PCOS - An Updated Overview and Current Trends in Ultrasound Imaging

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ABSTRACT

BACKGROUND

Poly-Cystic Ovary Syndrome (PCOS) is a widespread complex endocrine disorder of women in the reproductive age group. It may present as mild menstrual disorder which affects metabolic functions severely. PCOS results in chronic anovulation. There is abnormal production of oestrogen and androgens due to imbalance of LH and FSH. LH/FSH ratio is elevated. Women with PCOS are prone to insulin resistance, type II diabetes mellitus, obesity and infertility, psychological disorder like depression, cardiovascular diseases, and endometrial and ovarian cancer. Presenting symptoms may be acne and hirsutism. To define PCOS, there has to be two of the three following features- menstrual irregularity, clinical and biochemical evidence of androgen excess and multiple cysts in the ovary.

PCOS is manifestation of various interrelated mechanisms; it may not be known which if any, is primary. Probably PCOS is common end result of different mechanisms and pathologies. There may be pituitary dysfunction resulting in high serum LH and high serum prolactin. Menstrual cycles may be anovulatory presenting as oligomenorrhea, secondary amenorrhea, cystic ovaries and infertility. Patients are prone to obesity which leads hyperglycaemia and elevated oestrogen and sometimes insulin resistance leading to type II diabetes mellitus, dyslipidaemia and hypertension.

However, despite significant progress in understanding the pathophysiology and diagnosis of the disorder, over the past 20 years, the disorder remains underdiagnosed and misunderstood. The diagnostic criteria are indefinite with numerous intricacies, PCOS remains a challenging area of research. The aim of this article is to review the present status and formulate an interesting clinically relevant research direction with emphasis on ultrasound imaging in diagnosis of polycystic ovary with stress on various aspects of 3D, colour & power Doppler study that is essential to move the field of PCOS forward.

KEYWORDS

PCOS, Poly Cystic Ovary, Ultrasound Imaging

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INTRODUCTION

PCOS is a heterogeneous disorder of functional androgen excess, detected clinically or by laboratory testing, with ovulatory dysfunction and polycystic ovarian morphology also affecting a large proportion of these patients. PCOS is a diagnosis of exclusion, with other androgen excess or related disorders to be ruled out. The diagnosis of PCOS is based on well-defined criteria, at present for utilization in clinical practice there are three major sets of diagnostic criteria available. Regional prevalence of PCOS depends on diagnostic criteria utilized and ethnicity. Targeted screening in women with isolated symptoms of acne, hirsutism, and irregular menstrual cycles should be practiced.

REVIEW OF LITERATURE

Diagnostic Criteria

Stein and Leventhal originally described the combination of oligo-ovulation and hyperandrogenism[1] in the year 1935. Description of the syndrome was based upon case reports in the literature. Abnormal uterine bleeding was the most common symptom associated with the condition. Over time, multiple efforts have been made to better characterize this syndrome to allow for better appreciation of this complex entity. For clinicians there are three major sets of diagnostic criteria in diagnosing PCOS.

The first set of criteria was proposed by National Institutes of Health (NIH) in Bethesda, Maryland, in 1990, but has been replaced in clinical practice by the relatively recently proposed Rotterdam criteria.

To date, three major criteria have been proposed, with other investigators proposing modifications of these. We will review the criteria arrived at a NIH/NICHD expert conference sponsored in 1990,[2] that proposed by an expert conference of the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) in 2003,[3] and that proposed by the Androgen Excess Society in 2006.[4]

National Institute of Health Criteria

The first useful definition of PCOS arose from the proceedings of an expert conference sponsored by the US National Institutes of Health (NIH) in April 1990. Participants were surveyed, and tabulation of the results indicated the features of PCOS were:

a) Hyperandrogenism and/or hyperandrogenaemia,
b) Chronic anovulation and
c) Exclusion of related disorders such as hyperprolactinemia, thyroid disorders, and congenital adrenal hyperplasia.[5] Polycystic ovaries were suggestive, not diagnostic, of the syndrome.

Three principal phenotypes of PCOS are recognized using the NIH 1990 criteria, including women with: (a) hirsutism, hyperandrogenaemia, and oligo-ovulation, (b) hyperandrogenaemia and oligo-ovulation, or (c) hirsutism and oligo-ovulation. Alternatively, fasting insulin levels were highest in patients with hirsutism, hyperandrogenaemia, and oligo-ovulation, and lowest in those women with oligo-ovulation and hirsutism only.

ESHRE/ASRM (Rotterdam) Criteria

Another expert conference was organized in Rotterdam in May of 2003 in part sponsored by ESHRE and ASRM. The proceedings of the conference noted that PCOS could be diagnosed, after the exclusion of related disorders, by two of three features:[6]

1. Oligo and/or Anovulation (up to 90% patients) - Oligomenorrhea with less than eight periods per year or amenorrhea with no periods for more than three months.
2. Hyperandrogenism (seen in approx. 60% patients) - Assessed clinically by: hirsutism, acne, alopecia or biochemically: raised circulating androgens.
3. Polycystic ovaries on Ultrasound (US): ovarian volume 10 cc or more and/or has >10 follicles of 2-9 mm in diameter per ovary. The prevalence of Polycystic ovary in PCOS patients is estimated to be 17-33%.

As for the NIH 1990 criteria, other disorders should be excluded. It should be noted that these recommendations did not replace the NIH 1990 criteria; rather they expanded the definition of PCOS.

AES 2006 Criteria

Because of the continuing controversy regarding the definition of the PCOS, the AES, an international organization dedicated to promoting knowledge and original clinical and basic research in every aspect of androgen excess disorders, charged a Task Force to recommend an evidence-based definition for PCOS, whether already in use or not, to guide clinical diagnosis and future research. The Task Force, after review of all available published data, proposed that PCOS should be diagnosed by the presence of three features: (a) androgen excess (clinical and/or biochemical hyperandrogenism), (b) ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology), and (c) exclusion of other androgen excess or ovulatory disorders.[6]

Diagnosis of PCOS

The diagnosis of PCOS needs: (a) to assess features suggestive of PCOS are present and (b) to exclude related androgen excess or ovulatory disorders. It will depend on chosen diagnostic criteria.

Assess whether Features of PCOS are Present

Features suggesting PCOS are: (a) long-term menstrual dysfunction or irregularity, suggestive of chronic ovulatory

dysfunction, (b) dermatologic signs suggestive of hyperandrogenism, like hirsutism, acne or alopecia, and (c) polycystic ovarian morphology on ultrasonography.

All women with menstrual dysfunction should be reviewed for hyperandrogenism presenting as acne, unwanted hair growth, scalp hair shedding or loss with a more in-depth evaluation for PCOS. Clinical signs of insulin resistance (e.g., acanthosis nigricans) needs more thorough evaluation for PCOS (and metabolic syndrome). Finally, in a patient with menstrual dysfunction, assessment of polycystic ovaries on Ultrasonography is needed to exclude PCOS.

Exclusion of Other Androgen Excess or Ovulatory Disorders

Diagnosis of PCOS needs exclusion of other disorders like 21-hydroxylase deficient NCAH (by a basal and/or stimulated 17-hydroxyprogesterone), androgen-secreting neoplasms (by history and clinical exam and appropriate studies in selected patients), adreno cortical hyperactivity (by clinical exam and appropriate testing), and drug-induced hyperandrogenism.

Laboratory and Radiological/Sonographic Evaluation

Women should undergo measurement of circulating TSH, prolactin, 17-HP levels. Androgen levels: measurement of circulating androgen levels (generally total and free testosterone, and DHEAS), assessment of TSH, prolactin, and 17-HP levels required. Ovarian Ultrasonography in assessing PCO is essential.

DIFFERENTIAL DIAGNOSIS

PCOS remains a diagnosis of exclusion, and it is useful to exclude other potential aetiologies that can present with the triad of polycystic ovaries, hyperandrogenism, and chronic anovulation. For instance, chronic anovulation alone may be due to failure or dysfunction of the hypothalamic-pituitary axis or to frank ovarian failure, states of steroid deficiency without androgen excess. In series of adult women presenting with amenorrhea alone, PCOS is present in about one-third of these patients,[7] but rises to 70% or more when other symptoms such as hirsutism are considered.[8] Other than PCOS, other potentially serious causes of hyperandrogenism include such disorders as Cushing's syndrome and an androgen-secreting tumour.[9] These disorders are acquired and are often preceded by a period of normal menses without symptoms of hyperandrogenism. In contrast, PCOS presents in the post menarche and tends to affect women throughout much of their reproductive life. Androgen secreting tumours are rare in this age group, are usually ovarian in origin, tend to have markedly elevated circulating androgen levels above the usual disorder that can present peripubertally in a similar indolent fashion as PCOS is 21-hydroxylase (21-OH) deficient non classic congenital adrenal hyperplasia (NCAH), also known late-onset congenital adrenal hyperplasia. These disorders account for 5-10% of all women with androgen excess.[10]

Normal Ovary

Normal ovary has a relatively homogeneous echotexture with a central, more echogenic medulla. Well-defined, small anechoic or cystic follicles may be seen peripherally in the cortex (Figure 1). The appearance of the ovary changes with age and with the phase of the menstrual cycle. During the early proliferative phase, many follicles that are stimulated by both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) develop and increase in size until about day 8 or 9 of the menstrual cycle. At that time one follicle becomes dominant, destined for ovulation, and increases in size, reaching up to 2.0 to 2.5 cm at the time of ovulation. The other follicles become atretic. A follicular cyst develops if the fluid in one of these non-dominant follicles is not resorbed. Following ovulation, the corpus luteum develops and may be identified sonographically as a small hypoechoic or isoechoic structure peripherally within the ovary. The corpus luteum involutes before menstruation.

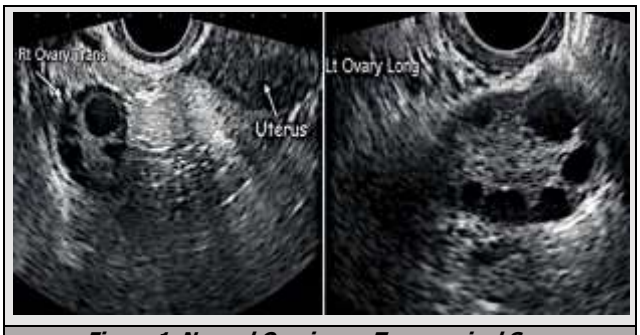

Figure 1. Normal Ovaries on Transvaginal Scan

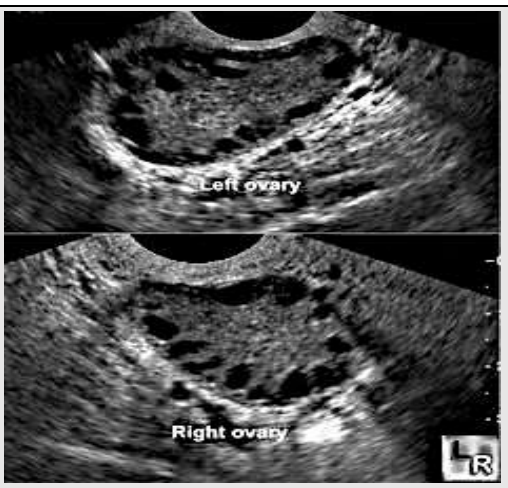

Figure 2. PCO with Cysts Arranged at the Periphery

Because of the variability in shape, ovarian volume has been considered the best method for determining ovarian size. The volume measurement is based on the formula for a prolate ellipse (0.523 x length x width x height). Studies have shown that ovarian volumes are larger than previously thought. In the first 2 years of life. The mean ovarian volume is slightly greater than 1 cc in the first year and 0.7 cc in the

second year. The upper limit of normal has been reported as 3.6 cc in the first 3 months, 2.7 cc from 4 to 12 months, and 1.7 cc in the second year. Ovarian volume remains relatively stable up to 5 years of age and then gradually increases up to menarche when the mean volume is 4.2±2.3 cc, with an upper limit of 8.0 cc.[11] In 87% pre menarchal & neonatal ovaries small follicles or cysts are present.[12] In adult menstruating female a normal ovary has a volume as large as 22 cc. In one study by transvaginal scan reported a mean volume of 6.8 cc with upper limit of 18 cc.[13]

Following menopause, the ovary atrophies and follicles disappear over the subsequent few years with ovary decreasing in size.[14]

Ultrasound Technique

This scan is done on day 2-3 of menstrual cycle. It was done by transvaginal route using a transducer with 8 MHz frequency. If trans-abdominal ultrasound scan is used, AFC (Antral Follicle Count) is not to be used as criteria to diagnose PCO (Polycystic ovary). Doppler is used to assess ovarian stromal vascularity. Spectral Doppler is used for quantitative assessment of the flows by measuring intra-ovarian resistance index (RI) and peak systolic velocity (PSV). For colour doppler, pulse repetition frequency (PRF) is set at 0.3, wall filters are lowest, with optimum gains and balance settings. For pulse Doppler PRF around 0.9-1.3 is set, and wall filters are set at 30 HZ as stromal flows on baseline scan are usually low-velocity flows.

Ovarian Volume is calculated by formula for ellipse (0.523 x length x width x height). Measure the largest longitudinal, transverse, and AP diameter of the ovary in centimeters (cm). 3D US provides a new method for objective quantitative assessment of follicle count, ovarian volume, and blood flow in the ovary.[15]

Volume histogram gives values of 3D power Doppler indices, VI (Vascularization Index), FI (Flow Index) and VFI (Vascularization-Flow Index). VI indicates 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.

Stromal Volume

Applying threshold volume on the same VOCAL (Virtual Organ Computer Aided Analysis) calculated volume will define stromal volume when threshold is set to differentiate follicles from rest of the ovarian tissues. When AFC is much more, as typically seen in polycystic ovaries, 3D US and advanced calculation software. Sono 3D volume acquisition of the ovary and volume calculation by VOCAL (virtual organ computer - aided analysis for volume) is a more reliable technique especially when the ovarian shape is not round or oval.

Antral Follicle Count (AFC)

Antral follicles are counted in the whole ovary by taking a 2D sweep across whole ovary and counting the follicles by eyeballing. But AFC is more, as typically seen in polycystic ovary 3D US & advanced calculation software Sono AVC is required. To use Sono AVC, region of interest is selected to include the whole ovary in all three orthogonal planes on acquired ovarian volume. The count is done automatically but post processing may be required. Automated 3D measures do provide reliable information on follicle number and size and appear to be more reflective of ovarian reserve and response.[16]

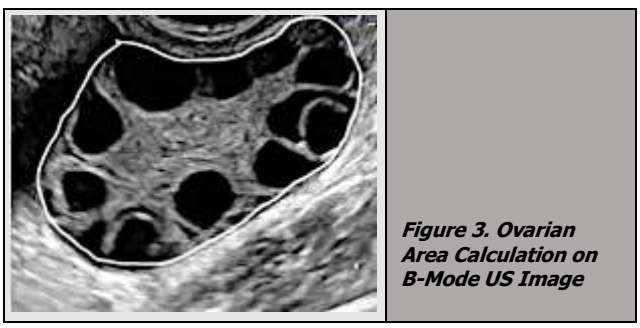

Figure 3. Ovarian Area Calculation on B-Mode US Image

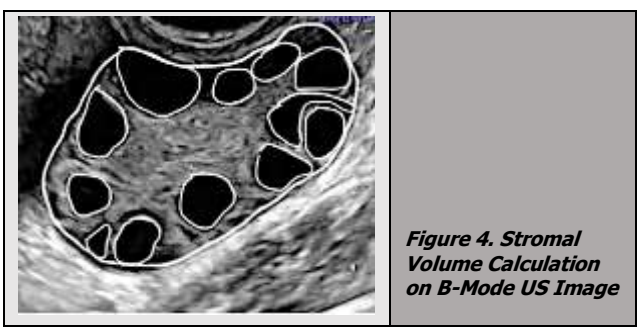

Figure 4. Stromal Volume Calculation on B-Mode US Image

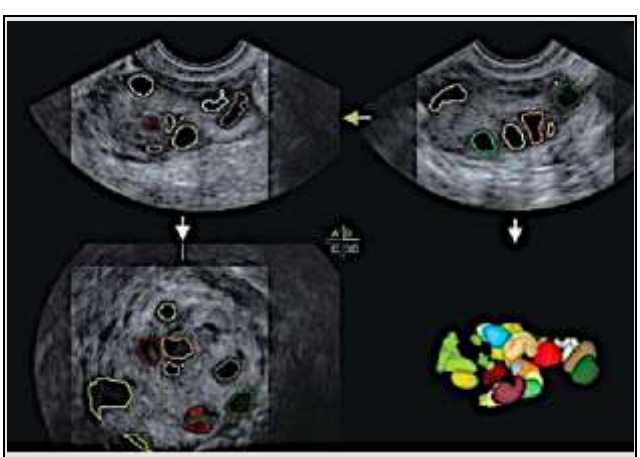

Figure 5. Colour Coded Antral Follicle on Sono AVC

Stromal Echogenicity and Polycystic Ovary Morphology (PCOM)

Stromal echogenicity is assessed against echogenicity of myometrium on B-mode US. Polycystic ovary morphology (PCOM) is more accurate for PCOS diagnosis for women between 30 and 39 years of age.[17] It has also been suggested that the threshold for PCOM should be revised regularly with advancing ultrasound technology and age-specific cut off values for PCOM should be defined.

Ultrasound Features and Review of Literature

Volume: Though 10 cc is the cut off defined in Rotterdam's criteria, ovarian volume 6.6 cc has shown 91% sensitivity and 91% specificity for polycystic ovarian' syndrome.[18] Polycystic ovary morphology is therefore a better discriminator than ovarian volume between women with polycystic ovary syndrome and control women.

The best sensitivity and specificity for diagnosis of PCOS were obtained using different threshold volume and AFC at different ages.

This study also quoted that the polycystic ovary morphology (PCOM) is more accurate for PCOS diagnosis for women between 30 and 39 years of age. It has also been suggested that the threshold for PCOM should be revised regularly with advancing ultrasound technology.

Therefore, now it is decided that ultrasound should not be used as one of two features to diagnose PCOS in females up to 8 years of gynaecological age. For diagnosis of PCOS in young adolescent female all the three features of PCOS according to Rotterdam criteria should be present.

The antral and atretic follicles may be peripherally arranged or are dispersed in the stroma and are named peripheral and general cystic pattern of PCO (polycystic ovary).[19] Lam et al. have concluded in their study that the current criteria will fail to identify milder forms of PCOS and further information, about the ovarian stroma and the degree of vascularization, is required. Hyperdense stroma and stromal abundance have been described with polycystic ovaries since the first definition of the syndrome by Stein-Leventhal. US to diagnose PCOS, a cardinal feature has been shown to be the presence of a bright, highly echogenic stroma and stromal echogenicity/total ovarian echogenicity was significantly higher in PCOS than controls.[20] Increased stromal echogenicity for diagnosis of PCOS has a sensitivity of 94% and specificity of 90%.[21] Stromal area of 4.6 cm^2 has 91% sensitivity and 86% specificity for diagnosis of polycystic ovarian syndrome. Ovarian area of 5.3 cm^2 has 93% sensitivity and 91% specificity for diagnosis of polycystic ovarian syndrome. Mean stromal area/mean ovarian area ratio of 0.34 and above has a specificity of 100% and this parameter may be used in routine clinical practice for improving US diagnosis of PCOS.[22] In a study by Franks et al., it has been well derived that PCOM in normal women is not a morphological variant of normal ovaries, but rather represents a functional entity - a silent form of PCOS.[23] Along with evaluation of ovaries on US, endometrial morphology and ovarian pathologies (if any) should be evaluated.

CONCLUSIONS

Assessment of anovulation and polycystic ovary (PCO) is very well possible on US. With advent of Transvaginal (TV) sonography and improved image resolution, better assessment of ovarian morphology is possible. 3D, colour and Power Doppler imaging, advanced calculation software (Sono AVC & VOCAL) have provided tools for more accurate assessment of number of follicles, ovarian volume, ovarian morphology & stromal volume. US remains a good tool for assessment of normal physiological changes and variations in volume and size of ovaries during puberty. Transvaginal sonography in adolescent has definite role in diagnosis of PCOS.

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