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ORIGINAL ARTICLE

Vascular effect of levonorgestrel intrauterine system on heavy menstrual bleeding: is it associated with hemodynamic changes in uterine, radial, and spiral arteries?

Hanifi Şahin[a], Arif Güngören[b], Burak Sezgin[c], Burak Ün[d], Eda Adeviye Şahin[a], Kenan Dolapçioğlu[b] and Rahime Nida Bayik[e]

[a]Department of Obstetrics and Gynecology, Malatya Education and Research Hospital, Malatya, Turkey; [b]Department of Obstetrics and Gynecology, Mustafa Kemal University Faculty of Medicine, Hatay, Turkey; [c]Department of Obstetrics and Gynecology, Faculty of Medicine, Muğla Sıtkı Koçman University, Muğla, Turkey; [d]Department of Obstetrics and Gynecology, Düziçi State Hospital, Osmaniye, Turkey; [e]Department of Obstetrics and Gynecology, Health Sciences University Ümraniye Education and Research Hospital, İstanbul, Turkey

ABSTRACT

The aim of this study was to evaluate the clinical and blood flow changes associated with the use of a levonorgestrel-releasing intrauterine device (LNG-IUD) in patients with idiopathic heavy menstrual bleeding (HMB). LNG-IUD was inserted into a total of 91 patients (39.5 ± 5.4 years) who were diagnosed with HMB. Uterine volume, ovarian volume, uterine, radial and spiral artery blood flow, Pictorial Blood Loss Assessment Chart (PBAC) scores, and other clinical and laboratory parameters were evaluated before and 12 months after insertion of LNG-IUD. Compared to pre-insertion values, LNG-IUD dramatically improved haemoglobin, PBAC scores, and endometrial thickness. Mean resistance indices of radial and spiral arteries significantly increased 12 months after insertion. Our study results suggest that a significant increase in the resistance indices of the intra-myometrial arteries in LNG-IUD users one year after insertion may be due to its local progestational effects, indicating a possible mechanism of LNG-IUD in reducing menstrual blood flow.

KEYWORDS
levonorgestrel-releasing intrauterine device; heavy menstrual bleeding; resistance index; pulsatility index

IMPACT STATEMENTS

- **What is already known on this subject?** The mechanisms of action of LNG-IUD on heavy menstrual bleeding include atrophy, decidualization and vascular changes of in the endometrium, resulting endometrial suppression. However, the exact mechanism to stop bleeding is not clear.
- **What do the results of this study add?** The present study suggests that one of the effects of the LNG-IUD on heavy menstrual bleeding is its ability to increase the resistance indexes of the intra-myometrial arteries.
- **What are the implications of these findings for clinical practice and/or further research?** These results will foster further studies on the effects of LNG-IUD on intra-myometrial arteries and will further assure clinicians on the vascular effect of LNG-IUD during management of heavy menstrual bleeding which includes hysterectomy as a final step.

Introduction

Heavy menstrual bleeding (HMB) is defined as excessive menstrual blood loss >80 mL per cycle which is associated with impaired physical, emotional, social wellbeing, and quality of life of a woman (Munro et al. 2012; Kai et al. 2016). HMB accounts for 10 to 35% of women (Mawet et al. 2014). The main aetiological factors include underlying uterine pathologies, coagulopathy, ovulation dysfunction, or iatrogenic causes (Munro et al. 2012).

Currently, medical treatment includes hormonal treatments; levonorgestrel-releasing intrauterine device (LNG-IUD), and combined hormonal contraceptives (Kai et al. 2016). The LNG-IUD offers a new therapeutic concept which combines a highly effective contraception with a blood loss-lowering treatment in both healthy women and those with HMB. The main mechanism of action of the LNG-IUD appears to be at the level of the endometrium, where the high dose of local progestogen causes decidualization, epithelial atrophy, and direct vascular changes (Cameron 2001).

In the majority of cases, Doppler flow ultrasonography does not show a significant change in the uterine artery flow between the copper intrauterine device (Cu-IUD) or LNG-IUD users (Zalel et al. 2002). However, a significant reduction in the sub-endometrial blood flow and endometrial thickness has been reported in the LNG-IUD users. In previous studies, reduced blood flow and endometrial thickness has been associated with morphological changes in the endometrial

CONTACT Arif Güngören arfgungoren@yahoo.com Department of Obstetrics and Gynecology, Mustafa Kemal University Faculty of Medicine, Hatay, Turkey

spiral arteries and capillaries (Zhu et al. 1989; Jones and Critchley 2000).

In the present study, we aimed to evaluate the LNG-IUD ability to decrease intramyometrial blood flow in HMB patients using colour Doppler transvaginal sonography (TVS).

Materials and methods

This longitudinal study was conducted at a tertiary centre between March 2011 and May 2013. A total of 91 women of reproductive age who were admitted to the Obstetrics and Gynaecology Department with complaints of HMB were recruited. Inclusion criteria were as follows: at least 18 years of age, not pregnant nor planning to become pregnant, not lactating, not menopausal, and a clinical diagnosis of functional HMB for at least six months. Exclusion criteria were as follows: a known or suspected pregnancy, prior endometrial ablation or curettage during the preceding three months; the use of a Cu-IUD or LNG-IUD within two months before screening, the use of other hormonal treatments including sex steroids, endometrial polyps, submucous myomas of any size or intramural or subserous myomas larger than 3 cm, adenomyosis, atypical hyperplasia or endometrial carcinoma, an abnormal PAP smear test or other evidence of cervical malignancy, abnormal uterine morphology, ovarian cysts $>$3 cm, a known or suspected hormone-dependent tumour, lower genital tract infection, pelvic inflammatory disease during the past three months, abnormal liver functions, renal insufficiency, uncontrolled hypertension, valvular disease, a body mass index (BMI) $>$30 kg/m^2, and hypersensitivity to the device material and/or LNG. A written informed consent was obtained from each patient. The study protocol was approved by the institutional Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

After a meticulous history taking and gynecological examination, laboratory testing including haemoglobin, haematocrit, prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalised ratio (INR) was performed in all patients 12 h before and after the LNG-IUD insertion. A cervical smear was performed to rule out cervical pathologies. Sonohysterography was used to measure the endometrial cavity for suspected cases. The Pipelle endometrial biopsy was performed to exclude endometrial hyperplasia or malignancies. The menstrual blood loss was quantified with the Pictorial Blood Loss Assessment Chart (PBAC) (Higham et al. 1990). HMB was defined as a menstrual blood loss of over 80 mL per cycle, and the menstrual flow was graded by self-assessment of the amount of menstrual loss using the PBAC including questions on the number and appearance of pads per cycle. A PBAC score of $\geq$100 is equivalent to a blood loss of $>$80 mL (Higham et al. 1990).

Each patient underwent a TVS examination using a 5-MHz transvaginal transducer (Voluson 730 Expert; General Electric Medical Systems, Little Chalfont, UK). All TVS examinations were performed by a single examiner, and each examination result was interpreted in real-time. The uterine and ovarian volumes were calculated using the formula for a prolate ellipsoid (volume $=$ 0.52 $\times$ length $\times$ anteroposterior diameter $\times$ transverse diameter). The cervical canal was accessed through the sagittal view using the pulsed wave Doppler to obtain the Doppler indices of the uterine artery at a sampling gate of 2 mm with an angle of insonation at less than 30°. The pulsatility index (PI) and resistance index (RI) were automatically calculated. Three similar consecutive waveforms were obtained, and the mean PI and RI of the uterine arteries were calculated.

The arcuate arteries of the uterine were visualised in the sagittal plane (anterior or posterior) to obtain radial artery Doppler findings and the intramyometrial flow velocity waveforms were detected through the radial artery exit. Three consecutive waveforms were visualised, and the PI and RI were calculated. Using Doppler examination of the spiral artery, the subendometrial region is consisted of a 5-mm hyperechoic halo, surrounding the hyperechogenic margin (basal endometrium). Colour Doppler ultrasound was used to evaluate the blood flow of the subendometrial region with a pulse repetition frequency of 3 cm/s and a colour gain of 80 $\pm$ 2 to obtain the blood flow of the small vessels. The spectral (radiating) fluctuations were obtained from the high colour-density vessels. The continuity of these fluctuations was confirmed. Three similar consecutive waveforms were obtained to calculate the PI and RI of the spiral artery and the mean values were recorded.

Following the insertion of LNG-IUD, all patients were scheduled for follow-up at one, six, and 12 months. All patients underwent Doppler TVS at baseline and at the end of 12 months in the late follicular phase.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 23.0 statistical software (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed in mean $\pm$ standard deviation (SD). After the normality testing, a paired sample t-test was used to analyse the significant differences. A p value of $<.05$ was considered statistically significant.

Results

Although 117 women were recruited during the study period, only 91 women completed one-year follow-up. Nine women underwent hysterectomy, the LNG-IUD was removed in three women due to excessive menstrual bleeding, three underwent spontaneous expulsion of the LNG-IUD after the insertion, and 11 were lost-to-follow-up. In total, 91 patients were included in the study.

The mean age of the patients was 39.5 $\pm$ 5.4 (range, 27 to 49) years. The mean parity was 3.1 $\pm$ 1.3 and the mean BMI was 22.8 $\pm$ 2.3 kg/m^2. The insertion of the LNG-IUD was made without anaesthesia in all patients.

The laboratory findings, PBAC scores, endometrial thickness, uterine and ovarian volume before and after the insertion of the LNG-IUD are shown in Table 1. Serum haemoglobin, haematocrit, international normalised ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (aPTT) levels were evaluated before and

Table 1. Clinical features and ultrasonographic findings of LNG-IUD users at 0 and 12 months.

Variable	Before insertion (mo 0)	Post insertion (mo 12)	p
Uterine volume (mL)	140 ± 21.5	135 ± 19.7	.071
Ovarian volume			
Right	17.3 ± 5.8	16.5 ± 5.3	.256
Left	16.8 ± 4.9	16.2 ± 5.1	.315
Endometrial thickness (mm)	8.1 ± 2.1	4.8 ± 1.1	**<.001**
Haemoglobin (g/dL)	9.2 ± 1.1	11.4 ± 1.0	**<.001**
Haematocrit (%)	27.5 ± 3.1	33.6 ± 2.2	**<.001**
PBAC score	228 ± 85	48 ± 22	**<.001**
PT (s)	12.1 ± 1.2	11.8 ± 1.1	.118
aPTT (s)	23.4 ± 2.2	23.2 ± 2.3	.186
INR	1.02 ± 0.37	0.98 ± 0.38	.281
HMB	91	0	**<.001**
Amenorrhea	0	17 (18.6%)	**<.001**
Spotting	0	19 (20.8%)	**<.001**
Infrequent bleeding	0	27 (29.6%)	**<.001**

LNG-IUD: Levonorgestrel-releasing intrauterine device; Mo: Month; PBAC: Pictorial Blood Loss Assessment Chart; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; INR: International normalised ratio; HMB: Heavy menstrual bleeding.
Bold values indicates statistical significance at $p < 0.05$.

Table 2. Changes in uterine, radial, and spiral artery blood flow after insertion of LNG-IUD.

Variable	Before insertion (mo 0)	Post insertion (mo 12)	p
Uterine artery RI			
Right	0.84 ± 0.04	0.84 ± 0.03	.264
Left	0.84 ± 0.03	0.83 ± 0.09	.380
Uterine artery PI			
Right	2.11 ± 0.32	2.09 ± 0.31	.141
Left	2.08 ± 0.31	2.10 ± 0.31	.131
Radial artery RI	0.68 ± 0.26	0.75 ± 0.25	**<.001**
Radial artery PI	1.51 ± 0.21	1.50 ± 0.17	.339
Spiral artery RI	0.58 ± 0.05	0.67 ± 0.03	**<.001**
Spiral artery PI	1.28 ± 0.15	1.26 ± 0.14	.385

LNG-IUD: Levonorgestrel-releasing intrauterine device; Mo: month; RI: resistance index; PI: pulsatility index.
Bold values indicates statistical significance at $p < 0.05$.

12 months after the insertion of the LNG-IUD. Serum haemoglobin and serum haematocrit levels increased from 9.2 ± 1.1 g/dL to 11.4 ± 1.0 g/dL ($p < .001$) and from 27.5 ± 3.1% to 33.6 ± 2.2% ($p < .001$), respectively at 12 months, compared to baseline.

The mean baseline uterine volume was 140 ± 21.5 mL. At 12 months, the mean uterine volume did not differ significantly (135 ± 19.7 mL; $p = .071$). The endometrial thickness (8.1 ± 2.1 to 4.8 ± 1.1 mm; $p < .001$) and the PBAC scores (228 ± 85 to 48 ± 22; $p < .001$) decreased at 12 months, compared to baseline.

Changes from baseline in the uterine, radial, and spiral artery blood flow are shown in Table 2. The RI and PI of the uterine arteries were not significantly different at 12 months compared to baseline. Only the RI measurements showed a significant increase in the radial and spiral arteries (0.68 ± 0.26 to 0.75 ± 0.25; $p < .001$ and 0.58 ± 0.05 to 0.67 ± 0.03; $p < .001$, respectively).

Discussion

To the best of our knowledge, there is no study examining changes in all three arterial (uterine, radial, and spiral) blood flows in HMB patients undergoing LNG-IUD treatment. The effects of this treatment on the intramyometrial blood flow have not been studied previously. Current literature regarding the changes in LNG-IUD in the uterine arterial blood flow are also conflicting. Our main hypothesis in the present study is to evaluate LNG-IUD ability to decrease intramyometrial blood flow in HMB patients. Our results revealed no significant changes in the uterine artery blood flow using the LNG-IUD insertion. However, a significant increase in the RI of the intramyometrial arteries (radial and spiral) was observed in LNG-IUD users one year after the insertion with decreased endometrial thickness and PBAC scores.

Although the exact mechanism by which LNG-IUD affects the endometrium to control uterine bleeding is still unclear, there are many Doppler flow studies examining the hemodynamic changes in LNG-IUD users. Controversial results have been reported in the literature. Despite its small sample size, in a study investigating the effect of LNG-IUD as a contraceptive method on the uterine artery blood flow, there was no significant difference in the uterine artery PI before and three months after the insertion (Pakarinen et al. 1995). However, in another study evaluating the effect of LNG-IUD on the uterine artery PI, it was suggested that continuous intrauterine release of progestin eliminated the vasodilatory effect of oestrogen (Jarvela et al. 1997). The aforementioned authors conducted another study one year later and examined the effect of LNG-IUD as a contraceptive device on the impedance to blood flow in the uterine arteries in 27 fertile women and found an increase in the mean uterine artery PI in the mid-luteal phase (Jarvela et al. 1998). The extent of this increase in the PI was associated with the serum levonorgestrel concentration. In another study investigating the local effects of LNG-IUD compared to Cu-IUD, no significant difference was found in the uterine artery RI between the two groups (Zalel et al. 2002). The aforementioned authors conducted another study one year later and compared the Doppler flow of the spiral arteries and cervical branch of the uterine artery 1–2 and 4–6 months after LNG-IUD insertion for contraception in 36 women (Zalel et al. 2003). The authors reported no significant change in the cervical branch RI values, although they observed a significant increase in the spiral artery RI. In addition, they reported a significant decline in the endometrial thickness 4–6 months after the insertion, consistent with our findings. In the present study, we also observed a significant decline in the endometrial thickness and an increase in the spiral artery RI one year after the insertion.

In another study comparing the PI and RI of the uterine artery between Cu-IUD and LNG-IUD users and examining whether these values differed before and after the insertion, no significant change of the uterine artery PI and RI values were found before and after the Cu-IUD users (Haliloglu et al. 2011). However, they found higher uterine artery RI values in the LNG-IUD users after one year of the insertion.

On the other hand, one study demonstrated that Doppler flow results showed no significant difference in the uterine artery PI and RI, consistent with our study results (Cihangir et al. 2013). In another longitudinal study involving 32 women using LNG-IUD for six months, it was reported that the LNG-IUD altered the endometrial thickness with a significant change in the uterine artery blood flow in women with prolonged bleeding (Bastianelli et al. 2014). More recently, a long-term, prospective, observational study involving 102 women with LNG-IUD, reported increased uterine artery RI and PI values at six and 12 months after the insertion (Rezk et al. 2017). In that study, a significant increase in the uterine artery RI values from baseline was observed at two and three years, although no significant increase was seen in the uterine artery PI values (Rezk et al. 2017).

Furthermore, several studies showed a decline in the subendometrial blood flow with decreased endometrial thickness in the LNG-IUD users (Jondet et al. 2005; Jimenez et al. 2008a, 2008b; Dane et al. 2009). In our study, we observed decreased endometrial thickness, consistent with the literature (Zalel et al. 2003, Haliloglu et al. 2011) In the literature, it was demonstrated that the uterine volume decreased with the use of LNG-IUD (Cihangir et al. 2013). In the present study, we observed a mild, but not a significant decrease in the uterine volume one year after the insertion.

In the present study, we also evaluated the effects of the LNG-IUD on coagulation parameters during one-year follow-up, considering many aspects of the HMB treatment. We observed no thromboembolism in any of the patients, and the use of LNG-IUD systemic haemostatic profile (INR, PT, aPTT) was no affected in LNG-IUD users over one-year study period. However, one study reported a significant reduction in the amount of fibrinogen with shortened PT and aPTT after 12 months of LNG-IUD use, suggesting that a short aPTT may imply a procoagulant status and may explain the relationship between thrombosis and LNG-IUD (Cihangir et al. 2013). However, we believe that this discrepancy may be due to the different study designs.

In our study, we demonstrated the efficacy of the LNG-IUD in reducing bleeding intensity over a period of 12 months for women with HMB. Our results are consistent with the findings of previous studies. It was shown that menstrual bleeding reduced by 86% with significantly decreased PBAC scores after the insertion of the LNG-IUD (Kucuk and Ertan 2008). In the aforementioned study, menstruation cessation was seen in almost all patients with HMB at six months. In addition, in a multi-centre study comparing LNG-IUD with hysterectomy, the median number of days of menstruation decreased from 7 days to 3 days at six months following the insertion of the LNG-IUD (Lahteenmaki et al. 1998). In this study, the expulsion rate of the LNG-IUD was found to be 3.6%, which is consistent with a previously reported rate of 4.2% (Sivin et al. 1991).

The strengths of the present study include its prospective design with a large sample size and intra-myometrial (radial and spiral) blood flow changes. However, the lack of a control group, relatively short follow-up, and the lack of an intention-to-treat analysis can be deemed as the main limitations.

Conclusion

In conclusion, our study results suggest that the significant increase in the RI of the intramyometrial arteries (radial and spiral) in the LNG-IUD users one year after the insertion may be due to its local progestational effects, indicating the mechanism of the LNG-IUD in reducing the menstrual blood flow. Nonetheless, further multi-centre, large-scale, prospective, randomized-controlled studies are needed to confirm these findings and to establish a definite conclusion.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Hanifi Şahin http://orcid.org/0000-0001-8522-9119
Arif Güngören http://orcid.org/0000-0002-8281-6630
Burak Sezgin http://orcid.org/0000-0003-2938-5816
Burak Ün http://orcid.org/0000-0002-8885-7062
Eda Adeviye Şahin http://orcid.org/0000-0003-4004-8167
Kenan Dolapçioğlu http://orcid.org/0000-0002-2296-9037
Rahime Nida Bayik http://orcid.org/0000-0003-1805-2178

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