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The efficacy, side-effects and continuation rates in women with symptomatic endometriosis undergoing treatment with an intra-uterine administered progestogen (levonorgestrel): a 3 year follow-up

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BACKGROUND: Side-effects and choice of drugs influence compliance during treatment for endometriosis. Progestogen administered by a device with a 5-year lifespan, has been shown to be an effective medical alternative with several advantages. The aims of this study were to investigate its efficacy, continuation rates and side-effects in women with endometriosis over a 3-year period. METHODS: Thirty-four women with laparoscopically confirmed minimal to moderate symptomatic endometriosis offered insertion of an intrauterine device at diagnostic laparoscopy were followed up at 1, 3 and 6 months, and then every 6 months for 3 years. A symptom diary for side-effects, documentation of symptoms on a visual analogue scale (VAS), a verbal rating scale (VRS) and quantified menstrual loss using the pictorial blood loss chart was used to assess response to treatment. RESULTS: The continuation rates were respectively 85%, 68%, 62% and 56% at, 6, 12, 24 and 36 months. Discontinuation rates were highest at <12 months, and most of these were for irregular and intolerable bleeding and persistent pain. An improvement in symptoms was observed throughout the 36 months. The greatest changes in pain assessed by either the VAS or VRS were between the pretreatment scores and those after 12 months (7.7 ± 1.3 versus 3.5 ± 1.8 for VAS, $P < 0.001$; and 25 ± 13.8 versus 14 ± 9.4 for VRS, $P < 0.002$). The monthly quantified blood loss fell from 204 (196) pretreatment to 60 (50) at 12 months ($P < 0.001$) and then to 70 (30) after 36 months. The most common side-effects were bleeding irregularities (14.7%), one-sided abdominal pain (11.8%) and weight gain (8.8%). CONCLUSIONS: Intrauterine progestogen is effective in symptom control throughout the 3 years on the device, and discontinuation is greatest between 3 and 6 months. For those patients with improvement in symptoms, it is an acceptable long-term alternative.

Key words: endometriosis/levonorgestrel/3 year follow-up

Introduction

Endometriosis, an estrogen-dependent condition, affects ~6–20% of women of reproductive age (Winkel, 2003). The most common symptoms are pelvic pain, and menstrual and sexual dysfunction. Therapeutic options include antiestrogens (e.g. progestogens, androgens such as danazol) and drugs that induce either a pseudomenopause (e.g. GnRH agonists) or a pseudo-pregnancy state (e.g. combined oral contraceptive pills) (Winkel and Scialli, 2001). More recently, the aromatase inhibitor anastrazole has been shown to be effective in women with refractory endometriosis (Takayama *et al.*, 1998; Ailawadi *et al.*, 2004). Though effective, most of these options are associated with systemic side-effects, which may affect compliance and preclude long-term use. Furthermore, the need for repeated or regular administration compromises compliance and therefore efficacy. This is more so with oral and depot progestogens, which although cheap and efficacious are associated with poorly tolerated side-effects of irregular vaginal bleeding, weight gain, fluid retention, seborrhoea and breast tenderness.

The advent of the levonorgestrel intrauterine system Mirena® provides an alternative route of delivering the 19-C progestogen (levonorgestrel) directly into the uterine cavity at a steady rate of 20 mg/day over a 5-year period (Bilian *et al.*, 1990; Andersson *et al.*, 1994). Since systemic levels following this route of administration are less than those achieved with oral (Nilsson *et al.*, 1980; Luciano *et al.*, 1988; Monghissi, 1999) or depot (Du *et al.*, 1999) progestogens, side-effects should theoretically be less severe (Van de Hurk and O'Brien, 1999). This has indeed been demonstrated to be the case when the device is used to treat women with menorrhagia, where it has been shown to be highly effective (Lahteenmaki *et al.*, 1998; Stewart *et al.*, 2001). Levonorgestrel delivered this way, however, has only recently been

demonstrated to alleviate symptoms of pelvic endometriosis during a period of either 6 months (Lockhat *et al.*, 2004) or 12 months (Vercelleni *et al.*, 1999) and also in women with adenomyosis and rectovaginal endometriosis (Fedele *et al.*, 2001).

Mirena confers several advantages over the oral or depot routes of administration. Apart from the fewer side-effects, there is no need for repeated administration, thus overcoming the problem of remembering to take the tablets regularly or the depot injection every 3 months, and there is no need for contraception. Although the device, which has a life span of 5 years, has been shown to control menorrhagia for this duration, such information is unavailable for its use in endometriosis.

We recently published our pilot data from an observational study of the effectiveness of this device on symptom control over the first 6 months (Lockhat *et al.*, 2004). We present here follow-up data on the evaluation of the efficacy of Mirena as a long-term (3 years) option for endometriosis concentrating on symptom control, side-effects and continuation rates.

Subjects and methods

The subjects were mainly women aged between 18 and 42 years who underwent a diagnostic laparoscopy for either known endometriosis, who had been previously treated but were representing with recurring symptoms, or suspected endometriosis based on a history of cyclical lower abdominal pain associated with deep dyspareunia and/or menorrhagia. The inclusion criteria included no hormonal therapy in the preceding 3 months, no immediate desire to conceive, no clinical history of pelvic inflammatory disease, no contraindications to the use of an intrauterine contraceptive device and laparoscopically diagnosed minimal to moderate endometriosis (American Fertility Society, 1985). Those with severe and extensive disease, including those with ovarian endometriotic cyst, dense adhesions and deep rectovaginal disease, were excluded as these are commonly treated by surgery in our unit. No additional surgical procedure was undertaken at the laparoscopy.

For the month preceding the Mirena insertion, each patient completed a diary for the generation of baseline variables, which were used for the assessment of response to treatment. Response to treatment was assessed by changes in the variables, which included the patient's perception of pelvic pain severity using a visual analogue scale (VAS), her rating of both types of pelvic pain (dysmenorrhoea and/or non-cyclical pelvic pain) on a verbal rating scale (VRS), a monthly pelvic pain and bleeding score.

The VAS was a subjective assessment of the pain on a scale of 0 (no pain) to 10 (most severe pain). It was recorded on a 10-cm ruler in the diary at each follow-up visit and reflected the severity of this symptom as perceived by the patient in the preceding month. A 4-point scale (0–3; where 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain) was used to rate dysmenorrhoea and/or non-cyclical pain on a daily basis. A monthly score was then generated from the summation of the daily VRS over a 28-day period (0 = no pain, 96 = maximum pain). Once again, this $VRS_{monthly}$ was only determined for the 28 days prior to the follow-up visit. Menstrual loss was quantified using the pictorial blood loss assessment chart (PBAC) described by Higham *et al.* (1990). A score of >100 was used to define menorrhagia. Only the loss in the month prior to a follow-up visit was quantified.

Follow-up visits after the Mirena insertion were initially after 1, 3 and 6 months, and thereafter every 6 months. A month before each visit, the patients completed a diary of their pain scores and menstrual loss. These were collected at the follow-up visit and new diaries given for the next visits. Each subject signed an informed consent to partake in the study, which was also approved by the local ethics committee.

Data analysis

SPS version 11.0 was used to record and statistically analyse the data. Values at the time of the insertion of the intrauterine system (i.e. time zero) were compared with those at different time points after insertion using the paired *t*-test or Wilcoxon rank analysis as appropriate. Additionally, perception by the patient of the efficacy of the device in pain control was evaluated at 1, 3, 6, 12, 18, 24, 30 and 36 months using a VAS, as well as overall satisfaction with the treatment (taking into account the undesirable side-effects) as indicated on a 4-point VRS.

Results

A total of 45 patients underwent the initial laparoscopy to diagnose and stage the endometriosis. Fifteen of these were known cases of endometriosis. Out of the remaining 30 undergoing the procedure on the basis of symptoms, 22 (73.3%) were newly diagnosed cases. Of the 37 women with endometriosis, three were excluded at the initial laparoscopy for the following reasons: Fitz–Hughes–Curtis syndrome (which was taken to indicate previous *Chlamydia trachomatis* infection) (one patient) and severe (American Fertility Society, 1985) disease requiring surgical intervention (two patients). The mean age of the remaining 34 women forming the subjects of the study was 31 ± 7.2 years (range 18–42). There were 13 patients with minimal disease, 15 with mild and six with moderate disease. The 6-month data on the effect of Mirena on endometriosis have already been published (Lockhat *et al.*, 2004).

The continuation rates and reasons for requesting for removal over the 3-year period are shown in Table I. The device was retained by 29 (85%) women at 6 months,

Table I. Indications for and timing of removal of Mirena over a period of 3 years

Indication for removal	Number	Time of removal (months)[a]
Personal	1	4
Pelvic pain	3	1, 3 and 4
Acne	1	5
Migraine headaches, weight gain, irregular bleeding	1	6
Weight gain and acne	1	6
Minimal/no improvement in pain and irregular bleeding	4	6
Irregular bleeding	1	15
Weight gain and persistent abdominal pain (functional ovarian cyst on scan)	1	18
Unacceptable spotting	1	20
Wanting to start a family	1	23
Total (%)	15 (44.1)	

[a]The time of removal (in months) is given as the total number of completed months after Mirena insertion.

Table II. Changes in the VAS, $VRS_{monthly}$ pain and menstrual scores during 3 years on Mirena

Months	0	3	6	12	18	24	30	36
No. of patients	34	34	29	23	23	21	21	19
VAS	7.7 (1.3)	6.1 (2.4)[a]	4.6 (3.0)[b]	3.5 (1.8)[c]	3.2 (2.0)[c]	2.8 (1.6)[c]	2.4 (1.3)[c]	2.7 (1.5)[c]
$VRS_{monthly}$	25 (13.8)	22 (15.7)[a]	19 (18.9)[b]	14 (9.4)[c]	11 (5.2)[c]	10 (3.7)[c]	10.4 (2.9)[c]	8.4 (3.5)[c]
Quantified monthly menstrual loss	204 (196)	129 (273)[b]	90 (157)[b]	60 (50)[c]	64 (32)[c]	58 (28)[c]	63 (40)[c]	70 (30)[c]

The *P*-values are for comparisons with pre-insertion values.
[a]$P > 0.05$;
[b]$P < 0.05$;
[c]$P < 0.002$.

23 (68%) at 12 months, 21 (62%) at 24 months and 19 (56%) at 36 months. There were five discontinuations before 6 months for personal reasons (one), pelvic pain (three) and acne (one). After 6 months, six requested removal because of weight gain and acne (one), migraine headaches, weight gain and irregular periods (one), and no improvement in symptoms and irregular bleeding (four). There were only four patients who requested the device to be removed after 12 months, the reasons being bleeding problems (two), weight gain and persistent abdominal pain that was thought to be related to a functional ovarian cyst (one), and planning to start a family (one). Out of a total of 15 discontinuations, five (33%) were for unacceptable irregular bleeding (unscheduled bleeding), most of which were within the first 6 months. Pelvic pain (20.6%) and weight gain (8.8%) were the second and third most common reason for requesting for removal, respectively. There were no expulsions over the 3-year period.

The changes in the VAS over the 3 years are shown in Table II. This fell continuously from a pre-insertion score of 7.7 (1.3) to a nadir of 2.4 (1.3) at 30 months and then rose slightly to 2.7 (1.5) at 36 months. The differences between VAS pre-insertion and subsequent follow-up scores after 6 months were all statistically significant ($P < 0.05$). The VRS for dysmenorrhoea fell throughout the 3 years on Mirena. The greatest change in VRS was achieved during the first 18 months on Mirena. Of the 27 patients experiencing moderate to severe dysmenorrhoea pre-insertion, 19 (70%) continued to have similar pains at 3 months ($P = 0.001$), 15 (51%) at 6 months ($P < 0.001$), seven (26%) at 12 months ($P < 0.001$) and only three (11.1%) at 18 months ($P < 0.0001$). At 24 months, only one patient continued to experience moderate, rather than severe, dysmenorrhea, which she found acceptable and hence retained the device. There were five (18.5%) discontinuations in these 27 cases, one each at 1, 3, 4, 6 and 18 months after insertion. The main reason for discontinuation was persistent pain. Overall, there was no consistent response pattern based on the stage or score of the disease; in the group of seven patients who experienced no effect of the treatment on pain, three had minimal, three mild and one minimal disease.

The total number of days of pain experienced during a 28-day period were determined from the diaries returned at the follow-up visits. This fell from a mean of 15.0 days (6.9) to 10.7 days (8.7) after 6 months therapy ($P < 0.05$) and to 6 days (3.4) after 12 months ($P < 0.001$).The mean score for pain per month (out of a total of 84) dropped from 25 (13.8) pre-insertion to 19 (18.9) 6 months later; this change was not statistically significant ($P = 0.076$). However, after 12 months, the mean score per month had dropped to 14 (9.4) and this change was statistically significant compared with pretreatment values ($P < 0.05$). There was a further statistically significant ($P < 0.001$) fall to 11 (5.2) after 18 months, but thereafter the fall was small and not statistically significant. The changes in the quantified menstrual loss from the PBAC chart are shown in Table II. This fell from 204 (196) pre-insertion to 90 (157) after 6 months of treatment ($P < 0.001$). There was further statistically significant ($P < 0.05$) reduction in the total blood loss after 12 months. Although this number did not change significantly over the remaining 2 years, most of them were reported as spotting rather than heavy bleeding.

Table III demonstrates the side-effects reported by the patients during the study period. The most common was irregular vaginal bleeding. There was a single case of severe depression, which responded well to a 3-month course of antidepressants. She was not willing to discontinue the device as it had significantly improved the quality of her life. The partners of two patients complained of discomfort during sexual intercourse caused by the strings of the device. Although these were shortened, the discomfort persisted but in a mild form, hence the patients retained the device. There were three cases of simple functional ovarian cysts diagnosed at laparoscopy and confirmed on ultrasound scan. Two of these presented with one-sided abdominal pain. All cases were monitored with serial ultrasound scan only.

Discussion

Our results confirm that this device is effective in symptom control for at least 3 years. The symptoms continued to improve, albeit less dramatically after the first 12–18 months on the device. Although a few of the patients experienced the typical systemic side-effects of progestogens, these were mild and tolerable. These results provide ample support for the use of this device in those women who are not immediately desirous of pregnancy. The benefits of using Mirena on even a short-term basis significantly outweigh the cost of a 6 months course of a GnRH agonist. The continuation rate after 3 years was 55.9%, similar to that in women using the device for contraception (Andersson *et al.*, 1994; Faculty of Family Planning and Reproductive Health Care Guidance, 2004) and as treatment of menorrhagia (Hurskainen *et al.*, 2004). It is, however, difficult to compare this with other

Table III. Side-effects reported during the 3-year period on Mirena

Side-effect	Number	Percent of the total ($n = (34)$ population
Irregular bleeding	5	14.7
One sided lower abdominal pain	4	11.8
Weight gain	3	8.8
Acne	2	5.9
Breast tenderness	2	5.9
Partner experiencing discomfort during sexual intercourse	2	5.9
Depression	1	2.9

medical treatment options, as these often involve a much shorter duration. An advantage of Mirena over other medical treatment options, which are usually short-term, is obviation of the need for repeated treatment (often with alternate regimens) where symptoms recur (in up 75% of patients within 5 years; Surrey and Hornstein, 2002) and the lack of need for additional contraception.

The main reasons for discontinuation were menstrual irregularities, persistent pelvic pain and weight gain. The menstrual problems were predominantly during the first 6 months on the device. These findings are not dissimilar to those in women on the device for contraception and the treatment of menorrhagia. In this study only two patients requested that the device be removed, for unacceptable spotting after the first 6 months. If this information is provided to patients during counselling and at follow-up visits, we would anticipate the continuation rates to remain high. Although there have been anectodal approaches to managing irregular bleeding in such women, such as the short-term use of the combined oral contraceptive pill, there are no studies on the best approach to treatment. Until this evidence is available, we would advocate a careful selection of patients, pre-insertion counselling supported by information leaflets and regular re-assuring follow-up visit during the first 6 months.

The most dramatic improvements in symptoms as determined by the VAS, VRS and quantified blood loss occurred during the first 12 months of therapy. Thereafter, there were no significant changes in the variables used to assess response to treatment over the remaining 24 months. Whether these improvements in symptoms will persist for the entire 5 years remains to be determined.

The proportion of women experiencing unacceptable unscheduled bleeding was similar to that reported by Vercellini and colleagues (Vercellini *et al.*, 1999; 2003). However, the proportion of those continuing with the device at 12 months was lower in our study compared with that reported previously (Vercellini *et al.*, 1999; 2003; Fedele *et al.*, 2001). The drop-out rates between 12 and 36 months were, however, higher in patients having the device as adjunct to surgery (Vercellini *et al.*, 2003) compared with our study, where it was used as the only treatment modality. These differences could partly be explained by the patients enrolled in these studies: a large proportion of our patients were undergoing treatment for the first time, while those in the other studies had already had other forms of treatment and were therefore more likely to tolerate side-effects, provided the treatment resulted in an improvement in their symptoms. Additionally, the numbers in our study are small.

The precise mechanism by which this device acts in pelvic endometriosis is uncertain. Several suggestions have been proposed including systemic (Luukkainen, 2000) and local (Pakarinen *et al.*, 1995; Jones and Critchely, 2000; Hurskainen *et al.*, 2000) actions. The systemic effects are most likely to be mediated via the suppression of ovulation. The critical systemic level of levonorgestrel required to achieve this is 200 pg/ml (Nilsson and Lukkainen, 1977). This level is achieved in most women during the first 3 months on the device, and falls thereafter. In fact, anovulatory rates of between 71% and 85% have been reported during the first 3 months on the device. It is perhaps only during this time that this mechanism influences patient's symptoms, since the ovulatory rate remains low in a large number of women (Lahteenmaki *et al.*, 2000).

Various potential local mechanisms have been proposed for the action of this device in women with endometriosis, but an exact understanding of these mechanisms remains unclear. We measured serum and peritoneal fluid levonorgestrel levels in this cohort during the second-look laparoscopy and demonstrated that the peritoneal fluid levels were approximately two-thirds of the serum levels. These laboratory data and discussions about the possible mechanisms of action of the device will be published separately (Lockhat *et al.*, 2005). A combination of a reduction in peritoneal fluid volume (Drake *et al.*, 1980; Khorram *et al.*, 1993) and a low concentration of peritoneal fluid macrophages (Ramey and Archer, 1993) and inflammatory markers (Haney and Weinberg, 1988; Kupker *et al.*, 1998) may be one of the mechanisms by which this device alters the symptom of pelvic pain. Whatever the case, it is likely that the device is effective through a combination of systemic and local mechanisms. The changes in the staging we demonstrated at 6 months (Lockhat *et al.*, 2004) suggest that there is likely to be a local effect on the condition, although this is by no means conclusive, since systemic levonorgestrel may also induce the same changes. Whatever the exact mechanism, the local effect of the progestogen on the endometrium resulting in hypomenorrhoea or amenorrhoea significantly improves the pain of dysmenorrhoea and menorrhagia.

Although it is perhaps not unreasonable to adduce from these findings that the improvement in symptoms was primarily a result of the levonorgestrel device, the placebo effect of the diagnostic laparoscopy cannot be eliminated. The only way to answer this question will be a randomized trial where one group receives the levonorgestrel intrauterine system and another a placebo intrauterine system. Since such a placebo device is currently not available, the copper intrauterine device may be used. We are currently undertaking such a randomized controlled trial with the gold standard for the medical treatment of endometriosis.

The results presented provide the first evidence to support the long-term use of this form of therapy in women presenting with symptoms of endometriosis. A better tool for the assessment of its overall effectiveness in these patients would have been a quality of life analysis. Unfortunately this was

not used in this study, but will now be used in subsequent studies. Whether the symptom control observed over the 3-year period reported here will persist for the remaining 2 years of the lifespan of the device remains unanswered. Since there are no forms of medical therapy that offer such long-term relief of symptoms, it will be difficult to undertake randomized, controlled and comparable studies. However, there is the need to gather more information on the long-term use of this device, especially in the older patient who may ultimately avoid the need for a hysterectomy.

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