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Effects of a Copper-Medicated Intrauterine Device on Ovarian Artery, Uterine Artery, and Intrauterine Blood Flow

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Key Words
Intrauterine device · Doppler · Uterine artery

Abstract
Aim: To determine the effect of a copper-medicated intrauterine device (IUD) on ovarian, uterine, arcuate, radial and subendometrial Doppler-derived indices of blood flow. ***Method:*** 23 regularly menstruating patients requested insertion of an IUD. All patients had a copper T (Nova T) IUD inserted between days 8 and 11 of the menstrual cycle. Ovarian, uterine, arcuate, radial and subendometrial artery pulsatility indices (PIs) were assessed by transvaginal color Doppler prior to insertion between days 8 and 11 of the menstrual cycle, and after 2 months in the same period of the cycle. Ovarian, uterine, arcuate, radial and subendometrial artery PIs were considered prior to and following IUD insertion. ***Results:*** No differences were recorded in any of the blood vessels sampled between pre- and post-insertion PIs. ***Conclusion:*** No significant change in ovarian or in uterine system vascular impedance is associated with the presence of a copper-medicated IUD.

Introduction

The mechanisms by which copper-medicated intrauterine devices (IUDs) have attained their high level of efficacy remain unknown despite over a generation of extensive use and research worldwide. It has been speculated that the modes of action involved include a spermatotoxic effect as well as inhibition of blastocyst implantation, or embryotoxicity [1]. Such a blocking reaction to the endometrial receptivity might occur as a result of a decrease in the amount of estrogen and progesterone receptors [2] or by inducing a local low-grade chronic inflammatory reaction [3–5]. When a low-grade inflammatory response is present, enhanced recruitment of lymphocytes as well as an elevated local humoral response may result in increased embryotoxicity due to multiple factors. Whatever the mechanism, copper might enhance this inflammatory response [6] and might induce vascular changes of the endometrium and myometrium. The lion's share of evidence regarding possible mechanisms of action is derived from various animal models. Differences between species in these mechanisms are significant and it is difficult to determine the relative weight of each of the possible mechanisms in humans.

Observational studies have determined normal blood flow parameters in the non-gravid uterine vessels as well

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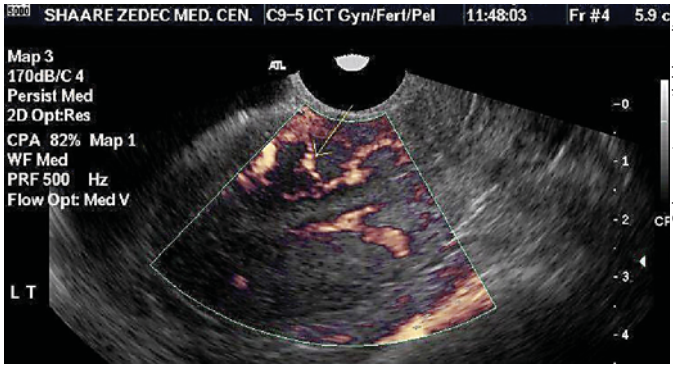

Fig. 1. Radial artery and subendometrial flow by transvaginal sonography.

as in its tributary vessels, the arcuate, radial, and subendometrial arteries. These have been found to be cycle-dependent [7–9]. When using Doppler indices to evaluate hemodynamics in the uterine arteries and its subsidiary vessels, the pulsatility index (PI) has been frequently used as a measure of downstream vascular impedance.

A literature search yielded one study [10] that examined the effect of a copper-medicated IUD on uterine artery blood flow, indicating no significant change in the uterine artery flow is affected by copper IUD insertion. Zalel et al. [11] found it is possible to measure subendometrial flow in all patients with a copper-medicated IUD. Not surprisingly, they were unable to detect spiral artery flow in most patients with a levonorgestrel-releasing IUD. This might be attributed to the down-regulation of estrogenic receptors causing thickening of the arterial walls, suppression of spiral arterioles and capillary thrombosis. It is conceivable that any effect an IUD might have on blood flow in the uterine artery system might be reflected in changes in blood impedance of the smaller intrauterine vessels with little detectable effect on flow in the uterine arteries themselves. We have studied the effect of IUD insertion on both uterine artery impedance and on that of its tributaries – the arcuate, radial and subendometrial arteries.

Materials and Methods

The study was carried out at the Shaare Zedek Medical Center, Jerusalem. A total of 23 women were enrolled in the study. Informed consent was obtained from each subject. Those eligible for inclusion into the trial were regularly menstruating patients who had elected to have an IUD (Nova T, Schering, Germany) inserted for contraception. Nulliparas and patients with a history of pelvic inflammatory disease were excluded. None of the patients had used non-steroid anti-inflammatory drugs prior to IUD insertion or within a week before the second sonogram. Insertion was performed between days 8 and 11 of menstruation. Prior to insertion a sonogram was performed to evaluate uterine position and size as well as to rule out any pelvic abnormalities. All patients had a color Doppler study of both uterine and ovarian arteries as well as of the arcuate, radial and subendometrial arteries. Methods for evaluating uterine and ovarian vascularity with transvaginal color imaging have been previously described [8–13]. As it was anticipated that it would not be possible to achieve in all cases low incidence angles for measuring blood flow, we chose not to measure velocities and use the PI. Doppler blood flow velocity waveform for the uterine artery was recorded by placing the sample gate on the ascending branch of the uterine artery at the level of the internal os as previously described. The ovarian artery was identified as the large vessel at the ovarian hilum. This location was selected to ensure the ovarian artery itself is sampled rather than a branch of the tubal or uterine arteries. Arcuate artery recordings were taken from the vessels parallel to and near the uterine serosal surface. Radial artery recordings were taken from vessels perpendicular to the uterine surface from within the myometrial substance and subendometrial measurements were taken in the areas just adjacent to the endometrial cavity (fig. 1). PIs were digitally calculated from a minimum of three good-quality waveforms, representative of three consecutive cardiac cycles. The maximum Doppler frequency shift was digitally traced and the mean PI calculated by the following standard equation: PI = peak systolic frequency shift – end diastolic frequency shift over mean frequency shift over the entire cardiac cycle. A second scan was performed between days 8 and 11 of the second menstrual cycle after IUD insertion. All scans were performed by a single experienced investigator (O.S.). To establish intra-observer variability, 10 cases were reviewed and the coefficient of variation calculated for the subendometrial and radial arteries, by comparing two sets of measurements per vessel.

All scans were performed transvaginally using a multifrequency 5- to 9-MHz probe with color duplex capability (carrier frequency 2.5 MHz) on an ATL HDI 3000 device (Advanced Technology Laboratories, Bothell, Wash., USA). Settings on measuring intrauterine vessels were set to the appropriate low velocities.

Results

Mean age for the study group was 31 ± 3.4 years. Mean parity was 3.6. Table 1 demonstrates pre- and post-insertion PI values for the various blood vessels. All blood vessels for all patients were sampled, except for subendometrial vessels for which pre-insertion measurements were unobtainable from 3 patients, and post-insertion measurements were unobtainable from 3 patients (2 of these from different patients). Intra-observer variation for the small subendometrial and radial arteries showed a good level of reproducibility of 0.92 and 0.95 respectively.

Table 1. Pre- and post-insertion PI values for the various blood vessels (mean PI ± SD)

	n	Pre-insertion	n	Post-insertion
Right ovarian artery	23	0.61 ± 0.078	23	0.61 ± 0.082
Left ovarian artery	23	0.62 ± 0.079	23	0.61 ± 0.082
Right uterine artery	23	2.10 ± 0.357	23	2.06 ± 0.415
Left uterine artery	23	2.12 ± 0.328	23	2.11 ± 0.363
Arcuate artery	23	1.78 ± 0.138	23	1.78 ± 0.1757
Radial artery	23	1.38 ± 0.382	23	1.33 ± 0.338
Subendometrial	20	1.26 ± 0.377	20	1.27 ± 0.4

The non-parametric Wilcoxon signed paired rank test was also applied to all pre- and post-insertion pairs. None of the differences between pairs was statistically significant.

Discussion

Our results are similar to those reported in the literature regarding ovarian, uterine and intrauterine PIs [7, 8]. Unlike Zalel et al. [11], who demonstrated flow in subendometrial vessels in all patients bearing a copper-medicated IUD, we were able to obtain measurable subendometrial signals in only 40 of 46 measurements, 20 pre-insertion and 20 post-insertion.

According to our results, no significant change in blood flow has been detected as a result of the presence of the copper-medicated IUD in either the large pelvic vessels (uterine and ovarian arteries) or in the small ones. This confirms the findings by Jarvela et al. [10] as to the uterine arteries. However, it might have been expected to detect decreased vascular impedance in the uterine small vessel circulation. Our inability to demonstrate such a change indicates that such low-grade inflammatory reaction, if it is indeed present, might induce little or no vascular change. A dominant body of evidence points to blastocyst implantation inhibition, or toxicity to the developing embryo, as likely mechanisms in the action of copper-medicated IUDs. Chronic inflammation might play an important role in achieving this effect. An inflammatory response typically implies increased blood flow to the affected organ. This increased flow has been measured by Doppler in laparoscopically proven pelvic inflammatory disease [14, 15]. It might be expected that the low-grade inflammation associated with the presence of an IUD would invoke increased vascularity and decreased vascular resistance in those vessels supplying the uterus, i.e. the uterine and ovarian arteries and the distal arcuate, radial and subendometrial arteries. The lack of vascular change can be considered evidence towards a decreased significance of the local endometrial effect of the copper-medicated IUD.

Most of the evidence on the mechanisms of action of IUDs [1] is from animal models and indeed, there are striking differences between species. In the ewe it is thought that the contraceptive effect of the IUD is entirely accounted for by inhibition of fertilization. In humans the data supporting the existence of inflammation are scarce and indirect. Parr and Shirley [16] examined inert IUDs contained in hysterectomy specimens. They were able to demonstrate that uterine extract from IUD-bearing specimens contained higher levels of inflammation marker, and such a level of inflammation might be toxic to mouse embryos. Spinatto [17] addressed this delicate and sensitive topic suggesting the weight of evidence pointing to post-fertilization mechanisms. His report triggered heated adversary responses on this ethically and morally charged issue. In our opinion it supplies little additional evidence in the favor of a post-fertilization mechanism.

IUDs are extensively used in both Europe and in the developing world. Many might find using a method of contraception, with a predominantly post-fertilization or post-implantation effect objectionable. *This is related to the morally and religiously charged question of 'the beginning of life'. If indeed the mechanism of action does not involve any significant inflammatory response, the likelihood of a pre-implantation mechanism of contraception is likely to be decreased. Those who consider the 'beginning of life' at implantation, might consequently, lower their objection to the use of the IUD.* Our study adds to the existing base of knowledge, an additional piece, suggesting a lesser role for a peri-implantation mechanism.

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