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Transvaginal Doppler Sonography for Evaluation of Irregular Uterine Bleeding with DMPA

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Abstract

Background: The main cause for discontinuation of DMPA use is irregular menstrual bleeding. The exact pathophysiological mechanisms of irregular bleeding have remained unclear. Transvaginal Doppler is a non invasive method for studying changes of blood flow which may highlight the underlying pathology in those cases with irregular uterine bleeding. The aim of the study was to quantify the uterine and subendometrial microvasculature in DMPA users with irregular bleeding pattern in comparison to DMPA users with amenorrhea.

Study Design: This is a case control study. Forty users of DMPA were divided into two groups: one group included 20 users with irregular uterine bleeding and the second group included 20 amenorrheic users. Pulsatility Index (PI) and Resistant Index (RI) of uterine and subendometrial blood vessels were determined. Power Doppler Energy (PWE) used to quantify the subendometrial area signal percentage.

Results: There is significant reduction of PI and RI in uterine artery and subendometrial microvasculature in cases with irregular uterine bleeding.

Conclusion: Irregular uterine bleeding with DMPA associated with increased perfusion of uterine and subendometrial blood vessels.

Key Words: DMPA – PI – RI – Subendometrial doppler.

Introduction

DEPO-PROVERA® (depot medroxyprogesterone acetate or DMPA intramuscular injection (150mg/mL), given once every 3 months exerts its contraceptive effect through the inhibition of gonadotropin secretion, which in turn prevents follicular maturation and ovulation and results in endometrial thinning [1]. Depot medroxyprogesterone acetate has been used for 40 years internationally. It is a convenient and long-acting method that provides highly effective contraception [2].

The most common side effect of DMPA use is irregular menstrual bleeding. Most women can expect some variation in menstrual bleeding patterns. Irregularities vary from woman to woman and may include prolonged menstrual bleeding, heavy bleeding, prolonged spotting, or spotting between periods.

The exact pathophysiological mechanisms of irregular bleeding have remained unclear. Several studies have been performed on endometrial morphology, histology, vascular microstructure and biochemistry, such as tissue factor, lipid peroxide, vitamin E, progesterone receptors, matrix metalloproteinases and the PGE2 and PGF2α [3-5].

Blood flow to the endometrium comes from uterine artery which divide before myometrial-endometrial junction into basal arteries that supply the basal portion of endometrium and the spiral arteries that continue upward to the endometrial surface. Considering that blood supply to the endometrium must go through the subendometrial area, vascularization of this area may be related to endometrial perfusion and hence any consequent endometrial vascular abnormalities [6].

Transvaginal Doppler is a non invasive method for studying changes of blood flow which may highlight the underlying pathology in cases with irregular uterine bleeding with DMPA.

The aim of the study was to quantify the uterine and subendometrial microvasculature in DMPA users with irregular bleeding pattern in comparison to DMPA users with amenorrhea.
Material and Methods

This is a case control study. Forty users of DMPA were divided into two groups: group 1 included 20 users with amenorrhea and group 2 included 20 users with irregular uterine bleeding. The users were collected from family planning clinic, woman’s Health Center, Assiut University Hospitals, Assiut, Egypt. Users with irregular uterine bleeding should have current bleeding without any use of hormonal treatment or other hemostatic agents that may alter the pattern of bleeding. A detailed menstrual and medical history was taken first. An informed consent was taken from each participant before being enrolled in the study.

Ultrasonographic study:

With longitudinal view of the uterus, the sub-endometrial area is the hypoechoic halo of 5mm width that regularly encircled the hyperechogenic margin (basal endometrium). Colour flow mapping (Siemens Ultrasound Sonoline G50) was used to determine the blood flow in the subendometrial areas. The pulse repetition for colour velocity was chosen in the range of 3 cm/second and the colour gain was adjusted to 80%±2% to optimize blood flow detection in the small vessels. Spectral waveforms were obtained from vessels of high colour intensity. After confirming that wave forms were continuous, at least three cardiac cycles were selected for calculation of Spiral artery pulsatility index (SA-PI) and resistance index (SA-RI). Angle should be kept at 0° because of the course of the small spiral arteries. The endometrial thickness was measured where the greatest in the sagittal section of the uterus. Uterine artery was visualized by colour Doppler lateral to the cervix with angle of insonation less than 30. Pulsatility Index (PI) and Resistance Index (RI) of uterine arteries were determined.

The settings for power Doppler sonography were standardized for the highest sensitivity in the absence of apparent noise, using a high pass filter at 50 Hz, pulsed repetition frequency at 750 Hz and moderate to long persistence. Power Doppler Energy were classified into 5 categories according to the the subendometrial area signal percentage: I (<10%), II (10-25%), III (25-50%), IV (50-75%) and V (75%) [7].

Statistical analysis:

Student’s t test was used for comparing age and duration of use. The Wilcoxon-Mann-Whitney test was used to compare skewed data (PI, RI, and ET), whereas the chi-square test was used for categoric data (PDE). p value <0.05 was considered significant.

Results

The demographic and clinical characteristics of 40 women included in the study groups did not significantly differ (Table 1).

<table>
<thead>
<tr>
<th>Table (1): Clinical characteristics of the patients.</th>
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<tbody>
<tr>
<td>Group 1 Amenorrhea (n=20)</td>
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<tr>
<td>Age</td>
</tr>
<tr>
<td>Parity</td>
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<tr>
<td>Duration of use</td>
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Doppler blood flow in the cervical branch and in the spiral arteries were significantly higher in group 2 as indicated by the lower PI and decreased impedance to the flow (Table 2).

<table>
<thead>
<tr>
<th>Table (2): Doppler blood flow characteristics.</th>
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<tbody>
<tr>
<td>Group 1 Amenorrhea (n=20)</td>
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<tr>
<td>Endometrial thickness</td>
</tr>
<tr>
<td>SA-PI</td>
</tr>
<tr>
<td>SA-RI</td>
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<tr>
<td>UA RI</td>
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<td>UA PI</td>
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The number of cases with high grades of sub-endometrial flow (categories III-V) was significantly higher in group 2 (16 Vs 1, p=0.001). There was significant difference in the subendometrial power Doppler signals between both groups (p=0.001) (Table 3). With univariate analysis, the duration of DMPA use (as a dependant variable) significantly correlated to the categorized Power Doppler Energy (r=−0.882, p=0.001).

<table>
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<th>Table (3): Categorized Power Doppler Energy characteristics.</th>
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<tr>
<td>Group 1 Amenorrhea (n=20)</td>
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<tr>
<td>I</td>
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<td>II</td>
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<td>III</td>
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<tr>
<td>IV</td>
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<td>V</td>
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**Discussion**

Bleeding disorder was the main cause for discontinuation of DMPA in previous studies [8,9]. The underlying mechanism of irregular uterine bleeding with DMPA is still unclear. The aim of the study was to elucidate the hemodynamic changes of uterine and subendometrial blood vessels in amenorrheic and in cases with irregular uterine bleeding using DMPA.

Irregular uterine bleeding may be the end stage of a complicated chain of events. It is most probably initiated by endometrial exposure to progestogen that leads to inconsistent anovulation, altered exposure to estrogen and stimulation of the development of abnormal endometrial microvasculature. These vessels are either inherently fragile or grow to be more fragile secondary to exposure to an unfavorable environment [10].

In this study, we observed that blood perfusion in the spiral arteries significantly increased in patients experiencing irregular bleeding as indicated by significant reduction of pulsatility index and significantly decreased impedance to the flow. Power Doppler energy showed high grade of subendometrial flow (>25%) in the same group which correlated significantly with prolonged duration of use.

These data support the previous explanation of irregular uterine bleeding with use of progestogen only methods. It consistent with Runic, et al. study who noticed enlarged, dilated thin walled and fragile vessels after one year exposure to Norplant® implants [11]. Krikun, et al. suggested that irregular uterine bleeding during progestin only contraception may result from characteristically enlarged and permeable vessels that formed as result of the damage caused by free radicals which alter the balance of angioprotein 1, 2 and produces such vessels [12].

Contact hysteroscopy performed in 38 women with irregular uterine bleeding caused by DMPA or Norplant® revealed the higher frequency of visualization of ectatic superficial network of blood vessels (Type D=enelarged abnormally distributed superficial blood vessels) [10,13]. CD34 antigen immunohistopathological staining of the endometrium removed in DMPA users with irregular uterine bleeding revealed marked excess of mean vascular density relative to the control [10]. These findings are in accord with data obtained by our Doppler study.

Cases with amenorrhea using DMPA showed increased PI and an increase in RI in both subendometrial and uterine artery levels in our study. This lies in accordance with Dane et al, who observed the same hemodynamic changes in amenorrheic cases using DMPA or Levonorgestrel Intruterine system (LNG-IUS) [14]. Haberal, et al. observed a significant increase in RI of the uterine artery one year after insertion of LNG-IUS for treatment of menorrhagia [15]. Also Jimenez et al. found a significant increase in uterine artery PI and RI three months after insertion of a LNG-IUS for contraception [16].

From data obtained in our study and previous studies, Doppler velocimetry presents an important diagnostic dimension in evaluating the pathphysiologic mechanism in cases with irregular uterine bleeding using progestogen only method. But still unclear, why some women experiencing amenorrhea while others not, although using the same progestogenic method of contraception.

There are many regimens for treatment of bleeding abnormalities with DMPA use including administration of estrogen [17], mifepristone [18], tranexemic acid [19], inoxifen [20] and doxicyclin [21]. But the results of reviewing all of these regimen do not support its routine clinical use especially for long period [20]. The vascular changes we observed may open new diagnostic and therapeutic approaches that may help in establishing a novel solution for patients with bleeding disorders related to DMPA use.

There are two limitations of our study. First, is the small number of cases; another one is absence of endometrial biopsies. Future studies comparing Doppler studies and endometrial pathology would be valuable.

**Conclusion:**

Irregular uterine bleeding with DMPA associated with increased blood flow in the subendometrial and uterine vessels. Formation of new fragile subendometrial blood vessels is highly suggestive which may point to the possibility of trying antiangiogenic methods for treatment.

**References**


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