

Significance of Ovarian Stromal Blood Flow Measurement Between Fertile Women with Normal Ovaries and Primary Infertile Women with Polycystic Ovary Syndrome.

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Abstract:

Background: Polycystic ovary syndrome is the commonest endocrine disorder in women of reproductive age as this syndrome affect about 5-10% of premenopausal women.

Objective : To determine Doppler flow changes within ovarian stroma in women with polycystic ovary syndrome and compare the ovarian stromal blood flow and serum LH,FSH concentration in fertile women with normal ovaries and primary infertile women with polycystic ovary syndrome .

Method : Samples of women who will attend to our gynecologic clinic in Elwyia maternity teaching hospital in Baghdad/Iraq ,from beginning of March to end of September 2014. Fifty cases of fertile women with normal ovaries control group and fifty cases of study group .Primary infertile women with PCOS confirmed by clinical examination ,investigation (Day 2-4 FSH,LH) and transvaginal Doppler ultrasound to determine total antral (AFC) ,total ovarian volume ,total ovarian vascularization index (VI) ,flow index (FI) and vascularization flow index (VFI).

Results: The frequency and percentage of amenorrhea, hirsutism and infertility were increased among overweight PCOS patient . Patient with PCOS showed significantly higher serum LH concentration ,but serum FSH was significantly lower in PCOS than normal groups. Mean serum LH was significantly higher in overweight than normal weight PCOS patient . Fertile controls and PCOS women has similar total ovarian VI/FI/VFI after controlling the age of women .PCOS women had significantly higher total AFC, total ovarian volume than fertile controls. Total ovarian VI/FI/VFI were significantly higher in normal weight (BMI < 25Kg/m²) PCOS than their overweight (BMI ≥ 25 Kg/m²).

Conclusion : Fertile controls and PCOS women had similar total stromal ovarian 3D power Doppler indices (VI/VF/VFI) .Normal weight PCOS women had significantly higher total ovarian 3D power Doppler indices than their overweight counter parts.

Keywords : Ovarian stromal blood flow, PCOS , 3D power Doppler .

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I. Introduction

PCOS produces symptoms in approximately 5% to 10% of women of reproductive age. Approximately 20% of them will have polycystic ovaries on ultrasound scan It is thought to be one of the leading causes of female subfertility⁽¹⁾⁽²⁾. Women with may display a wide range of clinical symptoms but the usually present with one or more of the following: menstrual irregularities, infertility and symptoms associated with androgen excess⁽³⁾. PCOS is a heterogeneous disorder of uncertain cause.⁽⁴⁾⁽⁵⁾ There is strong evidence that it is a genetic disease. Such evidence includes the familial clustering of cases, greater concordance in monozygotic compared with dizygotic twins and heritability of endocrine and metabolic features of PCOS.⁽⁴⁾⁽⁵⁾⁽⁶⁾ Polycystic ovaries develop when the ovaries are stimulated to produce excessive amounts of male hormones (androgens), in particular testosterone, by either one or a combination of the following (almost certainly combined with genetic susceptibility⁽⁷⁾):

- the release of excessive luteinizing hormone (LH) by the anterior pituitary gland
- through high levels of insulin in the blood (hyperinsulinaemia) in women whose ovaries are sensitive to this stimulus⁽⁸⁾.

Also, reduced levels of sex-hormone-binding globulin can result in increased free androgens.

Not all women with PCOS have difficulty becoming pregnant. For those that do, anovulation or infrequent ovulation is a common cause.

Objectives: To assess Doppler flow changes within ovarian stroma in women with polycystic ovary syndrome and to determine whether these variables can be add to the clinical ultrasonographic and endocrine findings typical of PCOS and compare the ovarian stromal blood flow and serum LH,FSH concentration in fertile women with normal ovaries and primary in fertile women with polycystic ovary syndrome .

II. Patients and Methods

The study was conducted in Elwyia maternity teaching hospital in Baghdad during a period from beginning of March to the end of September 2014. A total of 100 women were selected from gynecology and infertility clinic of the hospital , Fifty of them with features of PCOS comprised the study group and fifty women served as the control group . A careful history was obtained from each of them and detailed clinical examination was performed for each of them with particular attention to infertility history ,menstrual history ,hair growth pattern ,weight gain ,change in voice , any symptoms and sign of endocrinopathies and drug history .Height and weight were measured and body mass index (BMI)was calculated . Investigation : hormonal analysis day (2-4) LH, FSH midluteal serum progesterone ,transvaginal and Doppler ultrasound done to them . Women in the study were divided into two major groups (study group who had PCOS (no.=50) and control group who did not had PCOS (n=50). The inclusion criteria :-

- 1- Reproductive age group (20-40 years) .
- 2- Primary infertility (defined as in ability of a couple to obtain a clinically recognizable pregnancy after 12 Months of unprotected intercourse) .
- 3- Menstrual disturbances :-oligomenorrhea (menses at interval of >35 days) or amenorrhea (cessation of menstruation >=6 months in individual who previously had experienced periodic menstruation)
- 4- Hirsutism :- had a score of >8 according to Ferriman-Gallwey scoring system .
- 5- Overweight : BMI >= 25kg/m²and normal weight :BMI<25Kg/m².

These criteria that included taken by history and clinical examination and by investigation :-

- 1- Hormonal analysis : (day 2-4)elevated LH ,low or normal FSH and low midluteal serum progesterone < 5 ng/ml which confirm anovulation .

- 2- Transvaginal ultrasound : ovarian morphology according to the Rotterdam criteria ,12 or more small follicles should be seen in an ovary develop to a size of 5-7 mm with an ovarian volume of at least 10 ml.

Ethical consideration: An informed verbal consent had been taken from each patient . The following hormonal measurement were done for all women in the study by radioimmunoassay . 1.LH 2- FSH, These tests were performed in the early follicular phase (Day 2-4) of the cycle in regularly cycling or oligomenorrhoeic women and randomly in amenorrhoeic women .

Transvaginal pelvic ultrasound examination with 3D color and pulsed Doppler measurements was performed for all women in the study on the same day of hormonal assay using (Siemens real time scanning system) and a trans vaginal probe with a center frequency of 6.5 MHz coupled with pulsed and color Doppler facilities . The procedure wholly explained to the patient ,then put in a waiting room for at least 15 minutes before being scanned and completely emptied the bladder. The patient assume lithotomy position during the examination.

A coupling gel was applied to the vaginal probe which was subsequently introduced into a protective rubber sheath. Additional gel was placed on the top of the probe for lubrication to be gently inserted into the vagina . The average duration of the procedure was 15-20 minutes after which the probe should be gently removed ,cleaned and sterilized .

The following were scanned systematically :-

- Morphology of urinary bladder ,uterus ,adenxae ,and cludesac was explored by B mode ultrasound graphic.
- Follicular number ,diameter and distribution were recorded with stromal eachogenicity subjectively assessed .

III. Results

Table (1) Demographic features of PCOS in both groups (mean ±SD)

Number of women	PCOS group	Control group
	50	50
Age(yr)	28.31±3.7	28.9±4
BMI (Kg/m ²)	28.6±41	26.8±3.8

Table (2) Clinical criteria of PCOS patients

Clinical Criteria	Number of patients	%
Amenorrhoea	14	28%
Oligomenorrhoea	36	72%
Primary Infertility	50	100%
Signs of hyperandrogenism		
Acne	13	26%
Hirsutism	34	68%
Overweight BMI ≥ 25 Kg/m ²	32	64%
Normal weight BMI<25 Kg/m ²	18	36%

Table (3) :Frequency and percentage of clinical criteria in PCOS patients with BMI ≥ 25 Kg/m² and BMI < 25 Kg/m² .

Clinical Criteria	PCOS group		
	No.	BMI ≥ 25 Kg/m ²	BMI < 25 Kg/m ²
Amenorrhoea	14	10 (71.43%)	4 (28.57%)
Oligomenorrhoea	36	21 (58.33%)	15 (41.67%)
Hirsutism	34	27 (79.41%)	7 (20.59%)
Primary infertility	50	32 (64%)	18 (36%)

Hormonal findings :

The mean serum LH concentration was significantly higher in PCOS group than those of the controls while FSH slightly lower or normal in PCOS group than normal fertile group (no significant difference) as shown in table (4).

Table (4) Hormonal findings in PCOS and control groups .

Hormone (mean ± SD)	PCOS	Control	P-value
LH	10.27± 4.2	4.9 ± 1.7	<0.0001
FSH	5.10 ± 1.2	6.20 ± 1.5	<0.046

The relationship between hormonal findings in PCOS patients with BMI is shown in table (5) .There was highly significant difference in mean serum LH concentration between overweight patients with BMI ≥ 25 KG/m² and normal weight BMI <25 Kg/m² while there was no significant difference in mean serum between these two group as shown in table (5) .

Table (5) Hormonal findings in overweight and normal weight PCOS.

Hormonal findings (mean±SD)	Overweight No.32	Normal weight No.18	P-value ANOVA
LH concentration (IU/L)	11.8 ± 2.9	6.3 ± 2.8	<0.0001*
FSH control (IU/L)	5.20 ± 3.3	5.10 ± 1.2	0.72 (NS)

The total antral follicle count : The total antral follicle count for PCOS group (37.8±11.2) was significantly higher than of the control group (12.0 ± 5.3) ,P-value <0.001

Doppler finding in the ovarian stroma : PCOS were significantly had higher total ovarian VI/FI/VFI than that of normal fertile group as shown in table (6).

Table (6) Total ovarian stromal power Doppler flow indices in PCOS and normal fertile control group .

Doppler indices (mean±SD)	PCOS	Control	P-value
Total ovarian VI%	3.69±0.103	2.65±0.09	0.023
Total ovarian FI(0-200)	57.52±47.09	51.26±20.01	0.001
Total ovarian VFI(0-200)	1.36±0.08	0.66±0.18	0.024

- The total ovarian stromal Doppler flow indices is significantly higher in PCOS with normal weight BMI < 25 Kg/m² than overweight BMI ≥ 25 Kg/m² show in table (7).

Table (7) Total ovarian stromal Doppler flow indices between PCOS with BMI < 25 Kg/m² and ≥ 25 Kg/m² .

Doppler indices	BMI < 25 Kg/m ²	BMI ≥ 25Kg/m ²	P-value
Total ovarian VI%	5.64±3.2	1.72±0.18	0.001
Total ovarian FI%(0-200)	60.76±53.01	48.60±47.67	0.001
Total ovarian VFI%(0-200)	1.75±0.61	0.45±0.06	0.001

In normal fertile control total ovarian VI/FI/VFI were not correlated with age of women and BMI .Age of women was negatively correlated with total AFC (r= 0.32 : p=0.001)and positively correlated with serum FSH concentration (r= 0.368 ; p < 0.001)only.

IV. Discussion

Polycystic ovarian syndrome has been a subject of intensive clinical and basic research over the past 15-20 years .The ultrasound criteria for diagnosing PCOS have evolved from simply increased ovarian dimensions to the recognition of a characteristic follicular pattern and ultrasound changes in the ovarian stroma

by color Doppler ultrasound . As all women were in reproductive age group had comparable age and BMI ,this eliminates the effect of these two factors on hemodynamic variables .

The frequency and percentage of hirsutism ,amenorrhoea and infertility were increased among overweight PCOS patients .This was consistent with the findings of Adem's⁽⁹⁾ et al and Arden's⁽¹⁰⁾

- Mean serum LH ,concentrations in PCOS was significantly higher than those of the controls ,but serum FSH was significantly lower in PCOS than normal groups .This goes with the finding of Battaglia et al.⁽¹¹⁾

- Mean serum LH was significantly higher in overweight than normal weight PCOS patients, while FSH showed no significant difference between normal and overweight PCOS patients as shown in table (4.5) .This goes with the finding of caro et al⁽¹²⁾ .

- Elevated serum LH concentration may be a cause of increased ovarian stromal blood flow in PCOS women through the action of prostaglandins (Aleem and Predanic, 1996)⁽¹³⁾ .A liner increase in the capillary cross-section area of the theca interna was observed after the LH surge in a spontaneay cycle and the increased in capillary area was attributed to the vasodilatation rather than increase in the number of vessels (Cavander and Murdoch ,1990)⁽¹⁴⁾

- In PCOS group, increased ovarian volume found in 28% of patients and the mean ovarian volume (13.7±4.6)cm³ was significantly higher than that of the controls (p< 0.001).

These values are within the range found by previous studies of Battaglia⁽¹¹⁾ et al Al-Rawiet al⁽⁵⁶⁾ ,Brano⁽¹⁵⁾ and Pan⁽¹⁶⁾ .

- Total ovarian 3D power Doppler indices were significantly higher in PCOS women than normal fertile controls but such significant difference in total ovarian 3D power Doppler indices could not be found between the two groups after adjusting for the difference in age of women .This goes with the findings of Jarvela et al (2002)⁽¹⁷⁾ ,who could not demonstrate that the stroma of polycystic ovaries was more vascularized than that of normal ovaries. It was also reported that performed 3D ultrasound examination during cycle days (8-16) in patients with PCOS and found that 14 patients with PCOS had a dominant follicle ,which would reduce the ovarian stromal blood flow.

In current study ,PCOS was defined in that study as the presence of ≥ 8 sub capsular follicles of 2.8 mm diameter in one 2D plane in ether of the ovaries. It was found significantly a higher ovarian stromal blood flow in normal weight PCOS women than their overweight counter patient .

The result, differed from that of Pan et al.(2002)⁽¹⁶⁾ ,different control group were used in these two studies . Fertile women with normal ovaries were selected while Pan et al .(2002) chosen infertile women with normal ovaries moreover Pan et al .(2002) found significant differences in age of women and BMI between in fertile women in the normal ovaries and PCOS but did not control these when comparing ovarian 3D power Doppler flow indices .

Ngetal (2004)⁽¹⁸⁾ study addressed the effect of age on ovarian stromal blood flow in normal fertile women revealed that total ovarian VI/FI/VFI were negatively correlated with age of women and positively correlated with total AFC . In PCOS women ,the relationship among the age of women ,total AFC and total ovarian VI/FI/VFI seemed to be different .Total ovarian VI/FI/VFI in PCOS women were positively correlated with BMI only but was not correlated with age of women and total AFC . The vascular impedance to blood flow was not influenced by total AFC and no correlation was found between serum hormone concentration (LH,FSH) and PI and RI of ovarian stromal vessels in PCOS women ,(Aleem and Predanic ,1996)⁽¹³⁾ .In contrast ,Dolz et al (1999)⁽¹⁹⁾ showed that the total AFC was directly related to the degree of intra ovarian flow pattern during color Doppler analysis .Only 2D ultrasound was use in these two studies (Aleem and Predanic ,1996, Dolz et al ,1999)⁽¹³⁾⁽¹⁹⁾ .

Ovarian stromal blood flow has been examined in assisted reproductive methods to predict the ovarian response to gonadotrophins (Zaidi et al ,1996,Bassel et al ,1997)⁽²⁰⁾⁽²¹⁾ . Ovarian stromal blood flow has been examined in assisted reproductive methods to predict the ovarian response to gon-adotrophins (Zaidi et al., 1996; Bassil et al., 1997; Kupesic and Kurjak, 2002. Popovic-Todorovic et al., 2003)⁽²⁰⁾⁽²¹⁾⁽²²⁾⁽²³⁾ . PCOS patients are more sensitive to the stimulation of gonadotrophins and are at higher risk of ovarian hyperstimulation syndrome (Aboulghar and Mansour, 2003)⁽²⁴⁾ . Increased ovarian stromal blood flow in PCOS patient, especially in normal weight PCOS women shown in current study, may lead to a greater delivery of gonadotrophins to the granulosa cells of the developing follicles. Therefore ; we should incorporate the assessment of the ovarian stromal blood flow in the management of PCOS women undergoing ovulation induction or ovarian stimulation in order to reduce the associated risk of ovarian hyper-stimulation syndrome. Further studies are still required .

V. Conclusions and recommendations

Conclusions:

1. Doppler assessment of vascular changes in the ovarian stroma can be evaluable addititional tool for diagnosis of polycystic ovary syndrome .
2. Overweight has a significant effect on blood flow in the ovarian stroma .

Recommendation :

1. Estimation of vascular changes in the ovarian stroma in patients with polycystic ovary syndrome could be useful in monitoring the response to different treatment modalities and may explain the response of failure of such treatment.
2. Further researches are needed to determine the value of hemodynamic changes in the ovarian syndrome in prediction of ovarian response to ovarian stimulation in ART technique and whether any association exists between ovarian hyper stimulation and these hemodynamic changes.

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