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Can We Predict Menorrhagia with Intrauterine Contraceptive Device (IUCD) Insertion?

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Abstract

Objective: Studying sub endometrial vascularity and blood flow in cases using intrauterine contraceptive devices for contraception with and without menorrhagia compared to cases not using intrauterine contraceptive devices. **Methods:** Three hundred and fifteen women attending gynecology and family planning outpatient clinics in the maternity hospital, Ain Shams University were included in the study. They were classified into three groups, 105 women using IUCD with menorrhagia (group I), 105 women using IUCD without menorrhagia (group II), and 105 normal controls not using IUCD (group III). After excluding local causes for bleeding, blood disease or any medical disorders, transvaginal ultrasound including three dimensional power Doppler (3DPD) ultrasound was done for all women. Right and left uterine artery pulsatility index (PI) and resistance index (RI) were calculated, subednometrial blood flow RI and PI were obtained then 3DPD Vascular indices (VI, FI and VFI) of subendometrial blood flow were obtained for all cases. Statistical analysis was done to compare between the three groups. **Results:** A significant statistical difference was found as regards subendometrial vascularity indices, while there was no difference as regards bilateral uterine arteries Doppler indices in the three groups. **Conclusion:** Subendometrial vascularity in cases of menorrhagia with IUCD was markedly higher than in cases without menorrhagia and cases with no IUCD. 3DPD may be used for selection of cases prior to insertion of IUCD.

Keywords

Intrauterine Contraceptive Devices, IUCD, 3D Power Doppler Ultrasound, Menorrhagia

1. Introduction

An intrauterine contraceptive device (IUCD) is one of the most frequently used

methods for birth control around the world [1]. However, menorrhagia is among its side effects. Menorrhagia may cause iron deficiency anemia and usually ends by removing the IUCD in the first year after its insertion in many cases.

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

Probably there is a relation between IUCD adverse effects and uterine vascularization. However, this association is neither well-known nor well-studied. Three dimensional power Doppler (3DPD) was widely introduced for studying subendometrial vascularity by quantitative indices, vascularization index (VI), flow index (FI), and vascularization flow index (VFI).

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 (I.U.C.D) insertion [3].

Several possible mechanisms may explain the cause of menorrhagia in patients using IUD. Among these theories, the increased production of prostaglandins in the endometrium which causes an increase in vascularity, vascular permeability, inhibit platelet activity and therefore, increase menstrual bleeding [4].

Probably there is a relation between IUD adverse effects and uterine vascularization. However, this association is neither well-known nor well-studied [3].

Only a few studies have demonstrated an increase in subendometrial vascularization in patients with IUD induced menorrhagia [5].

The three-dimensional power Doppler is based on three-dimensional reconstruction of vessels image, received from power Doppler system. The intensity of three-dimensional angiography Doppler signal is directly dependent from blood flow velocity. It enables quantitative evaluation of vessels in the area studied due to the use of angio histogram function in which 3-dimensional vascularization and blood flow indices [Vascular Index (VI)], Flow Index (FI) and Vascular Flow Index (VFI), are counted automatically [6].

2. Subjects and Methods

This cross sectional case control study was performed in Ain Shams University Maternity Hospital. Three hundred and fifteen women attending gynecology and family planning outpatient clinics were included in the study.

Women were divided into three groups, 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. 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 105 women without IUCD who attended outpatient clinic requesting copper IUCD insertion and not complaining of abnormal uterine bleeding.

Cases with acute or chronic pelvic pain, cases with pelvic inflammatory disease, benign or malignant genital tumors or any uterine congenital anomalies, cases with bleeding tendency, patients on anticoagulants, non steroidal anti inflammatory drugs and patients on hormonal therapy in the previous 3 months were all excluded from the study.

The study protocol was approved by the hospital research ethics board. Study participants were counseled and informed consent was obtained.

A complete history was taken including menstrual history before and after IUCD insertion, including duration and amount of menstrual flow, regularity and length of the cycle, inter menstrual bleeding or spotting or 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.

3. Ultrasound Examination

The ultrasound equipment used was Voluson E6 B12 system with 6 - 9 MHz transvaginal transducer. A 2-dimensional B-mode real-time sonographic examination of the uterus and adnexae 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. Then, the ultrasound machine was switched to the 3D mode with power Doppler and 3D multiplanar view was seen.

Sub-endometrial blood flow pulsatility index (PI) and resistance index (RI) were calculated. Volume analysis was activated using histogram facility of virtual organ computer-aided analysis (VOCAL) software program. The rotation steps were 30˚ rotation steps resulting in successive six images of the uterus with manual drawing of each image, 1 mm shell thickness was chosen. Finally the volume was automatically calculated by the machine and accepted then histogram option was activated vascularization index (VI) flow index (FI) and vascularization flow index (VFI) were calculated automatically (Figure 1), VI is the ratio of color voxels to all voxels in the region of interest it reflects the density of vessels in the volume analyzed. FI is the mean intensity of all the power Doppler voxels in the volume analyzed. It represents the energy reflected from the blood corpuscles in the vessels of the volume. VFI is the mean color volume in all gray and color voxels within the volume, thus, it represents a combination of both FI and VI.
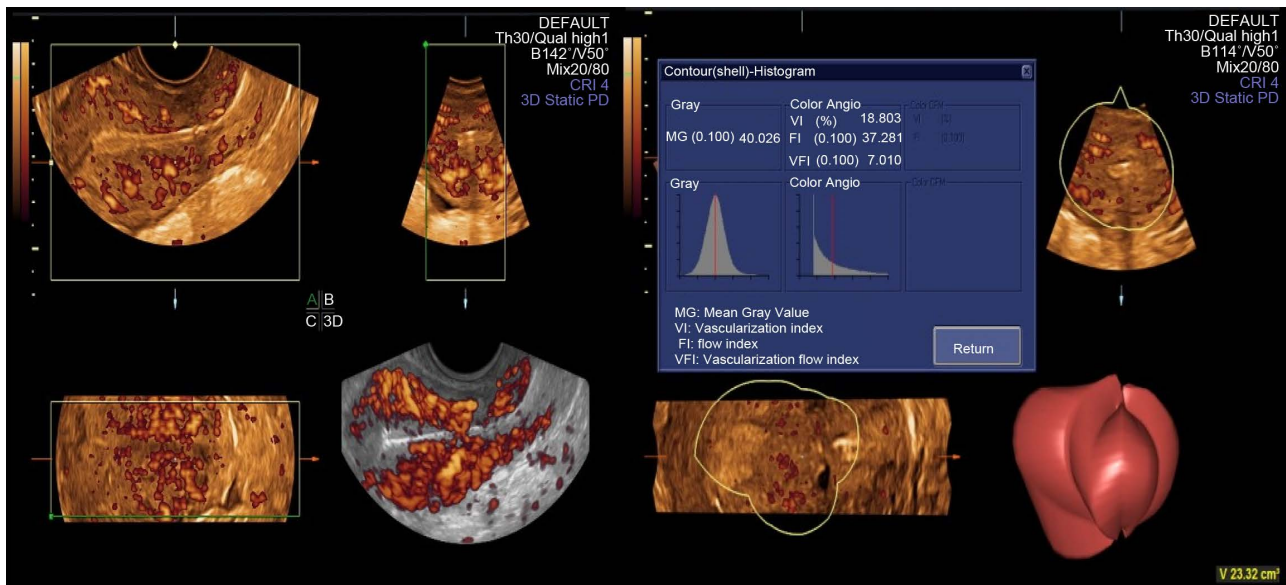
Figure 1. 3D power Doppler indices of subendometrium of a case of menorrhagia: VI: 18.8, FI: 37.28, VFI: 7.01. VI: Vascularization index, FI: flow index, VFI: Vascularization flow index.

4. Statistical Methods

Statistical analysis was done using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 13 (MedCalc© Software bvba, Ostend, Belgium).

Continuous numerical data were presented as mean and SD, and one-way analysis of variance (ANOVA) was used for comparison of the three study groups with application of the Student-Newman-Keuls test for post hoc pairwise comparisons, whenever the ANOVA revealed statistically significant differences among the groups.

Qualitative variables were presented as number and percentage and inter-group differences were compared using the Pearson chi-squared test.

Receiver-operating characteristic (ROC) curve analysis was used to examine the value of ultrasonic indices for prediction of menorrhagia in women using IUCD. The DeLong method was used for comparison of the areas under various ROC curves.

$P < 0.05$ was considered statistically significant.

5. Results

There was no significant difference between patients in the three study groups as regards age, body mass index and parity.

The mean uterine artery PI was significantly lower in women of group I (1.78 ± 0.33) than in women of groups II and III, (2.28 ± 0.35 and 2.33 ± 0.41), p-value < 0.001 (Table 1).

The mean uterine artery RI was significantly lower in women of group I (0.68 ± 0.09) than in women of groups II and III (0.87 ± 0.13 and 0.85 ± 0.11), p-value < 0.001 (Table 2).

Mean sub endometrial pulsatility index (PI) was significantly lower in women

of group I (1.84 ± 0.56) than in women of groups II and III (1.64 ± 0.41 and 1.93 ± 0.49), p-value < 0.001 (Table 3).

Mean subendometrial resistance index (RI) was significantly lower in group I (0.59 ± 0.12) than in women of groups II and III (0.87 ± 0.27 and 0.85 ± 0.32), p-value < 0.001 (Table 4).

Mean subendometrial vascularization index (VI) was significantly higher in women of group I (6.86 ± 2.9) than in women of groups II and III (2.61 ± 0.97 and 2.77 ± 1.5) p-value < 0.001 (Table 5).

Mean subendometrial flow index was higher in women of group I (36 ± 3.52) than in women of group II (29.26 ± 3.3) and III (28.8 ± 3.32), p-value < 0.001 (Table 6).

Mean subendometrial vascular flow index (VFI) was higher in women of group I (1.93 ± 1.03) than in women in group II (0.8 ± 0.21) and III (0.93 ± 0.57) p-value < 0.001 (Table 7).

Receiver-operating characteristic (ROC) curve was used for analysis of the

Table 1. Comparison of uterine artery pulsatility index (PI) in the three study groups.

Variable	Group I (n = 105)	Group II (n = 105)	Group III (n = 105)	*F* statistic	p-value⁹
Right Uterine artery PI	1.77 (0.36)*	2.26 (0.43)	2.22 (0.54)	32.097	**<0.001**
Left uterine artery P I	1.79 (0.52)*	2.30 (0.68)†	2.45 (0.52)	29.072	**<0.001**
Average UA PI	1.78 (0.33)*	2.28 (0.35)	2.33 (0.41)	77.986	**<0.001**

Data are presented as mean (SD). ⁹One-way analysis of variance (ANOVA). *p-value < 0.05 vs. IUD-O & Control groups (Student-Newman-Keuls test). †p-value < 0.05 vs. Control group (Student-Newman-Keuls test).

Table 2. Comparison of uterine artery RI in the three study groups.

Variable	Group I (n = 105)	Group II (n = 105)	Group III (n = 105)	*F* statistic	p-value⁹
Right Uterine artery RI	0.66 (0.09)*	0.89 (0.20)	0.86 (0.17)	59.686	**<0.001**
Left uterine artery R I	0.70 (0.13)*	0.86 (0.12)	0.85 (0.11)	58.018	**<0.001**
Average UA RI	0.68 (0.09)*	0.87 (0.13)	0.85 (0.11)	96.986	**<0.001**

Data are presented as mean (SD). ⁹One-way analysis of variance (ANOVA). *p-value < 0.05 vs. IUD-O & Control groups (Student-Newman-Keuls test).

Table 3. Comparison of subendometrial PI in the three study groups.

Variable	Group I (n = 105)	Group II (n = 105)	Group III (n = 105)	*F* statistic	p-value⁹
Subendometrial PI	1.64 (0.41)*	1.84 (0.56)	1.93 (0.49)	10.081	**<0.001**

Data are presented as mean (SD). ⁹One-way analysis of variance (ANOVA). *p-value < 0.05 vs. IUD-O & Control groups (Student-Newman-Keuls test).

data of all cases included in the study. Cut off values for prediction of menorrhagia in women with IUCD using uterine artery PI, RI, subendometrial blood flow PI, RI, VI, FI and VFI are mentioned in Figures 2-8, Table 8.

6. Discussion

The first published paper on actual IUCD insertions was made by Dr. Richard Richter in 1909 in Germany. The device he inserted was a ring made of silkworm gut, with 2 ends which protruded from the cervical os enabling him both to check the device and remove it. In the mid 1920s, Ernest Graefenberg added coiled metal ring made of an alloy of copper, nickel, and zinc. Graefenberg ring was widely used, however it was considered risky in continental Europe and in the U.S.. In 1959, Dr. Alan Guttmacher co-authored a paper in which the IUD was condemned for its ineffectiveness, potential source of infection, and its carcinogenic potential. Since 1960, various kinds of IUDs have been developed and renewed interest in IUCD [7].

Table 4. Comparison of subendometrial RI in the three study groups.

Variable	Group I (n = 105)	Group II (n = 105)	Group III (n = 105)	*F* statistic	p-value⁵
Subendometrial RI	0.59 (0.12)*	0.87 (0.27)	0.85 (0.32)	81.968	**<0.001**

Data are presented as mean (SD). ⁵One-way analysis of variance (ANOVA). *p-value < 0.05 vs. IUD-O & Control groups (Student-Newman-Keuls test).

Table 5. Comparison of subendometrial vascularization index (VI) in the three study groups.

Variable	Group I (n = 105)	Group II (n = 105)	Group III (n = 105)	*F* statistic	p-value⁵
Subendometrial VI	6.86 (2.90)*	2.61 (0.97)	2.77 (1.53)	107.929	**<0.001**

Data are presented as mean (SD). ⁵One-way analysis of variance (ANOVA). *p-value < 0.05 vs. IUD-O & Control groups (Student-Newman-Keuls test).
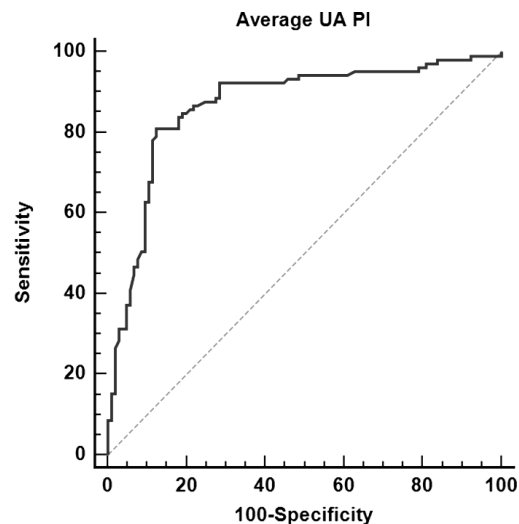
Table 6. Comparison of subendometrial flow index (FI) in the three study groups.

Variable	Group I (n = 105)	Group II (n = 105)	Group III (n = 105)	*F* statistic	p-value⁵
Subendometrial FI	36.56 (3.52)*	29.26 (3.39)	28.83 (3.32)	170.574	**<0.001**

Data are presented as mean (SD). ⁵One-way analysis of variance (ANOVA). *p-value < 0.05 vs. IUD-O & Control groups (Student-Newman-Keuls test).
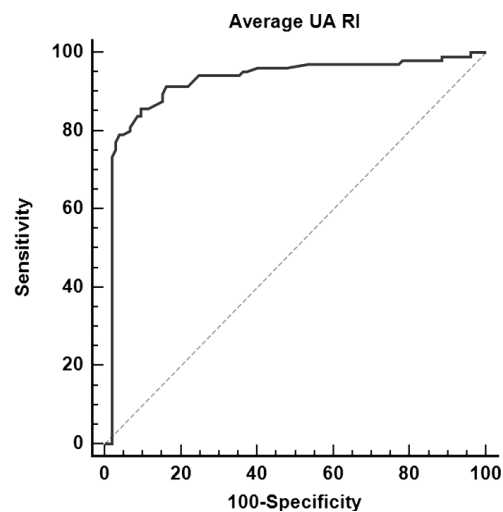
Table 7. Comparison of subendometrial vascularization flow index (VFI) in the three study groups.

Variable	Group I (n = 105)	Group II (n = 105)	Group III (n = 105)	*F* statistic	p-value⁵
Subendometrial VFI	1.93 (1.03)*	0.80 (0.21)	0.93 (0.57)	86.074	**<0.001**

Data are presented as mean (SD). ⁵One-way analysis of variance (ANOVA). *p-value < 0.05 vs. IUD-O & Control groups (Student-Newman-Keuls test).

Table 8. Doppler indices highly suggestive of menorrhagia after IUCD insertion.

Variable	Cut-off point	Sensitivity	Specificity
Average uterine artery PI	≤1.9	80.95%	87.6%
Average uterine artery RI	≤0.76	85.7%	90.4%
Subendometrial PI	≤1.83	67.6%	64.7%
Subendometrial RI	≤0.67	80.9%	91.4%
Subendometrial VI	≥4.1	87.62%	96%
Subendometrial FI	≥34	89.5%	95.24%
Subendometrial VFI	≥0.98	85.7%	87.6%

Figure 2. Receiver-operating characteristic (ROC) curve for prediction of menorrhagia in women with IUCD using UA PI. Area under the curve (AUC) = 0.869 (95% CI 0.816 to 0.911). Best cutoff point is PI of ≤1.9. This has a sensitivity of 80.95% and specificity of 87.62%. (UA PI: uterine artery pulsatility index).

Figure 3. Receiver-operating characteristic (ROC) curve for prediction of menorrhagia in women with IUCD using UA RI. Area under the curve (AUC) = 0.927 (95% CI, 0.883 to 0.958). Best cutoff point of RI is ≤0.76. This has a sensitivity of 85.71% and specificity of 90.48%. (UA RI: Uterine artery resistance index).
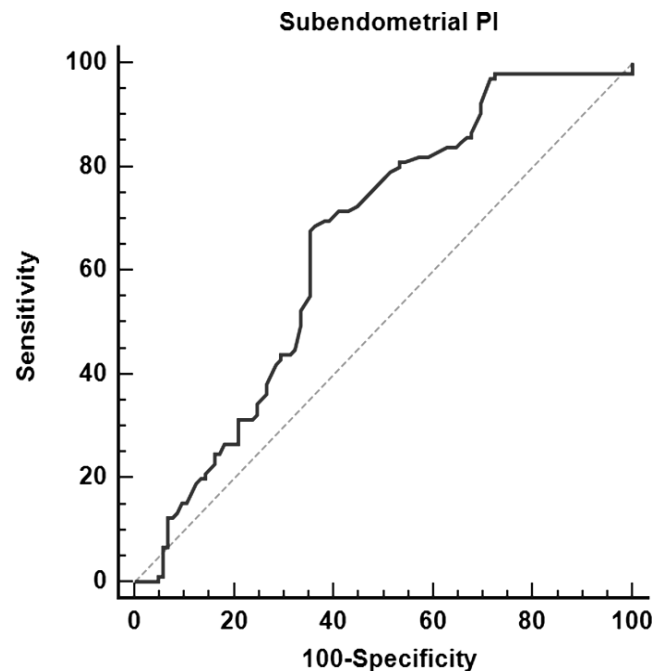
Figure 4. Receiver-operating characteristic (ROC) curve for prediction of menorrhagia in women with IUCD using subendometrial PI. Area under the curve (AUC) = 0.653 (95% CI, 0.585 to 0.718) of low predictive value. Best cutoff point of subendometrial PI is <1.83. This is has a sensitivity of 67.6% and specificity of 64.7%. (PI: pulsatility index).
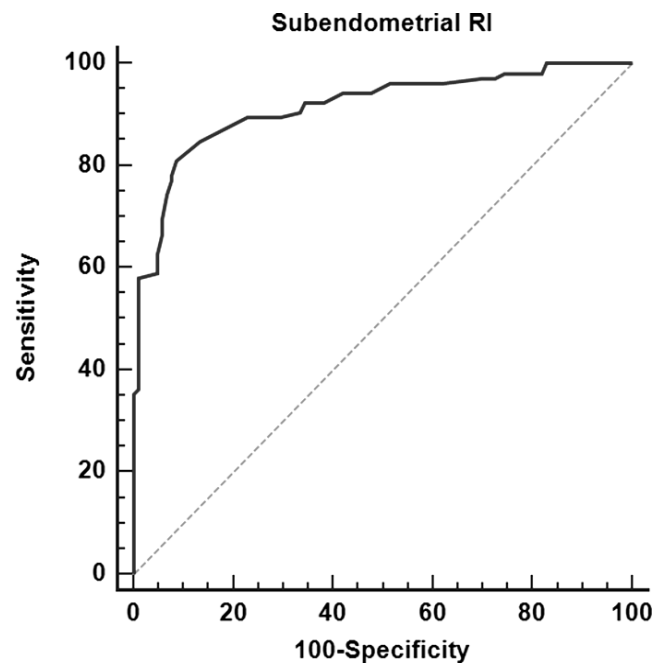

Figure 5. Receiver-operating characteristic (ROC) curve for prediction of menorrhagia in women with IUCD using subendometrial RI. Area under the curve (AUC) = 0.916 (95% CI, 0.870 to 0.950). Best cutoff point of subendometrial RI is ≤0.67. This has a sensitivity of 80.95% and specificity of 91.4%. (RI: resistance index).
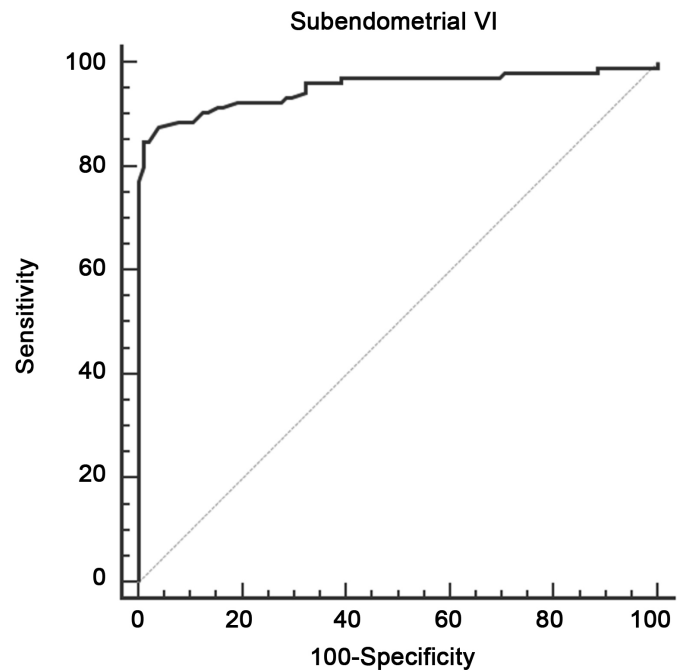
Figure 6. Receiver-operating characteristic (ROC) curve for prediction of menorrhagia in women with IUCD using subendometrial VI. Area under the curve (AUC) = 0.953 (95% CI, 0.915 to 0.977). Best cutoff point of VI is >4.1. This has a sensitivity 87.6% and specificity of 96.19%. (VI: Vacularization index).
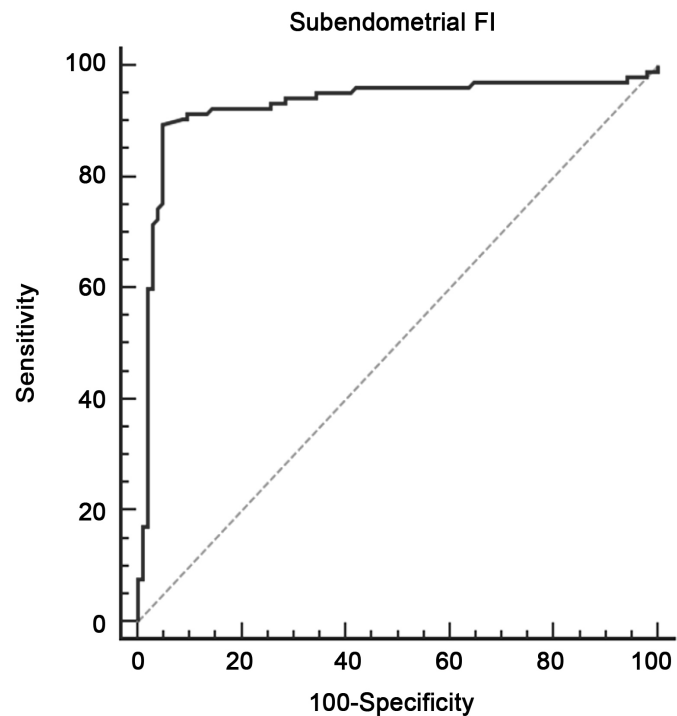

Figure 7. Receiver-operating characteristic (ROC) curve for prediction of menorrhagia in women with IUCD using subendometrial FI. Area under ROC curve (AUC) = 0.93 (95% CI, 0.887 to 0.961). Best cutoff point of FI is >34. This has a sensitivity of 89.6% and specificity of 95.4%. (FI: Flow index).
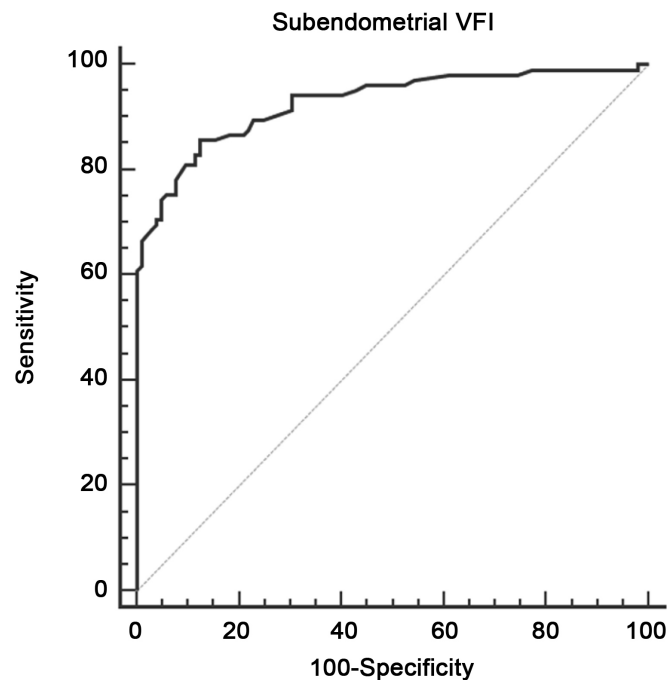
Figure 8. Receiver-operating characteristic (ROC) curve for prediction of menorrhagia in women with IUCD using subendometrial VFI. Area under the curve (AUC) = 0.929 (95% CI, 0.885 to 0.960). Best cutoff point of VFI is >0.98. This has a sensitivity of 85.7% and specificity of 87.6%. (VFI: Vascularization flow index).

Globally, 14.3% of women of reproductive age use intrauterine contraception (IUCD). In some countries, the percentage of women using IUC is <2%, whereas in other countries, it is >40% [8]. It was a widely accepted method for many women avoiding the systemic effects of hormonal contraception and the lower efficacy of the local methods or other physiological methods. However, IUCDs had their side effects, including the most common cause for discontinuation of using the method: menorrhagia. Excessive uterine bleeding up to iron deficiency anemia is among the most common causes of discontinuation of using the devices [9].

No proper patient selection for the method until now as the pathognesis of menorrhagia with IUCD is still unclear [1]. Some mechanisms were suggested for the pathogenesis of excessive bleeding with IUCD as a study of Xin *et al.*, reported that the 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 [4]. El-Sahwi *et al.* observed a significant rise in both PGF2*a* 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 post-insertion rise in prostaglandin concentration coincided with the phase of increased bleeding and pain [10]. Xin *et al.* 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 [4].

Trying to study the vasculature of the uterus and endometrium by assessment of uterine artery Doppler and subendometrial blood flow vascualrity by 2D and 3DPD, 315 cases were included in the current study, 105 with IUCD and menorrhagia, 105 with IUCD without menorrhagia, and 105 controls. The result of the current study showed that women in group I with menorrhagia had a significant increase in subendometrial vascularization index (VI), flow index (FI) and vascular flow index (VFI), and a significant decrease in subendometrial pulsitility index (PI), resistance index (RI) and uterine artery (PI) and (RI), in comparison with women in group II using copper IUD and not complaining of abnormal uterine bleeding and women in group III (control group). 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.

Usama *et al.* measured PI and RI of uterine arteries in 93 women divided into three groups, group I included 32 women complaining of menorrhagia with IUCD, group II including 30 women not complaining of abnormal uterine bleeding with IUCD and control group including 31 women not using IUCDs. The uterine artery PI and RI were significantly lower in group I compared to group II and group III. [2] The total number in their groups was 93; the total number in the current study was 315. They did not assess the sub endometrial vasuclarity, in the current study sub endometrial blood flow 2D and 3DPD parameters were assessed and revealed increased vascularity in cases of IUCD with menorrhagia.

El-Mazny *et al.*, measured PI and RI of uterine arteries, endometrial and subendometrial VI, FI, VFI in 120 women before and three months after the copper IUD insertion, concluded that there was a significant increase in the endometrial and subendometrial VI, FI and VFI in 47 women who had menorrhagia after IUD insertion compared to 73 women who were not complaining of abnormal uterine bleeding after insertion. Whereas the uterine artery PI and RI were not significantly different before and after IUD insertion [5]. The current study agree with the study of El-mazny *et al.* as regards the increase in the microvascularization in cases after inserting IUCDs, however they stated that it was not predictive for menorrhagia. In the current study, uterine artery and subendomertial vascularity Doppler parameters cut off values for prediction of menorrhagia were suggested. The current study included a larger number of total cases and larger number of menorrhagia cases, while their study—as a prospective study—depended only on the number of cases of menorrhagia among all the cases with IUCD, the number of menorrhagia cases in their study, forty seven cases may not express the whole population.

Jamenez *et al.* 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 [3].

Frajndlich *et al.* in 2000 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 [11], in the current study we preferred to include genuine cases presenting with menorrhagia not on medical treatment to avoid any effect on the results of Doppler of the endometrium.

In agreement also with the results of Momtaz *et al.*, they 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 [12].

Yigit *et al.* 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 [13]. Although their results of decreasing RI and PI agree with the results of the current study and many other studies, but their note of increasing PI and RI after the insertion of IUCD is of debate.

In contrary to results of the current study, desauza and Geber, 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 [1]. It should be mentioned that they compared the group before and after insertion after 30 days, and that duration may not be enough for detectable changes by Doppler ultrasound. And that they did not select cases with menorrhagia, in the current study 105 cases presented with menorrhagia were included in the study, and all cases passed 3 months duration of insertion.

In contrary to the results of the current study, Jamenez *et al.* found no statistically significant differences in uterine artery PI and RI between women with IUD induced bleeding and women using IUD with normal menstruation [3]. El-Mazny *et al.* also reported that were no statistically significant differences in uterine artery PI and RI before and after Copper IUD insertion in patients with IUD induced menorrhagia [5].

From the current study and previous studies, the copper IUD may be the cause for a modification in subendometrial mcirovascularization of those patients who presented with IUD-induced menorrhagia, through changes in the

production of prostaglandins leading to increase in subendometrial, and uterine artery blood flow.

Cut off values for uterine artery RI, PI, subendometrial RI, PI, VI, FI and VFI in the current study may be used for prediction of menorrhagia with IUCD insertion, however, further studies are needed with larger numbers and follow up pre and post insertion of IUCDs for a proper duration, as some cases develop menorrhagia after a longer duration.

7. Conclusion

Subendometrial vascularity in cases of menorrhagia with IUCD was markedly higher than in cases without menorrhagia and cases with no IUCD. 3DPD may be used for selection of cases prior to insertion of IUCD.

Conflicts of Interests

Authors state that there is no conflict of interest.

References

[1] De Souza, M.A. and Geber, S. (2006) Doppler Color Flow Analysis of the Uterine Arteries before and after Intrauterine Device Insertion: A Prospective Study. *Journal of Ultrasound in Medicine*, **25**, 153. https://doi.org/10.7863/jum.2006.25.2.153

[2] Fouda, U.M., Yossef, D. and Gaafar, H.M. (2010) Uterine Artery Blood Flow in Patients with Copper Intra Uterine Device-Induced Abnormal Uterine Bleeding. *Middle East Fertility Society Journal*, **15**, 168-173.
https://doi.org/10.1016/j.mefs.2010.07.003

[3] Jimenez, M.F., Vetori. D., Fagundes, P.A., Freitas, F.M. and Arbo, E. (1998) Effect of the Copper—Intrauterine Device (TCU 380A) on Subendometrial Micro-Vascularization and Uterine Artery Blood Flow. *Fertility Sterility*, **86**, 1780-1782.
https://doi.org/10.1016/j.fertnstert.2006.04.036

[4] Xin, Z.M., Cao, L.M., Xie, Q.Z., Sun, Y., Su, Y.C. and Guo, Y.H. (2009) Effects of the Copper Intrauterine Device on the Expression of Cyclooxygenase-1 and -2 in the Endometrium. *International Journal of Gynecology & Obstetrics*, **105**, 166-168.
https://doi.org/10.1016/j.ijgo.2008.12.018

[5] El-Mazny, A., Abou-Salem, N. and Elshenoufy, H. (2013) Three-Dimensional Power Doppler Study of Endometrial and Subendometrial Microvascularization in Women with Intrauterine Device-Induced Menorrhagia. *Fertility Sterility*, **99**, 1912-1915. https://doi.org/10.1016/j.fertnstert.2013.01.151

[6] Dubiel, M., Moszczynska, K., Breborowicz, G., *et al.* (2010) Three-Dimensional Power Doppler in Obstetrics and Gynecology. *Archives of Perinatal Medicine*, **16**, 109-112.

[7] Margulies, L. (1975) History of Intrauterine Devices. *Bulletin of the New York Academy of Medicine*, **51**, 662-667.

[8] Buhling, K.J., Zite, N.B., Lotke, P. and Black, K. (2014) INTRA Writing Group. Worldwide Use of Intrauterine Contraception: A Review. *Contraception*, **89**, 162-173. https://doi.org/10.1016/j.contraception.2013.11.011

[9] Pinter, B. (2002) Continuation and Compliance of Contraceptive Use. *European Journal of Contraception and Reproductive Health Care*, **7**, 178-183.

https://doi.org/10.1080/ejc.7.3.178.183

[10] El-Sahwi, S., Toppozada, M., Kamel, M., Gaweesh, S., Riad, W., Ibrahim, I., *et al.* (1987) Prostaglandins and Cellular Reaction in Uterine Flushings. *Advances in Contraception*, **3**, 291-302. https://doi.org/10.1007/BF01849285

[11] Frajndlich, R., von Eye Corleta, H. and Frantz, N. (2000) Color Doppler Sonographic Study of the Uterine Artery in Patients Using Intrauterine Contraceptive Devices. *Journal of Ultrasound in Medicine*, **19**, 577-579. https://doi.org/10.7863/jum.2000.19.8.577

[12] Momtaz, M., Zayed, M., Rashid, K. and Idriss, O. (1994) Doppler Study of the Uterine Artery in Patients Using an Intrauterine Contraceptive Device. *Ultrasound in Obstetrics* & *Gynecology*, **4**, 231-234. https://doi.org/10.1046/j.1469-0705.1994.04030231.x

[13] Yigit, N., Kacar, M., Yigit, H., Kosar, P. and Kosar, U. (2009) The Effects of Copper Contraceptive Intrauterine Device on the Uterine Blood Flow: A Prospective Transvaginal Doppler Study. *Journal of Clinical Ultrasound*, **37**, 380-384. https://doi.org/10.1002/jcu.20587