Original Article

Uterine Artery and Arcuate Vessels Doppler in Patients with Abnormal Uterine Bleeding Using Copper Intrauterine Contraceptive Device (IUCDs) and Combined Oral Contraceptive Pills (COCPs)

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ABSTRACT

Objectives: The aim of our study was to perform a comparative evaluation of the uterine and arcuate vessels Doppler indices in four groups of women: Intrauterine contraceptive device (IUCD) users with and without abnormal uterine bleeding (AUB), combined oral contraceptive users and women not using any contraceptive.

Materials and Methods: This prospective longitudinal analytic study was conducted in a tertiary university hospital during the period between September 2018 and March 2019. The study included 160 women with ages ranging from 20-35 years enrolled in 4 groups. Group 1: patient on IUCDs with AUB (n=40) Group 2: Patients on IUCD without AUB (n=40) Group 3: Patients on COCPs and without AUB (n=40) Group 4: Women not using aby contraceptive (n=40). The uterine artery and arcuate vessels were identified by transvaginal (TVUS) at the level of the internal os of the cervix. Real-time imaging and pulsed wave transvaginal Doppler assessment of the blood flow was performed to measure the blood flow indices.

Results: There was a statistically significant difference between the three patients' groups and the control group in endometrial thickness ($p=0.004$), uterine artery PI ($p<0.001$) , arcuate vessel PI ($p<0.001$) and arcuate vessel RI ($p<0.001$). However there was no significant difference regarding uterine artery RI ($p=0.112$). Additionally, there was statistically significant difference between endometrial thickness ($p<0.001$), uterine artery PI ($p=0.036$), arcuate vessel PI ($p<0.001$) and arcuate vessel RI ($p<0.001$) when comparing the groups IUCD with and without AUB. Yet, there was no statically significant difference regarding uterine artery RI. Finally, ROC curve analysis showed the optimal cutoff values for the uterine artery PI (1.9), the arcuate vessels PI (0.9) and the arcuate vessels RI (0.49) to predict AUB in patients with IUCD.

Conclusion: We identified a correlation between increased bleeding and Doppler indices. Most of the uterine artery and arcuate vessels Doppler indices were lower in the group with IUCD and AUB than in non-bleeding group. Thus the blood flow is increased during bleeding in women with IUCD-induced AUB than in those with normal menstruation. This indicates that there is an increase in uterine blood flow occurs in cases of IUCD - induced abnormal uterine bleeding.

Key Words: Arcuate vessels, AUB, Doppler, IUCD, uterine artery

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INTRODUCTION

Around 14.3 % of middle-aged women resort to intrauterine contraceptive devices (IUCDs) for contraception. This percentage might increase in some countries to reach 40%.[1] The copper IUCD, is utilized by nearly 150 million women worldwide. It is a safe, reversible, cheap and a reliable method with a long action up to twenty years for some forms.[2] It works by different mechanisms; mainly causing an intrauterine local inflammatory response that leads to lysosomal activation. Such inflammatory actions are spermicidal.[3] Not uncommonly this IUCD causes many side effects such as abnormal uterine bleeding (AUB), pelvic pain, dysmenorrhea and might be displaced by the effect of uterine contractions.[4]

On the other hand, combined oral contraceptive pills (COCPs) are considered an oral form of contraception containing an estrogen as well as a progestin. Their most important mode of action is by inhibiting the ovulation process through suppression of the hypothalamus and pituitary gland. The estrogen component mainly suppresses the follicle stimulating hormone (FSH) release and stabilizes the endometrium preventing breakthrough bleeding while

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the progestin component causes a compaction effect on this endometrium preventing intermenstrual bleeding.[5] They have their own side effects as contraceptive failure, deep venous thrombosis (DVT) and other thromboembolic events, vascular cerebral strokes and occasionally heart attacks.[6]

Abnormal uterine bleeding (AUB) is defined as vaginal bleeding arising from the uterus occurring for a longer duration than the usual or at an irregular time; not related to menstruation. This haemorrhage may be heavy with blood clots and might occur often or randomly. It can be due to the reflection of vascular changes in the uterus in patients utilizing IUCDs or on COCPs. Doppler ultrasonography can evaluate these vascular changes in the both the uterine and arcuate arteries. Such an assessment can be of aid in predicting the development of AUB.[7,8,9]

Thus, in this study we attempted to perform a comparative evaluation of uterine and arcuate arteries Doppler indices in four groups of women: IUCDs users with and without AUB, COCPs users and women not using any contraceptive. Our aim was to identify a correlation between increased bleeding and such Doppler changes.

PATIENTS AND METHODS

This was a prospective longitudinal cohort study conducted in the department of Ob/Gyn Cairo University after obtaining a departmental ethical comittee approval, during the period between September 2018 and March 2019. The study included 160 women with ages ranging from 20-35 years. The included patients were categorized into one of four groups as follow.

Group 1: Women who had an IUCD (Cu T380) inserted 6 months to 3 years ago with AUB either heavy menstrual bleeding, intermenstrual bleeding or both (n=40). We defined heavy menstrual bleeding as menstrual blood lasting 8 days or more and /or presence of blood clots with the menstrual flow. We defined intermenstrual bleeding after cessation of the regular menses or any irregular bleeding

Group 2: Women who had an IUCD (Cu T380) inserted 6 months to 3 years ago with no AUB (n=40)

Group 3: Women who were steadily and till date using cyclic COCPs within 6 month to 6 years without AUB (n=40)

Group 4: (control) Women not using any contraceptive for the past 6 months and with no AUB (n=40)

We excluded:

1. Patients with any local cause of bleeding such as fibroids, polypi, tumors, cervical ectopy and adenomyosis.

2. Patients with bleeding disorders such as an idiopathic thrombocytopenia purpura, hemophilia.

3. Patient with a niche >5 mm depth at the site of cesarean scar.

4. Patients on anticoagulation therapy.

5. Patients with displaced IUCDs > 4mm from fundal endometrium.

6. Non complaint users of COCPs in the past 3 months or patients who have received gestagens for any reason in the past 3 months.

7. Patients who were on hemostatics as tranexamic acid, amino caproic acid or ethamsylate

8. Patients with recent history of PID.

9. Third degree RVF uterus.

10. Patients with a positive pregnancy test.

All patients provided their written consent after the purpose of the study was clearly explained. A blood sample was sent to the laboratory to exclude any pregnant patients and patients with low platelet count. Then a general examination was performed including body mass index (BMI) and presence of purpura or erythema. Vaginal examination followed to detect the position and size of the uterus, adnexa and cervical speculum examination to exclude local cause of bleeding. Transvaginal ultrasound was performed postmentrually from day 9-14 in the lithotomy position after full evacuation of the bladder using Voluson GE E8 with 7.5 MHz vaginal probe. For patients who had intermenstrual bleeding the scan was performed when the patient was off bleeding. First we excluded the presence of local causes of bleeding as fibroids, ademomyosis or polypi and then checked the position of IUCD if present and measured the endometrial thickness. Doppler blood flow assessment of the uterine artery and arcuate vessels was performed by the same observer using the same equipment.

The probe was placed in the lateral fornix and the uterine artery was plotted at the level of the internal os using color Doppler at the level of the internal os of the cervix. Real-time imaging and pulsed wave Doppler assessment of the blood flow was obtained. The pulsatility index (PI) and the resistive index (RI) were calculated 3 times on each side and the average calculated. On each assessment at least three waveforms were assessed for each vessel. The arcuated vessels were then plotted using color Doppler and pulsed wave assessment was repeated as in the uterine artery. (Figure 1 and 2).

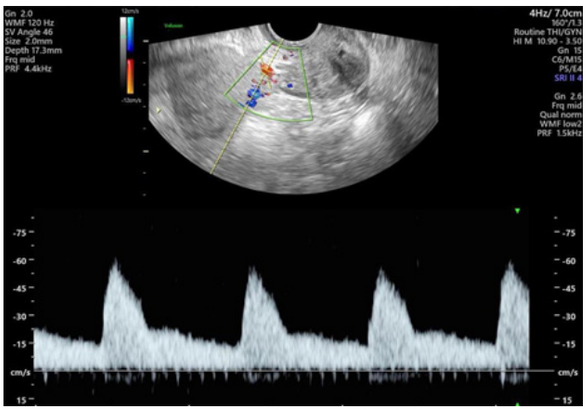

Fig. 1: Uterine artery Doppler; a sagittal view of the uterus with color Doppler visualizing the uterine artery at the level of the internal os.

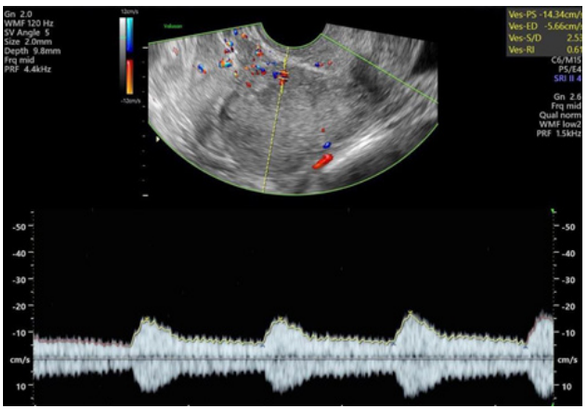

Fig. 2: Arcuate vessels Doppler; a sagittal view of the uterus with color Doppler visualizing the uterine vessels within the myometrium.

Categorical data were displayed as frequencies and centiles. Pearson Chi-square test had been used to compare these data. Numeric values were displayed as means and SD. Comparison between groups was done using statistical tests (Mann Whitney U-test, Student T test). Receiver operating characteristic (ROC) curves were created to determine the sensitivity and specificity of the Doppler indices to get cut-off values. Two-tailed *p value <0.05* will be considered significant.

RESULTS

We approached 234 patient and excluded 74 patients most of which either had a misplaced IUCD or an associated pathology that might have been the cause of bleeding. Finally, we analyzed 160 patients (40 in each group). There was no significant difference in the baseline characteristics between all the groups as shown in (Table 1).

Table 1: Comparison of different clinical variables among all study groups

Variable	IUCD with AUB	IUCD without AUB	COCP	Control	*P value*
Age (years)	27.9 ± 4.2	28.3 ± 4.5	28.1 ± 4.3	29.2 ± 4.4	0.78
BMI(kg/m$^{2)}$	27.5 ± 3.6	24.9 ± 3.1	27.4 ± 3.3	25.3 ± 2.8	0.56
Gravity	2.40 ± 1.15	2.83 ± 1.31	2.65 ± 1.35	1.38 ± 1.48	0.63
Parity	1.90 ± 0.95	2.5 ± 1.26	2.18 ± 0.98	0.80 ± 1.06	0.48
Contraception duration (yrs)	1.91 ± 0.80	2.03 ± 0.80	2.03 ± 0.90	-	0.89
No. of C.S	0.65 ± 0.73	0.60 ± 0.982	0.88 ± 0.97	0.20 ± 0.46	0.57

There was a statistically significant difference between the three patients' groups and the control group in endometrial thickness (*p=0.004*), uterine artery PI (*p<0.001*), arcuate vessel PI (*p<0.001*) and arcuate vessel RI (*p<0.001*). However there was no significant difference regarding uterine artery RI (*p=0.112*) as shown in (Table 2).

Table 2: Comparison of different ultrasound variables among all study groups

Variable	IUCD with AUB	IUCD without AUB	COCP	Control	*P value*
Endometrial thickness (mm)	5.53 ± 2.01	4.13 ± 0.80	4.38 ± 1.54	4.95 ± 1.97	0.004
Uterine Artery PI	1.65 ± 0.34	1.94 ± 0.66	1.73 ± 0.41	1.24 ± 0.70	<0.001
Uterine Artery RI	0.81 ± 0.17	0.86 ± 0.25	0.90 ± 0.28	0.78 ± 0.16	0.112
Arcuate Vessel PI	0.75 ± 0.26	1.53 ± 0.86	0.72 ± 0.13	0.67 ± 0.41	<0.001
Arcuate Vessel RI	0.35 ± 0.15	0.73 ± 0.34	0.29 ± 0.10	0.43 ± 0.28	<0.001

When we focused on the groups with IUCD we found that there was statistically significant difference between endometrial thickness (*p<0.001*), uterine artery PI (*p=0.036*), arcuate vessel PI (*p<0.001*) and arcuate vessel RI (*p<0.001*) in both groups. However there was no statically significant difference regarding uterine artery RI as shown in (Table 3). So most of the Doppler indices (Mean± SD) were lower in women using IUCD with bleeding than women of control group.

Table 3: Comparison of IUCD with AUB and IUCD without AUB

Variable	IUCD without bleeding group	IUCD with bleeding	*P value*
Endometrial thickness (mm)	4.13 ± 0.80	5.53 ± 2.013	0.001
Uterine Artery PI	1.94±0.66	1.65±0.34	0.036
Uterine Artery RI	0.86±0.25	0.81±0.17	0.205
Arcuate Vessel PI	1.53±0.86	0.75±0.26	<0.001
Arcuate Vessel RI	0.73±0.34	0.35±0.15	<0.001

As for the uterine artery PI, the ROC curve showed that the area under the curve was 0.63 to predict AUB in women with IUCD with an optimal cutoff value of 1.9 and with a sensitivity of 82.5% and a specifity of 50%. (CI=0.0.510/0.762) (*P=0.036*). Regarding the arcuate vessel PI the area under the curve was 0.79 to predict AUB with an optimal cutoff value of 0.90 and with a sensitivity of 85% and a specifity of 75%. (CI= 0.688/0.910) (*P <0.001*). Finally, regarding the arcuate vessel RI the area under the curve was 0.83 to predict AUB with an optimal cutoff value of 0.49 and with a sensitivity of 87.5% and a specifity of 80% (CI= 0.739/0.935) (*P <0.0001*). (Table 4) and (Figure 3).

Table 4: Cut-off values for statisticaly significant doppler ultrasound variables between IUCD with AUB group and IUCD without AUB.

Variable	AUC	*P. value*	95% Confidence Interval		cutoff value	Sensitivity (%)	Specificity (%)
			Lower Bound	Upper Bound			
Uterine artery PI	0.63	0.036	0.510	0.762	1.90	82.50	50.00
Arcuate Vessel PI	0.79	< 0.001	0.688	0.910	0.90	85.00	75.00
Arcuate Vessel RI	0.83	< 0.001	0.739	0.935	0.49	87.50	80.00

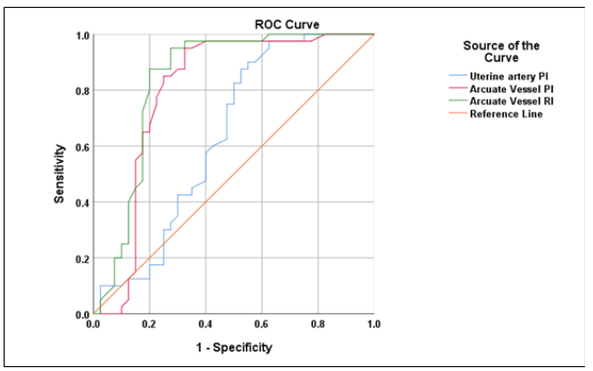

Fig. 3: ROC curve for significantly different Doppler variables between IUCD group with AUB and IUCD without AUB.

DISCUSSION

Heavy menstrual bleeding and intermenstrual bleeding are most common side effects related to IUCDs with menstrual blood being commonly doubled after insertion causing iron deficiency anemia in many patients. Ten to 15 percent of users discontinue the IUCD due to this indolent problem[10]. Thus, uterine artery Doppler changes to the (RI), (PI) were readily investigated to identify vascular hemodynamic changes to the uterus in such patients[11]. We aimed in this study to check the hypothesis that AUB induced by copper IUCD usage occurs secondary to blood flow increase in the uterine artery as well as the arcuate vessels and to test whether transvaginal Doppler might be applied to identify women at risk of AUB.

We found that the mean uterine artery and arcuate vessel PI in addition to arcuate vessel RI were statistically and significantly higher when compared to the nonbleeding control group. This could be attributed to the pelvic congestion which commonly occurs with IUCDs. This

agrees with a recent study that showed that such effect was related to the duration of IUCD usage.[12]

In contrast Frajndlich *et al*., in 2000[13], demonstrated that transvaginal Doppler examination of uterine artery in 101women (74 IUCD users and 24 controls) showed that the RI and PI were lower in the IUCD users. However not all patients in this study had AUB while some of those who had bleeding were on medications to control the bleeding.

We also found that there was significant difference between endometrial thickness ($p<0.001$), uterine artery PI ($P=0.036$), arcuate vessel PI ($p<0.001$)) and arcuate vessel RI ($p<0.001$) in the IUCD without bleeding group and IUCD with bleeding group. However there was no significant difference regarding uterine artery RI ($p=0.205$). This agrees with an earlier study that calculated the uterine artery PI and RI in 68 women (44 IUCD and 24 control). In that study both the PI and RI were lower in women IUCD user with AUB than in those without AUB. Moreover, there were no significant differences in PI and RI values between women using IUCD with no AUB and women in the control group.[14] We also agreed with Jarvela *et al*.[15] who evaluated the Doppler effects of the copper IUCD on the uterine artery in 21 women with no AUB. The authors did not find any significant changes in uterine artery RI after the insertion of the IUCD.

In contrary to our results a study in 2008 found no differences in uterine artery PI nor the RI between women with IUCD induced vaginal bleeding and IUCD users with normal menses.[16] Also, our results do not agree with De Souza *et al*[17], who prospectively evaluated the uterine artery RI and PI in over 100 patients before and 30 days after IUCD insertion. They concluded that the IUCD did not interfere with the uterine vascular resistance one month post insertion. Perhaps this is due to the short time interval which does not allow for changes or complications to happen.

Other studies evaluated the effect of IUCD on pain and bleeding[18]. They performed transvaginal Doppler ultrasound examinations on 120 women before and after IUCD insertion. No significant major changes in uterine artery blood flow were detected in women experiencing heavy menstrual bleeding, or pain following IUCD insertion.

We also tried to estimate cut off values for vascular predictors of AUB in IUCD users. To the best of our knowledge this was not attempted before, as many authors did not find significant vascular changes in IUCD users.[18].

The contrast and divergence between the results of this study and those previously reported by the other authors might be the effect of several variables as the patient selection, the skills and experience of the observer, study methods, duration of IUCD usage, time of observation during the cycle and the sample size. We assume that we performed this study by a skilled observer with proper sample size selection and thus consider this our main point of strength. However, our work could not be without limitation, and we believe that the variation in the insonation angle of the Doppler beam (which was not standardized or precisely determined) to be our main limiting factor. We also acknowledge that we did not take into consideration the duration of IUCD usage to be another important limiting factor. So further research should be conducted in this field taking into consideration the above limitations and detecting intra and interobserver variations of the calculated indices.

To conclude, we identified a correlation between increased bleeding and Doppler indices. AUB in IUCD user affects both the uterine artery and arcuate vessels Doppler indices due to the increase in blood flow when compared to normal menstruation. Most of the uterine artery and arcuate vessels Doppler indices were lower in the group with IUCD and AUB than in non-bleeding group. This indicates that the increase in uterine blood flow definitely occurs in cases of IUCD - induced abnormal uterine bleeding and might be the ground for therapeutic interventions.

CONFLICT OF INTEREST

There are no conflicts of interests.

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