Human Reproduction Vol.20, No.7 pp. 1993–1998, 2005 doi:10.1093/humrep/deh869
Advance Access publication March 24, 2005

Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis

Carlos A.Petta[1,4], Rui A.Ferriani[2], Mauricio S.Abrao[3], Daniela Hassan[1], Julio C.Rosa e Silva[2], Sergio Podgaec[3] and Luis Bahamondes[1]

[1]Human Reproduction Unit, Department of Obstetrics and Gynaecology, School of Medicine, Universidade Estadual de Campinas (UNICAMP), Campinas, [2]Department of Obstetrics and Gynaecology, School of Medicine, Universidade de São Paulo (FMUSP-RP), Ribeirão Preto and [3]Endometriosis Unit, Department of Obstetrics and Gynaecology, School of Medicine, Universidade de São Paulo (FMUSP-SP), São Paulo, Brazil

[4]To whom correspondence should be addressed at: Caixa Postal 6181, 13084-971, Campinas, SP, Brazil. E-mail: cpetta@attglobal.net

BACKGROUND: The objective of this multicentre randomized, controlled clinical trial was to compare the efficacy of a levonorgestrel-releasing intrauterine system (LNG-IUS) and a depot-GnRH-analogue in the control of endometriosis-related pain over a period of six months. METHODS: Eighty-two women, 18 to 40 years of age (mean 30 years), with endometriosis, dysmenorrhoea and/or CPP, were randomized using a computer-generated system of sealed envelopes into either LNG-IUS ($n = 39$) or GnRH analogue ($n = 43$) treatment groups at three university centres. Daily scores of endometriosis-associated CPP were evaluated using the Visual Analogue Scale (VAS), daily bleeding score was calculated from bleeding calendars, and improvement in quality of life was evaluated using the Psychological General Well-Being Index Questionnaire (PGWBI). The pain score diary was based on the VAS in which women recorded the occurrence and intensity of pain on a daily basis. A monthly score was calculated from the result of the sum of the daily scores divided by the number of days in each observation period. RESULTS: CPP decreased significantly from the first month throughout the six months of therapy with both forms of treatment and there was no difference between the groups ($P > 0.999$). In both treatment groups, women with stage III and IV endometriosis showed a more rapid improvement in the VAS pain score than women with stage I and II of the disease ($P < 0.002$). LNG-IUS users had a higher bleeding score than GnRH-analogue users at all time points of observation with 34% and 71% of patients in the LNG-IUS and GnRH-analogue groups, respectively, reporting no bleeding during the first treatment month, and 70% and 98% reporting no bleeding during the sixth month. No difference was observed between groups with reference to improvement in quality of life. CONCLUSIONS: Both, the LNG-IUS and the GnRH-analogue were effective in the treatment of CPP-associated endometriosis, although no differences were observed between the two treatments. Among the additional advantages of the LNG-IUS is the fact that it does not provoke hypoestrogenism and that it requires only one medical intervention for its introduction every 5 years. This device could therefore become the treatment of choice for CPP-associated endometriosis in women who do not wish to conceive.

Key words: endometriosis/GnRH analogue/intrauterine levonorgestrel/pain

Introduction

Endometriosis is a common cause of chronic pelvic pain (CPP), affecting up to 10% of women of reproductive age. The percentage of women with cyclic and non-cyclic CPP who also have endometriosis has been estimated to be as high as 70–90% (Koninckx *et al.*, 1991; Carter, 1994; Ling, 1999). CPP in women with endometriosis significantly impairs patients' quality of life (Marques *et al.*, 2004). Several forms of therapy have been used to treat CPP associated with endometriosis, including surgical and medical treatments. The most commonly used drugs for the conservative treatment of this pathology include non-steroidal anti-inflammatory drugs, GnRH analogues, androgen derivatives, combined oral contraceptives and progestins (Gambone *et al.*, 2002). Because of the adverse effects of the medical treatments currently available, new therapeutic options, including the levonorgestrel-releasing intrauterine system (LNG-IUS), are being investigated (Fedele and Berlanda, 2004).

The LNG-IUS releases levonorgestrel (LNG) directly into the uterine cavity at a relatively constant rate of 20 μg/day for 5 years (Luukkainen *et al.*, 1990). Since it is a 19-nortestosterone derivative, LNG exerts strong progestational activity (Sitruk-Ware, 2004) and induces profound effects on the endometrium, which becomes atrophic and inactive, although ovulation is usually not suppressed (Nilsson *et al.*, 1980; Odlind, 1996). Depending on the methodology of evaluation of blood loss and the definition of amenorrhoea, complete inhibition of menstruation has been observed in 20–60% of LNG-IUS users (Nilsson *et al.*, 1980; Odlind, 1996; Hidalgo *et al.*, 2002). Previous studies have suggested that the LNG-IUS is able to relieve CPP and dyspareunia in women with endometriosis (Vercellini *et al.*, 1999, 2003) and to alleviate dysmenorrhoea associated with adenomyosis (Fedele *et al.*, 2001). In addition, one observational study showed an improvement in the staging of endometriosis after 6 months of use of the LNG-IUS (Lockhat *et al.*, 2004) and an improvement in the control of symptoms for 3 years following insertion (Lockhat *et al.*, 2005). However, these studies have been either non-comparative (Vercellini *et al.*, 1999; Fedele *et al.*, 2001; Lockhat *et al.*, 2004) or have been compared to expectant management only (Vercellini *et al.*, 2003), generally with a relatively small sample size.

The aim of this randomized comparative trial was to determine the effect of LNG-IUS compared to a GnRH analogue on endometriosis-associated CPP and quality of life, during 6 months of treatment.

Materials and methods

A total of 82 women aged 18–40 years were included in this randomized, controlled clinical trial conducted between February 2002 and May 2004. Admission criteria included a surgically and histologically confirmed diagnosis of endometriosis made 3 months to 2 years prior to enrolment in the study, complaints of cyclic CPP with or without dysmenorrhoea and a visual analogue scale pain score ≥3 during the pretreatment cycle. Three centres participated in the study and randomization was performed separately for each centre. A total of 39 women were randomized to the LNG-IUS group and 43 to the GnRH analogue group. All women gave their written informed consent and the study protocol was approved by the Institutional Review Boards of all the participating universities.

All the women had had regular menstrual periods (25–35 day intervals) for ≥3 months before entering the study, had not used any hormonal therapy for ≥3 months prior to the study, and had not taken long-acting progestins or GnRH analogue therapy in the preceding 9 months. None of the women had been breastfeeding or pregnant during the 3 months preceding the study, they had no history of osteoporosis, coagulation disorders, or contraindications to LNG-IUS as defined by the World Health Organization (2004).

Using a computer-generated system of sealed envelopes, patients were randomized to receive either an LNG-IUS (Mirena®; Schering Oy, Finland) or GnRH analogue (Lupron depot 3.75 mg; TAP Pharmaceuticals, USA), 6 ampoules, 1 ampoule i.m. every 28 ± 3 days. LNG-IUS was inserted or GnRH analogue treatment was initiated within the first 7 days of the menstrual cycle. No adverse events occurred during insertion of the LNG-IUS. Users of the GnRH analogue were advised to use a barrier method of contraception to prevent pregnancy during treatment. Patients were instructed to use no medication other than that provided during the study.

Follow-up visits were scheduled every 28 ± 3 days after initiation of treatment for at least six completed visits following randomization. Women randomized to use the LNG-IUS were allowed to keep the system after completion of the study and are being followed-up regularly at the same clinic. To assess the response to treatment, we evaluated the changes in the patient's daily perception of pelvic pain, daily bleeding score, daily occurrence of vasomotor symptoms, and their quality of life. All women received a pain score diary and a bleeding diary. Pain was evaluated by comparing the mean score recorded each month with the score registered in the month prior to study initiation.

The pain score diary was based on the VAS in which patients recorded the occurrence and intensity of their pain daily (Woodforde and Merskey, 1972). VAS consists of a subjective evaluation of the pain on a scale of 10 in which 0 is no pain and 10 the most severe pain (Howard, 2003). The score was recorded daily in the diary by marking a point somewhere along a 10 cm line. The monthly score was calculated as the result of the sum of the daily scores divided by the number of days in each observation period. Additionally, the participants were questioned about their cycle length before being admitted to the study and at every monthly follow-up visit. Bleeding patterns were assessed by the participants throughout the study on a daily basis and recorded in individual diaries. Bleeding was assessed as: 0 = no bleeding; 1 = spotting (light bleeding not requiring sanitary protection); 2 = light bleeding (light bleeding requiring sanitary protection); 3 = normal bleeding (bleeding similar to normal menstrual blood flow); and 4 = heavy bleeding (bleeding exceeding normal menstrual blood flow). No bleeding was defined as 30 consecutive days with bleeding score 0 (Rodriguez *et al.*, 1976; World Health Organization, 1986). The mean bleeding score was calculated by dividing the sum of the daily scores by the number of days in each observation period.

Patients were also asked specifically about the daily occurrence of vasomotor symptoms, vaginal dryness, mood changes, breast tenderness, peripheral oedema, and abdominal distension, and were requested to record the occurrence of these symptoms in the diary. At the pretreatment visit and at study completion (visit 6), volunteers answered the Psychological General Well-Being Index Questionnaire (PGWBI) (Dupuy, 1984) to evaluate their quality of life.

Sample size was estimated at a minimum of 32 women per study arm, based on a 100% improvement in clinical symptoms as observed previously by Fedele *et al.* (2001) and a maximum absolute difference of 20% between treatments. α was set at 0.05 and β at 0.20 (Pocock, 1987). For quantitative variables with normal distribution, the parametric *t*-test was used; in the case of the other variables, the non-parametric Mann–Whitney test was applied. For qualitative variables, χ^2-test or Fisher's exact test were used (Altman, 1999). For dependent variables with numerical scores referring to long-term measurement, multivariate analysis of variance (MANOVA) was used, with four sources of variation: stage of endometriosis (I and II versus III and IV), treatment, time (or period between visits), and interaction between treatment and time (Johnson and Wichern, 1982). For comparison between treatment groups, in which each visit was analysed separately, the non-parametric Mann–Whitney test was applied.

Results

A flow chart for the study is shown in Figure 1. Centre no. 1 recruited 13 women to the LNG-IUS group and 15 to

the GnRH analogue group; centre no. 2 recruited 23 and 25 women respectively; and centre no. 3 recruited three women to each group. Sixteen women were excluded prior to admission for the following reasons: menstrual disturbances ($n = 5$), depression ($n = 2$), uterine fibromas ($n = 3$), fibromyalgia ($n = 1$), and inability to attend scheduled follow-up visits ($n = 5$). There were no statistically significant differences between the two groups with respect to baseline data including stage of endometriosis, smoking habits, parity, and use of medication prior to study initiation (Table I). Mean ± SD age of subjects was 29.4 ± 4.8 years in the LNG-IUS group and 30.5 ± 6.4 years in the GnRH analogue group ($P = 0.392$). Body mass index (BMI, kg/m^2) was 23.8 ± 4.1 and 25.8 ± 6.4 (mean ± SD) in the LNG-IUS and GnRH analogue groups respectively ($P = 0.215$). In the month preceding treatment, 17 women in each treatment group presented VAS pain scores ≥3 and ≤7, while 22 and 26 women in the LNG-IUS and GnRH analogue groups respectively had VAS pain scores >7.

Data analysis did not follow intention-to-treat principles but included only those women who had completed the VAS pain diary correctly throughout the entire study period of 6 months ($n = 71$). Mean pretreatment VAS pain score was 7.3 ± 0.3 (± SEM) in both groups. A significant reduction in this score had already been achieved by the end of the first month of treatment in both groups and there was no difference between the two groups ($P > 0.999$). This therapeutic effect persisted throughout the 6 months of the study and there was no inter-group difference ($P > 0.600$) (Figure 2). From baseline to study completion (between visits 1 and 6), there was a 6-point (SEM = 0.3) decrease in VAS pain score in the LNG-IUS group and a 6-point (SEM = 0.2) decrease in the GnRH analogue group ($P = 0.656$). However, in 12 out of 34 users of the LNG-IUS and in 10 out of 37 users of GnRH analogue, VAS pain score remained >3 at the end of the first month of evaluation, whereas at the end of the 6th month of use only five and six women respectively in each group failed to achieve a VAS pain score <3. The reduction in the pain score at each month of observation was unrelated to the VAS pain score value recorded at baseline in either treatment group ($P = 0.556$). Multivariate analysis showed that, in both treatment groups, women with stage III and IV endometriosis experienced a faster improvement in VAS pain score than women with stages I and II of the disease ($P < 0.002$).

Analysis of all patients who completed the bleeding diaries correctly throughout the entire duration of the study revealed that bleeding scores were higher for LNG-IUS users than for GnRH analogue users at all periods of observation (Figure 3). Thirty-four per cent of LNG-IUS users and 71% of GnRH analogue users reported no bleeding during the first treatment period (between visits 1 and 2), 55 and 96% for the third period, and 70 and 98% for the sixth period respectively.

No difference was found between treatment groups with respect to side-effects such as complaints of abdominal distension ($P = 0.458$) or peripheral oedema ($P = 0.098$); however, between follow-up visits 2 and 6, more symptoms of breast tenderness were recorded in LNG-IUS users (data not shown). No serious adverse events were reported during the study period.

Compared to pretreatment values, the PGWBI scores of LNG-IUS users increased by 8.3 (SD ± 15) points, whereas the scores of GnRH analogue users increased 6.8 (SD ± 18.2) points. This increase was not significant in either group and there was no significant difference between the groups ($P = 0.474$). Table II presents PGWBI scores recorded during the pretreatment cycle (baseline) and at study completion visit (visit 6).

Discussion

As far as we know, this is the first randomized comparative trial of the LNG-IUS and GnRH analogue in the treatment of endometriosis-associated CPP and both treatments were found to be effective in controlling pelvic pain. Relief was achieved by the first treatment month and pain scores decreased significantly from a high level (score ≥7) to a lower level (score 2) in both groups during the treatment period. Although these findings are in agreement with previous studies that showed pain relief in women with endometriosis during the use of GnRH analogue (Prentice *et al.*, 2000; Schroder *et al.*, 2004) and LNG-IUS (Fedele *et al.*,

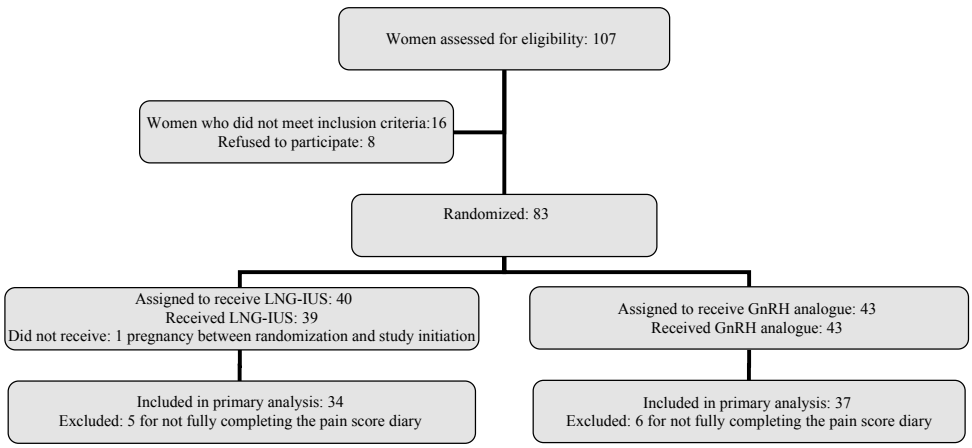

Figure 1. Study flow chart.

Table I. Distribution of women according to selected variables and treatment group (%)

Variables	Treatment group		*P*
	LNG-IUS ($n = 39$)	GnRH analogue ($n = 43$)	
Smoking			0.715[a]
Yes	8	12	
No	92	88	
No. of deliveries[b]			0.366[c]
0	63	56	
1	24	19	
≥ 2	13	26	
Stage of endometriosis			0.200[c]
I	8	16	
II	26	9	
III	31	33	
IV	36	42	
Baseline VAS pain score			0.344[d]
≥ 3–7	43	40	
> 7–10	57	60	
Use of medication in the month before study initiation			>0.999[d]
Yes	18	16	
No	82	84	

[a]Fisher exact test (2 × 2 table).
[b]One missing value in the levonorgestrel-releasing intrauterine system (LNG-IUS) group.
[c]Pearson χ^2-test.
[d]χ^2-test with Yates' correction (2 × 2 table).

2001; Vercellini *et al.*, 2003; Lockhat *et al.*, 2004), this is the first randomized clinical trial comparing the two medications.

GnRH analogues have long been used to treat endometriosis-associated CPP, principally because they provoke anovulation, hypoestrogenism with amenorrhoea, and a reduction in endometriotic lesions (Prentice *et al.*, 2000; Lockhat *et al.*, 2004; Schroder *et al.*, 2004). However, the main concerns with respect to hypoestrogenism are the induction of vasomotor symptoms and the effect on bone mineral density, including the risk of osteoporosis. For this reason, treatment with GnRH analogue alone is usually limited to a period of 6 months, although longer treatment with add-back hormone therapy is now common (Prentice *et al.*, 2000). In addition, GnRH analogues are an expensive medication, not readily available to women worldwide, especially in developing countries.

Endometriosis is an enigmatic disease, affecting up to 10% of women of reproductive age. There is a need, therefore, for better treatment options than the ones currently available, offering therapeutic efficacy over a longer period of time at an affordable cost, and with easy administration. Several possibilities are currently under investigation (Fedele and Berlanda, 2004). Although endometriosis is a frequent cause of infertility, not all patients with endometriosis wish to conceive and some contraceptive methods have been used to control pain, including the LNG-IUS (Vercellini *et al.*, 1996, 1999, 2003; Fedele *et al.*, 2001; Lockhat *et al.*, 2004, 2005). Previous reports on the effect of the LNG-IUS in the control of CPP in women with endometriosis have been encouraging (Vercellini *et al.*, 1999, 2003; Fedele *et al.*, 2001; Lockhat *et al.*, 2004, 2005) but large, randomized, comparative studies are needed.

Our study provides evidence that the LNG-IUS is as effective as GnRH analogue in the control of endometriosis-associated CPP and can be used to treat patients with this symptom. Compared to previous observational studies (Lockhat *et al.*, 2004), the present trial also included patients with more severe stages of the disease (stage III–IV) (American Fertility Society, 1985), although one previous study also included patients with stage I–IV (Vercellini *et al.*, 2003). In this study, duration of treatment was limited to 6 months because this is the maximum recommended duration of GnRH use; however, the therapeutic effect of the LNG-IUS is potentially much longer since the device has been approved for 5 years of use. Release of LNG from this device is almost 20 μg per day during the first year, slowly decreasing to 11 μg/day at 5 years of use (Luukkainen *et al.*, 1990). Despite the small amount of LNG released by the system, amenorrhoea is achieved in ~60% of women after 6 months of use and this percentage remains stable throughout the years of use (Hidalgo *et al.*, 2002). Therefore, based on the induced endometrial atrophy that provokes amenorrhoea, it is possible to speculate that the LNG-IUS may be effective

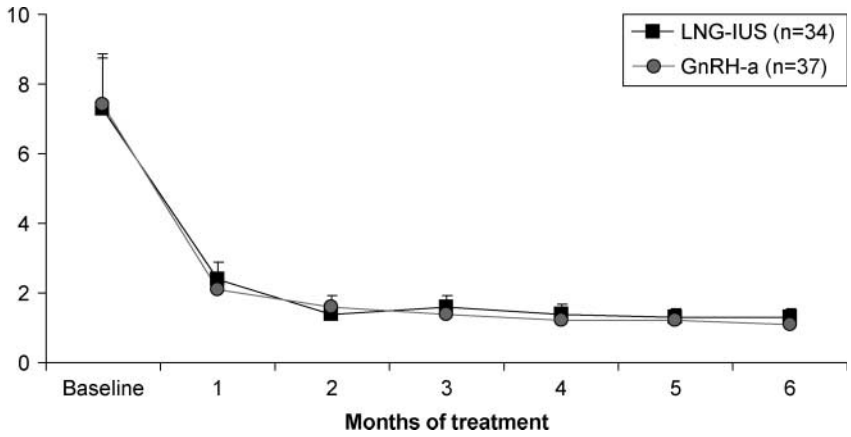

Figure 2. Changes in the visual analogue score pain scores between the two treatment groups. Values are mean ± SEM. *P*-value: not significant between both groups.

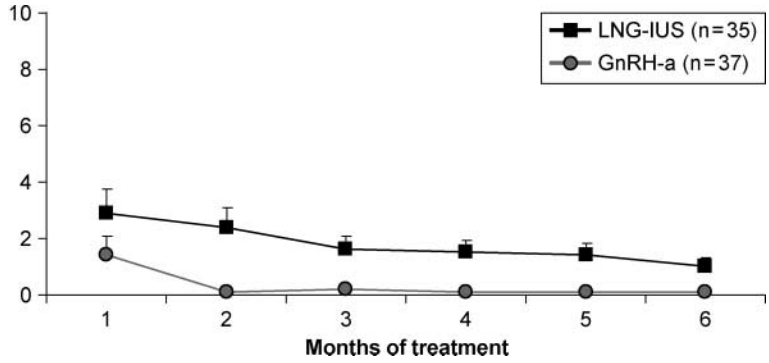

Figure 3. Changes in the bleeding scores between the two treatment groups. Values are mean ± SEM.

Table II. Changes in the the Psychological Well-Being Questionnaire Index (PGWBI) scores between the two treatment groups

Variable/score	Treatment group	
	LNG-IUS	GnRH analogue
$PGWBI_{baseline}$	($n = 39$)	($n = 42$)
Lower	37	50
Median	88	83
Higher	120	117
Mean ± SD	86.6 ± 17.6	85.8 ± 17.9
$PGWBI_{visit\ 6}$	($n = 38$)	($n = 30$)
Lower	48	39
Median	102	96
Higher	123	127
Mean ± SD	95.0 ± 19.0	93.0 ± 18.9

LNG-IUS = levonorgestrel-releasing intrauterine system.

in controlling CPP over the same period of time. It is important to note that the longer the effect on the control of pain, the more cost-effective the LNG-IUS will be. Moreover, the market cost of one LNG-IUS in Brazil is only a little higher than just one ampoule of the GnRH analogue.

Although effective in controlling CPP and reducing the stage of endometriosis (Lockhat *et al.*, 2004), the precise mechanism of action of the LNG-IUS in endometriosis is unclear and at the present moment can only be speculated. Previous studies have shown a decrease in the extension of recto-vaginal septum lesions as evaluated by ultrasonography (Fedele *et al.*, 2001), and a decrease in the severity of endometriosis at laparoscopy (Vercellini *et al.*, 2003; Lockhat *et al.*, 2004). The mechanism of action of the LNG-IUS on endometriosis is apparently different from that of GnRH analogue, as the former does not inhibit ovulation in the majority of women (Barbosa *et al.*, 1995), does not provoke hypoestrogenism (Nilsson *et al.*, 1980), and the concentration of LNG outside the uterus is very low and similar to serum levels (Nilsson *et al.*, 1982).

The adverse effects of the LNG-IUS and GnRH analogue were expected. It is important to note that although some adverse effects occurred in both groups, no woman in either treatment group discontinued the study because of side-effects. These women have a chronic disease that has a great impact on their quality of life (Marques *et al.*, 2004) and they are therefore presumably highly motivated to continue using the GnRH analogue or the LNG-IUS for the control of pain despite the occurrence of side-effects.

Higher bleeding scores were recorded in LNG-IUS users than in the GnRH analogue group. As observed in clinical trials on the use of the LNG-IUS for contraception (Hidalgo *et al.*, 2002; Baldaszti *et al.*, 2003), LNG-IUS users experienced light, irregular bleeding during the initial months of use, which decreased after the 3rd month of use. By study completion, 70% of the women were amenorrhoeic. In comparison, all GnRH analogue users became amenorrhoeic in a shorter time.

Endometriosis is a disease that impairs women's quality of life (Marques *et al.*, 2004). This study showed a slight increase in the PGWBI scores but no significant improvement in the psychological well-being of these women compared to pretreatment scores. It is important to note that a symptom such as pain may be part of a larger picture involving the emotional and general well-being of an individual. In addition, the PGWBI is a general measure of intra-psychic well-being and is not specific to any particular condition, which may represent a limitation of the instrument for the evaluation pursued in this study (Woodforde and Merskey, 1972).

Many women with endometriosis and pain no longer wish to become pregnant or may wish to delay pregnancy for some time. For these women, few long-term therapeutic options are available. Our results suggest that the LNG-IUS may be a possible treatment of choice since it offers the opportunity to use the same system for ≥5 years and provides highly effective contraception at the same time. In addition, in Brazil, the LNG-IUS is more cost-effective than GnRH analogue for the medical treatment of endometriosis-associated CPP. Its efficacy was similar to that of GnRH analogue over short-term use (6 months), but its long-term use still needs to be evaluated. Unfortunately this study was unable to identify a subset of women who were more likely to benefit from treatment with the LNG-IUS.

Acknowledgements

The levonorgestrel-releasing intrauterine system (Mirena®) and GnRH analogue ampoules were provided free of charge by Schering, São Paulo, Brazil. We thank Ms Maria Helena de Souza for the statistical analysis of data and Dr Tapani Luukkainen for his critical revision of the manuscript.

References

Altman DG (1999) Practical Statistics for Medical Research. Chapman & Hall/CRC, Boca Raton.

American Fertility Society (1985) Revised American Fertility Society classification of endometriosis. Fertil Steril 43,351–352.

Baldaszti E, Wimmer-Puchinger B and Loschke K (2003) Acceptability of the long-term contraceptive levonorgestrel-releasing intrauterine system (Mirena): a 3-year follow-up study. Contraception 67,87–91.

Barbosa I, Olsson SE, Odlind V, Goncalves T and Coutinho E (1995) Ovarian function after seven years' use of a levonorgestrel IUD. Adv Contracept 11,85–95.

Carter JE (1994) Combined hysteroscopic and laparoscopic findings in patients with chronic pelvic pain. J Am Assoc Gynecol Laparosc 2,43–47.

Dupuy HJ (1984) The psychological general well-being (PGWB) index. In Wenger NK, Mattson ME, Furberg CD, and Elinson J (eds) Assessment of Quality of Life in Clinical Trials. Le Jacq Publishing, New York, pp. 170–183, 353–356.

Fedele L and Berlanda N (2004) Emerging drugs for endometriosis. Expert Opin Emerg Drugs 9,167–177.

Fedele L, Bianchi S, Zanconato G, Portuese A and Raffaelli R (2001) Use of a levonorgestrel-releasing intrauterine device in the treatment of rectovaginal endometriosis. Fertil Steril 75,485–488.

Gambone JC, Mittman BS, Munro MG, Scialli AR and Winkel CA and Chronic Pelvic Pain/Endometriosis Working Group (2002) Consensus statement for the management of chronic pelvic pain and endometriosis: proceedings of an expert-panel consensus process. Fertil Steril 78, 961–972.

Hidalgo M, Bahamondes L, Perrotti M, Diaz J, Dantas-Monteiro CM and Petta CA (2002) Bleeding patterns and clinical performance of the levonorgestrel-releasing intrauterine system (Mirena) up to two years. Contraception 65,129–132.

Howard F (2003) Chronic pelvic pain. Obstet Gynecol 101,594–611.

Johnson RA and Wichern DW (1982) Applied Multivariate Statistical Analysis. Prentice Hall, Englewood Cliffs, New Jersey.

Koninckx PR, Meuleman C, Demeyere S, Lesaffre E and Cornillie FJ (1991) Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. Fertil Steril 55,759–765.

Ling F and Pelvic Pain Study Group (1999) Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. Obstet Gynecol 93,51–58.

Lockhat FB, Emembolu JO and Konje JC (2004) The evaluation of the effectiveness of an intrauterine-administered progestogen (levonorgestrel) in the symptomatic treatment of endometriosis and in the staging of the disease. Hum Reprod 19,179–184.

Lockhat FB, Emembolu JO and Konje JC (2005) 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. Hum Reprod in press.

Luukkainen T, Lahteenmaki P and Toivonen J (1990) Levonorgestrel-releasing intrauterine device. Ann Med 22,85–90.

Marques AA, Bahamondes L, Aldrighi JM and Petta CA (2004) Life Quality of Women with Endometriosis Assessed Through a Medical Outcome Questionnaire, Short-Form 36 (SF-36), in a Cohort Study of Brazilian Women. J Reprod Med 49,115–120.

Nilsson CG, Lahteenmaki T, Robertson DN and Luukkainen T (1980) Plasma concentrations of levonorgestrel as a function of the release rate of levonorgestrel from medicated intrauterine devices. Acta Endocrinol 93,380–384.

Nilsson CG, Haukkamaa M, Vierola H and Luukkainen T (1982) Tissue concentrations of levonorgestrel in women using a levonorgestrel-releasing IUD. Clin Endocrinol 17,529–536.

Odlind V (1996) Long-term experience of a levonorgestrel-releasing intrauterine system. Eur J Contracept Reprod Health Care 1,319–323.

Pocock SJ (1987) Clinical Trials: A Practical Approach. John Wiley & Sons, Chichester.

Prentice A, Deary AJ, Goldbeck-Wood S, Farquhar C and Smith SK (2000) Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. Cochrane Database Syst Rev (2),CD000346.

Rodriguez G, Faundes A and Atkinson LE (1976) An approach to the analysis of menstrual patterns in the clinical evaluation of contraceptives. Stud Fam Plann 7,42–51.

Schroder AK, Diedrich K and Ludwig M (2004) Medical management of endometriosis: a systematic review. Drugs 7,451–463.

Sitruk-Ware R (2004) Pharmacological profile of progestins. Maturitas 47,277–283.

Vercellini P, De Giorgi O, Oldani S, Cortesi I, Panazza S and Crosignani PG (1996) Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis. Am J Obstet Gynecol 175,396–401.

Vercellini P, Aimi G, Paonazza S, De Giorgi O, Pesole A and Crosignani PG (1999) A levonorgestrel-releasing intrauterine system for the treatment of dysmenorrhea associated with endometriosis: a pilot study. Fertil Steril 72,505–508.

Vercellini P, Frontino G, De Giorgi O, Aimi G, Zaina B and Crosignani PG (2003) Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study. Fertil Steril 80,305–309.

Woodforde JM and Merskey H (1972) Some relationships between subjective measures of pain. J Psychosom Res 16,173–178.

World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction (1986) The analysis of vaginal bleeding patterns induced by fertility regulating methods. Contraception 34,253–260.

World Health Organization (2004) WHO Medical Eligibility Criteria for Contraceptives, 3rd edn. WHO, Geneva.

Submitted on October 21, 2004; resubmitted on February 15, 2005; accepted on February 23, 2005