The effect of the levonorgestrel-releasing intrauterine system and the copper intrauterine device on subendometrial microvascularization and uterine artery blood flow

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Objective: To evaluate the effect of the levonorgestrel intrauterine system (LNG-IUS) and TCU 380A on the subendometrial vascularization and the uterine artery blood flow during the midluteal phase.
Design: Prospective clinical trial.
Setting: Teaching hospital.
Patient(s): The trial included 27 patients who received the LNG-IUS compared with 25 patients who received the TCU 380A.
Intervention(s): The subendometrial blood flow was evaluated using power Doppler analysis, uterine artery pulsatility index (PI), and resistance index (RI) just before inserting the intrauterine device in the midluteal phase and 3 months after.
Main Outcome Measurement(s): Power Doppler analysis, PI, RI, and endometrial thickness.
Result(s): There were no significant differences in subendometrial vascularization between the groups. Pulsatility index and RI variability (before and after) increased and endometrial thickness reduced in LNG-IUS users. We used the multiple logistic regression model to examine the potential confounding bias (age and parity). The LNG-IUS was independently associated with increased PI.
Conclusion(s): No subendometrial microvascularization difference was found between the groups. It is the first direct evidence that LNG-IUS reduced uterine artery blood flow, even after controlling for age and parity. (Fertil Steril® 2008;90:1574–8. ©2008 by American Society for Reproductive Medicine.)

Key Words: Intrauterine devices, LNG-IUS, TCU 380A, ultrasonography, Doppler, color, power Doppler, microvascular density

The levonorgestrel intrauterine system (LNG-IUS) was originally developed for contraception, but is also used to control excessive menstrual bleeding, and has brought about a significant change in side effects for intrauterine device (IUD) users. Fifteen percent of copper IUD users experienced increased menstrual blood loss. The LNG-IUS, contrarily, has markedly reduced blood loss (1) and other IUD-related side effects (2).

We and other investigators demonstrated that copper intrauterine devices do not induce any major changes in the uterine artery blood flow resistance (3, 4). However, in patients with increased menstrual pain after IUD insertion there seems to be a decrease in the uterine artery pulsatility index (PI) (3, 5). Using power Doppler analysis we also demonstrated an increase in subendometrial vascularization in patients presenting major side effects (dysmenorrhea or menorrhagia) (4).

In addition, the local endometrial effect was studied in several endometrial biopsies from LNG-IUS users, which showed a significant change in endometrial vascularization, as demonstrated by a decrease in the mean vascular density and an increase in the mean vessel area (6).

Indeed, there is some controversy regarding PI and resistance index (RI) in LNG-IUS users. Some studies suggest that there are no differences in PI before and after LNG-IUS insertion (7); others (8) demonstrate a PI increase in the midluteal phase.

The literature is absolutely scarce regarding the comparison of hemodynamic effects in LNG-IUS and copper IUD

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users (9). Some investigators found no evidence of any PI difference between the groups, but the spiral artery flow was significantly reduced in LNG-IUS users.

Moreover, subendometrial and uterine vascularization studies in patients with LNG-IUS lack methodologic and statistical consistence. Furthermore, the vast majority had no proper control of one of the most important confounding biases: the menstrual cycle phase in which the ultrasound (US) examination was performed.

The aim of this study is to evaluate the effect of LNG-IUS and TCU 380A use on the subendometrial vascularization and the uterine artery blood flow using power Doppler analysis and ultrasonography pulsed color Doppler during the precise midluteal phase.

MATERIALS AND METHODS

Design

We performed a prospective clinical trial.

Patients/Methodology

We prospectively enrolled 63 consecutive patients who wanted to use IUDs (LNG-IUS or TCU 380A). We evaluated subendometrial blood flow using power Doppler analysis, uterine artery blood flow using PI and RI, and endometrial thickness before IUD insertion and 3 months later.

The inclusion criteria were: regularly menstruating women (menstrual cycle varying between 24–35 days); normal serum TSH, FSH, and prolactin levels (as measured on day 3); and under 40 years of age. Contraceptive pills or any kind of hormonal medication had not been taken for at least 3 months before the study, and any IUD had necessarily been removed at least 3 months earlier. Patients were not allowed to use nonsteroidal anti-inflammatory drugs within 24 hours before any examination.

The exclusion criteria were: pregnancy, acute or chronic pelvic inflammatory disease, uterine bleeding, menorrhagia, copper allergy, cervicitis, dysplasia in the cervix, or genital tumor. All patients underwent a gynecologic examination and had a Papanicolaou smear taken in the previous 12 months.

All patients were examined daily with US after the eighth day of the cycle, and follicular development was observed to confirm ovulation; they were then examined in the midluteal phase, 6–9 days after ovulation, to obtain the power Doppler energy (PDE) measurement, PI, RI, and endometrial thickness (ET) by US scans. The study was approved by the Ethical Committee at the Hospital de Clínicas de Porto Alegre, institutional review board approval (number: 02-127), and informed consent was obtained from all patients.

Patients were continually allocated into two groups according to the IUD: LNG-IUS (group A) or TCU 380A (group B).

Three months after IUD insertion, also in the midluteal phase (6–9 days after ovulation, confirmed by US), the same study protocol was repeated with all subjects.

The sonographic equipment used consisted of a SONOACE 9900 (Medison SA, Korea). The PDE, PI, and RI were performed on a transvaginal route. The settings for power Doppler sonography were standardized for the highest sensitivity in the absence of apparent noise using a highpass filter at 50 Hz, pulsed repetition frequency at 750 Hz, and moderate long persistence. The lowest possible measurable velocity was below 5 cm/sec. The same investigator, using the same equipment and parameters, performed the sonography assessments so as to eliminate any interobserver variation. All exams were performed between 08:00 and 10:00 A.M. to avoid interference from the circadian rhythm (10).

Power Doppler energy was classified into five categories according to the subendometrial signal area percentage: I (<10%), II (10%–25%), III (25%–50%), IV (50%–75%), and V (>75%) (11).

Statistics

Student's *t* test was used for comparing age and body mass index (BMI). The Wilcoxon–Mann–Whitney test was used to compare skewed data (PI, RI, and ET), whereas the chi-square test was used for categoric data (PDE).

We used a multiple logistic regression model to examine outcome association (PI variability, before and after IUD insertion, categorized in percentile 50) and the independent variables: IUD (LNG-IUS or TCU 380A), age (years), and parity (0, 1, or >1). A value of $P<.05$ was considered statistically significant. The power calculation before this study protocol required the inclusion of 19 patients for a $P\beta = 80\%$.

RESULTS

A total of 63 patients were included in our prospective study. A total of 11 patients were excluded: two had large ovarian cyst before IUD insertion, one had uterine miomatosis, one had polycystic ovarian syndrome, and seven were anovulatory in two control cycles before IUD insertion. There were 27 patients in group A (LNG-IUS) and 25 patients in group B (TCU 380A).

The mean standard error of the mean age (years), BMI (kg/m^2), PI, and RI before IUD insertion was no different between the groups (Table 1).

There were no significant changes in the power Doppler subendometrial evaluation between groups after IUD insertion: P=.45 using the chi-square test (Fig. 1).

To evaluate the effect of the IUDs on uterine vascularization we analyzed the variability (%Δ) before and after IUD insertion in both groups. The PI and RI variability (before and after) were significantly increased in group A (LNG-IUS) (P=.001 and P=.046, respectively). Moreover, there

TABLE 1

The demographic characteristics, pulsatility index (PI), and resistance index (RI) of the 52 women before IUD insertion: mean (SEM).

	LNG-IUS (n = 27)	TCu 380A (n = 25)	*P* value
Age (years)	31 (1.08)	29 (1.15)	0.16
BMI (kg/m^2)	23 (0.82)	24 (0.91)	0.16
PI	2.47 (0.19)	2.87 (0.21)	0.16
RI	0.83 (0.02)	0.87 (0.02)	0.15

Student's *t* test.

Note: BMI = body mass index; IUD = intrauterine device; LNG-IUS = Levonorgestrel-releasing intrauterine system.

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TABLE 2

Comparison of %Δ (before and after IUD insertion) in the pulsatility index (PI), resistance index (RI), and endometrial thickness (ET) between LNG-IUS and TCu 380A users: mean (SEM).

	LNG-IUS users (n = 27)	TCu 380A users (n = 25)	*P* value
PI (%Δ)	0.65 (0.15)	−0.22 (0.21)	.001
RI (%Δ)	0.05 (0.01)	0.003 (0.01)	.046
ET (%Δ)	−3.15 (0.39)	1.88 (0.39)	<.001

Note: Wilcoxon-Mann-Whitney (WMW) test.
LNG-IUS = Levonorgestrel-releasing intrauterine system.

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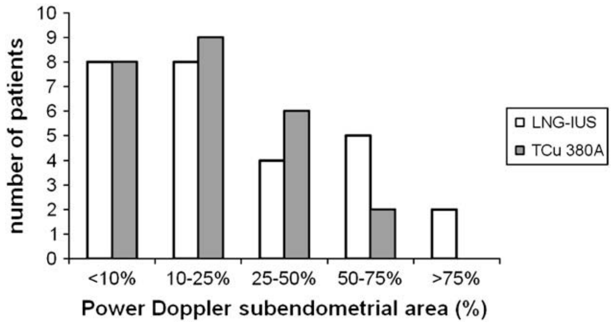
was a significant reduction in endometrial thickness in group A (LNG-IUS) ($P<.001$) (Table 2).

Using the univariate analysis, LNG-IUS IUD was significantly associated with an increase in PI variability ($P=.015$; odds ratio = 4.25; confidence interval: 1.33–13.56).

In addition, we used a multiple logistic regression model to examine any potential confounding bias. The PI variability (before and after), categorized in percentile 50, was the dependent variable, and IUD (LNG-IUS or TCU 380A), age (years), and parity (0, 1, or >1) the independent variables. Even after controlling for age and parity the association remained significant ($P=.014$) (Table 3): LNG-IUS is independently associated with an increased pulsatility index.

FIGURE 1

Subendometrial power Doppler analysis comparison between groups: LNG-IUS users and TCu 380A users. Chi-square test $P=.45$.



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DISCUSSION

We clearly demonstrated that there is a significant decrease in endometrial thickness after LNG-IUS insertion, probably related to the main LNG-IUS effect in endometrial morphology: glandular atrophy associated with pseudodecidualization (6). Moreover, it was not possible to detect the IUD effect on the uterine cavity by power Doppler analysis, as no changes were found in the power Doppler analysis, suggesting that power Doppler energy (in the midluteal phase) was not able to identify the local progestational effect on endometrium vascularization.

Copper IUDs do not induce any major changes in the PI and RI of the uterine artery either; however, copper

TABLE 3

Multiple logistic regression model.

Independent variable	Odds ratio	95% CI for exp B	*P* value
IUD (LNG-IUS or TCu 380A)	5.54	1.41–21.67	.014
Age (years)	0.99	0.89–1.12	.83
Parity	1	—	.15
Parity (1)	4.63	0.88–24.42	.071
Parity (>1)	1.37	0.27–7.03	.71

Note: Dependent variable: PI variablility (before and after IUD insertion). Independent variables: IUD type (LNG-IUS or TCu 380A), age (years), and parity (0, 1, or >2).
PI = pulsatility index; CI = confidence interval; IUD = intrauterine device; LNG-IUS = Levonorgestrel-releasing intrauterine system.

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IUD-related menorrhagia and pain might be caused by decreased vascular resistance in the uterine artery with increased uterine blood flow (3, 5, 12).

Others (13) evaluated the RI and PI before and 30 days after IUD insertion with no differences in the uterine artery blood flow. We have shown an increase in subendometrial vascularization in power Doppler analysis (4) in patients with major IUD-related side effects (dysmenorrhea or menorrhagia).

Several Doppler flow studies evaluated hemodynamic changes in LNG-IUS users. The uterine artery PI was not different before or 3 months after LNG-IUS insertion in 10 women of fertile ages (7). Contrarily, another study found that the LNG-IUS appears to be associated with an increase in blood flow resistance in the uterine arteries during the midluteal phase, and also appears to be dependent on the concentration of circulating levonorgestrel after 3 months of use (8).

The RI was increased in premenopausal women with menorrhagia after LNG-IUS insertion but not the PI and endometrial thickness (14). In addition, Doppler flow did not reveal any significant change in the uterine artery between the groups (LNG-IUS and copper IUD users), whereas there was a marked reduction in subendometrial blood flow (spiral artery) in LNG-IUS users (9).

However, most studies on subendometrial and uterine vascularization in patients with LNG-IUS lack methodologic and statistical consistence. Indeed, the vast majority did not properly control one of the most important confounding biases: the phase of the menstrual cycle in which the US examination was performed.

Some studies used a different duration of IUD use (9) or a short period of use (30 days) (13). In fact, the local progestative effect of LNG-IUS on the endometrium was already manifested within a period of 3 months or more after insertion (15), and there were differences in endometrium when comparing the first 3 months with long-time users (16).

We performed this study in view of the different results regarding uterine and subendometrial blood flow in IUD users. It is the first study using precise midluteal phase: ovulation was confirmed by daily US. We observed a significant increase in the PI and RI difference after IUD insertion in LNG-IUS users meaning that levonorgestrel circulating levels affect uterine vascularization. Moreover, only one study evaluated the uterine blood flow in copper IUD and LNG-IUS users (9) and appeared to be contradictory: it did not reveal any significant change in the uterine artery between groups, but lacks precision in midluteal phase definition and also used different durations of IUD use.

We enrolled consecutive women without randomizing. There was no bias introduced because we controlled any likely confounding bias (age, parity) using a logistic regression model; furthermore, there were no demographic characteristic differences.

Our study brings some important evidence to clarify the physiopathology of LNG-IUS and TCU 380A changes in menstrual patterns and side effects in IUD users. As already assessed by Järvelä I et al. (14), the levonorgestrel circulating levels may antagonize normal uterine response to the midluteal rising estradiol levels leading to a decrease in uterine blood flow. Postmenopausal estrogen therapy has been shown to increase endometrial thickness and reduce uterine artery PI. This effect was gradually abolished within 6 months of LNG-IUS insertion, which is in accordance with our results: LNG-IUS increased PI and RI.

The PI and RI were also studied in premenopausal women with menorrhagia after LNG-IUS insertion (15) with RI increasing, but not PI and endometrial thickness. It has been shown earlier that levonorgestrel circulating levels tend to decline during when LNG-IUS (17) is being used. Accordingly, it is possible that the increase in PI and RI observed in our study could be only temporary.

The increased impedance in uterine artery blood flow, demonstrated in our study, is one hypothesis to explain the action mechanism in pelvic pain relief in endometriosis (18, 19) medicated with LNG-IUS: a reduction in pelvic vascular congestion.

In conclusion, LNG-IUS reduced uterine artery blood flow as evidenced by the RI and PI variability ($\%\Delta$) before and after IUD insertion using pulsed color Doppler ultrasonography. It is important to emphasize, however, that the multiple logistic regression model demonstrated that, even controlling for age and parity, a significant increase in the PI difference was associated with LNG-IUS. The use of PI and RI variability ($\%\Delta$) and the precise midluteal phase makes those differences evident. Moreover, there are no differences between LNG-IUS and copper IUD users in the subendometrial microvascularization, as evidenced by power Doppler analysis.

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