Provisionally accepted for publication

ORIGINAL ARTICLE

Uterine Artery Doppler Indices: Pulsatility Index and Resistance Index as Predictive Tools to Menstrual Changes Related to Levonorgestrel Intrauterine System versus Copper Intrauterine Contraceptive Device Among Egyptian Women: A Cohort Study

Short title: Levonorgestrel IUD and Uterine Artery Doppler Effects on the Menstrual Pattern

Doi: 10.36129/jog.2022.88

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ABSTRACT

Objective. This study aims to assess the predictive value of the uterine artery Doppler indices (pulsatility and resistance) using transvaginal ultrasound following the insertion of an intrauterine device (IUD), either the levonorgestrel intrauterine system (LNG-IUS) or the Cu-IUD and to correlate the findings of the impedance indices to the changes in the menstrual pattern.

Materials and Methods. A prospective cohort study was conducted between March 2019 and March 2021 that included healthy women who visited our family planning clinic and were willing to use an intrauterine contraceptive device. Of the 365 women who initially opted for this contraceptive method, 340 were enrolled. The participants were divided into two groups: (LNG-IUS) group, LNG-IUS users; (Cu-IUD) group, Cu-IUD users. The decision was made based on the women's clinical circumstances and preferences. Then, the transvaginal ultrasonographic examination was performed after the deployment of the IUD and at three- and six-month follow-up intervals. Measurement tools included uterine Doppler impedance indices, and changes in the menstrual patterns were examined serially and recorded.

Results. The analysis showed a significant difference between the two groups. Women in (LNG-IUS) group experienced irregular vaginal bleeding at a rate of 28.2% compared to 35.2% in (Cu-IUD) group (P = 0.001), and amenorrhea was statistically reported at a rate of 67.7% in (LNG-IUS) group compared to 7.05% in (Cu-IUD) group at the end of the study (P = 0.001). The uterine artery pulsatility index (PI) was significantly associated with abnormal bleeding at a cut-off of 1.29 with an area under the curve (AUC) of 0.92, a sensitivity of 89%, and a specificity of 100%. In contrast, uterine artery resistance index (RI) was significantly

correlated with abnormal bleeding at a cut-off of 0.61 with an AUC of 0.11, a sensitivity of 95%, and a specificity of 100%.

Conclusions. Our results confirmed our assumption that the LNG-IUS, a hormonal contraceptive device unlike the Cu-IUD, significantly altered the blood flow of the uterine artery and menstrual pattern.

Key words

Copper IUD; LNG intrauterine system; transvaginal Doppler ultrasound; pulsatility index; resistance index.

INTRODUCTION

In low-resource countries like Egypt, the copper intrauterine device (Cu-IUD) is one of the most acceptable and cost-effective methods. More importantly, it has a low failure rate as a long-acting reversible contraceptive method, ranging from 0.2% to 1.0%. However, irregular vaginal bleeding or heavy menstrual bleeding is frequently encountered, and 10–20 % of women discontinued its use during the first year [1]. Conversely, the hormonal IUDs, specifically levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena, Schering AG, Berlin, Germany), were associated with a decrease in menstrual flow. A recent meta-analysis reported that LNG-IUS is a more effective treatment for heavy menstrual bleeding than other medical treatments, in addition to its contraceptive role [2]. Several mechanisms have been proposed to explain the value of LNG-IUS use in treating heavy vaginal bleeding. It is a long-acting, hormonal IUD that releases levonorgestrel (LNG) at a rate of 21 mcg/day after 24 days; this rate is reduced to about 11 mcg/day after five years and 7 mcg/day after eight years. Following the publication of the effectiveness of its long-term use, the US Food and Drug Administration (FDA) approved its contraceptive use for up to 8 years in 2021 [3]. The uterine artery Doppler indices have been thoroughly studied before and after IUD deployment to predict menstrual pattern change. Some studies reported an increase in uterine artery Doppler indices, pulsatility index (PI), and resistance index (RI), after three months of LNG-IUS insertion [4-6], whereas others found no change in uterine artery circulation in LNG-IUS users three months after insertion [7-9]. Similarly, the results of Doppler indices of the uterine artery in Cu-IUD users were contradictory.

As a result of its hormonal effect, LNG-IUS exhibits a significant change in sub-endometrial vascularization with a decrease in mean vessel density and endometrial thickness and an apparent reduction in menstrual flow after one year of its insertion [10]. Menstrual flow increased significantly due to increased vascularity of the endometrium adjacent to the Cu-IUD, changes in microvascular permeability, and the inflammatory process of the copper component [11-13].

In this study, we hypothesize that by studying uterine artery Doppler indices before the insertion of an IUD, we can predict the changes in the menstrual pattern following the insertion based on the pathophysiology and morphological changes detected when studying the endometrium and its vascularity. Consequently, we could counsel women on appropriate contraceptive choices. Our study aimed to evaluate the influence of LNG-IUS compared to that of Cu-IUD on the Doppler indices of the uterine artery at intervals of three and six months after insertion and to correlate these results with the changes in the menstrual pattern.

MATERIALS AND METHODS

Study Design

This prospective cohort study was conducted at the family planning clinic at Zagazig University Hospital during the period from March 2019 to March 2021.

Population: A total of 340 participants were included in our study and signed informed consent before starting the study. Eligibility criteria were as follows: all enrolled women were between the ages of 20 and 40, planned to use an intrauterine contraceptive device, either LNG-IUS or Cu-IUD, and had not received any hormonal therapy in the previous three months. We excluded all women with unexplained abnormal uterine bleeding (AUB), untreated cervical or uterine pathology, Müllerian tract abnormality, pelvic inflammatory disease or a sexually transmitted infection within the last three months, active liver disease, and an allergy to levonorgestrel or copper.

The sample size was calculated based on a reported 20% difference between the two methods for side effects of abnormal bleeding. Thus, 170 women in each group were required for the study to accomplish a 95% confidence interval and a significance level of 5%. We initially recruited 365 women to enable dropouts. After meeting the eligibility criteria, women were allocated into one of the two groups according to clinical circumstances and women's preferences (Figure 1).

In (LNG-IUS) group, women received the LNG-IUS (Mirena, Bayer HealthCare, Berlin, Germany). In (Cu-IUD) group, women received the Cu-IUD (copper T-380 IUD, DPK, Egypt). Moreover, blinding was not possible due to the significant difference between the two types of IUDs.

Before taking part in the study, each woman signed an informed consent form. The assigned physician took a history that included age, parity, previous contraceptive methods, duration and amount of menstrual blood flow, intermenstrual spotting, bleeding, contact bleeding, medical, and disorders. Clinical evaluation includes a general, abdominal, pelvic, and speculum examination to rule out any local abnormal findings that could impede IUD insertion. Following the insertion, transvaginal ultrasound was performed with the women in a lithotomy position to allow easy manipulation of the vaginal probe at different angles. Ultrasound examination immediately following insertions using a transvaginal probe Voluson E8 (General Electric Ultrasound System) at a frequency of 7.5 MHz with color Doppler. To achieve consistency in the ultrasonographic assessment, we carried out all examinations using a single ultrasound sonographer. The pulsed wave Doppler was applied to a sampling gate of 2 mm with an insonation angle of less than 30°. The PI and RI were automatically determined from the mean of three similar waveforms. To avoid the bias of confounding factors, we asked the women to abstain from taking nonsteroidal anti-inflammatory drugs 24 hours before the examination. For pre-insertion and follow-up visits, ultrasound and Doppler examinations were performed within five days of menstruation. In women who developed amenorrhea, the examination was carried out at any time within the planned visiting time during which endometrial thickness measurements were recorded.

Doppler indices in the main uterine maternal artery on both sides were measured and the mean was obtained in Figure 3. The primary outcome was to measure the blood flow indices of the uterine artery to obtain the PI and RI according to the following equations: PI = (systolic velocity – diastolic velocity)/mean velocity and RI = (systolic velocity- diastolic velocity)/systolic velocity, respectively.

The mean PI and RI were calculated by combining three waveforms of the left and right uterine arteries and used for subsequent statistical analyses. At the same time, the secondary outcome for the measurements was the correlation between uterine artery Doppler indices, menstrual pattern changes, and the adverse effects of the assigned contraceptive method. The side effects were examined at follow-up visits with appropriate management of the reported symptoms. A healthcare professional records the patient's history at intake, including the volume (heavy, normal, or light), regularity (irregular, regular, or absent), frequency (frequent, normal, or infrequent), and duration (prolonged, normal, or shortened) of menstrual episodes. Each term could be interpreted, and the symptoms were accurately evaluated to see if they were related to the method used.

Definitions of menstrual abnormalities are as follows:

1. Menorrhagia is a term increasingly replaced by the expression “heavy menstrual bleeding” (HMB), in terms of a statistical “abnormality,” namely, a blood loss of >80 mL per cycle. In contemporary times, HMB has been defined as excessive menstrual blood loss (MBL) that disrupts the physical, social, emotional, and/or material quality of life.

2. Oligomenorrhea is defined as irregular and inconsistent menstrual cycles lasting from 36 to 90 days in length.

3. Amenorrhoea (absence of menstruation) is a complete absence of menstruation after puberty.

4. Unscheduled vaginal bleeding spotting is a breakthrough of minimal vaginal bleeding that does not require sanitary precautions.

The International Federation of Gynecology and Obstetrics (FIGO) proposed the "PALM-COEIN" system (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified), a comprehensive classification system aimed at facilitating both clinical care and research. It systematically classifies AUB into groups with distinctively different structural and functional causes.

Statistical Analysis

The data was recorded in tabular form and analyzed using SPSS version 22 (IBM, Armonk, NY, USA). Categorical variables were grouped as a number (percentage), and continuous variables as a median (interquartile range). The X^2 test was used to compare two qualitative variables, and the Mann–Whitney *U* test was used to compare two independent quantitative variables. The association between PI or RI and bleeding was assessed using Spearman’s correlation. Multiple logistic regression has been used to determine predictors of abnormal bleeding. The receiver operator characteristic (ROC) curve analysis was used to determine the optimal cut-off value and sensitivity and the specificity of PI and RI to anticipate bleeding. A P value of less than 0.05 was statistically significant.

RESULTS

A total of 365 women were initially enrolled in the study, while 340 women completed the study at the six-month follow-up (LNG-IUS group, n = 170; Cu-IUD group, n = 170) (Figure 1). The dropout was due to withdrawal from the study or complications following insertion, such as persistent pain or continuous bleeding. The demographic parameters of all

participants are shown in Table 1, including age, parity, or body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters).

Women who experienced abnormal bleeding in the LNG-IUS (20/170; 11.76%) were less than those who reported the same complaint in the Cu-IUD group (102/170; 60%) at the beginning of the study. Conversely, amenorrhea was statistically more common in (LNG-IUS) group (67.7%) than in (Cu-IUD) group (7.05%) at the end of the study ($P < 0.001$). In both groups, the number of women who reported abnormal bleeding decreased after six months.

Uterine artery PI and RI are summarized in Table 2. There was a significant difference between the two groups in the initial PI ($P < 0.001$) and RI ($P < 0.001$), both of which were higher in women in the LNG-IUS group. In both groups, PI and RI were significantly lower after three and six months than the initial Doppler indices (all $P < 0.001$).

Multiple logistic regression analysis of participant characteristics and abnormal bleeding revealed a significant correlation with PI ($P < 0.001$) and RI ($P < 0.001$) at baseline (Table 1). In ROC curve analysis, uterine artery PI correlated with abnormal bleeding at a cut-off value of 1.29 with an AUC of 0.92, a sensitivity of 89%, and a specificity of 100%. The RI of the uterine artery correlated with abnormal bleeding at a limit of 0.61 with an AUC of 0.1, a sensitivity of 95%, and a specificity of 100% (Figure 2 and Table 3). The most associated menstrual abnormalities were observed with LNG-IUS inter-menstruation spots and amenorrhea. Meanwhile, menorrhagia was commonly reported with Cu-IUD, as shown in Table 4.

DISCUSSION

Given our circumstances as a low-resource country, the local health authorities encourage using long-term reversible contraception methods to prevent unintended or mistimed pregnancy. Cu-IUD was the most accepted and widely used method among women in our region; however, women stop its use due to its side effects of heavy and/or irregular vaginal bleeding. IUD-induced bleeding was reported to be associated with decreased vascular resistance and increased blood flow to the uterus [14]. Momtaz et al. [15] 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 ((LNG-IUS) group), women using IUD without abnormal vaginal bleeding ((Cu-IUD) group), and women with AUB 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.

In our study, we found that unscheduled vaginal spotting and amenorrhea in new LNG-IUS users, unlike Cu-IUD users, are positively correlated with hemodynamic changes in the uterine artery Doppler indices with a significant increase in RI.

The effect of LNG-IUS on uterine artery impedance indices has been debated in various studies. Järvelä et al. [16] reported that uterine artery PI measurement was positively affected in 13 symptomatic postmenopausal women who received hormonal replacement therapy in the form of transdermal estradiol for one month before combining LNG-IUS. Meanwhile, in another study of 27 fertile women, LNG-IUS insertion increased RI of the uterine artery, which was associated with the midcycle elevation of estrogen and a simultaneous decrease in serum progesterone [13]. This could be attributed to the antiproliferative effect of progesterone on sub endometrial vasculature, which compacts the vasodilator effect of estrogen.

Our results agree with those of Jiménez et al. [14], who reported that after controlling all confounding factors like age and parity, LNG-IUS increased uterine artery impendence and PI after three months of its deployment. However, no changes were observed in Cu- IUD users in this study. This conclusion was also supported by Bastianelli et al. [17], who reported that LNG-IUS significantly altered both endometrial thickness and blood flow of the uterine artery in 32 women after insertion of medicated IUD at 1, 3, and 6 months. On the contrary, Zalel et al. [18] reported that uterine artery RI and PI in both LNG-IUS and Cu-IUD arms were similar before and after the insertion of the device.

Dane et al. [19] found no changes in LNG users' Doppler study, while the sub-endometrial vascularity decreased after the depo-medroxyprogesterone acetate injection. Finally, Cihangir et al. [20] measured PI and RI in 49 women over the 1-year duration and reported no significant change in measurement before and after LNG-IUS insertion. Briefly, our results supported the hypothesis that changes in the menstrual pattern of LNG-IUS users were due to changes in the uterine artery Doppler study. This agrees with the randomized study conducted by Rezk et al. [16], who studied 306 women after the insertion of a levonorgestrel-releasing intrauterine system (LNG-IUS) (n = 152) or Cu-IUD (n = 154) to investigate the effects of LNG-IUS and Cu-IUD on menstrual pattern and uterine artery Doppler indices. The reported abnormal bleeding after LNG-IUS insertion was positively correlated with a decrease in uterine artery Doppler indices; however, these changes were not recorded for Cu-IUD users.

Strengths and Limitations

The strength of the current study is that we avoided the distractors of the conflicting results of various studies, which could be due to variations in measurement time during the menstrual cycle and, most likely, a small sample size. Our study has some limitations: blinding was not possible due to the difference between the two methods in terms of cost and availability and the absence of long-term follow-up after one year.

CONCLUSION

Uterine artery Doppler is a simple tool for predicting menstrual pattern change after the insertion of an IUD. LNG-IUS-related menstrual abnormalities were associated with changes in uterine artery blood flow, which were not evident in Cu-IUD users.

RECOMMENDATION

Future research should focus on the predictive value of uterine artery Doppler indices before utilization of other long-acting reversible contraception methods to increase women compliance and eliminate cultural barriers to contraceptive use in terms of women’s beliefs about their own fertility and positive health effects.

COMPLIANCE WITH ETHICAL STANDARDS

Acknowledgment

The authors are grateful to all medical staff and participants who dedicated their effort and time to this study.

Authors contributions

ANE contributed to the conceptualization, data curation, investigation, methodology, validation, supervision, visualization, and writing, review, and editing process.

AMA contributed to the writing, review, and editing process and methodology

AMF contributed to the conceptualization, data curation, formal analysis, investigation, methodology, and writing the original draft.

Funding

This research did not receive any funds or financial support.

Ethical Approval

This study had been approved by the ethical committee according to the Declaration of Helsinki guidelines (no. ZU_IRB 51-24-6-3-2019).

Informed Consent

Patients who fulfilled the selection criteria were counseled and informed about the trial protocol, and written infromed consent according to the Declaration of Helsinki was signed.

Data Sharing

Data are available upon reasonable request to the corresponding author

Disclosure of Interests

The authors have no conflicts of interest.

Table Legends

Table 1: Uterine artery pulsation index and resistance index by the study group.

Table 2: Multiple logistic regression analysis of participant characteristics and abnormal bleeding.

Table 3: Sensitivity and specificity of Doppler indices of the uterine artery for predicting abnormal bleeding.

Table 4: The changes in a menstrual pattern associated with each group.

Figures Legends

Figure 1: Flowchart for consortia.

Figure 2: ROC curve analysis of the association between abnormal bleeding and pulsatility index (PI) and resistance index (RI) of the uterine artery.

Figure 3: Transvaginal ultrasound measurement of uterine artery Doppler PI and RI.

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Table 1 Multiple logistic regression analysis of participant characteristics and abnormal bleeding.

Characteristic	X^2	P value	Odds ratio (95% CI)
Age	0.725	0.398	1.02 (0.95–1.13)
Parity	4.19	0.069	0.75 (0.61–1.13)
BMI	0.499	0.477	0.97 (0.89–1.05)
Uterine PI	13.19	<0.002	5.84 (2.23–14.91)
Uterine RI	20.45	<0.001	8.24 (2.73–17.59)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; PI, pulsatility index; RI, resistance index.

Table 2 Uterine artery pulsatility index and resistance index by study group.

Index	Index (95% CI)	*P* value		Index (95% CI)	*P* value	Mann-Whitney *U*	*P* value
PI							
Initial	**1.81 (1.81–2.20)**			1.77 (1.76–1.91)		9.60	**<0.001**
3 months	1.82 (1.13–2.34)	<0.001		1.85 (1.27–1.94)	<0.001	1.21	**0.228**
6 months	1.9 (1.48–2.23)	<0.001		1.89 (1.31–2.29)	<0.001	2.14	**0.029**
RI							
Initial	0.76 (0.67–0.83)			0.69 (0.63–0.77)		5.83	**<0.001**
3 months	0.73(0.66-0.81)	<0.001		0.74 (0.60–0.89)	<0.001	0.937	**0.343**
6 months	**0.85 (0.81–0.88)**	**<0.001**		**0.77 (0.62–0.83)**	**<0.001**	**0.669**	**0.499**

Abbreviations: CI, confidence interval; Cu-IUD, copper intrauterine device; LNG-IUS, levonorgestrel-releasing intrauterine system; PI, pulsatility index; RI, resistance index.
Versus the initial value.

Table 3 Sensitivity and specificity of uterine artery Doppler indices to predict abnormal bleeding.

AUC	0.92	**0.11**
Cutoff value	1.29	**0.61**
Sensitivity, %	89	**95**
Specificity, %	**100**	**100**

Abbreviations: AUC, area under the curve; PI, pulsatility index; RI, resistance index.

Table 4 the changes in the menstrual pattern associated with each group.

	Group I (170)		Group II (170)			
	Freq	%	Freq	%	X test	P value
Amount:						
Decreased	**104**	**61.17**	**23**	**13.5**	**Chi test not valid**	
Not changed	**26**	**15.29**	**45**	**26.47**		
Increased	**20**	**11.76**	**102**	**60**		
Intermenstrual Spotting:						**P<0.001**
-ve	**122**	**71.7**	**110**	**64.3**	**Chi=16.6**	
+ve	**48**	**28.2**	**60**	**35.2**		
Oligomenorrhea:						
-ve	**50**	**29.4**	**134**	**78.8**	**Chi =90.78**	**P<0.0001**
+ve	**120**	**70.6**	**36**	**21.1**		
Amenorrhea:						
-ve	**55**	**32.3**	**158**	**92.95**	**Chi =73.19**	**P<0.0001**
+ve	**115**	**67.7**	**12**	**7.05**		

Figure 1: Flow diagram for study selection