The effects of a copper-intrauterine device on the uterine artery blood flow in regularly menstruating women

I.Järvelä, A.Tekay and P.Jouppila

Department of Obstetrics and Gynecology, Oulu University Hospital, Finland

The aim of the study was to evaluate the effect of a copper-intrauterine device (IUD) on uterine artery blood flow during the midluteal phase and on the first day of the menstrual cycle using pulsed colour Doppler ultrasonography. Twenty-one regularly menstruating women (18–45 years) who were willing to use copper-IUD contraception participated in the study. The patients were first examined without the IUD in the midluteal phase 6–9 days before the expected onset of menstruation and on the first day of menstruation, after which the IUD was inserted. Three months later the patients were examined again on the corresponding cycle days. The patients estimated the level of dysmenorrhoeic pain with a scoring system. Transvaginal ultrasonography with colour flow imaging was used to measure the pulsatility index (PI) in the uterine arteries. There were no significant changes in the uterine artery blood flow after the insertion of the IUD during menstruation or in the midluteal phase. In patients with increased IUD-related pain during menstruation (n = 5), however, there was a decrease in PI (2.87 ± 0.52 versus 2.41 ± 0.23, P = 0.05) after IUD insertion. The decrease in the mean PI was present in all five patients. In conclusion, copper-IUD does not induce any major changes in the resistance of the uterine artery blood flow, although during menstruation in patients with increased menstrual pain after IUD insertion there seems to be a decrease in the uterine artery PI.

Key words: intrauterine device/menstrual pain/pulsatility index/transvaginal ultrasound/uterine artery

Introduction

Although the intrauterine device (IUD) has been used for over 30 years, its mode of action as a contraceptive still remains poorly defined. The IUD induces changes in endometrial activity and in the composition of uterine fluid, resulting in the inhibition of sperm function and blastocyst implantation and, at times, in side-effects (e.g. menorrhagia and dysmenorrhoea) (Johannisson, 1987; Ortiz and Croxatto, 1987; Alvarez et al., 1988; Mandelin et al., 1997). The morphological features of endometrium exposed to an IUD are manifestations of localized mechanical trauma, foreign body response and impaired haemostasis (Sheppard, 1987). It seems that the principal antifertility mode of action of the IUD is by a method other than the destruction of live embryos (Alvarez et al., 1988).

The effect of an IUD on uterine blood flow is not known. It has been found in studies utilizing pulsed colour Doppler ultrasonography that there are changes in uterine blood flow during menstrual cycles without contraception (Steer et al., 1990; Sladkevicius et al., 1993). The blood flow resistance in the uterine artery is lowest in the mid- (Steer et al., 1990) and late luteal phase (Sladkevicius et al., 1993), which probably indicates an increased blood flow in the uterus at the time of implantation of the blastocyst (Steer et al., 1990; Sladkevicius et al., 1993). The highest blood flow resistance in the uterine artery is on the first day of menstruation (Sladkevicius et al., 1994). The blood flow resistance is even higher in patients with dysmenorrhoeic pain during the first day of menstruation than in eumenorrhoeic patients (Pirhonen and Pulkkinen, 1995), indicating that decreased blood flow is involved in the pathophysiology of primary dysmenorrhoea (Dawood, 1993).

The aim of this study was to evaluate the effect of copper-IUD on uterine artery blood flow using pulsed colour Doppler ultrasonography during the midluteal phase and on the first day of the menstrual cycle.

Materials and methods

The study population consisted of 21 women who were willing to use copper-IUD contraception. It was necessary that the patients were menstruating regularly (i.e. a menstrual cycle varying between 24–35 days) and that they were 18–45 years old. The exclusion criteria were pregnancy, acute or chronic pelvic inflammatory disease, metrorrhagia for unknown reason, cervicitis, dysplasia in the cervix, genital tumour, copper allergy, Wilson’s disease, abnormalities in blood clotting and severe dysmenorrhoea. Laparoscopy was not performed, so that cases of endometriosis may have been included. Also contraceptive pills had not been taken during the previous 3 months and any previous IUD had been removed at least 1 month earlier. The patients were not allowed to use non-steroidal anti-inflammatory drugs (NSAID) within 24 h of any examination. All patients underwent a gynaecological examination and had a Papanicolaou smear taken during the previous 12 months. Patients gave their informed consent, and the trial was approved by the ethical committee of the medical faculty of Oulu University.

The patients were first examined in the midluteal phase 6–9 days before the expected onset of menstruation. The second examination took place on the first day of menstruation, after which a copper-T IUD (CuNovat, Leiras, Turku, Finland) was inserted. The third examination took place 3 months later during the first day of the menstrual cycle, with the IUD in situ. The fourth examination took place in the midluteal phase, 6–9 days before the expected onset...
of the next menstruation, in the same menstrual cycle as the third examination. The patients estimated the level of dysmenorrhoeic pain using a scoring system (1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) at the moment of the examination on the first day of menstruation. The purpose of this was to divide the patients into groups according to whether or not the IUD induced advanced menstrual pain. Blood samples were obtained at the examinations conducted in the midluteal phase to define oestriadiol and progesterone values. Oestriadiol and progesterone were analysed using a radioimmunoassay technique (SPECTRIA, Orion Diagnostica, Turku, Finland). The lowest quantifiable concentrations of the methods were 10 pmol/l for oestriadiol and 0.8 nmol/l for progesterone. The progesterone concentration during ovarioly cycles was determined to be 20 nmol/l or more. The Doppler parameters of the patients with ovulatory cycles were analysed separately.

The patients were examined using a pulsed colour Doppler ultrasound device (Toshiba SSA-270A, Toshiba Co., Tokyo, Japan) equipped with a 6 MHz curvilinear transvaginal probe (PVF-651VT). The minimum measurable velocity was 0.2 cm/s. The maximum acoustic output power for the colour Doppler transducer was 84 MW/cm² (I SPTA) and the pulsed repetitive frequency was between 2 and 10 kHz.

The uterus and the ovaries were first visualized using conventional B-mode ultrasound to rule out any pathology. The endometrial thickness was measured as the thickest part in the longitudinal section including both endometrial layers. The flow velocity waveforms of the main uterine artery were obtained on both sides at the level of the inner cervical os just beside the cervix. Three similar and optimal consecutive waveforms were analysed. The pulsatility index (PI) was calculated electronically according to the formula:

\[
PI = \frac{S - D}{A}
\]

where \(S\) is the maximum, \(D\) the minimum and \(A\) the mean maximum Doppler shift frequency throughout the cardiac cycle. The mean PI was calculated by combining three waveforms of the left and right uterine artery and was used for subsequent statistical analysis. All the measurements were done by the same examiner (I.J.).

The sample size was estimated according to formula \(n > 2\sigma\beta^2 / d_n^2\), where \(\sigma\) stands for SD, \(d_n\) for estimated mean difference, and \(z_{\beta}\) for standardized normal deviate exceeded (in either direction) with the probability \(2\alpha\) (for \(2\alpha = 0.05, z_{2\alpha} = 1.96\)) (Armitage and Berry, 1987). We estimated the mean difference to be one \(\sigma (\approx SD)\), which was expected to be 0.5 in the light of our previous observations.

The statistical analysis was performed on a personal computer using Statistical Package for Social Sciences (SPSS) for MS Windows release 7.0. Departure from the normal distribution was assessed using the Kolmogorov-Smirnov test. For normal distributed data we used the paired \(t\)-test and for skewed data the Wilcoxon test. The relationship between PI and hormone concentration and pain was analysed using Pearson’s correlation coefficient. \(P < 0.05\) was considered significant. All values given are means (± SD).

### Results

The mean age of the patients was 35 years (range 25–44 years) and mean parity was 2 (0–4). There were 2 primigravid and 19 multigravid women. The mean length of the menstrual cycle without the IUD was 28 (24–35) days and with the IUD it was also 28 (24–32) days (not significant: NS); the duration of menstrual bleeding was 5 (3–7) and 6 (3–10) days \((P < 0.05)\), respectively. The mean cycle day for the measurement in the midluteal phase without the IUD was 21 (16–27), and with the IUD 3 months later it was 20 (16–25) (NS).

Three out of 21 patients felt that the amount of menstrual bleeding was less after IUD insertion, three out of 21 patients felt that it was the same, and 15 out of 21 patients felt that the amount had increased. One patient discontinued the use of IUD after 3 months because of excessive menstrual bleeding.

On the first day of menstruation at the time of examination before IUD insertion, 17 out of 21 patients had no pain and four out of 21 mild pain. With the IUD, 14 out of 21 patients had no pain, six out of 21 had mild pain, and one out of 21 had severe pain. The IUD increased pain during menstruation in five patients, while in 16 patients the pain was the same or less.

On the first day of menstruation, the uterine artery PI ± SD was 2.34 ± 0.55 without the IUD and with the IUD 2.17 ± 0.44 (NS) (Table I). The endometrial thickness was 5.2 ± 2.0 mm before and 7.9 ± 2.2 mm after IUD application \((P < 0.001)\).

There was a negative correlation between the change in pain and the change in PI induced by IUD \((R = -0.446, P < 0.05)\) on the first day of menstruation. According to this, we divided the patients into two groups for further statistical analysis, the first having no change in menstrual pain \((n = 16)\) and the second having increased menstrual pain \((n = 5)\) after IUD insertion.

In the group with no change in menstrual pain there was no change in the uterine artery PI after IUD application \((2.17 ± 0.45\) versus 2.10 ± 0.47) on the first day of menstruation (Table II). In the group with an increase in menstrual pain after IUD application there was decrease in PI \((2.87 ± 0.52\) versus 2.41 ± 0.23, \(P = 0.05)\) (Table II). In all five patients with an increase in pain there was a decrease in the mean PI after IUD insertion during menstruation. There was a difference in the PI without the IUD between these groups \((P < 0.05)\) but not with the IUD (Table II).

The endometrium was thicker in both groups with the IUD but there was no difference between the two groups (Table III). The mean uterine artery PI ± SD was 2.27 ± 0.52 before and 2.53 ± 0.58 after the application of the IUD during the midluteal phase (NS). Correspondingly, endometrial thickness was 8.4 ± 3.6 mm and 8.0 ± 1.5 mm (NS), oestriadiol 308 ± 136 pmol/l and 323 ± 179 pmol/l (NS), and progesterone 28.2 ± 15.8 nmol/l and 16.2 ± 14.2 nmol/l \((P < 0.01)\), respectively (Table IV). There was no correlation between hormone levels and PI in the midluteal phase.

With a progesterone concentration of 20 nmol/l considered as a minimum limit for the ovulatory cycle, there were 15 patients with progesterone concentration above this limit before the insertion of the IUD. In the presence of IUD, the progesterone concentration was above 20 nmol/l in seven patients. Six patients had ovulatory cycles both before and after IUD insertion. There was no change in uterine artery PI, endometrial thickness, oestriadiol or progesterone values in these patients (Table V).

### Discussion

According to the results obtained in this study, it would appear that an IUD does not cause any significant changes in uterine
Effects of IUD on uterine artery blood flow. There may be, however, differences in patients according to whether or not the IUD induces side-effects.

It has been suggested that IUD-related side-effects, such as secondary dysmenorrhoea and metrorrhagia, may be caused by an increased uterine secretion of prostanoids leading to impaired haemostasis and abnormal uterine activity (Dawood, 1993). In previous studies concerning the effect of IUD on the biosynthesis of prostaglandins in the endometrium, Green and Hagenfeldt (1975) and Hillier and Kasonde (1976) found no change in the biosynthesis of prostaglandin F$_{2\alpha}$ (PGF$_{2\alpha}$) but an increase in the biosynthesis of prostaglandin E$_2$ (PGE$_2$). El-Sahwi et al. (1987) observed a significant rise in both PGF$_{2\alpha}$ and PGE$_2$ concentrations in the uterine wash 3 months

| Table I. Uterine artery pulsatility index (PI) and endometrial thickness on the first day of menstruation |
|-------------------------------------------------|------------------|------------------|------------------|
| Without copper-IUD | With copper-IUD | $P$-value |
| Uterine artery PI ($n = 21$) | $2.34 \pm 0.55$ | $2.17 \pm 0.44$ | NS |
| Endometrial thickness (mm) ($n = 21$) | $5.2 \pm 2.0$ | $7.9 \pm 2.2$ | $< 0.001$ |

The results are expressed as mean ± SD. IUD = intrauterine device; NS = not significant.

| Table II. Uterine artery pulsatility index (PI) on the first day of menstruation in patients with ($n = 5$) and without ($n = 16$) IUD-induced menstrual pain |
|---------------------------------|------------------|------------------|------------------|
| Without copper-IUD | With copper-IUD | $P$-value |
| IUD-induced pain ($n = 5$) | $2.87 \pm 0.52$ | $2.41 \pm 0.23$ | 0.05 |
| No IUD-induced pain ($n = 16$) | $2.17 \pm 0.55$ | $2.10 \pm 0.47$ | NS |

The results are expressed as mean ± SD. IUD = intrauterine device; NS = not significant.

| Table III. Endometrial thickness on the first day of menstruation in patients with ($n = 5$) and without ($n = 16$) IUD-induced menstrual pain |
|---------------------------------|------------------|------------------|------------------|
| Without copper-IUD | With copper-IUD | $P$-value |
| IUD-induced pain ($n = 5$) | $3.9 \pm 2.5$ | $7.7 \pm 2.6$ | $< 0.05$ |
| No IUD-induced pain ($n = 16$) | $5.6 \pm 1.8$ | $8.0 \pm 2.1$ | $< 0.001$ |

The results are expressed as mean ± SD. IUD = intrauterine device; NS = not significant.

| Table IV. Uterine artery pulsatility index (PI), oestradiol and progesterone values and endometrial thickness in the midluteal phase |
|---------------------------------|------------------|------------------|------------------|
| Without copper-IUD | With copper-IUD | $P$-value |
| Uterine artery PI ($n = 21$) | $2.27 \pm 0.52$ | $2.53 \pm 0.58$ | NS |
| Oestradiol (pmol/l) ($n = 20$) | $308 \pm 136$ | $325 \pm 179$ | NS |
| Progesterone (nmol/l) ($n = 20$) | $28.2 \pm 15.8$ | $16.2 \pm 14.2$ | $< 0.01$ |
| Endometrial thickness (mm) | $8.4 \pm 3.6$ | $8.0 \pm 1.5$ | NS |

The results are expressed as mean ± SD. IUD = intrauterine device; NS = not significant.

| Table V. The uterine artery pulsatility index (PI), oestradiol and progesterone values and endometrial thickness in the midluteal phase in six patients with ovulatory cycles before and after IUD insertion |
|---------------------------------|------------------|------------------|------------------|
| Without copper-IUD | With copper-IUD | $P$-value |
| Uterine artery PI | $2.45 \pm 0.52$ | $2.49 \pm 0.84$ | NS |
| Oestradiol (pmol/l) | $382 \pm 149$ | $342 \pm 127$ | NS |
| Progesterone (nmol/l) | $39.8 \pm 10.5$ | $31.5 \pm 7.8$ | NS |
| Endometrial thickness (mm) | $9.4 \pm 2.3$ | $9.0 \pm 1.9$ | NS |

The results are expressed as mean ± SD. IUD = intrauterine device; NS = not significant.
after IUD insertion but not in users who had used an IUD for at least 2 years; the temporary post-insertion rise in prostaglandin concentrations coincided with the phase of increased bleeding and pain.

The increased production and release of endometrial prosta-
glandins in primary dysmenorrhea gives rise to increased and abnormal uterine contractility (Dawood, 1993), which leads to experience of pain due to a decreased endometrial blood flow (Akerlund et al., 1976). Increased blood flow resistance in the uterus of patients with primary dysmenorrhea has also been shown in colour Doppler studies (Pirhonen and Pulkkinen, 1995). The pain is relieved by inhibiting the abnormal myometrial contractility with NSAID (Csapo et al., 1977), which are also capable of alleviating the pain and metrorrhagia induced by IUD (Ylikorkala et al., 1978; Davies et al., 1981; Roy and Shaw, 1981; Zhao et al., 1997).

According to our results there was no change during menstruation in the uterine artery PI after IUD application. When we related the change in pain to the change in PI, however, we found a negative correlation. 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. These patients had a higher PI level before the IUD insertion than the remaining patients. Our results are in accordance with the Doppler study performed by Momtaz et al. (1994), who found that the resistance in the uterine artery during menstruation was significantly lower in women with IUD-induced bleeding than in those without side-effects or in women not using any form of contraception.

It would appear that IUD-related side-effects during menstruation are more associated with an increased than with a decreased blood flow to the uterus. Our results also suggest that uterine blood flow in patients who experience increased menstrual pain after IUD insertion may differ from that of other women even before the IUD insertion. This may be a sign of uterine malfunction which makes these patients more prone to IUD-related side-effects.

We can only speculate on the metabolic and hormonal aetiology of the uterine haemodynamic findings of this study. If prostaglandins are involved in the pathogenesis of these side-effects as well as the regulation of blood flow to the uterus, the change in prostaglandin synthesis induced by an IUD could, according to our results, cause it to shift more to the production of vasodilatory than to vasoconstrictory prostaglandins.

Other vasoactive substances may also be involved, including nitric oxide (NO) which is a potent vasodilator produced by the vascular endothelium. NO is present in the human endometrium and myometrium (Telfer et al., 1995). There is evidence that NO may play a part in acute and chronic inflammation (Moncada and Higgs, 1993). The introduction of an intruterine device into the uterine cavity induces a foreign body reaction in the surrounding endometrium (Sheppard, 1987). NO is present in the foreign body inflammatory reaction around loosened joint replacement implants (Moilanen et al., 1997). Thus, it is possible that IUD also induces NO synthesis in the surrounding tissue. There is also a connection between NO synthesis and prostaglandin synthesis. NO directly interacts with cyclo-oxygenase, which is responsible for prostaglandin synthesis and causes an increase in enzymatic activity (Salvemini et al., 1993). There are no studies, however, concerning the effect of IUD on NO production by the endometrium.

There were no changes in midluteal PI values in the presence of the IUD, although the progesterone concentration was lower. We found no correlation between hormone concentrations and PI in the midluteal phase, as has been previously observed (Steer et al., 1990). The trend reported in previous studies measuring the hormonal values in menstrual cycles with and without the IUD is that there is no change in ovarian hormonal function induced by IUD (Faundes et al., 1980; Anttila et al., 1991). There is, however, evidence that endometrial sloughing among IUD users is initiated while serum progesterone and oestrogen are at a concentration characteristic of the late luteal phase of control cycles (in the absence of IUD), which results in a prolongation of the proliferative phase and in a shortening of the luteal phase, while the whole length of the menstrual cycle remains unchanged (Faundes et al., 1980; Anttila et al., 1991). We timed the point of measurement in the luteal phase according to the presumed onset of the next menstruation and not according to the ovulation of the ongoing menstrual cycle. Consequently, it is very likely that our measurements in the luteal phase with the IUD were performed a few days earlier than the assumed menstrual cycle day.

In order to exclude the possible effect of anovulation on our results concerning the luteal phase, we included six patients with an ovulatory concentration of progesterone both before and after IUD insertion for further statistical analysis, but we still observed no difference in the uterine artery PI. This further confirms our finding that copper-IUD does not have any significant effect on the blood flow to the uterus in the midluteal phase.

We performed the Doppler measurements in the main branch of the uterine arteries and the IUD did not alter the blood flow parameters. This may not hold true for the more distally located vessels, including radial and spiral arteries. When analysing the PI of the uterine artery at different levels in dysmenorrhoeic patients receiving NSAID, Pirhonen and Pulkkinen (1995) found that the most prominent changes occurred in the fundal part of the uterus. Since the distal branches of the uterine artery were not the objects of the present study, we cannot speculate on this possibility.

The endometrium was thicker at the phase of the initiation of bleeding with the IUD than without, but there was no change in the midluteal phase. We did not subtract the thickness of the IUD stem (2.3 mm) from the endometrial thickness measured after IUD application, since the IUD does not enlarge the cavity through the whole thickness of the stem but rather is partly embedded in the endometrium. Therefore the actual endometrial thickness after IUD application may be somewhat less than those we have reported. It may also be that endometrial sloughing is different during menstruation with an IUD in utero, as the IUD induces an increase in the fibrinolytic activity of the endometrium (Kasonde and Bonnar, 1976).

In conclusion, we found no major changes in the resistance of uterine artery blood flow after intruterine device insertion,
although blood flow seems to be affected in patients with IUD-related pain during menstruation.

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References

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Effects of IUD on uterine artery blood flow

1845