

Doppler Characteristics of Subendometrium and Uterine Hemodynamic Changes in Patients with Copper Intrauterine Device-induced Bleeding

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ABSTRACT

Background: The intrauterine contraceptive device is one of the most frequently used method of contraception all over the world. The most important adverse effects related to copper intrauterine contraceptive device use are excessive uterine bleeding and menstrual pain which are responsible for 5-15% removal rate of IUD during the first year of its insertion.

Objectives: The aim of the present study is to evaluate subendometrial blood flow in cases of menorrhagia after copper IUCD insertion in comparison to cases using IUCD and not complaining of abnormal uterine bleeding.

Patients and Methods: This study included 200 women; divided into two groups. Group I; included 100 women using copper intrauterine device and complaining of menorrhagia, Group II; included 100 women using copper IUD and not complaining of abnormal uterine bleeding.

Results: As regard to Doppler findings, it was noted that PI, RI of uterine arteries were significantly lower in group I in comparison to group II (p value <0.001), and by power Doppler energy women in group I with menorrhagia had a significant increase in subendometrial blood flow according to the subendometrial signal area percentage in comparison with women in group II using copper IUD and not complaining of abnormal uterine bleeding (control group). **Conclusion:** The results of our study revealed that uterine artery and subendometrial blood flow were increased in women with copper IUD induced menorrhagia in comparison to women with copper IUD and not complaining of abnormal uterine bleeding.

Keywords: Doppler, Subendometrium, Uterine Hemodynamic, Copper Intrauterine Device-induced Bleeding.

INTRODUCTION

The intrauterine copper devices are the most widely used method of long-acting reversible contraception with a very low failure of 0.2-1.0% ⁽¹⁾.

Side effects associated with IUD are mainly used for pelvic cramping, dysmenorrhea, heavy menstrual periods, and the discovery of uterine device expulsion may cause a stopover. Heavy menstrual periods are the most common cause of device removal ⁽²⁾. There are many possible mechanisms that explain the cause of menstruation in patients who use intrauterine contraception. Several studies have reported that intrauterine contraceptive inputs increase the production of prostaglandins in the lining of the uterus, which causes an increase in blood vessels, vascular permeability, inhibits platelet activity, and thus increases menstrual bleeding ⁽³⁾.

Probably there is relation between intrauterine device adverse effects and uterine vascularization. However, this association is neither well-known nor well-studied ⁽⁴⁾. Only a few studies have demonstrated an increase in subendometrial vascularization in patients with intrauterine device-induced menorrhagia ⁽⁵⁾. There are several mechanisms explaining the association of the pulsatility index (PI) and resistance index (RI) of uterine artery with menstrual blood loss.

It has been suggested that menorrhagia, may be caused by an increased uterine secretion of prostanoids leading to impaired hemostasis ⁽⁶⁾.

Temporary post-insertion rise in prostaglandin concentrations coincided with the phase of increased bleeding and pain. There is over expression of mRNA and protein of Cyclo-Oxygenase-2 (COX-2) enzyme leading to overproduction of prostaglandins in the endometrium after the insertion of copper intrauterine device (CIUD) ⁽⁷⁾.

Other vasoactive substances may also be involved, including nitric oxide (NO) which is a potent vasodilator produced the vascular endothelium. Nitric oxide (NO) is present in the human endometrium and myometrium ⁽⁸⁾.

There is evidence that nitric oxide (NO) may play a part in acute and chronic inflammation ⁽⁹⁾. The introduction of intrauterine device into the uterine cavity induces a foreign body reaction in the surrounding endometrium ⁽¹⁰⁾. Nitric oxide (NO) is present in the foreign body inflammatory reaction around loosened joint replacement implants. Thus, it is possible that Intrauterine device also induces nitric oxide (NO) synthesis in the surrounding tissue. There is also a connection between nitric oxide (NO)

synthesis and prostaglandin synthesis. Nitric oxide (NO) directly interacts with Cyclo-Oxygenase (COX), which is responsible for prostaglandin synthesis and causes an increase in enzymatic activity ⁽¹¹⁾.

There may be other vascular abnormalities caused by the formation of troubled blood vessels. In abnormal vessels, weakness of systole and dysfunction may cause menstrual thrombosis and decreased resistance ⁽¹²⁾.

The expression of vascular endothelial growth factor (VEGF) and its receptor, kinase insert domain-containing receptor (KDR) and microvessel density (MVD) were increased in endometrium after using copper intrauterine device ⁽³⁾.

The copper intrauterine device (CIUD) increases the subendometrial microvascularization of those patients who presented with intrauterine device-induced side effects (menorrhagia or dysmenorrhea), as evidenced by 2D power Doppler analysis. Based on these findings, uterine artery Doppler indices pulsatility index (PI) and resistance index (RI) were widely investigated in order to identify the uterine hemodynamic changes in patients with intrauterine device induced bleeding ⁽⁴⁾.

AIM OF THE WORK

To study hemodynamic changes by transvaginal Doppler ultrasound of subendometrial and uterine arteries blood flow in patients with copper intrauterine device-induced bleeding.

PATIENTS AND METHODS

This is a cross sectional case control study was performed at Bab El-Sha'eria Maternity Hospital, during the period between June 2016 and November 2018.

Two hundred women attending Gynecology and Family Planning Outpatient Clinics were included in this study.

The candidates were selected according to the following inclusion and exclusion criteria.

Inclusion criteria

- Regularly menstruating women before CIUD insertion.
- Age between 20 and 40 years.
- Hormonal treatment has not been taken at least three months before the study.
- Non steroidal anti-inflammatory drugs has not been taken 24 hours before the examination

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 anti-inflammatory drugs.

The study was conducted at Bab El-Sha'eria Maternity Hospital Outpatient Clinics on 200 women divided into two groups.

Group I (IUD-M) included 100 women (n=100) using IUCD and complaining of menorrhagia. Group II (IUD-C) included 100 women (n=100) using IUCD and without abnormal uterine bleeding.

Ethical considerations

The study was approved by the Ethical and Research Committee of the Council of Obstetrics and Gynecology Department, Al-Azhar University.

Full informed verbal explanation of the study aims and procedure was offered for all subjects participated in the study and verbal consent (agreement) attained.

Ultrasound examination:

After emptying the urinary bladder, the patient was examined in the dorsal position in the fetal unite with color Doppler machine.

Ultrasound examination was carried out between days 7-10 of the cycle. The ultrasound equipment used was (a Voluson E6 B12 and Mindray Dc 70) systems with 6-9 MHz transvaginal transducer. A 2-dimensional B-mode real-time sonographic examination of the uterus and adnexa was initially carried out to study uterine size and shape and exclude any uterine or ovarian pathology.

The color pulsed Doppler was activated in the 2D mode, the right and left uterine artery pulsatility index (PI) and resistance index (RI) were calculated.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. So, the p-value was considered significant as the following: P-value ≤0.05 was considered significant, P-value ≤0.001 was considered as highly significant, P-value >0.05 was considered insignificant.

RESULTS

Table (1): Comparison of uterine artery pulsatility index (PI) in the two study groups in premenstrual phase.

Variable	Group I (IUD-M) (n=100)	Group II (IUD-C) (n=100)	p-value
Right UA PI	1.79±0.36	2.28±0.43	<0.001
Left UA PI	1.81±0.52	2.32±0.69	<0.001

Data are presented as mean (SD).

¶Independent Sample t-test (t-test)

Both right and left uterine artery PI was significantly lower in women of group I than in women of group II.

Table (2): Distribution of the numbers of cases in each category in two groups

Signal area percentage	Group I		Group II		P-value	Sig.
	No.	%	No.	%		
<10 (Category I)	3	3.0%	33	33.0%	<0.001	HS
10 – 25 (Category II)	5	5.0%	30	30.0%	<0.001	HS
26 – 50 (Category III)	28	28.0%	19	19.0%	0.133	NS
51 – 75 (Category IV)	30	30.0%	14	14.0%	0.006	HS
>75 (Category V)	34	34.0%	4	4.0%	<0.001	HS

*:Chi-square test

Distribution of the number of cases in each category of subendometrial blood flow of two groups by transvaginal power Doppler classified into 5 categories according to subendometrial signal area percentage shows statistically significant difference except in category III was nonsignificant with higher number of cases in category VI, V in group 1 and higher number of cases in category I, II in group 2.

Table (3): Receiver-operating characteristic (ROC) curve analysis for prediction of menorrhagia in women with IUCD using UA PI

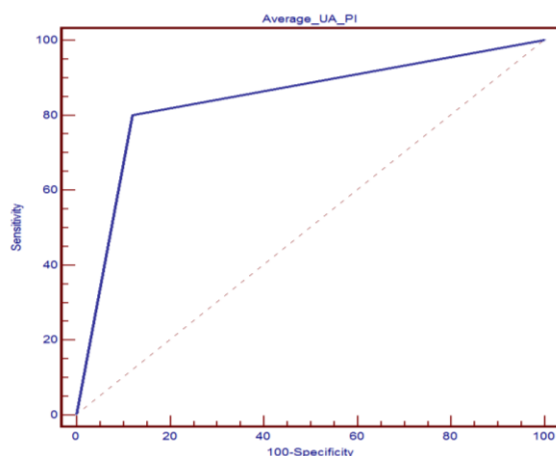
	Estimate	95% CI	p-value
AUC	0.88	0.82-0.92	<0.001
Youden index J	0.69		
Cut-off value (P.I)	≤1.93		
Sensitivity, %	81.76	72.82-88.88	
Specificity, %	88.50	80.60-94.13	
PPV	87.57	79.18-93.63	
NPV	82.92	74.54-89.59	

AUC: Area under the ROC curve

Youden index = (sensitivity + specificity) -1

PPV: Positive predictive value

NPV: Negative predictive value



95% CI: 95% confidence interval.

Figure (1): Receiver-operating characteristic (ROC) curve for prediction of menorrhagia in women with IUCD using UA PI.

Area under the curve (AUC) = 0.88 (95% CI 0.82 to 0.92). Best Cutoff point is PI of ≤ 1.93 . This has a sensitivity of 81.76% and specificity of 88.5%.

DISCUSSION

The use of copper IUD is a very common practice in family planning, although it has been used worldwide for decades, but many side effects are still reported after introduction, but the most common side effects associated with copper IUD is a comprehensive uterine hemorrhage which may lead to a high prevalence of this method. A major problem with the side effects of IUD is the inability to predict whether or not the patient is likely to have these effects. The main reason is that the cause of the disease is still unknown⁽¹³⁾.

There are several possible mechanisms that explain the cause of excessive bleeding in some patients using copper IUD, several studies reported that IUD insertion increase the production of prostaglandins in the endometrium which cause increased vascularity, vascular permeability and inhibit platelet activity and therefore increase menstrual bleeding⁽⁷⁾.

According to the results obtained in this study, it seems that the uterine arteries and subendometrial blood flow is significantly higher in women with copper IUD and complaining of menorrhagia than women using copper IUD with normal menstrual flow or women with normal menstruation and not using any contraceptive method.

The result of the current study showed that women in group I with menorrhagia had a significant increase in subendometrial blood flow calculated by power Doppler energy according to the

subendometrial signal area percentage in comparison with women in group II using copper IUD and not complaining of abnormal uterine bleeding (control group).

On comparing the results of current study with the results of other studies **El-Mazny et al.**⁽⁵⁾, measured PI and RI of uterine arteries in 120 women before and three months after the copper IUD insertion and concluded that there were not significantly different before and after IUD insertion in 47 women who had menorrhagia after IUD insertion compared to 73 women who were not complaining of abnormal uterine bleeding after insertion.

Jimenez et al.⁽¹⁴⁾ concluded that the copper IUD increases the subendometrial microvascularization of those patients who presented with IUD induced side effects (menorrhagia or dysmenorrhea) before and 3 months after IUD insertion. However uterine artery PI and RI were not altered after IUD insertion.

These two studies were prospective studies that measure subendometrial microvascularization before and after insertion of Copper IUD but the current study was cross-sectional study measuring subendometrial microvascularization in selected groups of patients after IUD insertion.

In agreement with the results of the current study: **Fouda et al.**⁽¹⁵⁾ measured PI and RI of uterine arteries in 93 women divided into three groups, group I 32 women were complaining

of menorrhagia, group II 30 women with CIUD and not complaining of abnormal uterine bleeding group III control group 31 women without CIUD. The uterine artery PI and RI were significantly lower in group I compared to group II and group III. However there were not statistically difference in PI and RI between women in group II and women in group III.

Frajndlich *et al.* ⁽¹⁶⁾ measured uterine artery RI and PI in 101 women, 74 women who were using copper IUCD and 27 controls who were not using any contraceptive method. The intrauterine contraceptive device users were divided into three groups; those with normal bleeding n=34, those with abnormal uterine bleeding without medication n=16 and those with abnormal bleeding corrected with use of prostaglandin inhibitors n=24. PI and RI were significantly lower in the group of women using intrauterine contraceptive devices who had abnormal bleeding than in all other groups.

Montaz *et al.* ⁽¹⁷⁾, measured PI and RI of uterine arteries in 68 women, including 44 using intrauterine contraceptive device and 24 control women who were not using a method of contraception. Both PI and RI were significantly lower in women with copper IUD-induced bleeding than in those using IUCD and not complaining of abnormal vaginal bleeding. In addition, there were no statistically significant differences in PI and RI in women using IUCD without complaining of abnormal vaginal bleeding and women in control group.

Yigit *et al.* ⁽¹⁸⁾ found that the PI and systole/diastole ratio in the uterine artery increased significantly 3-5 month after the insertion of a copper IUD. However, patients with increased bleeding scores had significantly lower uterine artery PI compared with those without increased bleeding scores.

In contrast to results of this study, **de Souza and Geber** ⁽¹³⁾ in 2006 measured the uterine artery PI and RI in both sides in 100 patients before and 30 days after insertion of Copper IUD, no statistically significant changes in PI and RI values were detected.

Jimenez *et al.* ⁽⁴⁾ reported that there were no statistically significant differences in uterine artery PI and RI between women with IUD induced bleeding and women using IUD with normal menstruation.

El-Mazny *et al.* ⁽⁵⁾ also reported that there were no statistically significant differences in

uterine artery PI and RI before and after Copper IUD insertion in patients with IUD induced menorrhagia.

Several hypotheses regarding the mechanism of bleeding induced by the IUD were proposed. Among the main suggested theories is the local inflammatory reaction in the endometrium, which is associated with increased prostaglandin synthesis and local vascular changes responsible for the development of menorrhagia. **El-Sahwi *et al.*** ⁽¹⁹⁾ observed a significant rise in both PGF₂ and PGE₂ concentrations in the uterine wash 3 months after IUD insertion but not in users who had used an IUCD for at least 2 years; the temporary postinsertion rise in prostaglandin concentration coincided with the phase of increased bleeding and pain. **Xin *et al.*** ⁽⁷⁾ found that there was over expression of mRNA and protein of COX-2 enzyme leading to over production of prostaglandins in the endometrium after the insertion of IUCD.

From the current study and previous studies, It is assumed that the copper IUD modifies subendometrial microvascularization of those patients who are presented with IUD-induced menorrhagia, through changes in the production of prostaglandins leading to increase in subendometrial, endometrial and uterine artery blood flow.

CONCLUSION

- Uterine arteries RI and PI were significantly lower in women with copper IUD induced menorrhagia.
- Subendometrial blood flow power Doppler energy were significantly higher in women with Copper IUD induced menorrhagia than women of group II.

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