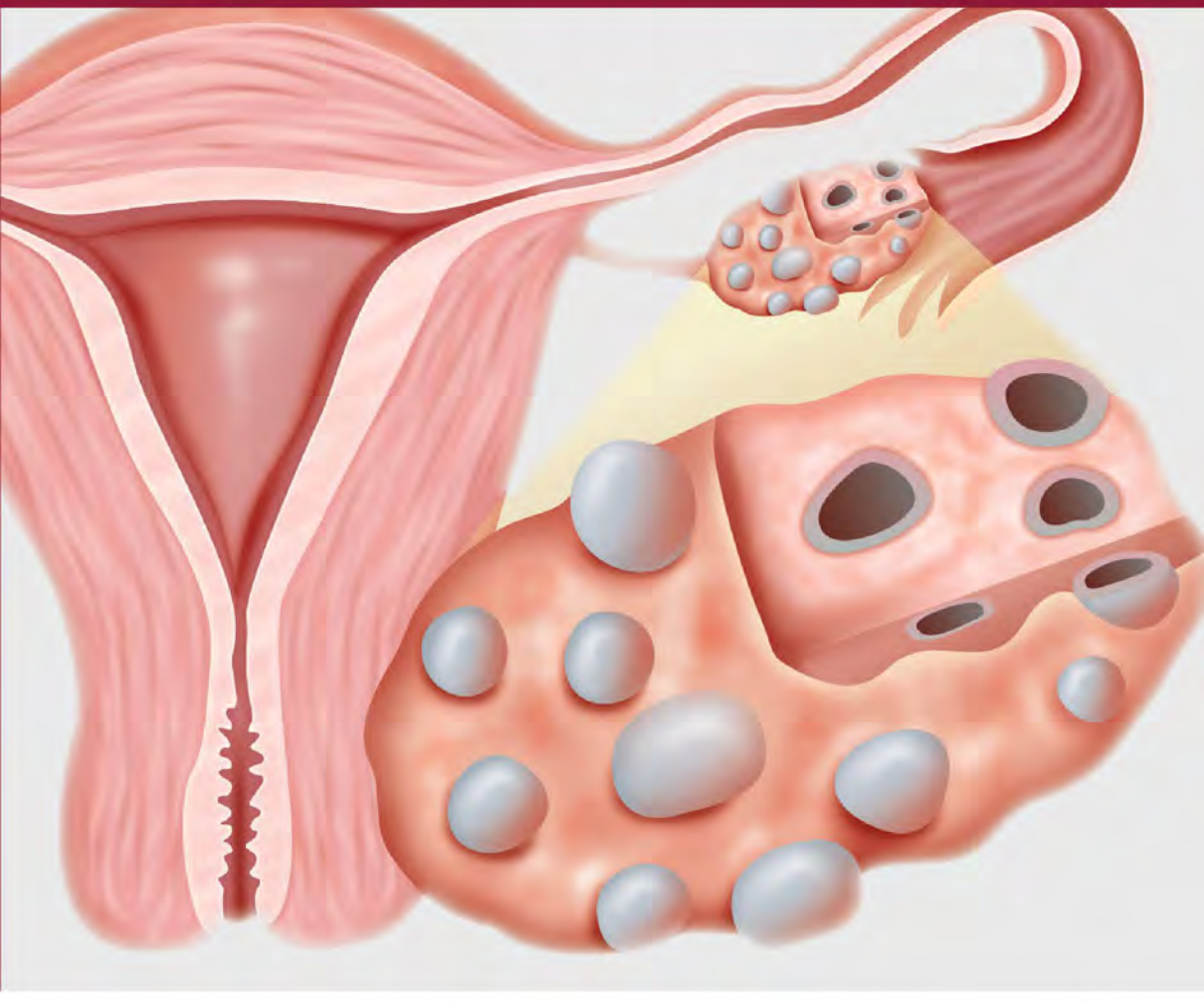
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Decoding Polycystic Ovarian Syndrome (PCOS)



Kanthi Bansal
Pooja Sharma Dimri
Apoorva Pallam Reddy

JAYPEE

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CHAPTER 4

Ultrasound in Polycystic Ovarian Syndrome

Sonal Panchal, CB Nagori

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a complex endocrine condition in which ovulatory dysfunction and androgen excess are cardinal features.[1] It affects about 10% of women in reproductive age.[2] Approximately 20–30% of women with infertility have polycystic ovaries and about half of these have signs and symptoms of PCOS. The earliest description of polycystic ovaries appears to date from 1845 as 'sclerocystic ovaries'.[3] Other names suggested are polyfollicular syndrome or ovarian dysmetabolic syndrome. Diagnosis of polycystic ovarian syndrome (PCOS) has always been a controversial and debatable issue. It has been defined in different ways by different college of thoughts European Society for Human Reproduction and Embryology (ESHRE)-American Society for Reproductive Medicine (ASRM), Androgen Society, etc. But as for the fertility group, most people still accept the ESHRE-ASRM consensus 2003 as a guideline. According to ESHRE/ASRM consensus 2003[4] the diagnosis of polycystic ovarian syndrome consists of at least two of the three following criteria:

1. Oligo and/or anovulation
2. *Hyperandrogenism:* Biochemical or clinical
3. Polycystic ovaries on ultrasound.

Therefore, the diagnosis of PCOS depends on clinical findings, laboratory testing and ultrasound.

TECHNIQUES FOR BASELINE SCAN OF OVARIES

B mode ultrasound assessment of the ovaries consists of assessment of ovarian diameters and volume and counting of antral follicles as quantitative and qualitative assessment of stromal density. Once the ovary is located, the probe is rotated to find out the longest diameter of ovary and is stored as one frame on a dual screen. Then probe is rotated 90° to get a true transverse axis of ovary. The largest longitudinal, transverse and AP diameter of the ovary is measured in centimetres (cm), and ovarian volume can be calculated by the formula (x x y x z x 0.523) **(Fig. 4.1)**.

Numbers of antral follicles are counted in ovary by performing a 2-dimensional sweep across the whole ovary. This method is very feasible and reliable when

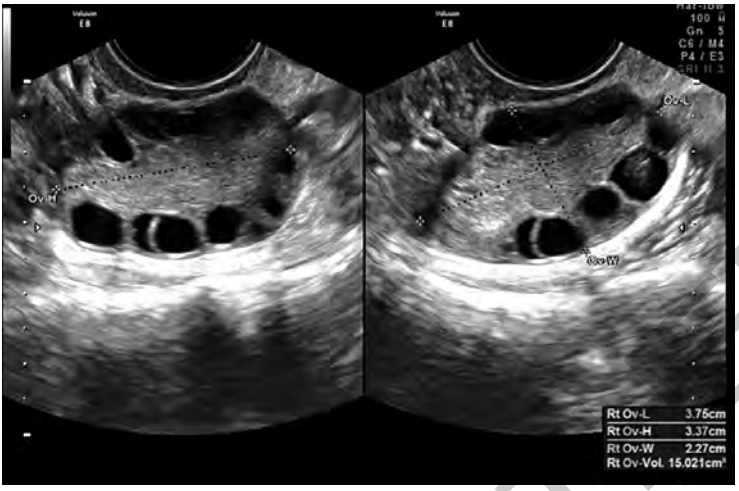


Fig. 4.1 Longitudinal and transverse sections of ovary

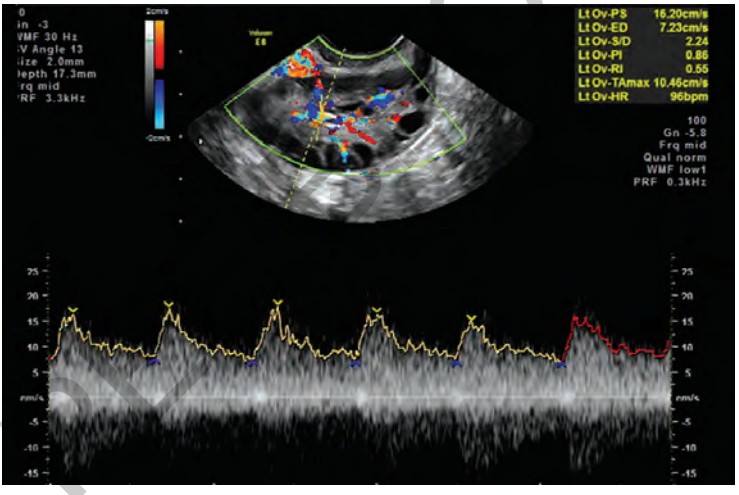


Fig. 4.2 Measuring ovarian stromal flows

number of antral follicles is approximately 10–15. But, when number of follicles is much more as in polycystic ovaries, the calculation using B mode scroll may be inaccurate.

Stromal echogenecity is compared with the echogenecity of myometrium, especially if ovary and uterus are at almost same depth from probe. Normally ovarian stroma is hypoechoic or isoechoic to myometrium, but in PCO it is hyperechoic as compared to the myometrium.

Color or power Doppler box is then placed on the ovary, so that whole ovary in included in colour box. Doppler is used to observe presence of vessels in ovarian stroma **(Fig. 4.2)**. The vessel that is close to any of the follicles is not a stromal vessel. If blood vessels are seen, pulse Doppler is used for quantitative assessment of the flows—intraovarian resistance index (RI) and peak systolic velocity (PSV).

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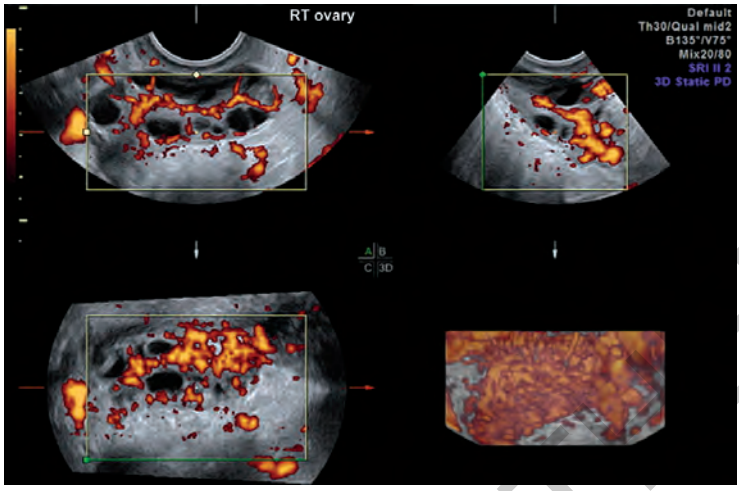


Fig. 4.3 3D power Doppler volume of ovary

For color Doppler pulse repetition frequency (PRF) is set at 0.3, wall filters lowest with optimum gains and balance settings. For pulse Doppler PRF is set at 1.3 usually but may be lowered of required and wall filters are set at 30 Hz, as stromal flows on baseline scan are low velocity flows. The vessel selected for interrogation is that which shows brightest color on color Doppler, though one may opt to take the readings for three different vessels that appear the brightest on color and take a mean of these values as stromal flows.

After having completed the Doppler study, volume studies are initiated. Three dimensional ultrasound provides a new method for objective quantitative assessment of follicle count, ovarian volume, stromal volume and blood flow in the ovary.[5] Power Doppler box is set to include whole ovary and then 3D volume of ovary is acquired **(Fig. 4.3)**. This volume of ovary is used to calculate ovarian volume, stromal volume, and to count number of antral follicles. Global vascular indices vascularity index (VI), flow index (FI) and vascularity flow index (VFI) may be calculated from the same ovarian volume.

Antral follicles can be counted by using inversion mode rendering **(Fig. 4.4)** or using a soft ware called Sono automated volume calculation (AVC) **(Fig. 4.5)**. Sono AVC is based on inversion mode rendering, but further color codes each follicle and also shows x, y and z diameters, mean diameter and volume of each follicle on result sheet **(Fig. 4.6)**. Region of interest (ROI) is selected to include the whole ovary in all three orthogonal planes on acquired ovarian volume and selecting the right/left ovary on the screen and initiating the soft ware will calculate the number of antral follicles. Postprocessing also may be done if the operator is not convinced with the calculations made by the scanner automatically.

A software called VOCAL (Volume calculation by computer) is used to define ovarian volume **(Fig. 4.7)**. VOCAL calculates volume of any structure by rotating it 180°. A rotating angle of 6°–30° can be selected. A circumference is drawn around the structure of interest at every step of rotation and at the end of 180°, total volume is calculated by the scanner computer. On this calculated ovarian volume with power Doppler, applying volume histogram assesses the global vascularity

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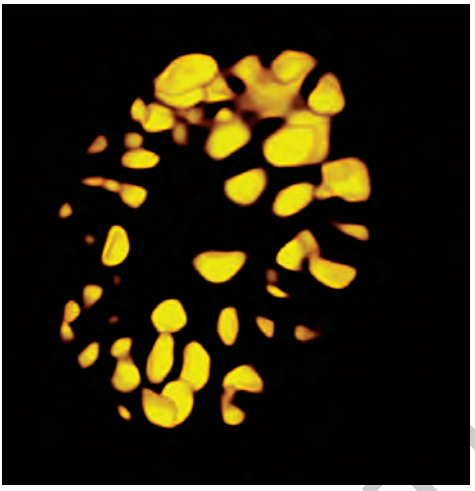


Fig. 4.4 Follicles as seen on inversion mode rendering

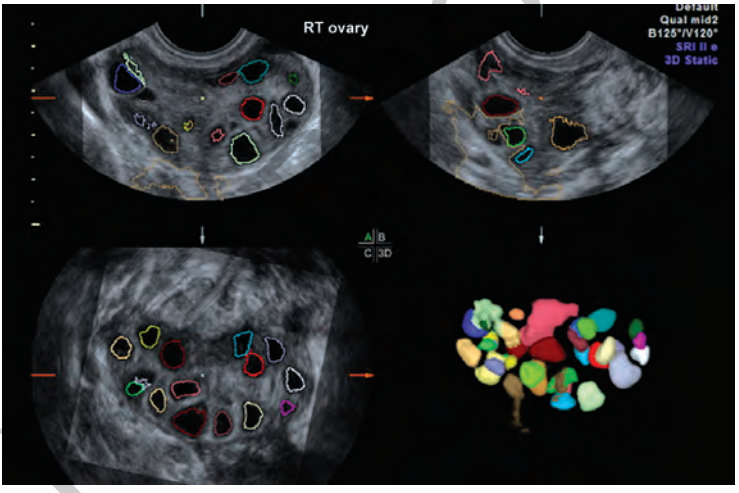


Fig. 4.5 Antral follicles as seen on Sono AVC

in the selected volume and presents it as vascularity index (VI), flow index (FI) and vascularity flow index (VFI) **(Fig. 4.8)**. VI is an index for abundance of flow in the selected volume, FI is an index for average intensity of flow in a selected volume and VFI is a perfusion index. Applying threshold volume on the same VOCAL calculated volume will define stromal volume when threshold is set to differentiate follicles from rest of the ovarian tissue **(Fig. 4.9)**.

ULTRASOUND CRITERIA OF POLYCYSTIC OVARY

As per ESHRE-ASRM 2003 consensus (Rotterdam criteria) polycystic ovary is defined as above 10 cc in volume and/or has more than 12 antral follicles. These seem to appear very clear and objective criteria for the diagnosis of polycystic

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Date of Exam: 22.04.2010 Page 3 / 4
Exam Type:

Name: NAYANA G 730 Pat. ID: D10878-10-03-04-5

Ovary: Left, Total#: 12						
Nr.	d(V) mm	dx mm	dy mm	dz mm	mn. d mm	V cm³
1	9.3	17.0	9.6	5.8	10.8	0.42
2	7.6	10.7	8.2	5.2	8.0	0.23
3	7.4	11.0	7.5	5.7	8.1	0.21
4	5.8	6.9	6.4	4.7	6.0	0.10
5	5.7	13.5	7.7	4.2	8.5	0.10
6	5.7	6.6	6.2	4.7	5.8	0.10
7	5.4	6.8	6.6	3.9	5.8	0.08
8	5.0	7.6	5.4	3.7	5.6	0.07
9	4.6	5.6	4.5	4.1	4.7	0.05
10	3.0	5.4	3.0	1.8	3.4	0.01
11	2.2	3.3	2.1	1.6	2.4	<0.01
12	2.1	3.2	2.3	1.7	2.4	<0.01

Ovary: Right, Total#: 10						
Nr.	d(V) mm	dx mm	dy mm	dz mm	mn. d mm	V cm³
1	13.1	20.7	15.6	7.9	14.7	1.18
2	9.7	13.6	11.7	6.5	10.6	0.48
3	8.6	10.7	9.0	7.0	8.9	0.33
4	7.2	10.1	7.2	5.5	7.6	0.20
5	7.0	9.6	6.6	5.8	7.3	0.18
6	5.1	7.2	5.7	3.4	5.4	0.07
7	4.7	6.2	5.2	3.4	4.9	0.05
8	4.2	5.7	4.6	3.1	4.4	0.04
9	3.2	3.6	3.4	2.8	3.3	0.02
10	3.1	3.7	3.0	2.7	3.1	0.02

Endo Thickness 4.89 mm

Pelvic Floor

funneling yes no

urethral kinking yes no

Fig. 4.6 Result sheet of Sono AVC

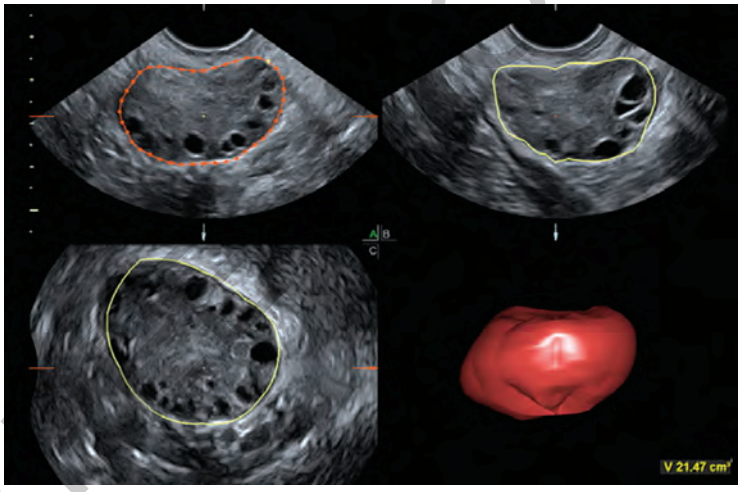


Fig. 4.7 Ovarian volume calculated by VOCAL

ovaries evidently. But then the problem is that ovaries of significant percentage of the patients diagnosed as polycystic ovarian syndrome do not fulfil these criteria on one hand and on the other hand several patients whose ovaries show these characters otherwise do not show any clinical signs and symptoms of polycystic ovarian syndrome. These mean both these ultrasound features need to be evaluated for their relevance to polycystic ovaries and polycystic ovarian syndrome.

OVARIAN VOLUME

'Enlarged spherical ovaries >10 cc on ultrasound, has shown good correlation between diagnosis of polycystic morphology and histopathological criteria for

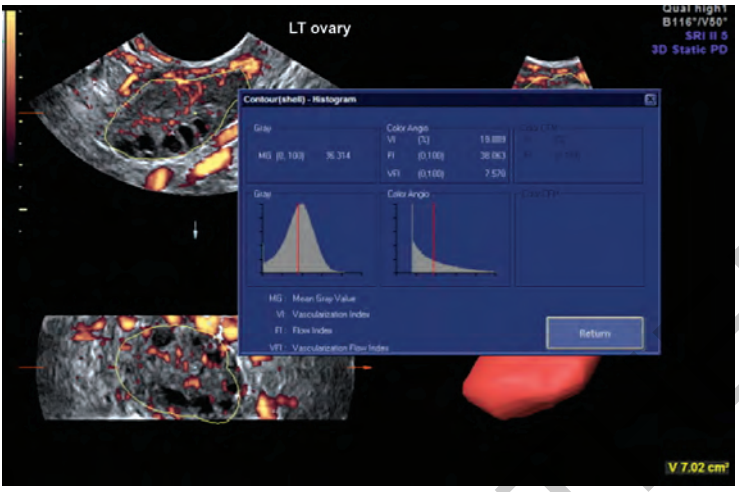


Fig. 4.8 3D power Doppler volume histogram of ovary

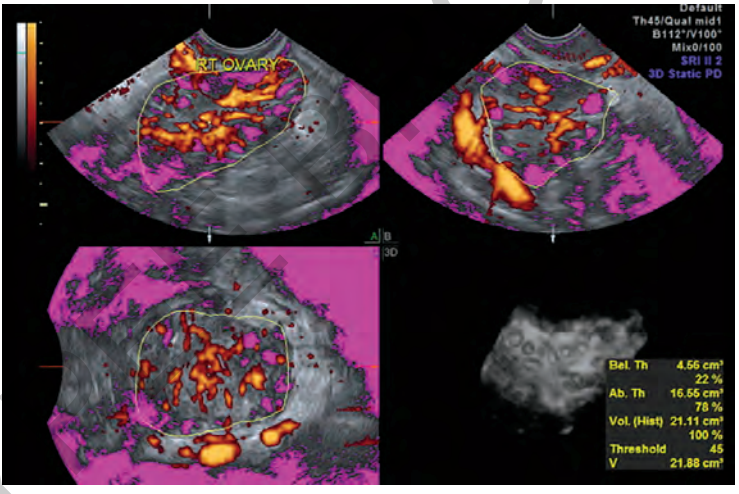


Fig. 4.9 Stromal volume calculated using threshold volme after VOCAL of ovary

polycystic ovaries.'[6] But the ovarian volume setting the threshold at 7 cc offered the best compromise between specificity (91.2%) and sensitivity (67.5%). In comparison, specificity and sensitivity were 98.2% and 45% respectively with threshold at 10 cc.[7] Ovarian volume 6.6 cc has shown 91% sensitivity and 91% specificity for polycystic ovarian syndrome.[8] Moreover, according to S. Kupesic, ovaries that are normal in volume can be polycystic as demonstrated by histological and biochemical studies (in 20%). Polycystic ovarian morphology has therefore been found to be a better discriminator than ovarian volume between polycystic ovarian syndrome and control women.[9] This discussion indicates that ovarian volume alone cannot be used as a parameter for diagnosis of polycystic

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ovaries. Therefore, morphological features of polycystic ovaries like number and arrangement of the follicles and stromal characteristics need consideration.

Antral Follicle Count

Antral follicle count (AFC) of 12/more (2–9 mm) has been used as a characteristic for polycystic ovaries according to Rotterdam criteria. Setting the threshold at 12 for 2–9 mm FNPO offered the best compromise between specificity (99%) and sensitivity (75%).[10]

The mean follicular number per ovary (FNPO) of follicles 2–5 mm in size was significantly higher in polycystic ovaries than in controls, while it was similar within 6–9 mm range. Within 2–5 mm range, significant relationship was found between FNPO and androgens but FNPO in the range of 6–9 mm was significantly and negatively related to body mass index and fasting serum insulin level.[11] Obesity and IR may enhance follicular excess by dysregulation of AMH through pathway of hyperandrogenemia.[12]

Though a study by Dewailly et al. in 2011 shows that FNPO > 19 had a sensitivity of 81% and specificity of 92% for PCO. And adding AMH >35 pmol/L as an additional parameter will increase the sensitivity to 92% and specificity to 97%.[13] The higher number is because of increased resolution of new scanners to identify follicles smaller than 2 mm. According to a study in 2013, an average value of 26 or more follicles per ovary is a reliable threshold for detecting polycystic ovaries in women with frank manifestation of PCOS. Sensitivity and specificity for diagnosis of PCOS for FNPO (26) was 85% and 94% and for OV (10 cc) was 81% and 84%. But the same study has also quoted that the lower follicle threshold may be required to detect milder variants of the syndrome.[14]

Moreover, polycystic ovaries with advancing age may show lesser number of follicles. AFC also thus cannot be used as the characteristic of polycystic ovaries. This indicates even antral follicle count cannot be diagnostic of PCO. Moreover, PCOM (size and follicle number) though is consistently found in PCOS patients, it may be seen in 25% of normal controls also.[15]

Stromal Abundance

Though not included in the Rotterdam criteria, stromal abundance is an important feature of PCO. Hyperdense stroma and stromal abundance have been described with polycystic ovaries since the first definition of the syndrome by Stein-Levanthal. Patients having long standing PCOS and long standing anovulation have denser stroma. Most severe form of stromal abundance, hyperthecosis, presents large ovaries with almost absence of cystic lesions: solid looking ovaries **(Figs 4.10A and B)**.

PATHOPHYSIOLOGY AND ULTRASOUND FINDINGS

Polycystic ovaries are a result of chronic anovulation. Mildly raised androgen levels, in early follicular phase in PCOS patients, leads to recruitment of several follicles. It is believed that androgen leads to early follicular development, but further progression is not normal due to hyperinsulinemia and/or other metabolic influence linked to obesity.[16] All these follicles do not become dominant.

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Fig. 4.10A Solid looking polycystic ovary

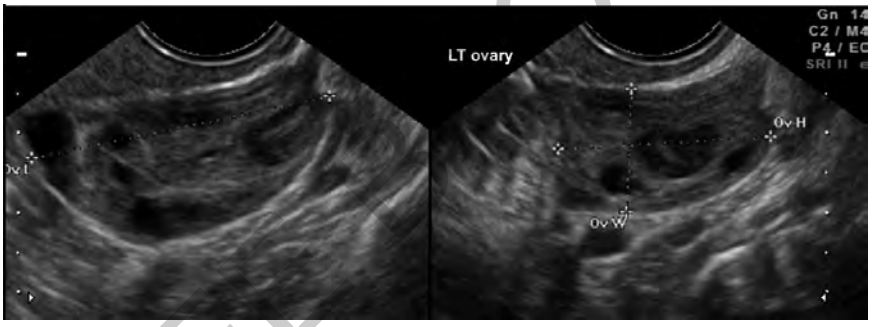


Fig. 4.10B Normal ovaries

This is because there is partial conversion of androgen to estrogen and there is also cumulative effect of minimal estradiol production by multiple follicles leading to negative feedback for FSH and positive feedback for LH. All these factors lead to maturation arrest of these follicles and premature luteinization leading to atresia. These luteinized atretic follicles ultimately contribute to the stroma leading to stromal abundance. Even when the cycle is ovulatory, in PCO patients the recruited antral follicles are more resulting in increase in atretic follicles which contribute to higher stromal density.

Stromal abundance can present as increased echogenecity because stroma is densely packed.

ASSESSMENT OF STROMAL ABUNDANCE

Polycystic ovaries show a hyperechoic stroma but assessment of this hyperechogenecity is subjective not only to the operator but also to equipment settings.[17, 18] Though ovarian stroma can be stamped as hyperecoic when it is more echogenic than myometrium. This hyperechogenecity is especially useful for its

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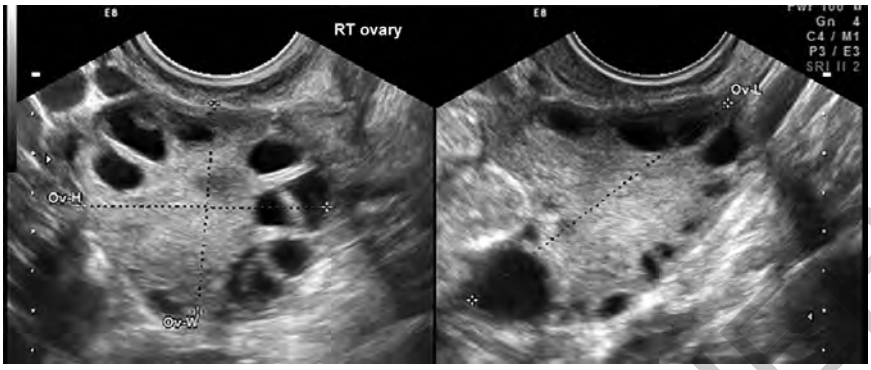


Fig. 4.11A Dense hyperechoic stroma of polycystic ovary

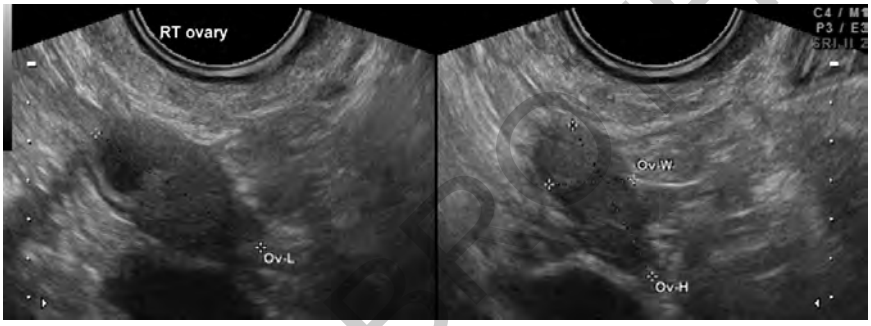


Fig. 4.11B Low reserve ovaries: small size and <3 antral follicles

differentiation from multicystic ovaries that are normally seen in adolescence and have multiple follicles, of variable sizes and nonhyperechogenic stroma. Increased stromal echogenecity for diagnosis of PCO has a sensitivity of 94% and specificity of 90%[19] **(Figs 4.11A and B)**.

But recent studies have shown that mean stromal echogenecity or total ovarian echogenecity as measured by histogram are not different in controls and PCOS. But Stromal index (stromal echogenecity/total ovarian echogenecity was significantly higher in PCOS than controls.[20]

Not only the echogenecity but also total stromal volume is also increased in polycystic ovaries. This can be measured on ultrasound as stromal area in the most longitudinal section of ovary on 2D US. As for echogenecity, this also has been found to be sensitive for diagnosis of polycystic ovarian disease. Stromal area : 4.6 cm^2 has 91% sensitivity and 86% specificity for diagnosis of PCOS. The ovarian area can also be measured in this same section. Ovarian area of 5.3 cm^2 has 93% sensitivity and 91% specificity for diagnosis of PCOS.[21]

But the ratio of stromal area to ovarian area has been found to be more reliable. **(Box 4.1)** stromal area/ovarian area (S/A) ratio also has a strongest correlation with S. androgens especially testosterone and androstenedione and insulin.[22] Stromal area/ovarian area ratio of > 0.34 is diagnostic of PCOS and can be correlated with S. androstenedione. Mean stromal area/mean ovarian area ratio of 0.34 and above also has a specificity of 100% in the same study.[23]

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BOX 4.1 Sensitivity for diagnosis of polycystic ovarian syndrome

• Ovarian volume	13.21 cc	21%
• Ovarian area	7 cm^2	4%
• Stromal area	1.95 cm^2	62%
Stromal/total area	0.34	100%

TABLE 4.1 Ovarian volume on sonography

Ovarian volume	*Right*	*Left*
Normal	5.3 ± 2.0 cc	5.7 ± 1.6 cc
PCOD	12.2 ± 4.7cc	10.5 ± 3.6 cc[20]

STROMAL ABUNDANCE AND HORMONAL IMPLICATIONS

The proportion revealed between the stroma and the ovary surface in the median section (S/A ratio) had been indicated as a reliable marker for hyperandrogenism. Hyperandrogenic subjects showed higher values of stromal area and S/A ratio, with no difference in ovarian volume and ovarian area.[24] S/A has also been found to be the best significant predictor of elevated androgen and testosterone levels. This parameter may be used in routine clinical practice for improving US diagnosis of PCOS.[23] Stromal to ovarian ratio is lower in normal females. Stromal abundance may be better assessed by stromal volume than with stromal area. Stromal volume can be assessed by using threshold volume on vocal calculated ovarian volume.

3D ultrasound provides a new method for objective quantitative assessment of follicle count, ovarian volume, stromal volume and blood flow in the ovary.[25] Ovarian volume calculation by 3D US has been found to be useful over 2D evaluation of ovarian long diameter or volume by 2D US.

Right ovary is larger in PCOS patients, whereas left ovary is larger in normal patients **(Table 4.1)**.

Theca cells of PCOS women hyper respond to gonadotrophins (LH) and produce excess androgens. This is due to an escape of their normal down regulation to gonadotrophins. This dysregulation is linked to excess of insulin and IGF-1. Hyperinsulinemia is a key factor to the pathogenesis of PCOS. Insulin augments LH stimulated androgen production by stromal cells. Androgen in turn causes proliferation of stromal and theca cells. This leads to increased stroma in the PCO. Stromal volume was positively correlated with serum androstenedione concentrations in patients with polycystic ovarian syndrome.[26] Increased androstenedione secretion as shown earlier is due to hyperinsulinemia.[27]

A prospective study of 50 polycystic ovarian syndrome patients with 50 non PCOS patients was done over a period six months with clinical examination, baseline ultrasound scan with 2D and 3D ultrasound and fasting and postprandial insulin levels. Group A: 50 patients with normal ovulation, no hirsutism, normal menstrual cycle and normal ovarian size and group B: 50 patients with PCOS, according to Rotterdam criteria. Age range of patients for both groups was

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between 25 and 35 with mean age for group A was 30.4 years, mean age for group B was 29.7 years. Mean BMI in both the groups was 28, range from 25–32 kg/m^2. Patients with BMI < 25 kg/m^2, proven diabetes mellitus, other endocrinological derangement thyroid, adrenal, etc.), follicles larger than 9 mm or residual corpus luteum on day 3 and ovarian mass lesions (cystic/solid) were excluded from the study cohort. Ovarian volume and stromal volume were calculated by applying threshold volume to the VOCAL calculated volume. The threshold was set to differentiate follicles from stroma. Fasting and postprandial insulin levels were checked for all on the same day. Insulin estimation was done by chemiluminescence method. For postprandial insulin measurement patient was given 75 g of glucose after fasting blood sample and then blood sample for PP insulin was taken after 2 hours. The average values of ovarian and stromal volumes and AFC was checked for both ovaries in each patient. Two-tailed Pearson correlation was checked for ovarian volume, stromal volume and stromal volume to ovarian volume ratio with fasting insulin and postprandial insulin level each. Ovarian and stromal volumes were compared and correlated with both fasting and postprandial insulin levels. Positive correlation was seen between ovarian and stromal volumes and fasting and postprandial insulin levels. With Pearson correlation significance level of 0.01 (2-tailed) the correlation for:

- Ovarian volume to fasting insulin is 0.651
- Ovarian volume to PP insulin is 0.409
- Stromal volume to fasting insulin is 0.736
- Stromal volume to PP insulin is 0.428

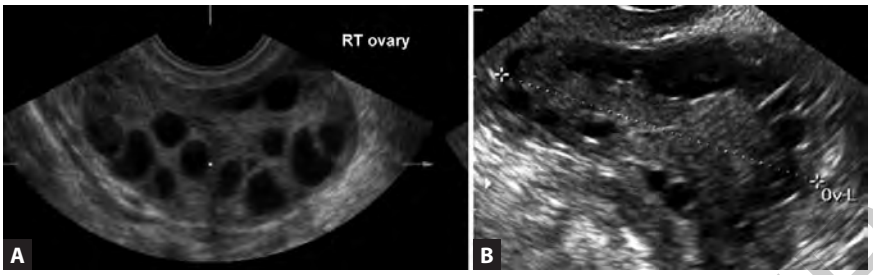
Stromal and ovarian volumes and AFC correlated significantly well with the fasting insulin levels, more than with postprandial insulin levels in obese PCOS patients. It is the stromal volume that can be best correlated with fasting insulin levels followed by ovarian volumes and AFC.[28]

A similar study has also been done earlier. Study by Pache et al. has shown that the degree of insulin resistance can be correlated with ovarian volume and stromal echogenecity.[29] A retrospective observational study done with 50 PCOS patients showing correlation between ovarian and stromal volumes with fasting and postprandial insulin levels. But in this study neither BMI, nor age group were defined. In PCOS patients a strong and similar correlation was seen between ovarian and stromal volumes to fasting and postprandial insulin levels.

ARRANGEMENT OF FOLLICLES

The antral and atretic follicles get arranged peripherally or are dispersed in the stroma and thus may categorize polycystic ovary as peripheral and general cystic pattern. In peripheral cystic pattern there is typical garland like arrangement of follicles and in generalized cystic pattern, the follicles can be seen throughout the ovary[30] **(Figs 4.12A and B)**. Though one school of thought believes that peripheral cystic pattern polycystic ovaries and generalized cystic pattern polycystic ovaries have different histopathological and endocrine bases.[31] According to another theory, the ovary is multifollicular in adolescence. Follicles that are < 9 mm are exposed to LH and undergo atresia and make stroma denser giving rise to generalized cystic polycystic ovary. As the disease progresses, gradually the follicles in the central part of the ovary, in the effort and process of recruitment

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Figs 4.12A and B (A) Generalized polycystic pattern; (B) Peripheral polycystic pattern: polycystic ovary

reach the periphery or are pushed out to periphery by expanding stroma. These undergo atresia ultimately leading to peripheral cystic polycystic ovary.[25,32] So multicystic ovary to generalized cystic PCO, and then to peripheral cystic PCO is a process of evolution of the disease.

Stromal Vascularity

Based on 3D US, women with PCOS have an increased stromal volume and vascularity. Even with same echogenecity, PCOS has more stromal flow. In polycystic ovaries even on 3rd day of the cycle intraovarian stromal flow is seen and they have moderate to low resistance flow with RI of 0.50–0.58.[33]

Elevated LH levels may be responsible for increased stromal vascularization due to neoangiogenesis, catecholaminergic stimulation and leukocyte and cytokine activation. This vascularity is inversely related to LH/FSH ratio. Tonic secretion of LH in early follicular phase in PCOS is also associated with theca and stromal cell hyperplasia and consequent androgen production. This androgen hypersecretion is responsible for not only increased follicular recruitment but also for vasoconstrictive effect on the uterine arteries. This effect is thought to be due to activation of specific receptors in arterial walls and collagen and elastin deposition in smooth muscle cells. Uterine artery PI is > 3 and sometimes the diastolic flow is absolutely absent. Even in later phases of the cycle this effect continues. This leads to inadequate perfusion of the endometrium and is thought to be responsible for blastocyst implantation failure and high abortion rate in PCOS.

Stromal Vascularity and Hormonal Implications

Looking to the hormonal correlation with the Doppler findings, it is evident that in patients in whom the hormonal milieu is worse the Doppler findings are more prominent. As discussed earlier the peripheral cystic pattern of PCO is an advanced stage then generalized cystic pattern and so the intraovarian vascularity and uterine artery resistance are more in peripheral polycystic ovaries than in generalized polycystic ovaries. In 22% of GCP PCO intraovarian vessels are not recognized.[34] Stromal vascularity is significantly higher in women with PCOS who are hyperandrogenic and lean rather than normoandrogenic and obese.[35] Fertile controls and PCOS women had similar total ovarian 3D

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Decoding
Polycystic Ovarian Syndrome (PCOS)

This is a comprehensive book about the common condition of polycystic ovarian syndrome (PCOS), affecting a vast majority of women. There have been a lot of changes in the understanding of etiology, manifestation and management of PCOS over the years. This book tries to capture all the aspects in exhaustive detail. The chapters have been penned by experts, who have shared their knowledge and experience. The information flows from basic to specific and is organized into sections, which makes it a pleasant reading. The text is supported with the scientific evidences, references, illustrations, diagrams, tables and boxes, to simplify and enhance the clarity.

It is a very useful book for the postgraduates, and will serve as a reference for the practitioners, enabling them to understand the complex condition and, in turn, treat the patients in a more holistic fashion.



Kanthi Bansal MD DGO FICOG is the Director of Safal Fertility Foundation and Bansal Hospital, Ahmedabad, Gujarat, India. This pioneering center is known for its high quality, success rates and ethical standards in the field of infertility. She runs the dedicated and unique polycystic ovarian syndrome (PCOS) and endometriosis clinic, where many adolescent girls suffering from PCOS and infertility are being suitably advised and managed. She has the distinction of producing the first IVF-ET baby of Gujarat. She has given the first single mother to India.

She is a visiting specialist to various centers in India for difficult infertility cases and repeated failed IVF cases. She has the centers at Ahmedabad, Bengaluru, Varanasi and Allahabad, India.

Publication of books has been very close to her heart, and she feels it is one of the best ways to propagate knowledge to the practicing doctors and postgraduates. Considering the same, she has published 10 books till date in the field of infertility management. She has been invited as a faculty to many international and national conferences, and to give orations at various organizations.

She is the Editor of the Journal of Endometriosis and Pelvic Pain Disorders, a Member of the National Advisory Board of the Journal of Human Reproductive Sciences, and a peer reviewer of renowned journals such as the Journal of Obstetrics and Gynecology of India (JOGI), and Journal of Reproductive and Stem Cell Biotechnology (JRSCB). She is the Organizing Co-Chairperson of the AICOG, 2017. She was the Chairperson of Endometriosis Committee, SAFOG, 2016; Chairperson of Endometriosis Committee, FOGSI (2011–2014); Joint Secretary, the Indian Society of Assisted Reproduction (ISAR); and the Vice President, Gujarat Chapter, ISAR.



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