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Original Research

Investigation of Doppler Indices in Copper Intrauterine Device-induced Heavy Menstrual Bleeding

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Abstract

Background: Copper intrauterine devices (IUDs) are one of the most commonly used methods of contraception all over the world. However, nearly 20% of users have their IUD removed due to increased or irregular uterine bleeding. We aimed to investigate if the occurrence of heavy menstrual bleeding (HMB) after application of IUDs could be predicted using transvaginal color Doppler ultrasonography in women without dysmenorrhea. **Method**: Fifty-five women with regular menstruation without dysmenorrhea who were willing to use an IUD were included in the study. The women were divided into two groups as those whose menstrual characteristics did not change after IUD insertion (group A, n = 31) and those who developed HMB secondary to IUD insertion (group B, n = 24). IUDs were inserted on the 2ndor 3rd day of menstruation in all women and color Doppler assessments of the uterine, arcuate, and utero-ovarian arteries were performed twice; the first measurement was performed just before IUD deployment and the second measurement was performed on the 2nd or 3rd day of menstruation after 2 months. After recording these two measurements, Doppler parameters were compared between the groups. **Results**: The first and the second pulsatility index (PI) and resistance index (RI) values of the uterine arteries were significantly lower in group B when compared with group A ($p < 0.05$). Likewise, the first and the second PI values of the arcuate arteries in group B were significantly lower than in group A ($p = 0.009$ and $p = 0.035$, respectively). The second RI measurements of the arcuate arteries were significantly lower in group B than in group A ($p = 0.037$); however, the first RI measurement of the arcuate arteries showed no statistically significant differences between the groups ($p = 0.073$). The first and the second PI and RI values of the utero-ovarian arteries showed no statistically significant difference between groups A and B. **Conclusions**: The results propose that low impedance to blood flow in the uterine and arcuate arteries prior to IUD insertion may help predict HMB secondary to IUD insertion in women without dysmenorrhea.

Keywords: color Doppler; copper intrauterine device; heavy menstrual bleeding; dysmenorrhea

1. Introduction

Copper intrauterine devices (IUDs) have been one of the most commonly used contraception methods in the world for many decades [1]. However, IUDs have common adverse effects such as increased blood loss during menstruation, menstrual disorders, pelvic pain, and dysmenorrhea [2]. Approximately 20% of users choose to have the device removed due to increased or irregular vaginal bleeding [3]. Nevertheless, not all types of intrauterine devices have the same side effects; contrarily, in a meta-analysis of randomized trials, the levonorgestrel-releasing intrauterine system (LNG-IUS) was reported to be reducing menstrual blood loss more than other medical treatments [4].

Several mechanisms had been suggested for this problem; however, it has not been elucidated to date. The mainly proposed mechanisms are capillary damage in the endometrium; increased vascularity of the endometrial tissue adjacent to the IUD; increased prostaglandin synthesis in the endometrium, which leads to increased endometrial blood flow and capillary permeability; endothelial vasodilator production by the uterus; imbalance in the prostaglandin-thromboxane ratio; and increased local fibrinolytic activity and epithelial surface erosion [5–7]. IUDs also cause an inflammatory response and the copper component may enhance this response and induce vascular changes of the endometrium and myometrium [2,7].

Considering that the blood flow changes of uterine circulation may reflect the adverse effects of IUDs, mainly heavy menstrual bleeding (HMB), the aim of this study was to determine if the occurrence of IUD-induced HMB was predictable before the insertion of IUDs using transvaginal color Doppler measurements of the uterine circulation [3,5]. For this purpose, uterine, arcuate, and utero-ovarian artery Doppler indices were assessed before and after the IUD deployment, excluding patients with previous or current IUD-induced dysmenorrhea.

2. Materials and Methods

The study was conducted in the obstetrics and gynecology clinic of Yüzyıl Hospital between May 2016 and June 2021. Fifty-five women with regular menstruation who were willing to use an IUD for birth control were in-

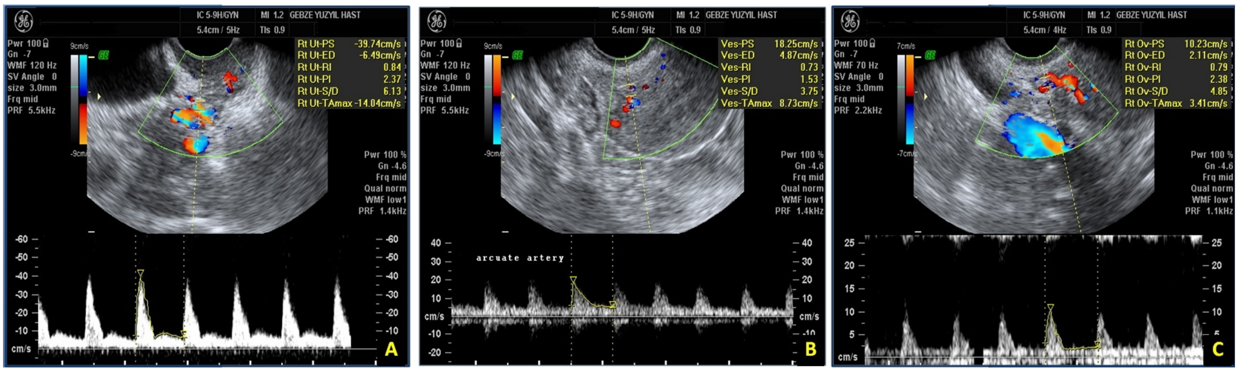

Fig. 1. Measurement of the Doppler indices. (A) Uterine artery. (B) Arcuate artery. (C) Utero-ovarian artery.

cluded in the study. After taking a detailed medical history of the patients, age, menstrual cycle characteristics and parities were recorded. IUD (SMB Copper T380A, Mumbai, India) insertion was performed on the second or third day of menstruation in all women.

The patients were evaluated in two groups; those whose menstrual characteristics did not change after IUD insertion (group A, n = 31) and patients who developed HMB after the insertion of the IUD (group B, n = 24). HMB was defined as; excessive menstrual blood loss that affects a woman's physical, social, emotional and/or material quality of life [8].

Color Doppler measurements of the uterine, arcuate, and utero-ovarian arteries were performed twice in each patient on both sides of the uterus using transvaginal color Doppler sonography; just before IUD insertion on the 2nd or 3rd day of menstruation (first measurement) and the 2nd or 3rd day of menstruation 2 months later (second measurement). Doppler measurements and ultrasonographic examinations were performed by the same physician (K.Ö.).

A Voluson 730 Pro ultrasound device (GE Medical Systems, Austria) with an IC 5-9H endovaginal probe was used for color Doppler measurements. Pulse repetition frequencies were set between 1.3–7 kHz to obtain a clear signal. For eliminating low-frequency signals, a wall filter was set between 120–190 Hz, as needed. One of the flow velocity waveforms was used for the measurement of the Doppler indices after obtaining five similar consecutive waveforms (Fig. 1). The pulsatility index (PI) and resistance index (RI) values were measured bilaterally for all three vessels, and the mean value of these measurements was recorded. The difference between the first and the second measurements of the groups was also compared. The mean value of Doppler indices was used for statistical calculations. The measurements were repeated three times consecutively for each artery and the average of these three measurements was recorded as the data to be used for statistical calculations. The formulas used for PI and RI values were [(maximal systolic flow-minimal diastolic flow)/mean flow] and [(maximal systolic flow-minimal diastolic flow)/maximal systolic flow], respectively.

Uterine arteries were detected at the level of cervicocorporeal junction, arcuate arteries were detected at the outer third of myometrium and utero-ovarian arteries were detected between the ovaries and the uterus.

All of the women had given birth at least once and all the deliveries were by the vaginal route. Exclusion criteria were previous surgery on the uterus or ovaries, congenital uterine anomalies, presence of uterine fibroids, abnormal uterine bleeding, women with ultrasonographic findings of adenomyosis, genital tumor, acute or chronic pelvic inflammatory disease, chronic pelvic pain, systemic diseases that could cause coagulopathy, and previous or current IUD-induced dysmenorrhea. Women with dysmenorrhea were excluded due to their potential effect on Doppler indices. Likewise, patients who developed dysmenorrhea after IUD administration were excluded because they could potentially affect post-insertion Doppler values. For this reason, although their menstrual characteristics did not change after IUD insertion other than dysmenorrhea, five women were excluded from group A and seven women were excluded from group B due to having HMB and dysmenorrhea at the same time. The patients were not taking oral contraceptive pills and the previous IUDs were removed at least 3 months before IUD insertion. Non-steroidal anti-inflammatory drugs (NSAIDs) were not allowed within 24 hours before each measurement.

The study was approved by the ethics committee of institute, and informed consent was obtained from all women before inclusion.

2.1 Statistical Analysis

The Number Cruncher Statistical System (NCSS 2007, Kaysville, Utah, USA) software package was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, and percentage, minimum, maximum) were used to evaluate the study data. The suitability of the quantitative data for normal distribution was tested using the Shapiro-Wilk test and graphical analysis. Student's *t*-test was used for the comparison of the normally distributed quantitative variables and the Mann-Whitney U test was used for the comparison

Table 1. Characteristics of the groups.

	Group A (n = 31)	Group B (n = 24)	p
	Min-max (median) Mean ± SD	Min-max (median) Mean ± SD	
Age (years)	19–40 (26) 28.26 ± 5.53	21–42 (28) 29.38 ± 5.78	**ᵃ0.469**
Parity	1–5 (2) 2.35 ± 1.31	1–4 (2) 2.25 ± 0.94	**ᵇ0.993**
Cycle duration (days)	23–35 (28) 28.74 ± 2.65	24–34 (29) 29.08 ± 2.62	**ᵃ0.636**
Body mass index	24–39 (29) 30.35 ± 4.21	24–36 (28) 30.92 ± 3.81	**ᵃ0.611**

[a]Student t-Test; [b]Mann Whitney U Test.

Table 2. Evaluation of uterine artery PI and RI values according to groups.

		Group A (n = 31) Mean ± SD	Group B (n = 24) Mean ± SD	[a]p
Uterine artery PI	First measurement	2.08 ± 0.45	1.77 ± 0.36	***0.010****
	Second measurement	2.25 ± 0.53	1.71 ± 0.29	***0.001*****
	[c]p	0.107	0.508	
	Difference (1st–2nd measurements)	0.17 ± 0.57	–0.06 ± 0.45	***0.108***
Uterine artery RI	First measurement	0.82 ± 0.06	0.77 ± 0.06	***0.002*****
	Second measurement	0.83 ± 0.07	0.77 ± 0.06	***0.001*****
	[c]p	0.347	0.896	
	Difference (1st–2nd measurements)	0.01 ± 0.07	0 ± 0.09	***0.494***

[a]Student t-Test; [c]Paired Samples t-Test; *$p < 0.05$; **$p < 0.01$.

of the non-normally-distributed quantitative variables between the two groups. The paired samples t-test was used for the first and second measurements of quantitative variables showing normal distribution. Statistical significance was accepted as $p < 0.05$.

In a study by Yiğit *et al.* [6], the descriptive values for post-insertion uterine artery PI levels in two groups with an increase in menstrual bleeding (n = 14) and no increase (n = 14) were found as 1.89 ± 0.27 and 2.27 ± 0.33, respectively. Based on these values, when the power of the test is 90% and the type I error is 0.05, the minimum sample size to be taken in our study was calculated as at least 19 women for each group (R 3.0.1. open-source program).

3. Results

The study was conducted with the participation of 55 patients who requested birth control with IUDs; 56.4% (n = 31) of the women were in group A and 43.6% (n = 24) were in group B. The mean age of the women was 28.75 ± 5.61 (range, 19–42) years. The mean parity numbers for groups A and B were 2.35 ± 1.31 and 2.25 ± 0.94, respectively.

There was no statistically significant difference between the mean ages, parity numbers, body mass indexes (BMI) and menstrual cycle durations of the two groups ($p > 0.05$) (Table 1). The first and the second PI and RI values of the uterine arteries were significantly lower in group B when compared with group A (Table 2).

The first and the second PI values of the arcuate arteries in group B were significantly lower than in group A ($p = 0.009$ and $p = 0.035$, respectively). The second RI measurements of the arcuate arteries were significantly lower in group B than in group A ($p = 0.037$); the first RI measurement of arcuate arteries showed no statistically significant differences between the groups ($p = 0.073$) (Table 3). The PI and RI values of the utero-ovarian arteries were not significantly different at the first and second measurements between groups A and B (Table 4). The PI and RI value differences between the first and second measurements of the uterine, arcuate, and utero-ovarian arteries were not statistically different among and between group A and group B patients (Tables 2,3,4).

4. Discussion

The results of this study showed that IUD insertion did not cause a significant change in uterine, arcuate, and utero-ovarian artery Doppler indices. Uterine and arcuate artery Doppler indices were significantly lower in women who developed HMB than those who did not before and 2 months after IUD insertion, except for the first measurement of arcuate artery RI. Doppler measurements of utero-ovarian arteries did not differ between the groups. Therefore, low Doppler indices of uterine and arcuate arteries on the 2nd or 3rd day of menstruation could be a useful method to identify women who will develop IUD-induced HMB.

Table 3. Evaluation of arcuate artery PI and RI values according to groups.

		Group A (n = 31) Mean ± SD	Group B (n = 24) Mean ± SD	ap
Arcuate artery PI	First measurement	1.90 ± 0.35	1.65 ± 0.35	***0.009****
	Second measurement	1.86 ± 0.39	1.61 ± 0.47	***0.035****
	cp	***0.579***	***0.749***	
	Difference (1st–2nd measurements)	–0.05 ± 0.47	–0.04 ± 0.6	***0.957***
Arcuate artery RI	First measurement	0.76 ± 0.06	0.73 ± 0.06	***0.073***
	Second measurement	0.75 ± 0.05	0.71 ± 0.08	***0.037****
	cp	***0.237***	***0.233***	
	Difference (1st–2nd measurements)	–0.02 ± 0.08	–0.03 ± 0.10	***0.738***

aStudent *t*-Test; cPaired Samples *t*-Test; $*p < 0.05$; $**p < 0.01$.

Table 4. Evaluation of utero-ovarian artery PI and RI values according to groups.

		Group A (n = 31) Mean ± SD	Group B (n = 24) Mean ± SD	ap
Utero-ovarian artery PI	First measurement	2.15 ± 0.47	1.94 ± 0.50	***0.116***
	Second measurement	2.11 ± 0.49	1.94 ± 0.45	***0.178***
	cp	***0.774***	***0.996***	
	Difference (1st–2nd measurements)	–0.03 ± 0.66	0 ± 0.69	***0.854***
Utero-ovarian artery RI	First measurement	0.79 ± 0.08	0.78 ± 0.07	***0.324***
	Second measurement	0.80 ± 0.06	0.77 ± 0.08	***0.096***
	cp	***0.749***	***0.783***	
	Difference (1st–2nd measurements)	0.01 ± 0.11	–0.01 ± 0.11	***0.674***

aStudent *t*-Test; cPaired Samples *t*-Test; $*p < 0.05$.

In previous studies, IUD-induced bleeding, increased menstrual bleeding or menorrhagia terms were used for HMB which is the current terminology. IUD-induced bleeding was reported to be associated with decreased vascular resistance, which causes increased blood flow to the uterus in women using IUDs [3,5]. Momtaz *et al*. [3] measured uterine artery Doppler indices between days 1 and 5 of the menstrual cycle in three groups of women; healthy women who did not use IUDs (group 1), IUD-using women without abnormal vaginal bleeding (group 2), and women with abnormal uterine bleeding who were IUD users (group 3). They identified that the PI and RI values of group 3 were lower than those of women in groups 2 and 1. Based on their results, they suggested that a low PI (e.g., <2) value might be related to IUD-induced bleeding. However, the authors posed a question: did the low PI value exist before IUD insertion or was it a direct result of their use in women who were prone to developing IUD-induced bleeding? [3]. The current study's results propose an answer to this question: low uterine artery PI values exist before IUD insertion in women who experience IUD-induced HMB. Frajndlich *et al*. [5] assessed the uterine artery Doppler indices in women with IUDs. Doppler measurements were performed on the 2nd and 3rd day of menstruation. The authors stated that uterine artery Doppler indices (PI and RI) were significantly lower in the IUD users who had IUD-induced bleeding compared with the control group. Like Momtaz *et al*. [3], they also suggested that uterine artery PI <2 might be related to IUD-induced bleeding . Similar to these findings, the mean uterine artery PI value after IUD insertion was found to be below 2 in those who developed IUD-induced HMB (1.71 ± 0.29) in the current study. The current study's results support the findings of the above-mentioned studies regarding low PI and RI values of uterine arteries when compared with a control group in IUD-induced HMB. However, these studies were conducted in women who were users of IUDs at the time of the study and did not aim to predict the occurrence of IUD-induced HMB.

Considering previous studies that evaluated Doppler measurements before and after IUD insertion, uterine artery Doppler indices were found not to change 1 month after IUD insertion in the study of de Souza *et al*. [2] in which Doppler assessments were performed between the 5th and 8th days of menstruation. Shen *et al*. [7] reported similar results to Souza *et al*. [2], where they evaluated uterine, arcuate, radial, subendometrial, and ovarian artery Doppler indices in asymptomatic patients and they found no significant change in the blood flow of these vessels before and after IUD insertion, between the 8th and 11th days of menstruation. Mutlu *et al*. [9] observed no significant changes in uterine artery blood flow in women experiencing increased menstrual bleeding or dysmenorrhea after IUD insertion. Also, Jiménez *et al*. [10] reported no significant difference in uterine artery blood flow after IUD insertion. Rezk *et al*. [11] randomized 306 multiparous women desiring intrauterine contraception who were assigned to a levonorgestrel-releasing intrauterine system (LNG-IUS) (n

= 152) or a copper IUD (Cu-IUD) (n = 154) to compare the effects of LNG-IUS and Cu-IUD on menstrual changes and uterine artery Doppler indices. Uterine artery PI and RI values were measured before insertion, and 3 and 6 months after insertion. LNG-IUS-related abnormal bleeding (mainly irregular bleeding) was positively correlated with a decrease in uterine artery Doppler indices, but a similar change was not detected for Cu-IUD users. The current study's results are in-line with the findings of these studies because the results showed that the Doppler indices of uterine, arcuate, and utero-ovarian arteries did not change significantly after IUD insertion.

The Doppler index values of the uterine artery and its myometrial branches before IUD insertion were reported not to be significantly different between women who did and did not experience increased dysmenorrhea or menstrual bleeding after IUD insertion [6,9]. Similarly, Jiménez *et al*. [10] stated that Doppler analysis of the uterine artery and subendometrial vascularization before IUD insertion did not differ between women with and without IUD-related adverse effects. However, in these studies having dysmenorrhea was not an exclusion criterion. Doppler measurements during menstruation and including patients with dysmenorrhea may affect the results and show higher index values because increased impedance to blood flow in the uterine, arcuate, radial and spiral arteries has been identified in patients with primary dysmenorrhea [12,13]. Considering these findings, it can be proposed that uterine blood flow is altered in patients with dysmenorrhea. For this reason, solely Doppler findings of women with and without IUD-induced HMB were compared in the current study, excluding patients with previous or current IUD-induced dysmenorrhea. This may be a possible explanation for the conflicting results compared with the literature.

When the etiology of menorrhagia is evaluated, mainly mechanisms that cause vasodilatation are prominent such as increased PGE2 or PGI2 production, increased expression of endothelial nitric oxide synthase (eNOS), reduced endothelin (ET) levels, and enhanced neutral endopeptidase (NEP) activity [5,14,15]. In the current study, no decrease in Doppler indices was detected in women with IUD-induced HMB after IUD insertion, which could be anticipated regarding these mechanisms. The lack of evidence that IUDs cause vasodilatation in the uterine, arcuate, and utero-ovarian arteries suggests that these mechanisms may affect smaller subendometrial vessels, as indicated in previous studies [10,16].

The small number of women included in the study and not including the smaller vessels such as radial and spiral arteries for Doppler measurements are the limitations of our study. However, the strength of our study is that it is the only study to evaluate uterine artery, arcuate artery, and utero-ovarian artery Doppler indices in women without dysmenorrhea aiming to determine if IUD-related HMB could be predicted based on the Doppler indices of these vessels. On the other hand, it is a fact that the assessment of Doppler indices is not easy to implement on a large scale, particularly in low-income countries where ultrasound devices are not widespread and the use of IUD is frequent.

The current study's results indicate that a pre-insertion cut-off value for uterine and arcuate artery Doppler index values may help predict IUD-induced HMB in women without dysmenorrhea.

5. Conclusions

This study's results propose that IUDs do not cause a significant change in the uterine, arcuate, and utero-ovarian artery blood flow, but women with lower Doppler indices of the uterine and arcuate arteries before IUD insertion are more prone to developing HMB. Thus, we can conclude that low pre-insertion uterine and arcuate artery Doppler values may have a role in the prediction of IUD-induced HMB in women without previous or current IUD-induced dysmenorrhea. LNG-IUS may be preferred in patients who are predicted to develop HMB because they are a highly effective and easy-to-use treatment option for HMB.

Author Contributions

KÖ designed the research study. KÖ performed the research. KÖ and FŞ analyzed the data. KÖ and FŞ wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Written informed consent was obtained from all women before inclusion. The study was approved by the institute's ethics committee.

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Conflict of Interest

The authors declare no conflict of interests.

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