship between

menstrual blood loss and the number of days bleeding (Haynes et al, 1977, Chimbira et al, 1980(b)), the majority of these women (58%) bled for over seven days per cycle, which is an inconvenience in itself. Furthermore, 27% of the women in employment regularly took time off work, another indication of severity, and most described "flooding". In contrast to those in medical trials, half of these women had irregular bleeding (usually with a shortened cycle) and the majority had some degree of dysmenorrhoea on questioning. Recent guidelines drawn up by the British Society for Gynaecological Endoscopy (1993) suggested that only women with regular bleeds and no dysmenorrhoea should be treated by hysteroscopic surgery - it can be seen that this would have eliminated 72% of these women and the operations would not therefore be a real alternative to hysterectomy. This sort of assertion cannot be made in an unsubstantiated way, but should be determined by the results of trials such as this.

Many other symptoms were extremely common in this group of women - half had flushes preoperatively, the majority had at least one premenstrual symptom, half had urological complaints, a quarter bowel symptoms, and half dyspareunia. Many of these problems have been attributed in the past to hysterectomy (DeNeef and Hollenbeck, 1966, Riedel et al, 1986, Menon et al, 1987, Smith et al, 1970, Hanley, 1969, Farghaly et al, 1986, Parys et al, 1989, Taylor et al, 1989, Amias, 1975, Utian, 1975), although prospective studies often fail to confirm this (Richards, 1974, Coppen et al, 1981,87, Jequier, 1976, Dennerstein et al, 1977, Chynoweth and Abrahams, 1977, Martin et al, 1980). In 83% either the woman or her partner had been sterilised, so the factor of future conception and contraception was largely irrelevant.

Conclusion.

Most women had a long-standing history of menstrual problems. Symptoms other than menorrhagia were very common preoperatively. There were no significant differences between women in the three arms of the trial for any variables, ensuring that the randomisation process had given equivalent groups for postoperative analysis.

OPERATIVE DETAILS.

Despite understanding the nature of the trial, two women in each group refused the allocated treatment. The decision was made not to carry out preoperative hysteroscopy, which might have biased recruitment to the trial, and it was accepted that some hysteroscopic treatments might not be possible because of unexpected findings. Cervical incompetence was not a problem that had been anticipated, but prevented adequate hysteroscopy and treatment in one woman. There were no problems in two women who had had a previous cone biopsy, however. Large submucous fibroids were found in four women, and in two, after a further injection of Zoladex, a two-stage procedure was performed, the other two (one of whom had actually been randomised to hysterectomy) underwent hysterectomy. These are the only cases where preoperative hysteroscopy might have altered management - either to hysterectomy, or a planned two-stage procedure. On two occasions the laser was out of order - in one the patient had been forewarned and TCRE was carried out instead. Most units would only have one or other treatment option, so on occasion treatment would have to be deferred because of equipment failure. All women were analysed by the group to which they were assigned.

At the time of abdominal hysterectomy, bilateral oophorectomy was carried out in six cases, although significant pathology was not found in any of the removed ovaries. The true incidence of ovarian carcinoma developing after hysterectomy is unknown (Studd, 1989), but these women now have to take hormone replacement therapy or risk the long-term complications of early menopause. The best method of performing hysterectomy is now being hotly debated, mainly because of the advances made in laparoscopic surgery. It has been argued that this trial should have been a comparison of vaginal hysterectomy, or even subtotal abdominal hysterectomy, with endometrial ablation. However, the standard operation for menorrhagia in this hospital, as in most in the United Kingdom, has been total abdominal hysterectomy, and the trial set out to compare the new methods with current practice.

The preoperative diagnosis in these women was dysfunctional uterine bleeding, but only one third of the hysterectomy group (and therefore by implication all women) had no histological abnormality, although in the majority of cases the abnormality was small fibroids, often not recognised macroscopically. This is a similar incidence to other studies (Miller, 1946, Grant, 1984, Lee et al, 1984). Endometriosis was found in 8% of cases. This does not necessarily mean that preoperative laparoscopy should be carried out more frequently, as it is often an incidental finding in women with no symptoms (Mahmood et al, 1991). The case of endometrial cancer emphasises the importance of obtaining endometrium for histology prior to hysteroscopic surgery, particularly ELA, as histology of endometrial chips after TCRE can reveal unsuspected malignancy (Dwyer et al, 1991, Rankin and Steinberg, 1992).

When the operative details in the two groups were compared, although the time taken in theatre (including anaesthetic time) was significantly shorter statistically in the hysteroscopy group, and again in the TCRE group compared to ELA, this was just a matter of 10 to 15 minutes and therefore probably not clinically significant. With experience the time taken for TCRE and ELA decreases, but other members of staff in training will balance this out. The important saving was in time spent in hospital, which was markedly different in the two groups. In this study, as the treatment was relatively new and because of the geography of Grampian region, very few women were treated as day cases, although these procedures are ideal for day case surgery in fit women. The time spent in hospital by the hysterectomy group was longer than necessary - at least two consultants admitted women routinely two days before operation, and many women would have preferred to go home sooner. Earlier discharge from hospital is now normal practice, because of pressure on beds and resources. Postoperative pain and analgesic requirements were significantly reduced following hysteroscopic surgery, as would be expected, although a quarter of women still required injectable analgesia.

In the hysterectomy group the major complications were anaesthetic problems in two cases and emergency laparotomy in three cases; minor morbidity was much more frequent, with infection occurring in 47% and haemorrhage requiring blood transfusion in 5%. Although this complication rate appears very high, it is comparable to other studies (White et al, 1971, Ledger and Child, 1973, Amirikia and Evans, 1979, Dicker et al, 1983, Gambone et al, 1990, Dwyer et al, 1993).

There was only one major complication in the hysteroscopic surgery group. Although the exact cause is not known, the most likely explanation is that there was full thickness

laser treatment at the cornual angle where the myometrium is thinnest. The events were very similar to a previous case report (Perry et al, 1990). It emphasises the care needed when treating this area, whether with laser, resection or rollerball. In contrast to other studies (Hallez et al, 1987, Brooks et al, 1989, Garry et al, 1991, Magos et al, 1991, Sturdee and Hoggart, 1991, Pyper and Haeri, 1991, MacDonald et al, 1992, Rankin and Steinberg, 1992, Dwyer et al, 1993), there was only one uterine perforation, and this was with a dilator, not the hysteroscope, with no concomitant extrauterine damage. This was perhaps in part due to good preoperative preparation of the endometrium, allowing excellent visibility in most cases, and the smaller loop size compared with the urological instruments originally used for TCRE. Although it was not a comparative study, a single injection of an LHRH analogue appears to give adequate endometrial preparation in the majority of cases, with no troublesome side-effects apart from hypooestrogenic flushes.

Primary haemorrhage was not a problem with these procedures - although a Foley catheter was inserted in three cases, this was a precaution rather than necessity. Infectious morbidity occurred in 15% - although this was significantly less than in the hysterectomy group, the differences were mainly in the incidence of urinary and wound infections, the incidence of pelvic infection (defined in this group as foul-smelling discharge and/or pain requiring antibiotics) being similar to the hysterectomy group. This incidence is much higher than in other reports (Goldrath, 1990, Davis, 1989, Garry et al, 1991, Brooks et al, 1989, Dwyer et al, 1993), and many others do not mention infection. MacDonald et al (1992) identified more cases in the UK survey, but it seems that there is under-reporting of this complication, which is potentially serious and has led to death from septicaemia on at least three occasions (unpublished reports).

Clinically significant fluid overload has been a problem with ELA (Goldrath et al, 1981,90, Garry et al, 1991, Bent and Ostergard, 1990, Lomano et al, 1986, Baggish and Boltoyannis, 1988, Gimpelson, 1988(a), Davis, 1989, Goldfarb, 1990, Feinberg et al, 1989) and TCRE (Townsend et al, 1990, Sturdee and Hoggart, 1991, Baumann et al, 1990, Magos et al, 1991, Pyper and Haeri, 1991), although this usually only occurs if over two litres of saline or glycine are absorbed (Baumann et al, 1990). In this study only seven women absorbed over two litres, although the operation was occasionally stopped before completion due to rapid fluid absorption - usually associated with fibroids and bleeding. In no case was there a clinical problem - perhaps as an intravenous bolus of frusemide was given at the end of the operation in eight cases with excessive absorption.

Although most complications were minor, the decreased incidence of early postoperative morbidity is a major advantage of hysteroscopic surgery over hysterectomy.

Conclusion.

Preoperative hysteroscopy is not essential, but women should be warned that it might not be possible to complete hysteroscopic surgery as a one-stage procedure. Hysteroscopic surgery results in a much reduced hospital stay compared with hysterectomy, with consequent savings to the health service. Although major complications are rare with all three procedures, there is significantly more minor morbidity, particularly infection, following hysterectomy.

POSTOPERATIVE RECOVERY.

The one month postoperative visit was principally to pick up early complications of the operations, and to assess the normal course of events following hysteroscopic surgery. This usually consists of up to two weeks of vaginal bleeding, followed by up to four weeks of vaginal discharge, often profuse and watery, with a bleed like a period at four to six weeks. Cramp-like lower abdominal pain often occurs, but usually only during the first week. Other authors have had similar findings (Goldrath et al, 1981, Baggish and Boltoyannis, 1988, Bent and Ostergard, 1990, Daniell et al, 1986, Magos et al, 1989, Townsend et al, 1990, Vancaillie, 1989, Fraser et al, 1993).

Following hysterectomy, pain (principally wound pain) lasted significantly longer. Urinary and bowel symptoms are also common. Another source of discomfort was "wind" which a third of women described as "severe".

Very few women had returned to work within a week, and only a third within two weeks, of hysteroscopic surgery, but often the general practitioner had advised otherwise, or a period of holiday had been added on by the patient. At four weeks 27 women (26%) had not returned to work, three had not returned by three months, but all had returned by six months. Surprisingly, two women returned to work within four weeks of hysterectomy, even though they are usually advised not to return before six weeks. Within three months, 59% of women had returned to work, and all but one of the rest returned between three and six months. In contrast, Gath et al (1982) found that over 75% were back to full functional and occupational level by three months after hysterectomy. This represents another major difference between the two types of operation.

Conclusion.

The shorter time taken to recover completely and return to work is one of the most significant advantages of hysteroscopic surgery over hysterectomy, with financial implications for both employers and women themselves. However, other factors are important in the decision to return to work, resulting in wide variation between individuals.

HYSTEROSCOPY FOLLOWING TCRE AND ELA.

Hysteroscopy is not possible in around 20% of women after hysteroscopic surgery. This may be because of an isolated stenosis at cervical level, or possibly obliteration of the entire uterine cavity. Repeat conservative surgery would probably be extremely difficult in these women. Hysteroscopy is possible in around 80% of women, and most of these women would therefore be suitable for repeat hysteroscopic surgery should it prove necessary.

In contrast to hysterographic findings, genuine adhesions appear to be rare following these procedures. This is not therefore classical Asherman's syndrome. The commonest finding is a completely white cavity, with no visible endometrium, although this may be demonstrated histologically (Magos et al, 1989(b)). Patches of endometrium are another common finding. It may be that these women will present as late treatment failures, although there is no evidence as yet to support this.

Endocervical and intra-cavitary stenosis and adhesions were more common following TCRE. This may be due to the relatively small numbers, but may represent a true

difference in healing following the two procedures. There were no other differences in the findings between patients treated by the two methods.

One of the long-term concerns about hysteroscopic surgery is that endometrial cancer may develop and be diagnosed later than usual because of sequestration behind adhesions. As adhesions are an uncommon finding at hysteroscopy, it may be that there is no basis for concern, and that should cancer develop, bleeding will be revealed rather than concealed. However, as endometrium is often still present, combined hormone replacement therapy rather than unopposed oestrogen should be given to women after TCRE or ELA whether or not they are amenorrhoeic.

Conclusion.

There were no obvious differences in the appearance of the uterine cavity following ELA and TCRE. Intra-uterine adhesions were rare, the common finding being an open, white cavity, which was usually associated with a good clinical outcome.

EFFECT OF SURGERY ON MENSTRUAL SYMPTOMS.

Hysterectomy of course guarantees amenorrhoea, which cannot be improved upon in the treatment of menorrhagia, so it becomes a matter of what percentage of this group of women become amenorrhoeic or hypomenorrhoeic after hysteroscopic surgery. This is complicated by the fact that assessment of menstrual loss is subjective and therefore unreliable, although each woman can compare her own periods before and after surgery.

The first assessment was at six months, as gradual improvement was found to occur before this time. Six women had had a hysterectomy by this time, usually because the original procedure had been incomplete or refused, but one because of symptoms in the early postoperative period, giving a 5% "failure rate". If women with continuing heavy periods are also included, the "failure rate" at six months was 20%, giving an 80% "success rate". The amenorrhoea rate of 20% is similar to other reports of three to six month results (Lomano et al, 1986), better than some (Davis, 1989, Dwyer et al, 1993) but lower than others (Daniell et al, 1986, Loffer, 1987, Baggish and Boltoyannis, 1988, Magos et al, 1989(b), Vancaillie, 1989, Boto et al, 1989, McLucas, 1990), although most of these series are of small numbers. Further surgery for continuing menstrual problems was usually requested between six and 12 months, emphasising the importance of longer term follow up than the studies mentioned above.

If continuing heavy periods or repeat surgery are taken as treatment failure, the failure rate at 12 months was 28%; if those successfully retreated by hysteroscopic methods are excluded, the failure rate was 17%. Although this may at first seem disappointing, 83% success is a great improvement on the results obtained with any medical therapy available at present. At 12 months, the amenorrhoea rate of 22% is similar to other reports of women followed up for 12 months or more (Magos et al, 1991, Fraser et al, 1993), less than others (Goldfarb, 1990, Goldrath, 1986(a),90, Gimpelson, 1988(a), Bent and Ostergard, 1990, Garry et al, 1991, DeCherney et al, 1983,87, Townsend et al, 1990) and better than some (Slade et al, 1991). At least one of these authors (Garry - personal communication) includes women with a brown discharge only in the "amenorrhoea" group, whereas in this study they were included in the

"hypomenorrhoea" category. This may explain the differences in outcome between the various papers mentioned above.

The overall success rate of 83% is similar to other longer term reports (Magos et al, 1991, Gannon et al, 1991, Goldfarb, 1990, Fraser et al, 1993), better than others (Gimpelson, 1988(a), Bent and Ostergard, 1990) and not as good as some (Goldrath, 1990, DeCherney et al, 1983,87, Garry et al, 1991, Townsend et al, 1990) although there were variable follow up intervals in these reports, from three months to 11 years. The other difference between this group of women and other studies (with the exception of the two other randomised trials) is that they did not choose the treatment and therefore were perhaps less motivated than those who did for it to succeed.

The majority of women in this study had dysmenorrhoea prior to surgery, and this usually improved postoperatively. However in 17% of the conservative surgery group at six months and 10% at 12 months it became more severe, and in four women laparoscopy was performed for pain. There was no evidence of haematometra in these women, although this did occur in one case. There has been anecdotal evidence of increased pain after ELA (Lomano et al, 1986) and TCRE (Magos et al, 1991, Slade et al, 1991) and seven women in the Bristol trial (Dwyer et al, 1993) had increased dysmenorrhoea following TCRE. This has led to the British Society for Gynaecological Endoscopy advising against hysteroscopic surgery in women with dysmenorrhoea, especially if premenstrual. However, pain is even more subjective than menorrhagia, and is known to persist after hysterectomy (Riedel et al, 1986, Stovall et al, 1990). Indeed, 15% of women in this study continued to have abdominal pain after hysterectomy. From the evidence of this trial, women can be reassured that pain is more likely to improve than deteriorate. Possible reasons for increased dysmenorrhoea

postoperatively could be altered prostaglandin production, or small "pockets" of endometrium continuing to bleed into fibrous scar tissue. This is a topic worth further research.

Conclusion.

Hysterectomy guarantees amenorrhoea, but not relief from pain. A proportion of women treated hysteroscopically, 11% in this study, request hysterectomy because of continuing menstrual symptoms. A further 11% requested a repeat hysteroscopic procedure for symptoms, usually with a good result. Despite this, hysteroscopic surgery appears to be a valuable alternative to hysterectomy in the majority of women with DUB, and also leads to relief of dysmenorrhoea in most cases.

EFFECT OF TREATMENT ON OTHER SYMPTOMS.

Urinary symptoms.

The women in this study had a high incidence of preoperative urinary symptoms, the commonest being stress incontinence, frequency and urgency. This has been noted by other authors (Jequier, 1976, Kilkku, 1985, Parys et al, 1989). No urodynamic investigations were carried out, so the true incidence of bladder dysfunction and genuine stress incontinence is not known, but in one prospective study with a similar incidence of symptoms, 39% of women had abnormalities (Parys et al, 1989). The only difference between the two groups at six and 12 months was in the incidence of urge incontinence at 12 months. These findings would tend to refute the argument that hysterectomy causes urinary symptoms because of altered anatomy, denervation or even

oestrogen deficiency (Hanley, 1969, Smith et al, 1970). Although the incidence of overall symptoms in both groups was significantly higher at six and 12 months, this was probably a design fault in the questionnaire, which did not adequately define nocturia. The only other symptoms to alter significantly were an increase in urge incontinence in the hysterectomy group at 12 months and a decrease in stress incontinence in the hysterectomy group at six months. This adds further confusion to the nature of the association between urinary symptoms and hysterectomy, but confirms that prospective randomised studies are essential in the study of postoperative bladder function.

Bowel function.

The incidence of bowel symptoms was lower than that of urinary symptoms, constipation being commoner than diarrhoea. No enquiry was made into other symptoms, such as those of the irritable bowel syndrome, which might have been valuable. The only significant change in frequency of symptoms was at one month, when, as might be expected, the incidence was higher in the hysterectomy group. These findings would not support the hypothesis (Taylor et al, 1989) that denervation at hysterectomy causes constipation, and again shows that prospective rather than retrospective studies are essential.

Dyspareunia.

Sexual function will be discussed more fully in the psychology section. The incidence of dyspareunia in these women was high - only 53% of sexually active women never experienced pain on intercourse. There was no difference between the groups or before

and after surgery in the incidence of this symptom, suggesting that anatomical change after hysterectomy does not lead to dyspareunia, but also that removal of the uterus does not lead to resolution of this complaint. One of the arguments for the recent development of laparoscopic supracervical hysterectomy is the preservation of sexual and urinary function. From the evidence of this trial comparing a group of women with conservation of the cervix with a group having had a total hysterectomy, this is not necessary.

Premenstrual symptoms.

These are discussed in the psychology section relating to the menstrual distress questionnaire. As this did not specifically ask about cyclical symptoms, women were also asked directly about breast discomfort, abdominal bloating, irritability and depression, and headaches occurring for part of every month. Similar to the menstrual distress questionnaire findings, breast symptoms, bloating and irritability were less common at six months in the hysterectomy group, but differences had mainly resolved by 12 months. Symptoms were less common in both groups postoperatively, with the exception of breast discomfort in the conservative group. This confirms the findings of other studies, one of hysterectomy (Osborn and Gath, 1990), one of ELA (Lefler, 1989) and one of rollerball ablation (Fraser et al, 1993), which showed a decrease in postoperative premenstrual symptoms. Dwyer et al (1993) also found that premenstrual bloating and breast tenderness were significantly less common at four months in women following hysterectomy, but found no difference in mood change, which improved in both groups to a similar degree. This suggests that symptoms are not related to ovarian function, as was previously thought, but either to the physical presence or psychological effects of menstruation.

Flushes.

Some of the studies which proposed that hysterectomy caused flushes or premature ovarian failure were based on postoperative symptoms (DeNeef and Hollenbeck, 1966, Riedel et al, 1986, Menon et al, 1987). A poor relationship between flushes and oestrogen level has been noted (DeNeef and Hollenbeck, 1966, Richards, 1974, Riedel et al, 1986, Menon et al, 1987). In this study, preoperative flushes were common, and unrelated to age. The incidence was unchanged postoperatively, with no difference between the two groups (except perioperatively due to the effect of the LHRH-agonist analogue used to prepare the endometrium in the hysteroscopic surgery group). This suggests that there is no early effect of hysterectomy on ovarian function (Coppen et al, 1981), although no hormone estimations were carried out in this study. Longer term follow up of these women, including hormone studies, is being undertaken to confirm or refute claims that hysterectomy causes premature ovarian failure (Siddle et al, 1987) or an increase in cardiovascular disease (Centerwall, 1981, Gordon et al, 1978, Punnonen et al, 1987), since for the first time there is a control group with the same underlying condition, DUB, which might itself possibly be a risk factor.

PSYCHOLOGY.

The psychological measures used in this study show a relatively high level of preoperative psychological morbidity in this group of women. The higher level of neuroticism and introversion in women with DUB has been noted previously (Coppen, 1963, Greenberg, 1983, Gath, 1987), as has the increased level of anxiety and depression (Ballinger, 1975, Worsley, 1977, Greenberg, 1983, Byrne, 1984, Salter, 1985, Gath, 1987, Martin, 1977, Gath, 1982, Ryan, 1989). However, the majority of

studies have not assessed the effect of treatment on psychological status. The only prospective studies have been of the effect of hysterectomy, and these are relatively few (Coppen et al, 1981, Tsoi et al, 1984, Chynoweth and Abrahams, 1977, Meikle et al, 1977, Martin et al, 1977, 1980, Gath et al, 1982, Ryan et al, 1989), the remainder of studies of hysterectomy and psychological factors being retrospective. If controls were used for comparison in these studies, they were women undergoing cholecystectomy (Bragg, 1965, Meikle et al, 1977) sterilisation (Meikle et al, 1977) or women who had not had a hysterectomy (Richards, 1973). Until the recently published randomised trial of TCRE and hysterectomy from Bristol (Dwyer et al, 1993) which used the GHQ, there had been no prospective randomised studies comparing the psychological effect of two forms of therapy for DUB.

At one month following the operation, there is probably the greatest difference in physical recovery between the two types of treatment, yet it is interesting to note that there was no difference between the anxiety and depression scores in the two groups, as measured by the HAD scale, or between the psychological distress scores of the PAIS. These were all significantly lower than the preoperative scores, at a time when neither group can be aware of the clinical effect of treatment on their symptoms. At six months the hysterectomy group continued to show improvement on the HAD scale, whereas the scores were significantly higher in the conservative treatment group. There was, however, no difference between the groups in the psychological distress score of the PAIS. In contrast, Dwyer et al (1993) found that 39% of women scored highly on the GHQ preoperatively, but although improvement was seen in both groups at four months, there was a greater improvement following TCRE than hysterectomy (25% were high scorers in the hysterectomy group, 8% in the TCRE group).

By twelve months, there was again no difference between the two groups on the HAD scale, or on the PAIS subscale. The differences in the two groups at six months are possibly related to persisting symptoms in some of the women treated by hysteroscopic surgery, which have been adequately dealt with by 12 months. The scores at six and 12 months were not statistically different to one month, suggesting that both treatments have a beneficial effect on psychological well-being, that this effect is seen early following treatment, and is then sustained. The low number of 'cases' in the women postoperatively, especially in those with low scores preoperatively, does not support the long-held belief that hysterectomy causes psychiatric disorders (Melody, 1962, Barker, 1968, Richards, 1973, Chynoweth and Abrahams, 1977, Kaltreider et al, 1979), but rather the more recent view that psychiatric symptoms can be alleviated by operative treatment of DUB (Coppen et al, 1981, Tsoi et al, 1984, Martin et al, 1980, Gath et al, 1982, Ryan et al, 1989). There were more 'cases' in those with high scores preoperatively, confirming previous findings that postoperative morbidity correlates with preoperative status (Tsoi et al, 1984, Martin et al, 1980, Ryan et al, 1989).

The "premenstrual syndrome" is hard to define, and claims have been made that up to 95% of women suffer from it. No definite pathophysiological cause has yet been identified, and this has led to the suggestion that it is psychologically based. (Magos and Studd, 1984). The women in this study had a high preoperative incidence of premenstrual-type symptoms. Although they were not (for the reasons previously given) asked about the cyclicity of the symptoms, they did not experience the 'control' symptoms to anything like the same degree. None of these operations should affect ovarian cyclical function, which has been thought to be the hormonal cause of premenstrual symptoms, but symptoms improved significantly postoperatively in both

groups, as previously noted (Lefler, 1989, Osborn and Gath, 1990). In the categories of pain, water retention and mood, the scores were significantly better in the hysterectomy group at six months. These findings suggest that either the origin of symptoms is not the ovary but the uterus, or, perhaps more likely, that the abolition of menstruation removes the recognisable 'trigger' for the cyclical symptoms, as has been previously noted in women following hysterectomy (Osborn and Gath, 1990). At 12 months there were no significant differences between the two groups, but since a higher proportion of the conservative group were amenorrhoeic because of subsequent therapy, perhaps the situation at six months is a truer reflection.

The significant differences in the PAIS work and family relationship sections at one month reflect the very different convalescence periods following hysterectomy and hysteroscopic surgery. However, there were no significant differences at six and 12 months, and no differences in the marital state scores at any time interval, suggesting that treatment of this kind does not disrupt social functioning for more than a short period, as found previously following hysterectomy (Gath et al, 1982, Ryan et al, 1989).

As with most other prospective studies (Chynoweth and Abrahams, 1977, Martin et al, 1980, Coppen et al, 1981) there was no consistent effect of hysterectomy (or hysteroscopic surgery) on sexual function, with the majority of women experiencing no change, and no differences between the two groups for any of the dimensions. This implies that physical changes such as altered anatomy or presence or absence of the cervix are not important factors, as was suggested by Zussman et al (1981).

Conclusion

Both forms of therapy for DUB appear to have an equally beneficial effect on psychological symptoms and premenstrual symptoms, which are common preoperatively, with minor differences in favour of hysterectomy at six months after treatment. Apart from the first few weeks following the operation, there were no differences in social or sexual functioning between the two groups of women.

PATIENT SATISFACTION

At 12 months, only five women said they were dissatisfied with the overall effects of treatment. This is a common finding in studies of patient satisfaction, as many factors such as attitudes to staff and the hospital are also taken into account when answering the question. Other studies of satisfaction after hysterectomy have shown levels to be high (Gath et al, 1982, Schofield et al, 1991, Dwyer et al, 1993), as are levels after hysteroscopic surgery (Magos et al, 1991, Rankin and Steinberg, 1992, Dwyer et al, 1993). However, women in the hysterectomy group were more likely to say they were very satisfied (89%) than the conservative group (78%) - this is similar to the Bristol study, which reported 94% versus 85% satisfaction (Dwyer et al, 1993).

The majority found the operation they had had "acceptable", with, perhaps surprisingly, no difference between the two groups at one month, but a significant difference in favour of hysterectomy at six months, presumably due to the delay involved in finding out whether the conservative procedures had been successful.

At 12 months the great majority of women felt their general health was the same or better than the year before, but with a significant difference in favour of hysterectomy. This is in contrast to Chynoweth and Abrahams (1977), who found that 26% of women felt their physical health deteriorated after hysterectomy.

The majority felt the operation had cured or significantly improved their original symptoms, but even in the hysterectomy group, some women said there had been no effect - in other words, amenorrhoea was not the only expectation in these women. There were significant differences in favour of hysterectomy at both six and 12 months. At six months 32% of the hysteroscopy group felt there had been no effect or insufficient improvement, but those who were unhappy usually opted for further treatment and only 11% said the same at 12 months (compared to 5% in the hysterectomy group).

Most women would recommend the same operation to a friend. At one month, there was a significant difference in favour of hysteroscopic surgery, due to the short recovery time, but by six and 12 months there were no significant differences between the two groups, with around 70% recommending the same, 10-15% recommending the other form of treatment, and the rest unsure. Dwyer et al (1993) found 95% would recommend the same operation, but probably did not include a "don't know" option.

In terms of patient satisfaction and preference therefore, neither type of operation had a clear advantage over the other, with the majority of women happy with the treatment they had received.

Conclusion.

Whichever of these results is taken to indicate "satisfaction", although satisfaction is in general significantly higher after hysterectomy, at least 70%, and perhaps as high as 96%, of women at present undergoing hysterectomy for DUB will be satisfied with the outcome of hysteroscopic surgery.

PREDICTIVE FACTORS FOR OUTCOME.

A significant proportion of women undergoing hysteroscopic surgery require a second procedure, either a repeat hysteroscopic operation or hysterectomy, for continuing symptoms. Although this does not appear to affect patient satisfaction to a great degree, it adds to the cost of the operation from the point of view of the health service, as well as the inconvenience to the woman herself. Many women are prepared to accept that further treatment may be necessary, but if there were a method of identifying those with a poorer chance of success, they might be better able to make an informed choice about whether to opt for hysterectomy in the first instance.

From this trial it was not possible to identify factors in the history, operative findings or psychological characteristics which differed between women having a successful outcome and those where the treatment was not successful. This tends to refute the suggestion that younger women, those with dysmenorrhoea or premenstrual symptoms, those with fibroids or possible adenomyosis should not be offered the chance of hysteroscopic endometrial ablation. Further follow-up and data from the second phase study of ELA and TCRE may however add to the information available about early and late treatment failure after conservative surgery.

Conclusion.

No predictive factors for good or poor outcome after hysteroscopic surgery were identified in this group of women.

CHAPTER 15. CONCLUSIONS AND IMPLICATIONS

In summary, the results of this trial with regard to the aims set out in the introduction were:

1) to compare the complication rates of hysterectomy, endometrial laser ablation and transcervical resection of the endometrium

Major complications were rare after all three operations, but minor morbidity was significantly more common following hysterectomy. There were no significant differences between ELA and TCRE.

2) to compare postoperative recovery after hysteroscopic surgery with that following hysterectomy

The time taken to recover completely and return to work after surgery was significantly reduced following hysteroscopic operations.

3) to compare the efficacy of hysteroscopic surgery with hysterectomy in the relief of dysfunctional uterine bleeding and other related symptoms

Hysteroscopic surgery is successful in the relief of DUB in around 80% of women at present treated by hysterectomy. Both types of operation are equally successful in relieving dysmenorrhoea.

4) to compare the effect of hysteroscopic surgery and hysterectomy on other symptoms

Premenstrual symptoms improved significantly in both groups, with a difference in favour of hysterectomy at six months, but no difference between the groups at 12 months. Neither type of operation had significant effects on urinary or bowel symptoms, dyspareunia or menopausal symptoms.

5) to compare the effects of the two types of operation on psychosocial factors

Anxiety and depression improved significantly postoperatively, with a difference in favour of hysterectomy at six months, but no difference between treatments at 12 months. With the exception of the first postoperative month, no other effects of either operation on psychosocial function were demonstrated.

6) to compare patient satisfaction with the two types of operation

Patient satisfaction was significantly higher following hysterectomy, but between 70 and 95% of this group of women were satisfied following hysteroscopic surgery.

7) to identify, if possible, predictive factors, in the history, examination, operative findings or psychosocial characteristics of women, for a good or poor outcome after hysteroscopic surgery

No predictive factors for outcome were identified.

IMPLICATIONS.

There has been debate recently about the best method of performing hysterectomy for DUB. Subtotal hysterectomy, vaginal hysterectomy, or laparoscopically assisted hysterectomy have all been proposed as "better" than total abdominal hysterectomy. The latter is however, the most common method in use in the UK at this time. We have again demonstrated its merits as a safe, effective operation with a high rate of patient satisfaction. If any of the above alternatives can decrease the infectious morbidity or reduce the postoperative recovery time, without increasing the major complication rate, this would be of great benefit. There is therefore further scope for randomised trials including hysterectomy as an option.

Hysteroscopic surgery is, however, a valuable alternative to hysterectomy, and should perhaps be offered to all women with DUB requiring operative treatment, as around 80% will have a satisfactory result, with a greatly reduced complication rate and a much shorter hospital stay and convalescence period. They should however be warned that there is no guarantee of amenorrhoea, and further treatment may be required. It is certainly an alternative to major surgery in women unfit for hysterectomy.

Hysteroscopic surgery is extremely attractive to many women who at present would not consider hysterectomy, and once readily available, many more women may come forward for treatment. Such treatment should not be lightly undertaken, as there are possible operative complications and a proportion require eventual hysterectomy. Perhaps randomised trials of hysteroscopic surgery versus medical treatment should be considered.

From the findings of this trial so far, there is nothing to choose between the two hysteroscopic operations. A second-phase study is being undertaken at present, continuing to randomise only between ELA and TCRE, to increase the power of the study in detecting significant differences in complications or outcomes between the two methods. Included in this trial is a randomised placebo-controlled study of antibiotic prophylaxis.

The women treated in this trial will continue to be followed up for life, to increase the state of knowledge about long-term implications of both hysterectomy and hysteroscopic surgery.

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Appendix 1.

HAD Scale

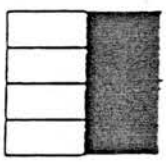
TWELVE MONTH QUESTIONNAIRE

Study no: **Date:**

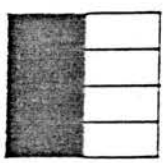
Please read each item and tick the box opposite the reply which comes closest to how you have been feeling *in the past week*. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick only one box in each section

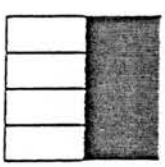
I feel tense or 'wound up':
- Most of the time .....
- A lot of the time .....
- Time to time, Occasionally .....
- Not at all .....



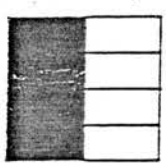
I still enjoy the things I used to enjoy:
- Definitely as much .....
- Not quite so much .....
- Only a little .....
- Hardly at all .....



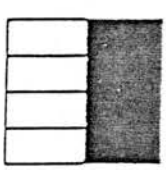
I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly .....
- Yes, but not too badly .....
- A little, but it doesn't worry me .....
- Not at all .....



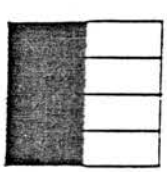
I can laugh and see the funny side of things:
- As much as I always could .....
- Not quite so much now .....
- Definitely not so much now .....
- Not at all .....



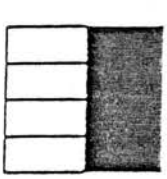
Worrying thoughts go through my mind:
- A great deal of the time .....
- A lot of the time .....
- From time to time but not too often ...
- Only occasionally .....



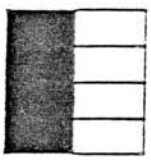
I feel cheerful:
- Not at all .....
- Not often .....
- Sometimes .....
- Most of the time .....



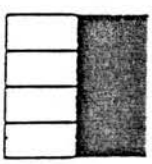
I can sit at ease and feel relaxed:
- Definitely .....
- Usually .....
- Not often .....
- Not at all .....



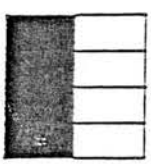
I feel as if I am slowed down:
- Nearly all the time .....
- Very often .....
- Sometimes .....
- Not at all .....



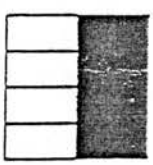
I get a sort of frightened feeling like 'butterflies' in the stomach:
- Not at all .....
- Occasionally .....
- Quite often .....
- Very often .....



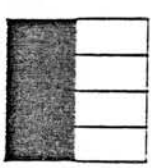
I have lost interest in my appearance:
- Definitely .....
- I don't take so much care as I should.....
- I may not take quite as much care .....
- I take just as much care as ever .....



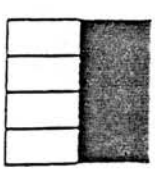
I feel restless as if I have to be on the move:
- Very much indeed .....
- Quite a lot .....
- Not very much .....
- Not at all .....



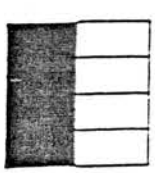
I look forward with enjoyment to things:
- As much as ever I did .....
- Rather less than I used to .....
- Definitely less than I used to .....
- Hardly at all .....



I get sudden feelings of panic:
- Very often indeed .....
- Quite often .....
- Not very often .....
- Not at all .....



I can enjoy a good book or radio or TV programme:
- Often .....
- Sometimes .....
- Not often .....
- Very seldom .....



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Appendix 2.

EYSENCK PERSONALITY QUESTIONNAIRE

Answer YES or NO to each question. Please answer all questions.

1. Do you have many different hobbies?
2. Do you stop to think things over before doing anything?
3. Does your mood often go up and down?
4. Have you ever taken the praise for something you knew someone else had really done?
5. Are you a talkative person?
6. Would being in debt worry you?
7. Do you ever feel "just miserable" for no reason?
8. Were you ever greedy by helping yourself to more than your share of anything?
9. Do you lock up your house carefully at night?
10. Are you rather lively?
11. Would it upset you a lot to see a child or an animal suffer?
12. Do you often worry about things you should not have done or said?
13. If you say you will do something, do you always keep your promise no matter how inconvenient it might be?
14. Can you usually let yourself go and enjoy yourself at a lively party?
15. Are you an irritable person?
16. Have you ever blamed someone for doing something you knew was really your fault?
17. Do you enjoy meeting new people?
18. Do you believe insurance schemes are a good idea?
19. Are your feelings easily hurt?
20. Are all your habits good and desirable ones?
21. Do you tend to keep in the background on social occasions?
22. Would you take drugs which may have strange or dangerous effects?
23. Do you often feel "fed-up"?
24. Have you ever taken anything (even a pin or a button) that belonged to some-one else?
25. Do you like going out a lot?
26. Do you enjoy hurting people you love?
27. Are you often troubled about feelings of guilt?
28. Do you sometimes talk about things you know nothing about?
29. Do you prefer reading to meeting people?
30. Do you have enemies who want to harm you?
31. Would you call yourself a nervous person?
32. Do you have many friends?
33. Do you enjoy practical jokes that can sometimes really hurt people?
34. Are you a worrier?
35. As a child did you do as you were told immediately and without grumbling?
36. Would you call yourself happy-go-lucky?
37. Do good manners and cleanliness matter much to you?
38. Do you worry about awful things that might happen?
39. Have you ever broken or lost something belonging to someone else?
40. Do you usually take the initiative in making new friends?
41. Would you call yourself tense or "highly-strung"?
42. Are you mostly quiet when you are with other people?
43. Do you think marriage is old-fashioned and should be done away with?
44. Do you sometimes boast a little?
45. Can you easily get some life into a rather dull party?
46. Do people who drive carefully annoy you?
47. Do you worry about your health?

48. Have you ever said anything bad or nasty about anyone?
49. Do you like telling jokes and funny stories to your friends?
50. Do most things taste the same to you?
51. As a child were you ever cheeky to your parents?
52. Do you like mixing with people?
53. Does it worry you if you know there are mistakes in your work?
54. Do you suffer from sleeplessness?
55. Do you always wash before a meal?
56. Do you nearly always have a "ready answer" when people talk to you?
57. Do you like to arrive at appointments in plenty of time?
58. Have you often felt listless and tired for no reason?
59. Have you ever cheated at a game?
60. Do you like doing things in which you have to act quickly?
61. Is (or was) your mother a good woman?
62. Do you often feel life is very dull?
63. Have you ever taken advantage of someone?
64. Do you often take on more activities than you have time for?
65. Are there several people who keep trying to avoid you?
66. Do you worry a lot about your looks?
67. Do you think people spend too much time safeguarding their future with savings and insurances?
68. Have you ever wished that you were dead?
69. Would you dodge paying taxes if you were sure you could never be found out?
70. Can you get a party going?
71. Do you try not to be rude to people?
72. Do you worry too long after an embarrassing experience?
73. Have you ever insisted on having your own way?
74. When you catch a train do you often arrive at the last minute?
75. Do you suffer from "nerves"?
76. Do your friendships break up easily without it being your fault?
77. Do you often feel lonely?
78. Do you always practice what you preach?
79. Do you sometimes like teasing animals?
80. Are you easily hurt when people find fault with you or the work you do?
81. Have you ever been late for an appointment or work?
82. Do you like plenty of bustle and excitement around you?
83. Would you like other people to be afraid of you?
84. Are you sometimes bubbling over with energy and sometimes very sluggish?
85. Do you sometimes put off until tomorrow what you ought to do today?
86. Do other people think of you as being very lively?
87. Do people tell you a lot of lies?
88. Are you touchy about some things?
89. Are you always willing to admit it when you have made a mistake?
90. Would you feel very sorry for an animal caught in a trap?

Appendix 3.

MARITAL STATE QUESTIONNAIRE

Read each of the following statements carefully and decide which response best describes how you feel about your relationship with your partner. Each question is followed by a series of possible responses. Please tick the corresponding response.

- Strongly agree
- Agree
- Neither agree nor disagree
- Disagree
- Strongly disagree

1. My partner is usually sensitive to and aware of my needs
2. My partner doesn't seem to like me any more
3. We can 'agree to disagree' with each other
4. I am dissatisfied with our relationship
5. I sometimes feel lonely even when I am with my partner
6. We both seem to like the same things
7. I find it difficult to show my partner that I am feeling affectionate
8. I enjoy just sitting and talking with my partner
9. I find the idea of spending the rest of my life with my partner rather boring
10. I am totally committed to my relationship with my partner
11. Our relationship is still full of joy and excitement
12. I wish there was more warmth and affection between us
13. There is always plenty of 'give and take' in our relationship
14. I suspect we may be on the brink of separation

Appendix 4.

MENSTRUAL DISTRESS QUESTIONNAIRE

Here is a list of symptoms that women sometimes experience.

Please indicate whether you have had any of these symptoms at any time in the last thirty days and grade the severity by circling the relevant category

0 - did not have this symptom
1 - barely noticeable
2 - present, mild
3 - present, moderate
4 - present, strong
5 - acute or partially disabling

1	Unable to sleep	0	1	2	3	4	5
2	Crying	0	1	2	3	4	5
3	Forgetfulness	0	1	2	3	4	5
4	Loneliness	0	1	2	3	4	5
5	Feeling suffocated	0	1	2	3	4	5
6	Cramps (abdominal/pelvis/thighs)	0	1	2	3	4	5
7	Dizziness	0	1	2	3	4	5
8	Avoiding social activities	0	1	2	3	4	5
9	Anxiety	0	1	2	3	4	5
10	Backache	0	1	2	3	4	5
11	Fatigue	0	1	2	3	4	5
12	Nausea/vomiting	0	1	2	3	4	5
13	Restlessness	0	1	2	3	4	5
14	Difficulty concentrating	0	1	2	3	4	5
15	Breast pain/tenderness	0	1	2	3	4	5
16	Feeling of wellbeing	0	1	2	3	4	5
17	Buzzing or ringing in the ears	0	1	2	3	4	5
18	Irritability	0	1	2	3	4	5
19	Mood swings	0	1	2	3	4	5
20	Palpitations	0	1	2	3	4	5
21	Feeling sad/blue	0	1	2	3	4	5
22	Clumsiness	0	1	2	3	4	5
23	Numbness/tingling in hands or feet	0	1	2	3	4	5
24	Change in eating habits	0	1	2	3	4	5
25	Feeling tense	0	1	2	3	4	5
26	Blind spots/fuzzy vision	0	1	2	3	4	5
27	Bursts of energy/activity	0	1	2	3	4	5
28	Swelling abdomen/breasts/ankles	0	1	2	3	4	5

Appendix 5.

Psychosocial adjustment to illness scale

This questionnaire refers to the past 30 days. Tick one answer for each question

Section 1

1 Which of the following statements best describes your usual attitude about taking care of your health?

- I am very concerned and pay close attention to my personal health
- Most of the time I pay attention to my health care needs
- Usually, I try to take care of health matters but sometimes I just don't get around to it
- Health care is something that I just don't worry too much about

2 Your present illness probably requires some special attention and care on your part. Would you please select the statement below that best describes your reaction.

- I do things pretty much the way I always have done them and I don't worry or take any special considerations for my illness.
- I try to do all the things I am supposed to do to take care of myself, but lots of times I forget or I am too tired or busy
- I do a pretty good job taking care of my present illness
- I pay close attention to all the needs of my present illness and do everything I can to take care of myself

3 In general, how do you feel about the quality of medical care available today and the doctors who provide it?

- Medical care has never been better, and the doctors who give it are doing an excellent job
- The quality of medical care available is very good, but there are some areas that could stand improvement
- Medical care and doctors are just not of the same quality they once were
- I don't have much faith in doctors and medical care today

4 During your present illness you have received treatment from both doctors and medical staff. How do you feel about them and the treatment you have received from them?

- I am very unhappy with the treatment I have received and don't think the staff has done all they could have for me
- I have not been impressed with the treatment I have received, but I think it is probably the best they can do
- The treatment has been pretty good on the whole, although there have been a few problems
- The treatment and the treatment staff have been excellent

5 When they are ill, different people expect different things about their illness, and have different attitudes about being ill. Could you please check the statement below which comes closest to describing your feelings.

- I am sure that I am going to overcome the illness and its problems quickly and get back to being my old self
- My illness has caused some problems for me, but I feel I will overcome them fairly soon, and get back to the way I was before
- My illness has really put a great strain on me, both physically and mentally, but I am trying very hard to overcome it, and feel sure that I will be back to my old self one of these days
- I feel worn out and very weak from my illness and there are times when I don't know if I am really ever going to be able to overcome it

6 Being ill can be a confusing experience, and some patients feel that they do not receive enough information and detail from their doctors and the medical staff about their illnesses. Please select a statement below which best describes your feeling about this matter.

- My doctor and the medical staff have told me very little about my illness even though I have asked more than once
- I do have some information about my illness but I feel I would like to know more
- I have a pretty fair understanding about my illness and feel that if I want to know more I can always get the information
- I have been given a very complete picture of my illness and my doctor and the medical staff have given me all the details I wish to have

7 In an illness such as yours, people have different ideas about their treatment and what to expect from it. Please select one of the statements below which best describes what you expect about your treatment.

- I believe my doctors and medical staff are quite able to direct my treatment and feel it is the best treatment I could receive
- I have trust in my doctor's direction of my treatment; however, sometimes I have doubts about it
- I don't like certain parts of my treatment which are very unpleasant, but my doctors tell me I should go through with it anyway
- In many ways I think my treatment is worse than the illness, and I am not sure it is worth going through it

8 In an illness such as yours patients are given different amounts of information about their treatment. Please select a statement from those below which best describes information you have been given about your treatment.

- I have been told almost nothing about my treatment and feel left out about it
- I have some information about my treatment but not as much as I would like to have
- My information concerning treatment is pretty complete, but there are one or two things I still want to know
- I feel my information concerning treatment is very complete and up to date

Section 2.

1 Has your illness interfered with your ability to do your job?

- No problem with my job
- Some problems, but only minor ones
- Some serious problems
- Illness has totally prevented me from doing my job

2 How well do you physically perform your job now?

- Poorly
- Not too well
- Adequately
- Very well

3 During the past 30 days, have you lost any time at work due to your illness?

- 3 days or less
- 1 week
- 2 weeks
- More than 2 weeks

4 Is your job as important to you now as it was before your illness?

- Little or no importance to me now
- A lot less important
- Slightly less important
- Equal or greater importance than before

5 Have you had to change your goals concerning your job as a result of your illness?

- My goals are unchanged
- There has been a slight change in my goals
- My goals have changed quite a bit
- I have changed my goals completely

6 Have you noticed any increase in problems with your co-workers since your illness?
- A great increase in problems
- A moderate increase in problems
- A slight increase in problems
- None

Section 3.

1 How would you describe your relationship with your partner since your illness?
- Good
- Fair
- Poor
- Very poor

2 How would you describe your general relationships with the other people you live with?
- Very poor
- Poor
- Fair
- Good

3 How much has your illness interfered with your work and duties around the house?
- Not at all
- Slight problems, easily overcome
- Moderate problems, not all of which can be overcome
- Severe difficulties with household duties

4 In those areas where your illness has caused problems with your household work, how has the family shifted duties to help you out?
- The family has not been able to help out at all
- The family has tried to help but many things are left undone
- The family has done well except for a few minor things
- No problems

5 Has your illness resulted in a decrease in communication between you and members of your family?
- No decrease in communication
- A slight decrease in communication
- Communication has decreased, and I feel somewhat withdrawn from them
- Communication has decreased a lot, and I feel very alone

6 Some people with an illness like yours feel they need help from other people to get things done from day to day. Do you feel you need such help and is there anyone to provide it?
- I really need help; but seldom is anyone around to help
- I get some help, but I can't count on it all the time
- I don't get all the help I need all of the time, but most of the time help is there when I need it
- I don't feel I need such help, or the help I need is available from my family or friends

7 Have you experienced any physical disability with your illness?
- No physical disability
- A slight physical disability
- A moderate physical disability
- A severe physical disability

8 An illness such as yours can sometimes cause a drain on the family's finances; are you having any difficulties meeting the financial demands of your illness?
- Severe financial hardship
- Moderate financial problems
- A slight financial drain
- No money problems

Section 4.

1 Sometimes having an illness can cause problems in a relationship. Has your illness led to any problems with your partner?

- There has been no change in our relationship
- We are a little less close since my illness
- We are definitely less close since my illness
- We have had serious problems or a break in our relationship since my illness

2 Sometimes when people are ill they report a loss of interest in sexual activities. Have you experienced less sexual interest since your illness?

- Absolutely no sexual interest since illness
- A marked loss of sexual interest
- A slight loss of sexual interest
- No loss of sexual interest

3 Illness sometimes causes a decrease in sexual activity. Have you experienced any decrease in the frequency of your sexual activities?

- No decrease in sexual activities
- Slight decrease in sexual activities
- Marked decrease in sexual activities
- Sexual activities have stopped

4 Has there been any change in the pleasure or satisfaction you normally experience from sex?

- Sexual pleasure and satisfaction have stopped
- A marked loss of sexual pleasure or satisfaction
- A slight loss of sexual pleasure or satisfaction
- No change in sexual satisfaction

5 Sometimes an illness will cause an interference in a person's ability to perform sexual acitivities even though they are still interested in sex. Has this happened to you, and if so, to what degree.

- No change in my ability to have sex
- Slight problems with my sexual performance
- Constant sexual performance problems
- Totally unable to perform sexually

6 Sometimes an illness will interfere with a couples' normal sexual relationship and cause arguments or problems between them. Have you and your partner had any arguments like this, and if so, to what degree?

- Constant arguments
- Frequent arguments
- Some arguments
- No arguments

Section 5.

1 Have you had as much contact as usual with members of your family outside your household since your illness?

- Contact is the same or greater since illness
- Contact is slightly less
- Contact is markedly less
- No contact since illness

2 Have you remained as interested in getting together with these members of your family since your illness?

- Little or no interest in getting together with them
- Interest is a lot less than before
- Interest is slightly less
- Interest is the same or greater since illness

3 Sometimes, when people are ill, they are forced to depend on members of the family outside their household for physical help. Do you need physical help from them, and do they supply the help you need?
- I need no help, or they give me all the help I need
- Their help is enough, except for some minor things
- They give me some help but not enough
- They give me little or no help even though I need a great deal

4 Some people socialize a great deal with members of their family outside their immediate household. Do you do much socializing with these family members, and has your illness reduced such socializing?
- Socializing with them has been pretty much eliminated
- Socializing with them has been reduced significantly
- Socializing with them has been reduced somewhat
- Little or no socializing, or slight or no effect of illness

5 In general, how have you been getting along with these members of your family recently?
- Good
- Fair
- Poor
- Very poor

Section 6.

1 Are you still as interested in your leisure time activities and hobbies as you were prior to your illness?
- Same level of interest as previously
- Slightly less interest than before
- Significantly less interest than before
- Little or no interest remaining

2 How about actual participation? Are you still actively involved in doing those activities?
- Little or no participation at present
- Participation reduced significantly
- Participation reduced slightly
- Participation remains unchanged

3 Are you as interested in leisure time activities with your family as you were prior to your illness?
- Same level of interest as previously
- Slightly less interest than before
- Significantly less interest than before
- Little or no interest remaining

4 Do you still participate in those activities to the same degree you once did?
- Little or no participation at present
- Participation reduced significantly
- Participation reduced slightly
- Participation remains unchanged

5 Have you maintained your interest in social activities since your illness?
- Same level of interest as previously
- Slightly less interest than before
- Significantly less interest than before
- Little or no interest remaining

6 How about participation? Do you still go out with your friends and do those things?
- Little or no participation at present
- Participation reduced significantly
- Participation reduced slightly
- Participation remains unchanged

Section 7.

1 Recently, have you felt afraid, tense, nervous, or anxious?
- Not at all
- A little bit
- Quite a bit
- Extremely

2 Recently, have you felt sad, depressed, lost interest in things, or felt hopeless?
- Extremely
- Quite a bit
- A little bit
- Not at all

3 Recently, have you felt angry, irritable, or had difficulty controlling your temper?
- Not at all
- A little bit
- Quite a bit
- Extremely

4 Recently, have you blamed yourself for things, felt guilty, or felt like you have let people down?
- Extremely
- Quite a bit
- A little bit
- Not at all

5 Recently, have you worried much about your illness or other matters?
- Not at all
- A little bit
- Quite a bit
- Extremely

6 Recently, have you been feeling down on yourself or less valuable as a person?
- Extremely
- Quite a bit
- A little bit
- Not at all

7 Recently, have you been concerned that your illness has caused changes in the way you look that make you less attractive?
- Not at all
- A little bit
- Quite a bit
- Extremely