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Doppler study of the uterine artery in patients with copper intrauterine contraceptive device-induced abnormal uterine bleeding

دراسة دوبلر الشريان الرحمي للمريضات الواضعات اللولب الرحمي والمؤدي الى النزف الرحمي غير الطبيعي

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Abstract:

Objective: to evaluate the effect of copper intrauterine device (CIUD) induced abnormal uterine bleeding on uterine artery blood flow using pulsed color Doppler ultrasound.
Design: prospective clinical study.
Setting: Al-Zahra'a teaching hospital.
Patients and methods: ninety three women were examined by trans-vaginal color Doppler to detect the pulsatility index(PI) and resistance index(RI) in the uterine arteries. Women were divided into three groups: Group I. Included 31 women using CIUD and abnormal uterine bleeding. Group II. Included 32 women using CIUD with normal cycle. Group III. Was a control group that included 32 women with normal menstrual flow and not using any contraceptive methods.
Results: No significant differences in RI and PI were observed between group II and III, the comparism between group I and the other two groups revealed significantly lower mean RI and PI values for group I.
Conclusion: This results confirm the hypothesis that there is an increase in the uterine blood flow in women with CIUD- induced abnormal uterine bleeding.
Key words: CIUD, Doppler ultrasound.

الخلاصة:

في دراسة تقدمية أجريت في م. الزهراء التعليمي في النجف 93 امرأة من 18 إلى 40 سنة قسمت إلى ثلاث مجاميع. المجموعة الأولى اللواتي يستعملن اللولب مع نزف رحمي، المجموعة الثانية يستعملن اللولب مع دورة شهرية طبيعية، أما المجموعة الثالثة فهي نساء لا يستعملن أي موانع للحمل ولديهن دورة شهرية طبيعية. دوبلر سونار أثناء الطمث اجري للكل لقياس نسبة جريان الدم في الشرايين الرحمية ومقارنتها. كانت النتائج أن جريان الدم أكثر في المجموعة الأولى مقارنة بالمجموعتين الثانيتين، وهذا يثبت النظرية أن النزف الذي يحصل مع اللولب جزء منه سببه زيادة جريان الدم في الشرايين الرحمية.

Introduction:

Although the intrauterine device (IUD) has been used over 30 years, its mode of action as a contraceptive still remains poorly defined. It seems that the principal anti-fertility mode of action is by a method other than the destruction of live embryos (1). The plastic IUD induces changes in endometrial cavity and in the composition of uterine fluid, resulting in inhibition of sperm function and in side effects e.g. menorrhagia and dysmenorrhea(2).

Copper devices inhibit sperm motility and viability this reaction is enhanced by copper, which affects endometrial enzymes, glycogen metabolism and estrogen uptake and also inhibit sperm transport (3). So copper IUDs are highly effective contraceptives with failure rate of <0.5% (4).

Worldwide, the Copper T 380 is the first choice, as it has the lowest failure rate and the longest life span (4).

The most common copper IUD related side effect is excessive uterine bleeding. The menstrual blood loss is commonly doubled after the insertion of IUD 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 cupper IUD and within one year approximately 15% of women remove the IUD because of this problem (5). There are several possible mechanisms that explain the cause of excessive bleeding , several studies reported that IUD 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 (6).

Recent studies have reported that IUD causes cyclo-oxygenase isoenzyme 2 up-expression, the subsequent elevated prostanoids biosynthesis and signaling can promote the expression of pro-angiogenic factors, such as vascular endothelial growth factor VEGF), platelet-derived growth factor (PDGF), and angiopoietin-1 and 2 (6,7). Xin et al. reported that the expression of vascular endothelial growth factor and its receptor were increased in the endometrium after using CIUD(6).

Other vasoactive substances including nitric oxide (NO) which is potent vasodilator produced by the vascular endothelium, IUD induces NO synthesis in the surrounding tissue because it induce acute and chronic inflammatory reaction in the surrounding endometrium thus NO play a part in this inflammation. There is also connection between NO synthesis and prostaglandin synthesis as NO directly interacts with cyclo-oxygenase enzyme and causes an increase in enzymatic activity (8).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 (9).

Based on these findings, uterine artery Doppler indices, PI and RI, were widely investigated in order to identify a correlation between IUD-related bleeding and increase in the uterine artery blood flow (10), which is also the aim of our study now.

Materials and Methods:

This is a prospective clinical study was performed at AL- Zahra'a teaching hospital, during the period between February and December 2012.

A total of 95 women were divided into three groups:

Group 1:

included 31 women using copper intra-uterine device (CIUD) and complaining of menorrhagia or meno-metrorrhagia.

Group 2:

included 32 women using CIUD and not complaining of abnormal uterine bleeding, they attended outpatient clinic complaining of vaginal discharge or for routine checking of CIUD or requesting CIUD removal.

Group 3:

Control group which included 32 who were not using any kind of contraceptive method, include healthy women who attended the Family Planning Clinic, and not complaining of abnormal uterine bleeding.

The study protocol was approved by the hospital research ethics board.
Inclusion criteria were as follows:

- Regularly menstruating women before insertion of IUD.
- Age between 18- 40 yrs.
- Hormonal treatment has not been taken at least 2 months before the study and non- steroidal anti-inflammatory drug has not been taken 24 hours before the examination.

Exclusion criteria were as follows: Nullipara, pregnancy, present or past history of pelvic inflammatory disease, and presence of pelvic pathology as ovarian cysts, endometrial polyp, uterine fibroid.

All women included in the study were evaluated by history taking especially menstrual history (rhythm, regularity, duration of bleeding, the presence of inter-menstrual bleeding) pelvic pain and vaginal discharge. The history of any bleeding disorders, similar episodes of bleeding, any medication and previous operations were also included.

A systematic general examination was performed with special attention to medical problems that may cause a bleeding tendency (e.g. bleeding disorder, thyroid disorders, liver problem etc). A detailed gynecological examination for the presence of any pelvic or gynecological lesion was also performed.

All women had trans-vaginal ultrasound scan during the menstrual phase of the cycle (day 1- 5) using a pulsed color Doppler ultrasound device (Philips 6.5 MHz trans-vaginal probe). The uterus and the ovaries were first visualized to rule out any pathology, the endometrial thickness was measured as the thickest part in the longitudinal section including both endometrial layers, also see the accurate placement of the device inside the uterus and following this at the level of the internal cervical orifice the Doppler beam was adjusted by manipulation the probe so that the Doppler beam crossed the long axis of the uterine artery. Blood flow indices of the uterine artery were then calculated to obtain the pulsatility index (PI) and the resistance index (RI). The mean PI and RI were calculated by combining three waveforms of the left and right uterine artery and compared between different groups.

Statistical analysis:

was done by using SPSS (statistical package for social sciences) version 17. In which we use percentages, mean and standard deviation in addition to analysis of variance (ANOVA) test to determine the difference between the groups.

We set *P* value <0.05 as significant.

Results:

The study was conducted on 95 women divided into three groups. In group-1; 31 women were used CIUD with abnormal vaginal bleeding.
Group-2; 32 women with CIUD and had normal menstrual cycle.
Group-3; 32 women were requesting contraception with normal menstrual cycle as a control.

Table-1 shows the distribution of symptoms and reasons for medical consultation among women in different groups, all women in groups 2 and 3 had regular normal menstrual cycle.

Table (1) the cause of attendance to outpatient clinic

Group 1 (No. =31)	
Menorrhagia	23 (74.19%)
Meno-metrorrhagia	8 (25.81%)
Group 2 (no. = 32)	
Vaginal discharge	17 (53.1%)
Request CIUD removal	5 (15.6%)
Follow-up visit	10 (31.6%)
Group 3(no. =32)	
Request other contraception	14 (43.75%)
Request CIUD insertion	18 (56.25%)

Table-2 shows no significant differences between women in the three groups with respect to age, BMI, parity, and duration of IUD insertion.

Table (2) patient's characteristics of the three groups

Variables	**Group 1 (CIUD with abnormal bleeding)**	**Group 2 (CIUD without bleeding)**	**Group 3 (Control)**	**P-value**
	Mean±SD	Mean±SD	Mean±SD	
Age(year)	27.23±6.20	26.66±4.96	25.81±5.49	0.6
BMI Kg/m2	27.48±3.22	27.91±4.51	26.99±4.61	0.082
Parity	3.03±1.22	3.09±1.71	2.47±1.24	0.156
Duration of CIUD(year)	3.9±13.53	4.87±9.86	------	0.753

Table-3 shows mean RI and PI values for the three groups. No significant differences in uterine arteries RI (0.85, 0.88) and PI (2.45, 2.24) observed when group-2 and 3 were compared respectively, the comparison between group-1 and the other two groups revealed significantly lower mean RI (0.68) and PI (1.85) values for group-1 ($p< 0.05$).

Table (3) Doppler results of uterine artery

Variables	Group 1 (CIUD with abnormal bleeding)	Group 2 (CIUD without bleeding)	Group 3 (Control)
	Mean ±SD	Mean ±SD	Mean ±SD
RI	0.68±0.095	0.85±0.067	0.88±0.020
PI	1.85±0.339	2.45±0.243	2.24±0.311

Table (3) continued P value

	G1 vs. G2	G1 vs. G3	G2 vs. G3
RI	0.048	0.031	0.189
PI	<0.001	<0.001	0.5

Table-4 shows the endometrial thickness in the three groups, there was significant increase in endometrial thickness after IUD insertion whether associated with abnormal uterine bleeding or not (groups 1 and 2).

Table (4) endometrial thickness of three groups

Variables	Group 1 (CIUD with abnormal bleeding)	Group 2 (CIUD without bleeding)	Group 3 (Control)	P value
	Mean±SD	Mean±SD	Mean ±SD	
Endometrial thickness in mm	7.25±2.70	7.62±1.96	5.80±1.84	0.008

Discussion:

It has been suggested that IUD- related side effect, such as abnormal uterine bleeding may be secondary to a decrease in uterine arterial resistance and increase in uterine blood flow, which are both detected by color Doppler sonography (11).

Using trans-vaginal Doppler Steer and coworker have shown physiological variations in uterine blood flow during the normal menstrual cycle, (12) , in our study the women in all groups were examined during their period days to eliminate the effects of these physiological effects.

We found that there were no significant differences between the three groups regarding age, BMI, parity and duration of IUD.

The result of our study revealed that the uterine artery blood flow during menstruation is significantly higher in women with CIUD induced bleeding reflected as decreased uterine artery PI and RI compared to women with CIUD and normal menstrual loss or those without any contraception. There were no statistically significant differences in the uterine artery PI and RI between women using CIUD and not complaining from abnormal bleeding and women in control

group this indicate that the increase in uterine blood flow occurs only in case of women using CIUD complaining of abnormal uterine bleeding. Our results run in agreement with Usama et al.2010 (13) who found PI and RI were significantly lower in women with CIUD induced abnormal uterine bleeding. Amal El Anwar et al.2010 (11) found a significant increase in uterine artery blood flow in patients presented with CIUD side effects like bleeding and pain and they use 1.5 as a cut-off value for uterine artery PI for prediction of abnormal bleeding.

Momtaz et al.1994 (14) found both PI and RI were lower in CIUD induced bleeding women. Renato Frajinlich et al.2000 (15) found PI and RI were significantly lower in women with IUD induced bleeding and he concluded that patients with uterine artery pulsatility index less than 2 had a higher risk for development of IUD- induced bleeding. Ebru Coskun et al. , 2011 (16)found only the left uterine artery pulsatility and resistance indices decreased statistically significantly while other Doppler parameters showed no change.

In contrast to our results Jamenez et al. ,2008 (17) and Kmal et al. 2013(18) reported there were no significant differences in PI and RI between women with IUD-induced bleeding and those using IUD with normal menstruation.

We also found increase in endometrial thickness after IUD insertion, probably related to the presence of the IUD itself and not due to any IUD endometrial effects.

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 CIUD- induced menorrhagia, in addition prostaglandins are known to affect blood flow regulation in the uterine arteries (6). Other vasoactive substance is nitric oxide(8). Women with menorrhagia also show significant increase in endothelial cell proliferation reflecting disturbed angiogenesis.

On these basis of these observation and our present study it is possible that CIUD induces changes in the production prostaglandins and stimulates angiogenesis in the endometrium leading to an increase in uterine blood flow.

Conclusion:

The results of our study confirm the hypothesis that there is an increase in the uterine blood flow in patients with CIUD- induced abnormal uterine bleeding.

Recommendations:

1- Trans-vaginal Doppler can be used to identify women at risk of developing abnormal uterine bleeding after CIUD insertion. Low PI and RI in women may be associated with higher risk for development of CIUD- induced bleeding.
2- Uterine arteries Doppler blood flow can also be used to detect CIUD-associated pain, needs other study.

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