

Effect of the copper-intrauterine device (TCu 380A) on subendometrial microvascularization and uterine artery blood flow

During this cohort study, the copper-intrauterine device (IUD) did not modify subendometrial microvascularization. However, subendometrial blood flow increased in patients who experienced IUD-induced side effects. (*Fertil Steril*® 2006;86:1780–2. ©2006 by American Society for Reproductive Medicine.)

The most important copper-intrauterine device (IUD)-related side effects are uterine bleeding and/or menstrual pain. These side effects are responsible for a removal rate of 5% to 15% during the first year after IUD insertion. Probably there is a connection between IUD adverse effects and uterine vascularization. However, this association is neither well-known nor well-studied.

Copper-IUDs do not induce any major changes in the resistance of the uterine artery blood flow. Nevertheless, in patients with increased menstrual pain after IUD insertion, there seems to be a decrease in the uterine artery pulsatility index (1). Moreover, levonorgestrel-releasing IUDs appear to be associated with an increased blood flow resistance in the uterine arteries during the luteal phase (2).

The objective of this study was to evaluate the effect of the copper-IUD on subendometrial vascularization and uterine artery blood flow, using power Doppler energy and ultrasonography pulsed color Doppler during the midluteal phase.

MATERIALS AND METHODS

The study population consisted of 25 volunteer women. The inclusion criteria were: [1] regularly menstruating women (menstrual cycle varying between 24–35 days), and [2] normal serum TSH, FSH, and prolactin levels (as measured on day 3).

Contraceptive pills or any kind of hormonal medication had not been taken for ≥ 3 months prior to the study, and

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any IUD had necessarily been removed ≥ 3 months earlier. Patients were not allowed to use nonsteroidal antiinflammatory drugs (NSAIDs) within 24 hours prior to any examination.

The exclusion criteria were pregnancy, acute or chronic pelvic inflammatory disease, menorrhagia for unknown reason, copper allergy, cervicitis, dysplasia in the cervix, or genital tumor.

All patients were examined daily with ultrasound (US) after the eighth day of the cycle, and follicular development was observed to confirm ovulation. Patients were then examined in the midluteal phase, 6–9 days after ovulation, to obtain the power Doppler energy (PDE) measurement, pulsatility index (PI), resistance index (RI), and endometrial thickness by US scans.

The study was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre (institutional review board equivalent; no. 02-127), and informed consent forms were obtained from all patients.

Three months after the copper IUD (TCu 380A) insertion, still during the midluteal phase (6–9 days after ovulation, confirmed by US), all subjects repeated the same study protocol.

The sonographic equipment used consisted of a Sonoace 9900 (Medison SA, Seoul, 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 high-pass filter at 50 Hz, pulsed repetition frequency at 750 Hz, and moderate long persistence.

The lowest possible measurable velocity was < 5 cm/s. The same investigator (P.A.P.F.), using the same equipment and parameters, performed all US assessments so as to eliminate any interobserver variation. All examinations were carried out between 8:00–10:00 AM.

Power Doppler energy was classified into five categories according to the subendometrial signal area percentage: I

TABLE 1

Logistic regression, with dependent variable of IUD-induced side effects of dysmenorrhea or menorrhagia.

Independent variable	Odds ratio	95% confidence interval for exp B	P value
PDE	9.1659	1.0280–81.7246	0.047
Age (y)	0.8550	0.6814–1.0729	0.176
Parity	2.4571	0.1509–40.0168	0.530

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(<10%), II (10–25%), III (25–50%), IV (50–75%), and V (>75%) (3).

Afterwards, patients were divided into two groups: the first comprised patients who presented with IUD-induced pain or bleeding ($n = 7$), and the second included those who did not present IUD side effects ($n = 18$). For further analysis of the IUD-induced side-effects subgroup, we divided PDE into two groups: the first contained those patients with minor subendometrial vascularization (PDE classification I and II), and the second included those with major subendometrial vascularization (PDE classification III and IV).

The two-tailed Wilcoxon test was used to analyze skewed data (PI, RI, and endometrial thickness), whereas the marginal homogeneity test was used for categorical data (PDE). For comparison among scores of the PI, RI, endometrial thickness and PDE in groups with and without IUD-induced side-effects, the Wilcoxon-Mann-Whitney and χ^2 or Fisher's exact test were used.

Logistic regression was used to investigate any confounding bias. The power calculation before this study protocol required the inclusion of 24 patients for a $P\beta = 80\%$, considering PI and RI as the primary endpoints.

RESULTS

The median and 25th–75th percentiles of age (years) and body mass index (BMI) (kg/m^2) were 30.00 (range, 24.50–33.00) and 23.45 (range, 20.24–27.68), respectively. Regarding parity, 6 (24%) had no parity; 8 (32%) had a parity of 1; 6 (24%) had a parity of 2; 4 (16%) had a parity of 3; and 1 (4%) had a parity of 5. Regarding occurrences of abortion, 17 patients (68%) reported no occurrences; 6 patients (24%) reported 1 occurrence; and 2 patients (8%) reported 2 occurrences.

There were no significant changes in power Doppler subendometrial evaluation before and after the IUD insertion ($P=1.00$). The pulsatility and resistance indexes were not significantly different before and after the IUD insertion ($P=.40$ and $P=.19$, respectively). However, endometrial thickness (median: 25th–75th percentiles) was less before (7: 6–9 mm) than after IUD insertion (9: 7.5–10 mm) ($P<.001$).

Seven of 25 patients either felt that the amount of menstrual bleeding had increased, or had severe menstrual pain 3 months after the IUD insertion (5 with pain, and 2 with bleeding). The IUD was then removed from two patients who experienced side effects: one due to excessive menstrual bleeding, and the other due to severe pain. Subgroup analysis showed increased subendometrial blood flow after IUD insertion in patients who suffered from side effects when compared to patients who presented no side effects ($P=.016$).

To control for a possible confounding bias, we used logistic regression: IUD-induced side effects was the dependent variable, and PDE, age, and parity were the independent variables. Even after controlling for age and parity, the association remained significant ($P=.047$) (Table 1). There were no differences in uterine artery PI ($P=.71$), RI ($P=.30$), and endometrial thickness ($P=.33$) in patients who suffered from side effects 3 months after IUD insertion, compared to patients with no side effects.

Moreover, in the group that presented IUD-induced side effects, there was no difference in PDE ($P=.97$), in RI ($P=.95$), and in PI ($P=.72$) before IUD insertion.

DISCUSSION

The purpose of our study was to elucidate the uterine hemodynamic effects of the copper IUD. The copper-IUD modified the subendometrial microvascularization of those patients who presented with IUD-induced side effects (dysmenorrhea or menorrhagia), as evidenced by power Doppler analysis, even after controlling for age and parity.

The uterine artery blood flow was not altered after IUD insertion, as evidenced by RI and PI using pulsed color Doppler ultrasonography. We did not find changes in power Doppler analysis, RI, and PI prior to the IUD insertion, suggesting that PDE, RI, or PI (in midluteal phase) could not predict which patient would be more prone to IUD-related side effects.

We found a significant increase in endometrial thickness after IUD insertion, probably related to the presence of the IUD itself and not due to any copper-IUD endometrial effect. We did not subtract the thickness of the IUD stem

(2.3 mm) from the total endometrial thickness measured in the midluteal phase. Therefore, the actual endometrial thickness after IUD insertion may be somewhat less than what we have reported.

We hypothesized that the effect of a copper-IUD in the uterine cavity could be detected by power Doppler analysis. Utilizing power Doppler sonography, we were able to obtain an in vivo quantification of subendometrium vascularity, an area containing rather weak vascular signals, which are difficult to detect with conventional color Doppler (4, 5). Probably PDE, and not PI nor RI, was associated with IUD side effects for the reason that PDE quantifies the microvasculature, whereas PI and RI measure the blood flow pulsatility and resistance, respectively.

Color Doppler studies (6) showed an increased blood flow resistance in the uterus of patients with primary dysmenorrhea. Studies with color Doppler also showed that there was no change in uterine artery PI during menstruation after IUD insertion (1), but there was a decrease in PI after IUD insertion in patients with increased menstrual pain, suggesting a low-resistance increased blood flow to the uterus (1, 7). It appears that IUD-related side effects during menstruation are more associated with increased blood flow to the uterus.

Järvelä et al. (1) also suggested that uterine blood flow changes in patients who experience increased menstrual pain after IUD insertion. This finding may be a sign of uterine-microvasculature malfunction that makes these patients more prone to IUD-related side effects. We found, in agreement with that study (1), an increased blood flow in patients with IUD-induced side effects.

Also, the levonorgestrel-releasing intrauterine system appears to increase blood flow impedance in the uterine artery in the midluteal phase. Concomitant with the change in blood flow resistance, there is a decrease in midluteal serum P concentrations (2). Administration of NSAIDs, although effective in relieving menstrual pain in patients both with and without an IUD, reduced uterine blood flow resistance only in the absence of an IUD (8). We could control the carry-over NSAID effect, not including those patients who received this drug ≥ 24 hours before our protocol.

To exclude a possible effect of menstrual cycle day from our results, all patients were examined daily by US, and follicular development was observed to confirm ovulation. Patients were examined again in the midluteal phase, 6–9 days after ovulation. The control examination was done in the same patients (paired sample), to avoid any confound-

ing bias by the same investigator. It is important to emphasize, however, that the logistic regression analysis demonstrated that, even controlling for age and parity, subendometrial vascularization was the only variable associated with dysmenorrhea or menorrhagia.

In conclusion, the copper-IUD modified the subendometrial microvascularization of those patients who presented with IUD-induced side effects (dysmenorrhea or menorrhagia), as evidenced by power Doppler analysis. Uterine artery blood flow and subendometrial vascularization were not altered after the IUD insertion, as evidenced by RI and PI using pulsed color Doppler ultrasonography and power Doppler analysis.

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