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● *Original Contribution*

UTERINE ULTRASONOGRAPHIC CHANGES DURING ENDOMETRIOSIS TREATMENT: A COMPARISON BETWEEN LEVONORGESTREL-RELEASING INTRAUTERINE DEVICES AND A GONADOTROPIN-RELEASING HORMONE AGONIST

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Abstract—We compared the effects of levonorgestrel-releasing intrauterine devices (LNG-IUD) and a gonadotropin-releasing hormone agonist (GnRHa) on uterine volume, uterine arteries pulsatility index (PI) and endometrial thickness before and after six months of endometriosis treatment. Sixty women aged 18–40 y were allocated randomly to one of two groups: LNG-IUDs were inserted in 30 women, and GnRHa monthly injections were performed on the other 30. All 60 women were submitted to transvaginal 2-D ultrasound scans on the day that the treatment started and then six months later. Measurements of uterine arteries PI, uterine volume and endometrial thickness were performed at both evaluations. The use of LNG-IUDs significantly decreased endometrial thickness (pre = 6.08 ± 3.00 mm, post = 2.7 ± 0.98 mm; mean ± SD), as did the use of GnRHa (pre = 6.96 ± 3.82 mm, post = 3.23 ± 2.32 mm). The uterine volume decreased in the GnRHa group (pre = 86.67 ± 28.38 cm^3, post = 55.27 ± 25.52 cm^3), but not in the LNG-IUD group (pre = 75.77 ± 20.88 cm^3, post = 75.97 ± 26.62 cm^3). Uterine arteries PI increased for both groups; however, the increase was higher in the GnRHa group (0.99 ± 0.84 *vs.* 0.38 ± 0.84, $p = 0.007$; PI increase in GnRHa and in LNG-IUD groups, respectively). In conclusion, levonorgestrel released directly onto the endometrium by the LNG-IUD induced smaller uterine changes than did the hypoestrogenism induced by GnRHa. Nevertheless, both promoted similar effects on endometrial thickness. (E-mail: wpmartins@gmail.com) **© 2008 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Levonorgestrel, Hormone-releasing intrauterine device, Gonadotropin-releasing hormone, Endometriosis, Doppler ultrasonography.**

INTRODUCTION

Endometriosis is the presence and proliferation of functional endometrial glands and stroma outside the uterine cavity. It is a chronic and recurrent disease that induces an inflammatory reaction (Child and Tan 2001). The prevalence of endometriosis may be as high as 10% in women of reproductive age (Eskenazi and Warner 1997). When considering women complaining of pelvic pain only, the prevalence is higher: 90% among women with dysmenorrhea, 42% among women with deep dyspareunia and 39% among those with nonmenstrual pelvic pain (Jamieson and Steege 1996).

Gonadotropin-releasing hormone agonists (GnRHa) have been shown to relieve pain in patients with endometriosis (Bergqvist et al. 1998). However, the use of GnRHa for longer than six months is not recommended because of concerns regarding adverse sequelae of prolonged hypoestrogenism (Friedman et al. 1994). The levonorgestrel-releasing intrauterine device (LNG-IUD) has been reported recently as an option for endometriosis pelvic pain treatment (Lockhat et al. 2005; Petta et al. 2005; Vercellini et al. 2003b) and may be used for a longer period of time.

Among uterine changes induced by GnRHa, uterine volume reductions are especially common. The use of

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GnRHa for one year caused a 36% decrease in uterine volume in patients with uterine fibroids (Friedman et al. 1991) and a 34% decrease in uterine volume when used for only eight weeks before hysterectomy for nonfibroid-related uterine bleeding (Weeks et al. 1999). In addition, a 20% increase in the uterine arteries pulsatility index (PI) was noticed. The effect of LNG-IUDs on uterine volume remains controversial: LNG-IUD yielded a 25% decrease in uterine volume and a 30% decrease in endometrial thickness when used for one year by premenopausal women complaining of menorrhagia. However, no significant change in the PI of uterine arteries was found (Haberal et al. 2006). Two other studies reported different results: no significant uterine volume reduction was found after six months of LNG-IUD insertion (Rosa e Silva et al. 2005) or even after one year (Grigorieva et al. 2003). The objective of the present study was to compare the effects of levonorgestrel (approximately 20 μg/d) released by an LNG-IUD and GnRHa on uterine volume, uterine artery PI and endometrial thickness during six months of endometriosis treatment.

MATERIALS AND METHODS

Subjects

Seventy-nine women aged between 18 and 40 y complaining of pelvic pain were invited to participate in this study. Endometriosis was classified based on previous laparoscopic findings according to the Revised American Society for Reproductive Medicine classification of endometriosis (ASRM 1997). All women had regular periods (25 to 35 d). Exclusion criteria were: use of depot medroxiprogesterone acetate or GnRHa within the last nine months, use of any other hormonal medication within the last three months, breast-feeding, being or wishing to become pregnant, presence of osteoporosis, clotting disorders or any event that might be considered a contraindication for the use of LNG-IUDs, as defined by the World Health Organization medical eligibility criteria for contraceptive use (WHO 2004). The research protocol was conducted in accordance with the guidelines of the World Medical Association Declaration of Helsinki (WMA 2004) and was approved by the local Institutional Review Board. Written informed consent was obtained from all selected subjects.

Using a computer-generated system of sealed envelopes, 61 patients were randomized to receive either an LNG-IUD (Mirena®; Schering Oy, Finland; 31 women) or monthly (28 $\pm$ 3 d) GnRHa injections (Lupron Depot 3.75 mg; TAP Pharmaceuticals, Lake Forest, IL, USA; 30 women). The LNG-IUD was inserted within the first 7 d of the menstrual cycle on only 30 women, because one became pregnant before insertion. No adverse events occurred during LNG-IUD insertions. The GnRHa treatment was initiated on 30 women. Subjects receiving GnRHa were advised to use condoms to prevent pregnancy during treatment. Patients were instructed to use no other medication during the study period.

Ultrasound

Women from both groups were submitted to transvaginal ultrasound scans. The examinations were performed by the same observer (LAM) using the 5–9 MHz vaginal probe of the HDI-3500 ultrasound machine (Ultramark HDI 3500; ATL, Bothell, WA, USA). The first vaginal scan was performed on the day of the LNG-IUD insertion or on the day of the first GnRHa injection. The second scan was performed six months later on the GnRHa group. For the LNG-IUD group, the patients were also evaluated approximately six months after the first exam: 22 patients within menstrual cycle days 10–12 and eight amenorrheal women (at least 60 d after their last menstrual period). Oligomenorrhea was observed in 15 patients.

Uterine diameters were assessed on the ultrasound scans to calculate the uterine volume (cm^3) = length (cm) $\times$ height (cm) $\times$ width (cm) $\times$ 0.5236 (Yaman et al. 2003). The uterine length was measured as the straight-line distance from the external cervical os to the uterine fundus on the longitudinal plane; when the angle between the corpus uteri and the uterine cervix was $<120^{o}$, the sum of the distances (from the internal to the external cervical os and from the internal os to the uterine fundus) was used. The height was assessed in the thickest uterine segment by tracing a line perpendicular to the endometrium on the same plane; the width was measured at the widest portion of the uterus on the uterine transversal plane. Endometrial thickness was measured at the thickest portion of a longitudinal section including both endometrial layers, but did not include the LNG-IUD (Fig. 1). For the uterine artery evaluation, a 2–4 mm Doppler gate was positioned on the ascending branch of the uterine artery at the level of the internal cervical os on a longitudinal plane for both uterine arteries (Haberal et al. 2006). The uterine arteries PIs were then calculated using the built-in ultrasound system software, with at least three similar consecutive waveforms: PI = (peak systolic velocity – end diastolic velocity)/time averaged maximum velocity (Gosling et al. 1971). The PI values obtained from right and left uterine arteries were then averaged for each subject.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). After tests of normality, pretreatment values for uterine volume, endometrial thickness and uterine artery PI were compared between the two groups using an unpaired *t*-test.

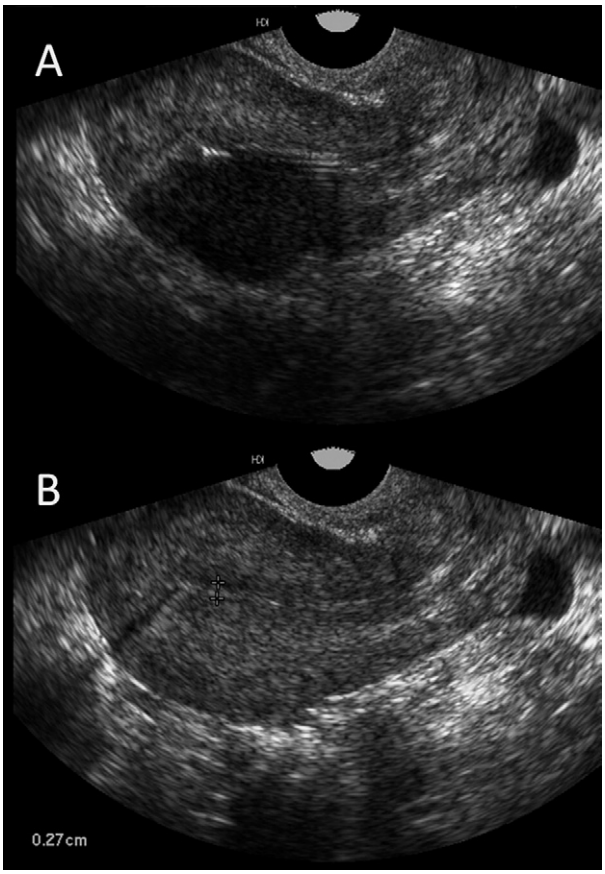

Fig. 1. Longitudinal plane of the uterus. (a) IUD and the typical posterior acoustic shadow. (b) Measurement of endometrial thickness just lateral to the IUD.

Pretreatment and posttreatment values within each group were compared using a paired *t*-test. The changes between pretreatment and posttreatment values (posttreatment value – pretreatment value) were compared between the groups by unpaired *t*-test. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

There were no significant differences between the two groups regarding the subject characteristics before admission (age 32.3 ± 3.4 y *vs.* 31.8 ± 4.1 y, $p = 0.609$; uterine volume: 75.8 ± 20.9 cm^3 *vs.* 86.7 ± 28.4 cm^3, $p = 0.096$; endometrial thickness: 6.1 ± 3.0 mm *vs.* 7.0 ± 3.8 mm, $p = 0.313$; uterine arteries PI: 2.43 ± 0.71 *vs.* 2.14 ± 0.59, $p = 0.085$; LNG-IUD *vs.* GnRHa respectively, *p*-value obtained from unpaired *t*-tests). In addition, no significant difference was observed concerning endometriosis classification during previous laparoscopy (stage II: 5 women (16%) *vs.* 4 women (14%); stage III: 8 women (27%) *vs.* 10 women (33%); stage IV: 17 women (57%) *vs.* 16 women (53%); LNG-IUD *vs.* GnRHa respectively, $p = 0.363$ by chi-square test).

The uterine volume decreased for the GnRHa group, but not for the LNG-IUD group. The endometrial thickness exhibited a similar decrease for both groups. The uterine arteries PI increased in both groups, but the increase was significantly higher in the GnRHa group (Table 1).

DISCUSSION

GnRHa is one of the most widely used medical therapies for endometriosis. This agent induces medical hypoestrogenism by down-regulating hypothalamic–pituitary GnRH receptors, thus causing decreased gonadotropin secretion, suppression of ovulation and reduced serum estrogen levels (Child and Tan 2001). GnRHa is associated with hypoestrogenic side effects, including hot flashes, vaginal dryness, loss of libido and emotional instability. When used for a long period, it is associated with substantial bone mineral density reduction (Valle and Sciarra 2003). For this reason, treatment with GnRHa alone is usually limited to a period of six months. Longer treatments using GnRHa combined with add-

Table 1. Uterine volume, endometrial (End.) thickness and uterine arteries PI: Comparison between the values found during the pretreatment evaluation (Pre) and six months after LNG-IUD or GnRHa treatment (Post)

	LNG-IUD ($n = 30$)			GnRHa ($n = 30$)		
	Pre	Post	*p*	Pre	Post	*p*
Uterine volume (cm^3)	75.8 ± 20.9	76.0 ± 26.6	0.946†	86.7 ± 28.4	55.3 ± 25.5	<0.0001†
Change*	0.2 ± 16.3			–31.4 ± 23.7		<0.0001‡
End. thickness (mm)	6.1 ± 3.0	2.7 ± 1.0	<0.0001†	7.0 ± 3.8	3.2 ± 2.3	<0.0001†
Change*	–3.4 ± 2.8			–3.8 ± 3.6		0.633‡
Uterine arteries PI	2.43 ± 0.71	2.81 ± 0.97	0.018†	2.14 ± 0.57	3.13 ± 0.92	<0.0001†
Change*	0.38 ± 0.84			0.99 ± 0.84		0.0068‡

Data are given as mean ± SD.
* Change = (posttreatment value) – (pretreatment value).
† *p*-value was obtained from paired *t*-test.
‡ *p*-value was obtained from unpaired *t*-test.

back hormone therapy are possible, but complicated and expensive (Crosignani et al. 2006).

Although endometriosis is a frequent cause of infertility, not all patients with endometriosis desire to become pregnant, and some contraceptive methods have been used to control pain, including the LNG-IUD (Vercellini et al. 2003a). The biological rationale for LNG-IUD use is that progestogens may prevent implantation and growth of engorged endometrium by inhibiting the expression of matrix metalloproteinase and angiogenesis. They also have several antiinflammatory effects that may reduce the inflammatory state generated by the metabolic activity of the ectopic endometrium (Vercellini et al. 2003a). Progestogens also have direct effects on the endometrium, causing marked decidualization and atrophy of both the eutopic endometrium and endometriotic lesions (Crosignani et al. 2006).

The uterine volume of women who used GnRHa for six months was reduced by approximately 36% (mean uterine volume: pre = 86.7 cm^3, post = 55.3 cm^3), reflecting systemic hypoestrogenism. This result is very similar to previous findings; considering GnRHa used in women with leiomyomata uteri, a 36% volume reduction was observed after 12 weeks, a 45% reduction after 24 weeks (Friedman et al. 1991) and a 36.8% reduction when GnRHa was used for six months (Kanelopoulos et al. 2003). Considering only women undergoing hysterectomy for nonfibroid-related uterine bleeding, the use of GnRHa for only eight weeks yielded a 34% reduction in uterine volume (Weeks et al. 1999). The time necessary to obtain the maximal uterine and fibroid volume reduction using GnRHa was found to be very short, approximately 19 d, with a 46.6% reduction in uterine volume (Flierman et al. 2005). This evidence suggests that hypoestrogenism is very effective for inducing uterine (and fibroid) reduction.

The uterine volume of women who used LNG-IUDs was not reduced (mean uterine volume: pre = 75.8 cm^3, post = 76.0 cm^3). This result is similar to previous data; the uterine volume was not reduced after three, six or even 12 months after the LNG-IUD insertion in 67 women with leiomyomas who had chosen this device for contraception (Grigorieva et al. 2003). No significant difference was observed in uterine volume six months after LNG-IUD insertion in the seven women with leiomyomas and increased menstrual flow (Rosa e Silva et al. 2005). However, a significant uterine volume reduction was observed 12 months after LNG-IUD insertion in 33 premenopausal women complaining of menorrhagia (Haberal et al. 2006). Nevertheless, age-related hypoestrogenism could be the cause of this uterine volume reduction in this last study. The mean age was 44.3 ± 7.6 y; three patients (9.1%) were already in menopause at the end of the study and there was no control group.

We evaluated the uterine artery PI because this is the most reliable transvaginal Doppler velocimetry measurement of the uterine arteries (Tekay et al. 1997). The PI increased 46% (from 2.14 to 3.13) in the GnRHa group. The increase in the uterine arteries PI secondary to GnRHa was similar to increases described in other studies (Battaglia et al. 1995; Weeks et al. 1999). This effect is probably because of the hypoestrogenism, because the posttreatment values were very similar to those found on postmenopausal women and a significant decrease in PI (65 to 74%) was observed when estrogen was used as hormonal therapy (Bonilla-Musoles et al. 1995; Jarvela et al. 1997). Furthermore, when using GnRHa, a direct correlation was observed between serum estradiol level and uterine arteries PI, indicating that the greater the fall in serum estradiol, the greater the increase in PI (Weeks et al. 1999).

The uterine arteries PI also increased in women who used LNG-IUDs, but the increase (15%) was significantly lower than that observed in women who used GnRHa. A comparable increase in PI (22%) was also observed six months after LNG-IUD insertion in postmenopausal women who had been using estrogen therapy for one month before its insertion (Jarvela et al. 1997). However, a study comparing women who used LNG-IUDs and copper IUDs found no significant difference in the resistance index of the uterine arteries (Zalel et al. 2002), and no change in uterine artery PI was seen one year after LNG-IUD insertion in premenopausal women (Haberal et al. 2006). There is one remaining weakness in our study: the lack of a control group without therapy. Further conclusions about the small increase in uterine artery PI related to LNG-IUDs, observed in our study, would be premature and the effects of LNG-IUD on uterine arteries of women of reproductive age remains inconclusive. However, it is clear that the increase in PI caused by LNG-IUD was smaller than that caused by GnRHa.

Both LNG-IUD and GnRHa induced comparable reductions in endometrial thickness. Among the patients treated with GnRHa, this atrophy was attributed mainly to hypoestrogenism. The mechanism by which this atrophy is produced in LNG-IUD users has not been clarified fully, but there is evidence that the presence of this system in the uterine cavity leads to glandular atrophy, pseudodecidualization of the stroma and vasodilatation, with thinning of the vessel walls associated with a reduction in vascular density (Jondet et al. 2005).

In summary, LNG-IUD did not induce the same uterine volume reduction and uterine artery PI increase as was observed for GnRHa. However, levonorgestrel released directly onto the endometrium resulted in sim-

ilar thickness reductions to those promoted by hypoestrogenism. Because both LNG-IUD and GnRHa can be used for the treatment of pelvic pain related to endometriosis, when choosing between these two therapies, their uterine effects might also be considered. One should preferentially opt for LNG-IUD when planning a long-term treatment because it lacks severe adverse effects such as bone density loss and it induces less uterine change. When there is a need to stop menstruation quickly or there is a desire to reduce uterine volume and increase the resistivity of uterine vessels, (*i.e.*, pre hysterectomy) GnRHa is more effective.

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