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EVALUATION OF SUBENDOMETRIUM BLOOD FLOW IN CASES OF EXCESSIVE MENSTRUAL BLEEDING AFTER INTRAUTERINE CONTRACEPTIVE DEVICE

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ABSTRACT

Background: There is several possible mechanisms that explain the cause of menorrhagia in patient using intrauterine contraceptive device (IUCD). Abnormal uterine bleeding may be excessive to the extent of causing iron deficiency anemia. The aim of the present study was to compare of the Doppler parameter of subendometrium and uterine artery of the patients that complain of excessive menstrual bleeding after IUCD insertion to other patients have no excessive menstrual bleeding. **Patients and methods:** This study includes 54 women divided into three groups. Group I; included 18 women using copper intrauterine device (Tcu 380A) and complaining of menorrhagia, Group II; included 18 women using copper IUCD and not complaining of abnormal uterine bleeding and group III; included 18 women not using any contraceptive method and not complaining of abnormal uterine bleeding. **Results:** There is statistically significant difference between the studied groups regarding left uterine artery RI and PI. The cutoff of sub-endometrial RI in prediction of excessive menstrual bleeding if IUD inserted is ≥0.755 with area under curve 0.701 at which sensitivity 77.8%, specificity 69.4%, positive predictive value 56%, negative predictive value 86.2% and accuracy 72.2% ($p<0.05$). The best cutoff of uterine RI in prediction of excessive menstrual bleeding if IUD inserted is ≥0.775 with area under curve 0.807, at which sensitivity 77.8%, specificity 72.7%, positive predictive value 58.3%, negative predictive value 86.7% and accuracy 74.1% ($p<0.05$). **Conclusion:** Uterine arteries RI and PI were significantly lower in women with copper IUD induced menorrhagia. Subendometrial blood flow RI, PI were significantly lower in women with Copper IUD induced menorrhagia than women of group II and III.

Keywords: Subendometrium Blood Flow; IUCD; Menstrual Bleeding

INTRODUCTION

An intrauterine device is one of the most frequently used methods for birth control around the world **(1).** The most important copper intrauterine contraceptive device (IUCD) related side effects are excessive uterine bleeding and menstrual pain. The menstrual blood may be excessive to the extent of causing iron deficiency anemia **(2).** These side effects are responsible for a removal rate of 5% to 15% during the first year after intrauterine contraceptive device (IUCD) insertion **(3).**

There are several possible mechanisms that explain the causes of excessive menstrual bleeding in patients using IUCD Several studies reported that IUCD insertion increase the production of prostaglandins in the endometrium which cause an increase in vascularity, vascular permeability and inhibit platelet activity and therefore, increase menstrual bleeding **(4).**

Probably there is a relation between IUCD adverse effects and uterine vascularization. However, only a few studies have demonstrated an increase in subendometrial vascularization in patients with IUCD induced excessive menstrual bleeding **(5).** The color pulsed Doppler is activates in the 2D mode, the rightandthe left uterine artery pulsatilityindex (PI) and resistance index (RI) are calculate. Subendometrial blood flow PI and RI are calculate **(6).**

Therefore, this study aimed to compare of the Doppler parameter of subendometrium and uterine artery of the patients that complain of excessive menstrual bleeding after IUCD insertion to other patients have no excessive menstrual bleeding.

PATIENTS AND METHODS

This cross sectional case control study was performed at Zagazig out patients clinic, during the period between February 2021andAugust 2021 Fifty fourwomen attending Gynecology and family planning outpatient clinic were included in the study.

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Women were divided into three groups as follows: Group (I): included 18 women using copper T380 IUCD and complaining of menorrhagia. Group (II):included 18 women using CuT380 IUCD and not complaining of abnormal uterine bleeding. They attended the outpatient clinic complaining of vaginal discharge or inability to feel the threads of IUCD or requesting IUCD removal. Group (III): was a control group which included 18 women without IUCD who attended outpatient clinic complaining of vaginal discharge or requesting copper IUCD insertion and not complaining of abnormal uterine bleeding.

Inclusion criteria:

Women in age from 25 to 40 years old with regular menstrual cycle and body mass index < 30 kg/m^2.

Exclusion criteria:

Pregnancy, acute or chronic pelvic inflammatory disease, the presence of pelvic pathology as benign or malignant genital tumors or any uterine congenital anomalies. Patients on hormonal treatment in the last three months before the study. Bleeding tendencies and general causes as Von Willebrand disease … etc. Patients on anti–coagulant and non-steroidal antinflammatory drugs.

Clinical Assessment:

The study protocol was approved by the Zagazig University Institutional Review board. Study participants were counseled and informed written consent was obtained. Detailed clinical history was taken from the patients with special consideration to age, parity, duration of IUCD insertion and history of other contraception before insertion of IUCD.

Menstrual history before and after IUCD insertion was taken including duration and amount of menstrual flow, regularity and length of the cycle, intermenstrual bleeding or spotting contact bleeding. In addition, history of any drug intake, blood disease or any medical disorders were considered.

Clinical examination was done including general, abdominal and pelvic examination which included bimanual examination to detect any abnormal findings and speculum examination to detect the threads of the IUCD and exclude any local cause of bleeding as polyp and erosion.

Color Doppler blood flow assessment:

Ultrasoundexamination and Doppler assessment of subendometerium blood flow, right and left uterine arteries were carried out between days 7-10 of the cycle.

Doppler study was performed upon:the right and left uterine arteries. Also, Sub-endometrialblood flow.

The Doppler indices, which wereused are the pulsatility index (PI; A-B/mean) and the resistance index (RI; A-B/A), in which A was the maximum (systolic)Doppler frequency shift; Bwas the minimum (diastolic) Dopplerfrequency shift; and the mean represented the average Doppler frequency shift. Three waveforms werestudied for the sub-endometrial blood flow, right and left uterine arteries.

Statistical analysis:

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Chi square and Fisher exact test when appropriate. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests, independent sample t test were used. Kruskal wallis test and Turkey HSD were used. p value of one way ANOVA test was <0.05. ROC curve was used to calculate performance of cutoff of certain marker in diagnosis of health problem. The level statistical significance was set at P<0.05. Highly significant difference was present if p≤0.001.

RESULTS

The present study showed a statistically non-significant difference between the studied groups regarding age **(Table 1)**.There is statistically significant difference between the studied groups regarding right uterine artery RI and PI. On doing Turkey's HSD test, the difference is significant between group with IUD and manifested by excessive menstrual bleeding and the group with IUD and normal menstrual flow and control groups. RI was significantly higher in those with IUD and excessive menstrual flow and patients within this group had the lowest PI **(Table 2)**.

There is statistically significant difference between the studied groups regarding left uterine artery RI and PI. On doing Turkey's HSD test, the difference is significant between group with IUD and manifested by excessive menstrual bleeding and the group with IUD and normal menstrual flow and control groups. RI was significantly higher in those with IUD and excessive menstrual flow and patients within this group had the lowest PI **(Table 3)**.

The best cutoff of sub-endometrial RI in prediction of excessive menstrual bleeding if IUD inserted is ≥0.755 with area under curve 0.701, at which sensitivity 77.8%, specificity 69.4%, positive predictive value 56%, negative predictive value 86.2% and accuracy 72.2% (p<0.05) **(Table 4 , Figure 1)**.

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The best cutoff of uterine RI in prediction of excessive menstrual bleeding if IUD inserted is ≥0.775 with area under curve 0.807, at which sensitivity 77.8%, specificity 72.7%, positive predictive value 58.3%, negative predictive value 86.7% and accuracy 74.1% (p<0.05) **(Table 5 , Figure 2)**.

There is statistically non-significant correlation between duration of IUD and the studied Dopper parameters **(Table 6)**.

Table (1):Comparison between the studied groups regarding demographic data:

Parameter	Groups			Test	
	IUD with excessive bleeding group	IUD without excessive bleeding group	Control group	F	p
	N=18 (%)	N=18 (%)	N=18 (%)		
Age (year):					
Mean ± SD	32.67 ± 4.8	34.67 ± 4.03	32.44 ± 4.98	1.261	0.292
Min – max	25 – 40	27 – 40	26 – 39		

F One Way ANOVA test

Table (2) Comparison between the studied groups regarding right uterine artery Doppler:

Parameter	Groups			Test	
	IUD with excessive bleeding group	IUD without excessive bleeding group	Control group	F	P
	N=18 (%)	N=18 (%)	N=18 (%)		
RI:					
Mean ± SD	0.82 ± 0.13	0.73 ± 0.07	0.72 ± 0.09	25.94	<0.001**
Min – max	0.62 – 0.99	0.6 – 0.85	0.58 – 0.88		
Turkey's HSD	P_1<0.001**	P_2 0.224	P_3<0.001**		
PI:					
Mean ± SD	1.63 ± 0.21	2.1 ± 0.36	2.24 ± 0.2	6.362	0.003*
Min – max	1.26 – 1.98	1.23 – 2.92	1.94 – 2.61		
Turkey's HSD	P_1 0.011*	P_2 0.984	P_3 0.007*		

**p≤0.001 is statistically highly significant *p<0.05 is statistically significant F One way ANOVA test

Table (3) Comparison between the studied groups regarding left uterine artery doppler:

Parameter	Groups			Test	
	IUD with excessive bleeding group	IUD without excessive bleeding group	Control group	F	p
	N=18 (%)	N=18 (%)	N=18 (%)		
PI:					
Mean ± SD	0.81 ± 0.11	0.71± 0.12	0.72 ± 0.1	4.948	0.011*
Min –max	0.66 – 0.98	0.5 – 0.92	0.6 – 0.87		
Turkey's HSD	P_1 0.014*	P_2 0.895	P_3 0.044*		
RI:					
Mean ± SD	1.77 ± 0.33	2.33 ± 0.28	2.19 ± 0.55	9.226	<0.001**
Min – max	1.21 – 2.77	1.73 – 2.9	1.94 – 2.86		
Turkey's HSD	P_1 0.001**	P_2 0.606	P_3 0.008*		

**p≤0.001 is statistically highly significant *p<0.05 is statistically significant F One way ANOVA test

**p≤0.001 is statistically highly significant *p<0.05 is statistically significant F One way ANOVA test

Table (4) Performance of subendometrial RI in prediction of excessive bleeding if IUCD inserted among the studied participants:

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	P

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≥0.755	0.701	77.8	69.4	56	86.2	72.2%	0.001**

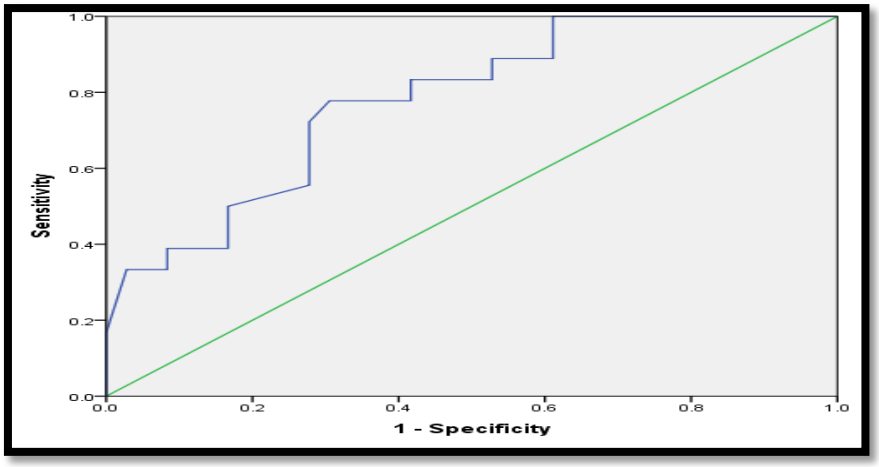

Figure (1) ROC curve showing performance of sub-endometrial RI in prediction of excessive bleeding if IUCD inserted among the studied participants

Table (5) Performance of uterine artery RI in prediction of excessive bleeding if IUCD inserted among the studied participants:

cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	P
≥0.775	0.807	77.8	72.7	58.3	86.7	74.1%	0.001**

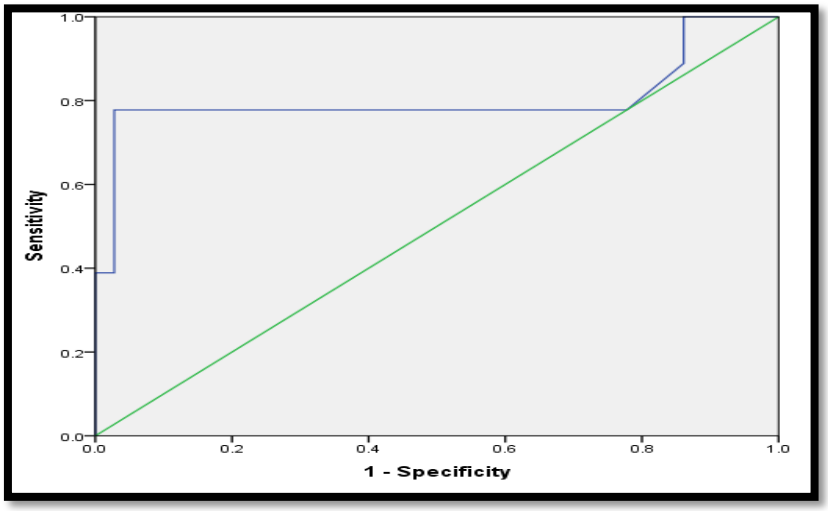

Figure (2) ROC curve showing performance of uterine artery RI in prediction of excessive bleeding if IUCD inserted among the studied participants

Table (6) Correlation between duration of IUD and doppler parameters:

	Duration of IUD	
	r	p
Sub-endometrial RI	0.128	0.5
Sub-endometrial PI	0.082	0.667
Right uterine artery RI	0.23	0.221
Right uterine artery PI	0.119	0.532
Left uterine artery RI	-0.033	0.862
Left uterine artery PI	0.229	0.223

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r Spearman rank correlation coefficient

DISCUSSION:

The menstrual blood loss is commonly doubled after the insertion of IUCD particularly during the first 3 to 6 months of use. Frequently, the menstrual blood may be excessive to the extent of causing iron deficiency anemia, women with heavy menstruation may not be able to tolerate the use of IUCD and within one year approximately 15% of women remove the IUCD because of this problem **(7).**

There are several possible mechanisms that explain the cause of excessive bleeding, several studies reported that IUCD insertion increase the production of prostaglandins in the endometrium which cause an increase in vascularity, capillary permeability, and inhibit platelet activity and therefore increase menstrual bleeding **(8).**

Two studies have reported that IUCD causes cyclo-oxygenase isoenzyme 2 up-expression, the subsequent elevated prostanoids biosynthesis and signaling can promote the expression of proangiogenic factors, such as vascularendothelial growth factor VEGF), platelet-derived growth factor (PDGF), and angiopoietin-1 and 2 **(9,10)**.

It is possible that there are also other vascular abnormalities resulting from disturbed angiogenesis, in abnormal vessels, poor contractibility and dysfunction of the haemostatic system may cause menorrhagia and decreased impedance **(11).**

We conducted this cross sectional case control study to assess uterine artery, subendometrial microvascularization indices in relation to heavy menstrual bleeding as a predictor the risk of bleeding after IUCD insertion. Patients dived to Group I included 18 women using CuT380 IUCD-induced HMB ,Group II included 18 women using CuT380 IUCD without HMB and Group III (control group) included 18 women without CUT380 IUCD.

In agreement with current study, **Anwar et al., (12)** cross sectional case control study was performed in Al Galaa Maternity Teaching Hospital, on three hundred and fifteen women divided into three groups as follows: Group (I): included 105 women using copper T380 IUCD and complaining of menorrhagia. Group (II): included 105 women using CuT380 IUCD and not complaining of abnormal uterine bleeding. And Group (III): was a control group which included 105 women without IUCD. They reported no significant differences between patients in the three groups with respect to age, parity, and body mass index.

In current study, uterine artery PI & RI significantly decreased with time in heavy and non-heavy menstrual bleeding cases. On the other hands, uterine artery PI & RI (basal and month-3) was significantly lower in heavy menstrual bleeding cases and their reduction was significantly higher in Heavy menstrual bleeding cases. There are several mechanisms explaining the association between the increase in the uterine blood flow and the increase in menstrual blood loss. Prostaglandins and prostacyclins play an important role in the IUCD-induced menorrhagia, in addition prostaglandins are known to affect blood flow regulation in the uterine arteries. Other vasoactive substance is nitric oxide. Women with menorrhagia also show significant increase in endothelial cell proliferation reflecting disturbed angiogenesis **(10)**.

There are also other possible mechanisms explaining the association of the PI of uterine artery with menstrual blood loss. Women with menorrhagia show a significant increase in endothelial cell proliferation, reflecting disturbed angiogenesis. It is possible that there are also other vascular abnormalities resulting from disturbed angiogenesis. In abnormal vessels, poor contractibility and dysfunction of the haemostatic system may cause menorrhagia and decreased impedance **(13).**

Indeed, there is some controversy regarding PI and resistance index (RI) in IUCD users. Some studies suggest that there are no differences in PI before and after insertion **(14).** Also **Järvelä et al., (15)** demonstrate a PI increase in the midluteal phase.

Furthermore another group assessed and evaluated the PI and RI of uterine arteries in 68 study subjects, involving 44 cases using intrauterine contraceptive device and 24 control study subjects not using a contraceptive method. Both the PI and RI were statistically significantly lower in cases with IUCD triggered bleeding than in those using IUCD and not complaining of abnormal vaginal bleeding. Moreover, there were no statistically significant differences observed in PI and RI between cases using IUCD without complaining of abnormal vaginal bleeding and women in the control research group. They mentioned that

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the PI was less than 2 in cases with IUCD triggered bleeding, whereas the mean PI in cases using IUCD without complications was 2.38 with the lowest PI being 1.98 **(16).**

Frajndlich et al. also measured the uterine artery RI and PI values in women with and without IUCD and found that the PI values of the women with IUCD having abnormal bleeding were significantly lower than those of the patients without IUCD. This was also valid for the patients with IUCD having no abnormal bleeding or patients treated with prostaglandin inhibitors due to abnormal bleeding. Based on this information, it was concluded that a lower resistance and an increased uterine artery blood flow correlated with the presence of an abnormal bleeding, and the PI valuesparticularly if lower than 2pose a significant risk for the bleeding induced by IUCD **(17)**.

Hurskainen et al. (18) measured the PI of uterine arteries, in 60 spontaneously menstruating women complaining of menorrhagia. A significant inverse correlation was found between uterine artery PI and the amount of menstrual blood loss, suggesting that women with lower uterine flow impedance bleed more

Jamenez et al. (19) reported that there were no statistically significant differences in PI and RI between women with IUCD-induced bleeding and women using IUCD with normal menstruation.

In comparison to the results of **Shen et al, (20)** who conducted a study at the Shaare Zedek Medical Center on 23 regularly menstruating women who was elected to have Cu medicated IUCD (Nova T) inserted for contraception. All patients had color Doppler study of both uterine arteries pre-insertion and post-insertion and their result was no significant change in blood flow has been detected as a result of the presence of Cu medicated IUCD in either uterine arteries which confirms our study regarding our control group (which showed no significant changes in PI or RI)

In contrary to the results of the current study, **Jamenez et al**. **(21)** found no statistically significant differences in uterine artery PI and RI between women with IUCD induced bleeding and women using IUCD with normal menstruation. **De Souza et al. (22)** compared the uterine artery PI and RI of 100 women before IUCD insertion and one month thereafter: the presence of the device did not interfere with the vascular resistance of the uterine arteries.

In current study, subendometrium PI & RI significantly decreased with time in heavy and non-heavy menstrual bleeding cases. Subendometrium PI & RI (basal and month-3) and their reduction were significantly lower in heavy menstrual bleeding cases. **Jamenez et al**. **(21)** concluded that the copper IUD increases the subendometrial microvascularization of those patients who presented with IUD induced side effects (menorrhagia) before and 3 months after IUD insertion

In addition, the result of the **Anwar et al., (12)** showed that women in group I with menorrhagia had a significant decrease in subendometrial pulsitility index (PI), resistance index (RI) in comparison with women in group II using copper IUCD and not complaining of abnormal uterine bleeding and women in group III (control group)**.**

CONCLUSION:

Uterine arteries RI and PI were significantly lower in women with copper IUD induced menorrhagia. Subendometrial blood flow RI, PI were significantly lower in women with Copper IUD induced menorrhagia than women of group II and III.

No Conflict of interest.

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