Quantification of Doppler signal in polycystic ovary syndrome using three-dimensional power Doppler ultrasonography: a possible new marker for diagnosis

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BACKGROUND: Differences in the ovarian stromal blood flow of women embarking on an IVF treatment, as assessed on day 2 or 3 of the menstrual cycle, using three-dimensional (3D) power Doppler ultrasonography to quantify the blood flow and vascularization, were compared. METHODS: The women were divided into two groups: group 1, 54 women with regular, ovulatory menstrual cycles and normal ovaries on ultrasound scan; and group 2, 25 women with polycystic ovary syndrome (PCOS). RESULTS: The quantification of Doppler signal in the ovarian stroma appeared to be greater in the PCOS group compared with the normal group. The mean of ovarian volume was significantly higher \( (P < 0.05) \) in women with PCOS compared with the normal ovaries. The vascularization flow index (VFI), flow index (FI), and vascularization index (VI), were significantly higher \( (P < 0.05) \) in the women with PCOS compared with the women with normal ovaries. CONCLUSIONS: This observation may help to explain the excessive response often seen during gonadotrophin administration in women with PCOS. We believe that a quantification study of the vascular flow, including the VI, FI, and VFI of the entire ovarian stroma using 3D power Doppler, is more accurate than the previously reported quantification analysis using 2D imaging, and may be a new parameter to assist in the ultrasound diagnosis of PCOS.

Key words: ovarian stroma/PCOS/power Doppler/stromal blood flow/three-dimensional ultrasound

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting female fertility (Kousta et al., 1999). However, the great variability in symptoms and clinical and biochemical manifestations of PCOS make the aetiology and pathophysiology unclear (Franks, 1994; Conway, 1996). Polycystic ovaries (PCO) have been reported to occur in about 20% of the general female population (Polson et al., 1988) and in up to 50% of women presenting to infertility clinics (Jacobs, 1987). Using high resolution ultrasonography, Adams (Adams et al., 1986) demonstrated PCO in 87% of those patients with oligomenorrhoea, in 26% of patients with amenorrhoea, and in 92% of women with idiopathic hirsutism.

Most investigators would agree that the blood flow and the vascular pattern of an organ are directly related to the organ’s morphology and function. Therefore, the clinician may consider an ability to detect alterations in an organ’s blood flow and vascular pattern a valuable tool in evaluating organic and functional anomalies. The ovary is an ideal organ for the application of these techniques, as there is a rapid and controlled sequence of cyclical events involving neoangiogenesis coupled with significant fluctuations in the local concentration of hormones known to affect the vasculature (Findlay, 1986).

In the early 1990s, better sensitivity was achieved with colour Doppler sonography. Now, transvaginal colour Doppler ultrasound, in combination with B-mode imaging, is increasingly used as a non-invasive method to assess blood flow changes in the pelvic organs. Among the newest technological advances in the evaluation of the vascular flow and flow pattern is the ability to evaluate using three-dimensional (3D) power Doppler, quantification of blood flow and vascularization, and the quantification of Doppler signal using a histogram software. In contrast to frequency-based colour Doppler sonography, which analyses the frequency shift of blood velocity information, power Doppler sonography uses the amplitude component of the signals received to present the number of moving blood cells. Power Doppler sonography has been found to be superior to frequency-based colour Doppler sonography, especially in situations of low-velocity blood flow (Rubin et al., 1994), with the potential to detect alterations in blood flow (Rubin et al., 1995), because it is more sensitive, less angle-dependent, and not susceptible to aliasing (Meyerowitz
et al., 1996). This allows the visualization of small vessels and lower flows (Chaoui and Kalache, 1998). All these features make this new method optimal for the 3D reconstruction of vessels. With the recent advent of 3D power Doppler ultrasonography, the quantification of the total blood flow of the ovaries becomes feasible.

If differences in vascularity can be demonstrated, this information might provide us with an additional parameter for the ultrasound diagnosis of the PCOS. Therefore, in the present study, we aimed to compare the characteristics of intra-ovarian blood flow intensity and vascularization in women with PCOS and normal controls using 3D power Doppler ultrasonography.

Materials and methods

Subjects

A total of 79 women who were about to undergo IVF treatment were recruited from the IVF centre of Cheng Kung University Hospital. Based on clinical menstruation history, physical examination, biochemical data, and ultrasound findings, the women were divided into two groups: group 1 consisted of 54 women (the normal group) who had regular spontaneous menstrual cycles ranging from 25 to 32 days. Transvaginal ultrasonography on day 2 or 3 of the cycle (i.e. the baseline ultrasound scan) showed normal ovaries, and they underwent IVF procedure because of tubal factor or male factor only; group 2 consisted of 25 women (the PCOS group) with polycystic ovaries on the baseline ultrasound scan, a history of oligomenorrhea/amenorrhoea, clinical evidence either of acne, alopecia, obesity (BMI >25 kg/m²), or hirsutism as defined by the presence of excessive body hair distributed in an androgen-dependent pattern (O’Driscoll et al., 1994; Timpatanapong and Rojanasakul, 1997). In addition, women in the PCOS group had either elevated concentrations of serum testosterone or a LH/FSH ratio >1. For inclusion in this group, women were required to have at least one of the abnormal clinical findings and at least one abnormally elevated laboratory value. This study was approved by the Institutional Review Board of National Cheng Kung University Hospital, and informed consent was given by all subjects.

3D power Doppler ultrasound examination and histogram analysis

Patients underwent transvaginal ultrasonography, on day 2 or 3 of their menstrual cycle, prior to starting treatment with a gonadotrophin hormone releasing hormone agonist for pituitary desensitization. All ultrasound examinations were performed using a conventional 3D power Doppler ultrasound equipment (Voluson 530D®; Medison-Kretz, Seoul–Zülpich, Korea–Austria). All the quantitative measurements were performed by one of the authors (Y.-C.C). To determine the intra-observer error, another 10 healthy post-menopausal women were evaluated by two consecutive measurements of the bilateral ovarian stroma blood flow by the same operator in this study (Y.-C.C). During the examination, the Doppler settings were not changed. The region of interest included the whole ovarian region and excluded the supplying vessels.

After weighing the total colour percentage and flow amplitudes in the total volume of interest (Pairleitner et al., 1999), the VOCAL (virtual organ computer aided analysis) software (Medison-Kretz) for the 3D power Doppler histogram analysis is then used to analyze with computer algorithms to form indices of blood flow and vascularization. In brief, as reported by Pairleitner et al. (1999), the vascularization index (VI) indicates the proportion of the volume showing a flow signal in the total volume of the ovary. It does not contain any information on flow signal and intensity. The flow index (FI) is an average of the intensity of flow signal inside the ovary that carries no significance by itself. The vascularization flow index (VFI) is a combination of the information of vessel presence and amount of flow made by multiplying the FI and VI. During the analysis and calculation, the manual mode of VOCAL program was used to cover the whole 3D volume of the ovary. For further details, please refer to the manual of the manufacturer. The setting condition for this study was: Angio Mode: Cent, FRQ, Mid. Frame filter: 3. Line density: 254. Enhance: 3. Far gain: Max 62. Persist: 0.3/0.4. Quality: 12. Density: 6. Enhance: 3. Balance: G > 192. Reject: 79.

Statistical analysis

The ultrasonographic and flow data from the right and left sides of the ovaries were evaluated with a Student’s t-test for paired samples. Since no significant differences were found between right- and left-side values, the average from both sides was used as a single parameter. The Wilcoxon test was used to evaluate non-parametric variables bilaterally. As no statistically significant differences existed between the right and left sides, the value used was the sum of both sides divided by two. Data are represented as mean ± SD. Comparisons between the two groups were performed using an analysis of variance. An independent-sample t-test was used to compare the variables. P values < 0.05 were considered to be statistically significant.

Results

The demographic and hormonal data of these two groups are shown in Table I. A statistically significant difference was noted in age and body mass index (BMI) between the PCOS group and the normal controls. There was a tendency toward a larger BMI in the PCOS group. There was no significant difference in serum estradiol and LH concentrations between the two groups. As expected by virtue of the study design, statistically significant differences (P < 0.05) existed in the serum LH/FSH ratio (0.93 ± 0.48 versus 0.64 ± 0.57) and testosterone concentrations (1.11 ± 0.48 versus 0.39 ± 0.30) between the PCOS and the normal controls (Table I). Ultrasonographic and power Doppler signal parameters also showed statistically significant differences between the two groups (Table II). Mean ± SD ovarian volume was significantly higher (P < 0.05) in women with PCOS (12.94 ± 4.27 ml) compared with normal ovaries (6.10 ± 3.41 ml). The VFI, FI and VI were all significantly higher (P < 0.05) in women with PCOS (2.10 ± 1.32, 50.26 ± 3.02, and 3.99 ± 2.38 respectively) compared to women with normal ovaries (0.80 ± 0.97, 44.44 ± 5.42, and 1.44 ± 1.20). The 3D power Doppler ultrasonography histogram analysis in PCOS patient was demonstrated in Figure 1. The 3D power Doppler ultrasonography histogram analysis in normal patients was demonstrated in Figure 2. The difference in volume distribution between these two groups is shown in Figure 3. The VFI distribution data of these two groups are demonstrated in Figure 4, then FI in Figure 5, and VI in Figure 6.

Reliability assessment

For intra-observer error, there was a good correlation of the consecutively repeated measurements for right ovary (r = 0.986) and left ovary (r = 0.991), and there was no
significant difference between the two repeated measurements ($P > 0.05$). In addition, because all the measurements were performed by the same operator in this study (Y.-C.C), there was no interobserver error for this study.

**Discussion**

Power Doppler ultrasound, also known as colour power angiography or colour Doppler angio, has been in clinical practice for several years (Bude *et al.*, 1994; Rubin *et al.*, 1994; Chui *et al.*, 1997). Power Doppler ultrasound has the advantage of being more sensitive to low flow, and thus overcomes the angle-dependence and aliasing of standard colour Doppler. It displays the total flow in a confined area, giving an impression similar to that of angiography. This implementation of the 3D display permits the physician to see three dimensions on the screen interactively, rather than mentally assembling the sectional images. Thus, the 3D power Doppler system may be used to measure blood flow changes in PCOS (Zaidi *et al.*, 1995; Battaglia *et al.*, 1995, 1996; Aleem and Predanic, 1996; Dolz *et al.*, 1999), because the 3D power Doppler histogram analysis can quantify the whole ovarian stroma Doppler signal via a 3D reconstructive figure, which can really reflect the whole stroma flow data while 2D power Doppler cannot.

The aetiology of PCOS is unclear. Women with PCOS may have a variety of clinical symptoms or signs, and more likely have a higher concentration of LH, an elevated LH/FSH ratio, and an elevated concentration of testosterone (Adams *et al.*, 1986; Yen, 1986; Jacobs, 1987; Franks, 1991). Ovarian volume is also likely to be greater in women who fulfill the ultrasonographic criteria for PCOS. Our study results reveal the same findings in the PCOS group, which had a higher LH/FSH ratio, and testosterone and ovarian volume, than the normal group. It is well documented that women with PCOS are at increased risk of developing ovarian hyperstimulation syndrome during ovarian stimulation for IVF (MacDougall *et al.*, 1992; Rizk *et al.*, 1997). Early Doppler ultrasound studies have demonstrated increased stromal vascularity in polycystic ovaries (Battaglia *et al.*, 1995; Zaidi *et al.*, 1995). One hypothesis is that the increased blood flow and the increased vasculature seen in the stroma of these ovaries may be responsible for the increased risk of ovarian hyperstimulation syndrome. Thus, increasing research interest in the ovarian stroma has highlighted the need for a reliable and objective method of stromal analysis, because stromal hyperechogenicity (Adams *et al.*, 1985) is a notoriously subjective parameter.

### Table I. Demographic and hormone data between the two groups

<table>
<thead>
<tr>
<th></th>
<th>Normal ($n = 54$)</th>
<th>PCOS ($n = 25$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.89</td>
<td>28.20</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.99</td>
<td>24.25</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>35.87</td>
<td>42.61</td>
<td>NS</td>
</tr>
<tr>
<td>FSH (mU/ml)</td>
<td>6.92</td>
<td>4.80</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LH (mU/ml)</td>
<td>3.96</td>
<td>4.61</td>
<td>NS</td>
</tr>
<tr>
<td>Testosterone (ng/ml)</td>
<td>0.39</td>
<td>1.11</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>0.64</td>
<td>0.93</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Group differences were compared by independent-sample $t$-test. Significance: $P < 0.05$.

BMI = body mass index; PCOS = polycystic ovary syndrome (PCOS).

### Table II. The ovarian volume and power Doppler signal parameters between the PCOS and normal controls

<table>
<thead>
<tr>
<th></th>
<th>Normal ($n = 54$)</th>
<th>PCOS ($n = 25$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>6.10</td>
<td>12.94</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>VFI</td>
<td>0.80</td>
<td>2.10</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>FI</td>
<td>44.44</td>
<td>50.26</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>VI</td>
<td>1.44</td>
<td>3.99</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Group differences were compared by independent-sample $t$-test. Significance: $P < 0.05$.

VFI = vasculation flow index; FI = flow index; VI = vasculation index.
Figure 1. Three-dimensional (3D) power Doppler ultrasonography histogram analysis in a polycystic ovary syndrome (PCOS) patient.

Figure 2. 3D power Doppler ultrasonography histogram analysis in a normal control.

ultrasonographic visualization improves, stromal characteristics may become more important than follicular pattern for the diagnosis of PCOS (Pache et al., 1992; Dewailly et al., 1994). Sophisticated new computerized ultrasound systems can now be used to measure the area and volume of the ovary and may provide a valuable opportunity for truly objective comparative studies of the normal ovary and PCOS.

With the recent advances of 3D ultrasound, its clinical application has been applied in many fields of obstetrics and gynaecology. Over the past decade, we have investigated and
validated the clinical use of 3D ultrasound in many fields (Kuo et al., 1992; Chang et al., 1997a, 1997b, 1997c, 2000a, 2000b, 2000c; Chou et al., 1997; Liang et al., 1997a, 1997b, 1998; Wu et al., 1997, 1998; Lin et al., 1998; Wang et al., 1999; Chuang et al., 2000; Lai et al., 2000, 2001; Yu et al., 2000). To the best of our knowledge, this study is the first one to report a significant increase in the indices of the Doppler signal in the ovarian stroma of PCOS patients compared with ovaries from normal patients using 3D power Doppler ultrasound. We found significantly increased ovarian stromal VFI, FI, VI, and ovarian volume within the PCOS group. Although the implication of this finding in ovulation induction treatment is unknown, it may help to explain the excessive response often seen in women with PCOS when they are administered gonadotrophins. The presence of an increased stromal Doppler signal in the PCOS group, compared with women with normal ovaries, supports the notion that PCOS is a primary disorder of the ovary. In conclusion, the detection of an increased ovarian stromal Doppler signal by 3D power Doppler ultrasound may be a possible new ultrasound marker in the diagnosis of PCOS. In addition to our previous 3D ultrasound series and other investigators’ conclusions (Platt, 2000; Bega et al., 2001; Pretorius and Nelson, 2001), we believe that 3D power Doppler ultrasound may provide substantial assistance to the management of the PCOS and is worthy of further research.

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References


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