Effect of Laparoscopic Ovarian Drilling on Ovarian and Uterine Doppler Flow Indices Using 3-Dimensional Power Doppler in Clomiphene Resistant PCOS

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Abstract

Background: It is assumed in polycystic ovary syndrome (PCOS) that follicular development, maturation, ovulation and implantation are impaired due to hormonal imbalance and vascular impairment of the ovarian and uterine vasculatures. The mechanism of action of laparoscopic ovarian drilling (LOD) is largely unexplained. To date, only limited studies have been conducted utilizing 3D ultrasonography to investigate the 3D ultrasound features of PCOS in relation to this fertility treatment.

Objective: To determine the effect of LOD on ovarian and uterine blood flow and vascularity as assessed by 3-Dimensional power Doppler ultrasonography in Clomiphene citrate (CC) resistant women with PCOS.

Study Design: Prospective study.

Patients and Methods: 60 CC resistant women with PCOS were scheduled for LOD. Three ovarian Doppler indices—vascularization index, flow index, and vascularization flow index, in addition to the resistance index of the uterine artery—were measured before and a month after LOD. All patients were followed-up through 6 months after the operation to detect the outcome of the laparoscopic drilling.

Results: Doppler indices of ovarian blood flow showed a highly significant decrease in the PCOS group after LOD. Decrease in uterine artery Doppler indices following LOD failed to reach statistical significance.

Conclusion: LOD is shown to reduce ovarian vascularization in CC resistant women with PCOS. The data could contribute greatly to our knowledge on ovarian physiology, resumption of menstrual cyclicity and fertility after the commonly used ovarian surgery.


Introduction

POLYCYSTIC ovary syndrome (PCOS) is a heterogeneous, multifactorial, complex genetic and endocrine disorder, characterized by menstrual disturbances, clinical and biochemical manifestations of hyperandrogenism and polycystic ovaries.

Women with PCOS have significant differences in intraovarian and uterine artery hemodynamics, both at a baseline ultrasound scan and during clomiphene induced menstrual cycle, compared to women with normal ovaries. These differences are likely to be due to a primary disorder within the polycystic ovary and their different hormonal status.

Increased ovarian stromal blood flow is emerging as a new parameter to assist in the ultrasound diagnosis of polycystic ovaries [3]. Power Doppler ultrasound is more sensitive than color Doppler imaging at detecting low velocity flow, and thus it overcomes the angle dependence of standard color Doppler and provides improved visualization of small vessels [4].

Uterine blood flow plays an important role in uterine receptivity and increased values of pulsatility index (PI) of uterine artery have been reported in infertile couples. The presence of a pathologic uterine perfusion in PCOS patients may contribute to the reduced chance of conception and to the increased risk of miscarriage that characterized these patients.

The first line treatment of anovulatory infertility in PCOS patients is clomiphene citrate. Laparoscopic ovarian drilling (LOD) has been shown to be an effective means of inducing ovulation in these patients when clomiphene citrate fails [8].

The mechanism of action of LOD is largely unexplained. In particular, it is not known whether LOD exerts its action through a direct effect on the ovary or through a systemic endocrine mechanism [6].
Material and Methods

A prospective study was conducted from May 2012 to August 2013, at the Obstetrics and Gynecology department of Kasr El Ainy Hospital, Cairo University, Egypt. Approval was received from the Ethics Committee of the Cairo University.

A total of 60 women with PCOS and previous CC failure (these patients had failed to ovulate after being given 250mg per day of clomiphene citrate for 5 days during 6 consecutive cycles) attending the infertility clinic were invited to participate in the study. Written informed consent was obtained from each participant after an information sheet had been provided. The patients had the right to refuse participation in the study or to withdraw at any time without being denied their full regular clinical care. Other inclusion criteria included age range from 18 to 34 years, and BMI of 25 to 35. Other causes of infertility were excluded.

All participants met the Rotterdam consensus criteria 2003 for the diagnosis of PCOS. To make a diagnosis of polycystic ovaries from transvaginal scanning, 12 or more follicles measuring 2-9mm in diameter or increased ovarian volume (>10cm³) must be present.

Examinations were performed with a Kretz Voluson 730D ultrasound scanner (Kretztechnik, Zipf, Austria). In all patients, identical preinstalled instrument settings were used. After visualizing the ovary in 2-D B mode, the mobile sector for angio mode was switched on and set up to cover the region of interest, then the 3-D volume mode was engaged. The volume sector angle was preset to 90°, and the fast volume acquisition setting was selected to avoid motion artifacts. The acquired 3-D volumes were stored then analyzed later by the same observer (A.T.) by using the VOCAL imaging program (Virtual Organ Computer-aided AnaLysis). The longitudinal view was used as a reference image, and the rotation step was selected as 30°, resulting in the definition of six contours for each ovary. Once a contour was defined in all image planes, the volume of the ovary was obtained. After definition of the contour, the VOCAL program automatically calculates indices for gray-scale and color-scale voxels.

According to these values, three indices were calculated: The vascularization index (presence of blood vessels in the tissue region of interest) (VI), flow index (average intensity of flow in the vessels scale 1-100) (FI) and vascularization flow index (feature of both vascularization and flow) (VFI). Ovaries were examined bilaterally, and the average value from both sides was used as a single parameter.

The ascending branch of the uterine artery was then visualized laterally to the cervix at the level of internal os in longitudinal plane, with the angle between the ultrasound beam and the vessel close to 0. At least three similar consecutive waveforms of good quality were obtained from each side, the RI was automatically calculated for each side, and the mean of the two measurements was calculated for each woman.

LOD was carried out in the early follicular phase of the menstrual cycle. Ovarian drilling was performed by using an ErbotomTUR10109 electrosurgical unit and a Corson needle electrode. A unipolar electrocautery needle was used to puncture the ovary at a right angle to a depth of about 8mm. The punctures were placed evenly around the ovary taking care to avoid the hilum. Coagulating current was applied once the needle was within the ovarian stroma. One or both ovaries was punctured at 4-6 points depending on the size of the ovary, using a power setting of 40W for each puncture for 2 to 3 seconds. Irrigation fluid was used immediately after each treatment to cool the ovary.

Three-dimensional CPA and histogram analysis of intraovarian circulation and RI measurements of the uterine arteries were performed in all patients before laparoscopic electrocautery as well as at 1 month after the procedure (if menstrual cycle had resumed, this was performed on cycle day 3).

For statistical analysis of the ovarian and uterine flow parameters before and after LOD, paired t-test was applied, and data were expressed as mean ± SD. For comparing categorical data, Chi square (χ²) test was performed. p-values of <0.05 were considered to be statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

We found that 56.7% of the 60 cases had good spontaneous ovulation by good folliculometry following laparoscopic ovarian drilling. These cases were referred as favourable cases.

Comparing Doppler Indices (mean ± standard deviation) in Patients with PCOS before and after LOD, there is a highly significant decrease in ovarian stromal blood flow indices (Vascularity
Index, Flow Index and Vascularity Flow Index) following LOD (p-value <0.001) (Table 1).

In this study, although a reduction in the mean value of uterine artery Resistance Index was reported after LOD, it failed to reach statistical significance. (p-value 0.296) (Table 1).

Comparing Doppler Indices (mean ± standard deviation) in favourable and unfavourable patients with PCOS before and after LOD, there was no significant change for the favourable patients than the unfavourable patients before or after LOD regarding ovarian vascularity index (p-value 0.869 and 0.243 respectively), ovarian stromal flow (p-value 0.479 and 0.516 respectively) or ovarian stromal vascularity flow index (p-value 0.749 and 0.806 respectively) (Table 2).

There was no significant change in uterine resistance for the favourable patients than the unfavourable patients before or after LOD (p-value 0.664 and 0.496 respectively) (Table 2).

Table (2): Comparing Doppler indices in favourable and unfavourable patients before and after LOD.

<table>
<thead>
<tr>
<th></th>
<th>Before LOD</th>
<th>After LOD</th>
<th>p-value</th>
<th>Significance</th>
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<tr>
<td></td>
<td>Mean±SD</td>
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<tr>
<td>Uterine Artery:</td>
<td></td>
<td></td>
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<tr>
<td>RI</td>
<td>Favorable</td>
<td>0.997±0.18</td>
<td>0.664</td>
<td>NS</td>
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<tr>
<td></td>
<td>Unfavorable</td>
<td>0.987±0.17</td>
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<tr>
<td>Ovarian Stroma:</td>
<td></td>
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<td></td>
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<tr>
<td>VI</td>
<td>Favorable</td>
<td>4.50±1.02</td>
<td>0.869</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Unfavorable</td>
<td>4.56±0.65</td>
<td></td>
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</tr>
<tr>
<td>FI</td>
<td>Favorable</td>
<td>51.51±2.00</td>
<td>0.479</td>
<td>NS</td>
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<tr>
<td></td>
<td>Unfavorable</td>
<td>51.16±2.10</td>
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<tr>
<td>VFI</td>
<td>Favorable</td>
<td>2.58±0.39</td>
<td>0.749</td>
<td>NS</td>
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<tr>
<td></td>
<td>Unfavorable</td>
<td>2.67±0.40</td>
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Correlating between favourable and unfavourable as regards Doppler indices pre LOD, ovarian stromal vascularity index (p-value 0.869), ovarian stromal flow (p-value 0.479) and ovarian stromal vascularity flow index (p-value 0.749) were not significantly reduced (Table 3).

Uterine resistance was not significantly higher for the favourable patients than the unfavourable patients before LOD (p-value 0.664) (Table 3).

Table (3): Correlating Doppler indices between favourable and unfavourable Pre LOD.

<table>
<thead>
<tr>
<th></th>
<th>Favourable</th>
<th>Unfavourable</th>
<th>p-value</th>
<th>Significance</th>
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<tr>
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<tr>
<td>RI</td>
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<td>0.664</td>
<td>NS</td>
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<tr>
<td>Ovarian Stroma:</td>
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Discussion

This is a study of the effect of laparoscopic ovarian electrocautery on ovarian and uterine blood flow and vascularity as assessed by 3-D CPA in patients with PCOS.

With the introduction of 3-D power Doppler technique, a multiplanar display of the total vascularity and blood flow within a tissue region of interest can be studied interactively, and the rendered 3-D image resembles one created by using angiography.

Three-dimensional (3D) ultrasound is a relatively new imaging modality that has the potential to improve the sensitivity and specificity of ultrasound in the diagnosis of PCOS [7,8]. There are important parameters that may be relevant to our understanding of the pathogenesis and clinical presentation of PCOS and as prospective predictors of the response to the various treatments used in patients with PCOS [7,9].

To date, only limited studies have been conducted utilizing 3D ultrasonography to investigate...
the 3D ultrasound features of PCOS in relation to the various fertility treatments [9,10].

In the present study, we measured, evaluated and quantified ovarian and uterine blood flow with 3-D CPA histogram analysis before and after laparoscopic ovarian electrocautery in patients with PCOS. Thus, long-term follow-up and pregnancy rate were not considered.

The data could contribute greatly to our knowledge on ovarian physiology and could help understanding about the resumption of menstrual cyclicity and fertility after the commonly used ovarian surgery. The aim of our study, with this small sample size, was just to highlight possible tendencies of clinical interest.

It has been shown that in patients with polycystic ovarian syndrome, important changes in ovarian vascularization occur at the level of the intraovarian arteries. Zaidi et al., and Aleem et al., successively confirmed that, in patients with PCOS, significant changes occur within the intraovarian vessels. Furthermore, Zaidi et al., and Aleem et al., confirmed that Doppler analysis of ovarian stromal arteries in PCOS may be useful to improve the diagnosis, and to provide further information about the pathophysiology and evolution of the syndrome [3,11].

A smaller number of studies have used 3D power Doppler angiography, to examine the degree of vascularity of PCOs as a whole or within their stroma. Many of these studies have limited power because of small sample sizes and open inclusion/exclusion criteria that result in the recruitment of inappropriate controls. In addition, different criteria for the diagnosis of PCOS, variable Doppler settings and inconsistencies in the phase of cycle when the examinations were conducted militate against any worthwhile comparison. Interestingly, in contrast to the reported and commonly accepted observation of an increased blood flow within the PCOS [9,10], the study with the best design demonstrated no significant differences in total ovarian 3D power Doppler flow indices from those seen in fertile controls [12].

Amin et al., reported significant increase in Doppler indices (pulsatility index and resistance index) of ovarian stromal blood flow after LOD. This shows reduced ovarian blood flow velocities following LOD [13].

Parsanezhad et al., reported that six to ten weeks following diathermy the pulsatility index increased from 0.98±0.36 to 1.78±0.72 (p-value 0.001) and resistance index increased from 0.55±0.16 to 0.71±0.19 (p-value 0.001) and concluded that LOD in women with polycystic ovary syndrome may result in a decrease in ovarian stromal blood flow velocity. Changes in the Doppler parameters were significantly higher in women who ovulated and concluded that the measurement of ovarian stromal blood flow by colour Doppler may be of value in predicting the outcome of treatment [14].

Wu et al., have also demonstrated a reduced stromal blood flow (VI: 0.29±0.10 versus 1.01±0.37%, p<0.05; VFI: 0.13±0.05 versus 0.49±0.18, p<0.05) during the early follicular phase in 40 clomiphene-resistant women with PCOS 3 months after laparoscopic ovarian drilling. However, both groups of investigators have not prospectively examined the predictive values of these changes in ovarian volume and vascularization after laparoscopic ovarian drilling in its clinical responses [15].

In this study we agree with Amin et al., and Wu et al., the decrease in ovarian stromal blood following LOD. This may explain the reduced risk of ovarian hyperstimulation syndrome (OHSS). Another hypothesis is that a corrected stromal blood flow is due to a reduction in luteinizing hormone (LH) and testosterone (T). This reduction in LH and T subsequently results in a reduction of VEGF, an angiogenic factor thought to be responsible for increased Doppler indices [13,15].

Contrary to these studies, Vizer M et al., showed increased intraovarian flow intensity after laparoscopic ovarian electrocautery. It is thought that increased ovarian blood flow (FI and VFI) and partial neovascularisation (VI) around the developing follicles make ovarian tissue accessible to higher circulating levels of FSH. Subsequently, follicular development is triggered, and resumption of menstrual cyclicity and fertility may be achieved. The prevailing hypothesis is that the focal damage to the androgen producing theca cell component in the ovarian stroma decreases intraovarian androgen production. This restores an estrogenic milieu within the ovary that enables follicular maturation to resume [16].

Uterine blood flow play an important role in uterine receptivity and increased values of pulsatility index (PI) and resistance index (RI) of uterine artery have been reported in infertile couples and have been related to a decreased chance to conceive in cycles of assisted reproduction. Studies confirm that patients affected by PCOS have higher resistance in uterine arteries; however, they also demonstrate that PCOS itself does not predetermine a single uterine blood flow pattern [2].
Androgens are known to have direct vasoconstrictive effects on vascular tissues, thereby increasing vascular resistance. Nearly every study of the endocrine effects of LOD has demonstrated a significant reduction in serum LH and testosterone levels. These changes occur within the first 5 days postoperatively [17]. These changes may explain the reduction in uterine artery resistance index (RI) following LOD.

In this study, the mean value of Uterine artery RI was 0.99±0.17 before LOD and 0.96±0.18 after LOD. However this is not a significant decrease in resistance (p-value 0.296) following LOD.

Ozkan et al., reported that the Uterine RI and PI were positively correlated with LH. Reduction of LH post LOD was related to a reduction in Uterine Doppler indices. Few studies reported the direct effect of LOD on uterine RI and further studies are needed [18].

Conclusion:

3D ultrasound is a more appropriate tool to assess and study PCOS because it facilitates the quantitative measurement of total ovarian and stromal echogenicity, volume and blood flow in a way that has not been possible before [7,9].

Such parameters may not be available to all clinicians and are unlikely to be practically applicable in a clinical setting, but they are important in the research environment and may contribute to our understanding of this enigmatic disease.

Measuring ovarian stromal 3D power Doppler blood flow for women with anovulatory PCOS undergoing LOD may provide a useful tool in evaluating the outcome of LOD.

References

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الملخص العربي

الهدف: تحديد آثار تثبيت المبيض بالمناظر على تدفق الدم في الأوعية الدموية بالمبيض والرحم باستخدام الموجات فوق الصوتية 3D-الإبعاد.

(دوير) لدى النساء يتوافق مذابة المبيض الأنيتي تقاوم عقار الكولوبيفين ستات.

تقصيم الدراسة: دراسة مستقبلية.

المرضى وطرق: من المقرر 60 من النساء يتوافق مذابة المبيض الأنيتي تقاوم عقار الكولوبيفين ستات تثبيت المبيض بالمناظر. ثلاثة من مؤشرات الدوائر على الأوعية الدموية بالمبيض بالإضافة إلى مؤشر مقاومة تدفق الدم في الرحم، وتثبت نتائج قبل وبعد شهر من تثبيت المبيض بالمناظر. تم تأخير جميع المرضى لمدة 6 أشهر بعد عملية الكشف عن نتائج تثبيت بالمناظر.

النتائج: أظهرت مؤشرات الدوائر انخفاض كبير جداً في تدفق الدم في المبيض بعد تثبيت المبيض بالمناظر. انخفاض في مؤشرات دوائر الدم في الرحم بعد تثبيت المبيض بالمناظر تصل إلى الأهمية الإحصائية.

الخلاصة: يوجد انخفاض كبير جداً في تدفق الدم في المبيض بعد تثبيت المبيض بالمناظر. المؤشرات يمكن أن تساهم في معالجة مرض وظائف المبيض، استئصال دورة الشهرية والخصوبة بعد جراحة المبيض شائعة الاستخدام.