The local progestational effect of the levonorgestrel-releasing intrauterine system: a sonographic and Doppler flow study

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BACKGROUND: We aimed to evaluate the effect of the levonorgestrel-releasing intrauterine system (LNG-IUS) on the uterine vasculature and the endometrium. METHODS: The study was a prospective controlled study evaluating the local effects of LNG-IUS compared with the copper intrauterine device (IUD). Forty-seven women carrying LNG-IUS (group A) were compared with 35 women carrying copper IUD in a control group (group B). Clinical measures of menstrual bleeding, endometrial thickness and Doppler flow of the cervical branch of the uterine artery and spiral artery were evaluated and compared between the two groups. RESULTS: Doppler flow in the cervical branch of the uterine artery did not reveal any changes between the groups (resistance index \( R_I < 0.01 \) in both groups). Endometrial width was significantly thinner in group A (4.1 ± 0.2 mm) compared with group B (7.3 ± 0.2 mm) (\( P < 0.0001 \)). Subendometrial flow in the spiral artery was significantly reduced in 35 women of group A (75%) and in none of group B (\( P < 0.0001 \)). CONCLUSIONS: The present study offers an explanation for the oligomenorrhoea in LNG-IUS users, i.e. a local progestational effect on the endometrium with no change in the blood flow in the uterine artery. This should be presented to the women in the pre-contraceptive counselling in order to lessen the discontinuation rate.

Key words: contraception/Doppler flow/endometrium/LNG-IUS/ultrasonography

Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS) is a hormonally medicated intrauterine device (IUD). The introduction of LNG-IUS has brought a significant change in the side-effects for IUD users. Twenty per cent of conventional IUD users choose to have the device removed due to increased menstrual blood loss and abnormal uterine bleeding (Guillebaud et al., 1976). LNG-IUS, on the other hand, has caused a marked reduction in blood loss (Andersson and Rybo, 1990) and can even serve as an alternative approach to hysterectomy in cases with heavy menstrual bleeding (Lahteenmaki et al., 1998; Hurskainen et al., 2001).

Menorrhagia in IUD users can be caused by decreased vascular resistance in the uterine artery with concomitant increased blood flow to the uterus, changes which can be detected using colour Doppler flow (Kurjak et al., 1989; Momatz et al., 1994). However, only a few studies describe the haemodynamic changes in LNG-IUS users (Pakarinen et al., 1995; Jarvela et al., 1998).

Our aim was to evaluate the uterine blood flow in copper IUD and LNG-IUS users, and to try to determine the cause for the different bleeding pattern in both groups, especially the cause of amenorrhoea in the LNG-IUS users.

Materials and methods

We prospectively enrolled 47 consecutive women with LNG-IUS (Mirena™; Schering) (group A) and an additional 35 women with copper IUD (group B), matched according to the duration of IUD use. Our aim was to evaluate the uterine Doppler flow patterns, along with the morphological changes in the endometrium in both groups.

Two main parameters were examined. First, blood flow velocity waveforms were evaluated in the uterine artery on either side at the level of the inner cervical os, as well as in the spiral artery at the region of the endometrial cavity. Second, endometrial width was measured in both groups. It was measured as the thickest part in the sagittal section. In order not to include the device itself (copper as well as LNG-IUS) in the measurement and to avoid the acoustic shadowing created by the LNG-IUS, endometrial measuring was done at the side of the vertical arm.

Exclusion criteria in this study included use of any contraceptive pills during the previous 3 months, ingestion of any other medications, pregnancy, previous pelvic inflammatory disease, genital tumour or thromboembolic phenomena.

All patients enrolled gave their informed consent to participate in the study. Clinical parameters of degree of menstrual flow, intermenstrual bleeding, and cessation of menstrual bleeding were obtained using a simple questionnaire filled 1–2 months and 4–6 months after insertion. Menstrual flow was graded using a modified pictorial questionnaire.
including questions on the number and look of pads/tampons per menstruation (spotted, half-full and full) as well as occurrence of intermenstrual bleeding.

Ultrasonography was done using 4–8 MHz transvaginal transducer (Ultramark HDI 3000; ATL, Bothwell, WA, USA). All women were examined in the mid–late follicular phase (up to day 10 from the beginning of the menstrual cycle).

Blood flow velocity waveforms were evaluated in the uterine artery on either side at the level of the inner cervical os, as well as in the spiral artery at the region of the endometrial cavity. Blood flow patterns were displayed within a 90° sector. The spatial peak temporal average intensity was <100 mW/cm². The high-pass filter was set at the lowest available setting (to eliminate low-frequency signals originating from vessel wall movements) with sample volume size of 2–4 mm. When good colour signals were obtained, blood flow velocity waveforms were recorded. Uterine artery blood flow was evaluated according to the Pourcelot index. The resistance index (RI), defined as the difference between peak systolic and end diastolic flow divided by the peak systolic flow, was calculated. The mean value of three consecutive waveforms was obtained.

Results are given as mean ± SEM. All the variables were analysed for the normality of their distribution by the one-sample Kolmogorov–Smirnov test procedure. A significant difference was defined by the two-sided non-paired t-test, or the non-parametric Mann–Whitney test, as appropriate. Fisher’s exact test was used to compare the rate of outcome measures in different subgroups. All statistics were performed using SPSS for Windows version 8.0 (SPSS Inc., Chicago, IL). P < 0.05 was considered statistically significant.

Results
The LNG-IUS users (study group, group A) were compared with the copper IUD users (group B). The demographic, clinical and ultrasonographic characteristics of the 82 women are shown in Table I. The mean ± SEM ages of the women and mean parity were not different between the two groups (Table I). All women in group A were carrying the device for ≥3 months (mean duration 9 ± 1.7 months), whereas the duration of copper IUD use was 13 ± 1.5 months (not significantly different). There were no differences in the age or parity between the two groups.

Most (87%) patients using the LNG-IUS experienced amenorrhoea or only slight menstrual bleeding, whereas the women of group B complained of menorrhagia or intermenstrual bleeding (34%). Accordingly, endometrial thickness was significantly reduced in the LNG-IUS group (with mean thickness of 4.1 mm in group A versus 7.3 mm in group B) (P < 0.0001). By contrast, the RI of the cervical branch of the uterine artery in both groups did not change significantly (Table I).

When the existence of blood flow in the spiral artery was examined (at the subendometrial area), no blood flow was found in 35 (75%) women examined in group A while blood flow was found in all patients in group B.

Discussion
Levonorgestrel-releasing IUD (LNG-IUS) is a hormonally medicated IUD. It has a 32 mm long T-shaped plastic frame with a reservoir on the vertical stem of the intrauterine system containing 52 mg of levonorgestrel mixed with polydimethylsiloxane. This allows a steady, local release of 20 µg levonorgestrel per day through the rate-limiting surface membrane with a life-span of ≥5 years (Rybo et al., 1993). This special structure creates a unique ultrasonographic appearance as described in a former study (Zalel et al., 1999).

Abnormal uterine bleeding, such as menorrhagia and intermenstrual bleeding, is one of the most undesirable side-effects of the use of IUD. Hence, the advantage of the introduction of the new IUD, LNG-IUS, which, in addition to the better contraceptive effect, is characterized by reduction of menstrual blood loss, as well as the number of days of bleeding per cycle (Luukkainen and Toivonen, 1995).

The oligomenorrhoea or amenorrhoea in LNG-IUS users is hypothesized to be mediated by suppression of endometrial proliferation (Barbosa et al., 1995) as well as endometrial vascular changes that include thickening of the arterial walls, suppression of spiral arterioles and capillary thrombosis (Zhu et al., 1989).

Several Doppler flow studies evaluated the haemodynamic changes in LNG-IUS users. Pakarinen et al., who examined the impedance to uterine blood flow before and after the insertion of LNG-IUD in 10 women of fertile age, did not find any change in the uterine PI (Pakarinen et al., 1995). Jarvela et al. demonstrated an increase in the main uterine artery PI in the mid-luteal phase, but not on the first day of menstruation, and that the extent of increase in the PI correlated with serum levonorgestrel concentration (Jarvela et al., 1998).

Table I. Demographic, clinical and ultrasonographic characteristics of intrauterine device (IUD) users

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A: LNG-IUS (n = 47)</th>
<th>Group B: copper IUD (n = 35)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38 ± 0.7 (28–50)</td>
<td>36 ± 0.8 (24–46)</td>
<td>NS</td>
</tr>
<tr>
<td>Parity</td>
<td>2.8 ± 0.1 (1–5)</td>
<td>2.8 ± 0.1 (1–6)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of IUD use (months)</td>
<td>9 ± 1.7 (1–72)</td>
<td>13 ± 1.5 (1–30)</td>
<td>NS (0.07)</td>
</tr>
<tr>
<td>Rate of intermenstrual bleeding (%)</td>
<td>6/47 (13)</td>
<td>12/35 (34)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cessation of menstrual bleeding (%)</td>
<td>31/47 (66)</td>
<td>0/35 (0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Resistance index of the cervical branch</td>
<td>0.6 ± 0.01</td>
<td>0.6 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Subendometrial blood flow (%)</td>
<td>12/47 (25)</td>
<td>35/35 (100)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td>4.1 ± 0.2 (2–7)</td>
<td>7.3 ± 0.3 (4–11)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Two-tailed significance by Mann–Whitney test or Fisher’s exact test as appropriate.
LNG-IUS = levonorgestrel-releasing intrauterine system; NS = not significant.
IUD-related menorrhagia might be caused by decreased vascular resistance in the uterine artery with increased blood flow to the uterus (Momtaz et al., 1994). Frajndlich et al. have examined the Doppler sonographic changes in Women carrying copper IUD with and without abnormal bleeding. They found an increase in the uterine artery blood flow in women with abnormal uterine bleeding carrying IUD when compared with the control groups (Frajndlich et al., 2000).

We have conducted this study in view of the differing results regarding blood flow in LNG-IUS users, as well as in normal-bled and abnormal-bled women carrying copper IUD. Its main aim was to evaluate the Doppler flow patterns in the main uterine artery and the spiral artery, along with the sonographic appearance of the endometrium, in LNG-IUS versus copper IUD users.

According to the present results, Doppler flow did not reveal any significant change in the uterine artery (cervical branch) between the groups, whereas there was a marked reduction in the subendometrial blood flow only in the LNG-IUS users. Furthermore, this observation was reinforced by the significant reduction in endometrial thickness in LNG-IUS users (from a mean of 7.3 mm to 4.1 mm, \( P < 0.0001 \)).

We think, according to these study results, that the main effect of the LNG-IUS is due to its local progestational effect (i.e. no change in uterine blood flow along with marked reduction in spiral artery blood flow and endometrial width). These haemodynamic changes correlate well with the morphological changes in the endometrial spiral arterioles and capillaries (Zhu et al., 1989; Jones and Critchley, 2000). These authors have demonstrated a remarkable transformation of the endometrium, mediated by the local levonorgestrel delivery and manifested by extensively decidualized and atrophic morphology, significant reduction in steroid receptor content, resulting in the alteration of many progesterone-regulated locally acting mediators (Jones and Critchley, 2000). They have also stated that this phenomenon is independent of ovarian function and circulating sex steroid concentrations. In addition it should be acknowledged that levonorgestrel has androgenic and anti-estrogenic activities on the endometrium that result mainly from down-regulation of estrogen receptors (Jones and Critchley, 2000).

We agree with French et al., who stated that the amenorrhoea in LNG-IUS users is benign, end-organ suppression of bleeding, and associated with normal estrogen levels (French et al., 2000). Since the amenorrhoea was the main reason for discontinuation of the LNG-IUS in their study, and in view of our results, every effort should be made in the pre-contraceptive counselling to inform the patient of the possible amenorrhoea and to assure her that the main effect is benign and local. This may add to the data on the recovery of fertility after LNG-IUS discontinuation, which were reported to be very similar to copper IUD (Belhadj et al., 1986; Andersson et al., 1992). All these data can reassure the patients carrying LNG-IUS of the merely local effect of the device and thus may serve to provide reassurance at consultation and thereby decrease the rate of discontinuation.

References


Submitted on April 26, 2002; resubmitted on June 25, 2002; accepted on August 2, 2002.