

## EFFECT OF POLYCYSTIC OVARY SYNDROME ON THE MORPHOLOGY OF OVARY - A REVIEW

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*Polycystic ovary syndrome is one of the most common endocrine disorders, and the presence of polycystic ovary morphology is a cardinal feature of polycystic ovary syndrome. PCOS is a frustrating experience for women, often complex for managing clinicians and is a scientific challenge for researchers. Although PCOS is an endocrine disease, it affects many systems of the body resulting in reproductive, metabolic, and psychological consequences. The diagnosis of polycystic ovary syndrome relies on clinical, biological and morphological criteria. With the advent of ultrasonography, follicle excess has become the main aspect of polycystic ovarian morphology (PCOM). An increase in ovarian volume and/or area may also be considered accurate markers of PCOM. Measurements of ovarian volume and antral follicle count are of clinical importance as diagnostic features of PCOS and as a parameter in estimation of ovarian follicular reserve for prognostic purposes in infertility care.*

**Key words:** Polycystic ovary, Ultrasonography, Ovarian volume, ovarian area, Follicle count, Infertility, Morphology.

**INTRODUCTION**

PCOS is an ovarian dysfunction syndrome of which the main manifestations are menstrual disorder, continuous anovulation, hyperandrogenism and polycystic ovary etc. As PCOS patients suffer from long-term an ovulation and the endometrium lacks the effect of progestin due to long term exposure to estrogens, the morbidity of endometrial hyperplasia and endometrial cancer increases significantly, up to 23% (Park et al., 2011). Polycystic ovary syndrome (PCOS) was firstly defined by the presence of oligo/ amenorrhea and hyperandrogenism in association with polycystic ovary (PCOM) morphology seen at the time of surgery [Stein IF, 1935,] and, thereafter, observed by ultrasound [Adams J et al., 1986]. Moreover, PCO morphology is not pathognomonic of PCOS because it was also found in childhood, adolescence [Bridges NA et al., 1993], menopausal women [Birdsall MA and Farquhar CM, 1996], and in patients with clinical evidence of hyperandrogenism in absence of irregular menstrual cycles [Carmina E and Lobo RA, 2001]. The following criteria have sufficient specificity and sensitivity for the definition of PCO, the presence of at least 12 follicles in each ovary measuring 2–9 mm in diameter, and/ or increase in ovary size greater or equal to 10 ml [Balen et al.,]

In the adult non-pregnant state, the ovaries lie on each side of the uterus close to the lateral pelvic wall, suspended in the pelvic cavity by a double fold of peritoneum, the mesovarium, which is attached to the upper limit of the posterior aspect of the broad uterine ligament. They are dull white in colour and consist of dense fibrous tissue in which ova are embedded. Before regular ovulation begins they have a smooth surface, but thereafter their surfaces are distorted by scarring that follows the degeneration of successive corpora lutea. Their average dimensions are 4 × 2 × 3 cm in reproductively mature women; they more than double their size during pregnancy. In the neonate, their dimensions are 1.3 × 0.6 × 0.4 cm. Prior to the first menstrual period (menarche) the ovaries are about a third of the normal reproductive adult size; they gradually increase in size with body growth. After the menopause, the average size of the ovary reduces to 2.0 × 1.5 × 0.5 cm and further to 1.5 × 0.75 × 0.5 cm in late menopause [Standing S, 2008].

The ovaries are surrounded by a thin fibrous capsule, the tunica albuginea. Oogonia develop before birth from primordial germ cells. Before puberty, the ovary is smooth, but after puberty, the ovary becomes progressively scarred as successive corporal utea degenerate. After menopause, the ovary becomes shrunken and its surface is pitted with scars. The ovaries are the organs responsible for the production of the female germ cells, the ova, and the female sex hormones, estrogens and progesterone, in the sexually mature female [Richard S. Snell ,2012]

Each ovary is subdivided into the highly cellular cortex and a medulla, which consists mostly of a richly vascularised loose connective tissue. The blood vessels of the medulla are derived from the ovarian arteries. Histologically,

however, the division between the cortex and the medulla is indistinct. The ovarian cortex is composed of the connective tissue stroma that houses ovarian follicles in various stages of development. The ovarian medulla is a richly vascularised fibroelastic connective tissue housing connective tissue cells, interstitial cells, and hilus cells. The central region of the ovary, the medulla, is composed of fibroblasts loosely embedded in a collagen-rich meshwork containing elastic fibres. The medulla also contains large blood vessels, lymph vessels, and nerve fibres. The medulla of the premenstrual human ovary has a few clusters of epithelioid interstitial cells that secrete estrogens. In mammals having large litters, the ovaries contain many clusters of these interstitial cells, which collectively are called the interstitial gland. In humans, most of these interstitial cells involute during the first menstrual cycle and have little, if any, function. Hilus cells constitute another group of epithelioid cells in the ovarian medulla. These cells have a similar configuration of organelles and contain the same substances in their cytoplasm as Leydig cells of the testes. These cells secrete androgens. The ovarian cortex is composed of a connective tissue framework, the stroma (also known as the interstitial compartment), housing fibroblast-like stromal cells (also known as interstitial cells) as well as ovarian follicles in various stages of development [Leslie P.G and James L.H, 2006].

Ovarian size also varies with age, reaching a maximum during adolescence (1.3–3.8 years post-menarche), slowly decreasing during adulthood and rapidly shrinking after menopause. The finding of an elevated mean ovarian size during adolescence that decreases with each decade of life has been demonstrated using magnetic resonance imaging (MRI) and ultrasonography. Using MRI, Well et al. (2007) observed a marginal decrease in OV between the second and the fourth decades of life (from 9.5+3.3 ml to 8.5+3.3 ml, approximately a 10% reduction), with ovaries being half their size by the late fifth decade of life (Wellet et al., 2007). While the absolute size of the ovaries was notably smaller in similar studies using ultrasonography [Pavlik et al., 2000; Garel et al., 2001], the following changes in OV over the lifespan were noted by Pavlik et al. (2000) using ultrasound: age, 30 years, 6.6+0.2 ml; 30–39 years, 6.1+0.1 ml; 40–49 years, 4.8+0.0 ml; 50–59 years, 2.6+0.0 ml; 60–69 years, 2.1+0.0 ml; and ≥70 years, 1.8+0.1 ml. Evaluation of the ovarian size is accomplished with the formula for the volume of prolate ellipsoid (Volume=length x height x width x 0.5233). In premenopausal women, the normal ovarian volume is documented to be between 5.3 ml to 13.9 ml, while in postmenopausal the volume is less than 8ml [Joseph E et al., 2009].

In polycystic ovary syndrome (PCOS) the woman's levels of the sex hormones oestrogen and progesterone are out of balance. This leads to the growth of ovarian cysts (benign masses on the ovaries) [Tomlinson, J et al., 2010]. While the exact cause of PCOS is unknown; doctors believe that hormonal imbalances and genetics play a role. Women are more likely to develop PCOS if their mother or sister also has the condition. Overproduction of the hormone androgen may be another contributing factor. Androgen is a male sex hormone that women's bodies also produce. Women with PCOS often produce higher-than-normal levels of androgen. This can affect the development and release of eggs during ovulation. Excess insulin (a hormone that helps convert sugars and starches into energy) may cause high androgen levels. [Jaime Herndon, Polycystic Ovarian Syndrome].

## DISCUSSION

Diagnostic criteria and management procedures for polycystic ovary syndrome (PCOS) are highly controversial and hotly debated in the literature [Azziz R, 2006]. In clinical practice, transvaginal ultrasonography (TVUS) is the first choice imaging modality in evaluating the ovaries because of its high performance, availability, cost-effectiveness and patient friendliness. The major limitations of TVUS are its user dependency and the limitations in displaying a global view of the pelvis and large lesions of ovarian origin. Magnetic resonance imaging (MRI), with its excellent soft-tissue contrast resolution and characteristics, is a useful non-invasive alternative modality to TVUS, especially in adolescent and/ or very obese women [Barber TM, 2010].

For diagnosis of PCOS, the 2003 Rotterdam criteria require at least two of the following: oligomenorrhea or anovulation, clinical or biochemical signs of hyperandrogenism, and at least one polycystic ovary defined as the presence of 12 follicles 2–9 mm in diameter or ovarian volume >10 ml at ultrasonography [Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2003]. The fact that PCOS is often characterised by the presence of

insulin resistance and associated hyperinsulinaemia and most of the patients in clinical series are overweight or obese is significant. However, recent advancements in imaging technology has questioned the accuracy of these morphologic criteria, and higher thresholds of antral follicle counts have been proposed [Dewailly, et al. 2011].

The clinical significance of ovarian morphology alone or combined with other PCOS features is still unclear [Angela Falbo et al., 2009]. The following criteria have sufficient specificity and sensitivity for the definition of PCO, the presence of at least 12 follicles in each ovary measuring 2–9 mm in diameter, and/ or increase in ovary size greater or equal to 10 ml [Balen et al., 2003 ] Although increased stromal volume is a characteristic feature of PCO [Bucket WM et al., 2003], determination of ovarian size has been shown to be a good replacement for quantitation of stromal volume in clinical practice [Dewailly D et al., 1994]. This definition does not apply to women using oral contraceptives since the latter can alter ovarian morphology in normal women and possibly in subjects with PCO [Christensen JT et al., 1997].

The diagnosis of polycystic ovary syndrome (PCOS) relies on clinical, biological and morphological criteria. With the advent of ultrasonography, follicle excess has become the main aspect of polycystic ovarian morphology (PCOM). Since 2003, most investigators have used a threshold of 12 follicles (measuring 2–9 mm in diameter) per whole ovary, but that now seems obsolete. An increase in ovarian volume (OV) and/or area may also be considered accurate markers of PCOM, yet their utility compared with follicle excess remains unclear [Didier Dewailly et al., 2013]. The last major histological study dates back to 1982 (Hughesdon, 1982) and provides a detailed description of the 'polycystic' appearance of the ovaries as being simply an increase in the number of growing follicles measuring 10 mm in diameter.

With the advent of ultrasonography, follicle excess has become the main aspect of polycystic ovarian morphology (PCOM). An increase in ovarian volume (OV) and an increased ovarian area (OA) are also considered accurate markers of PCOM, provided the measurements are carried out on a median section of the ovaries. Histopathologic studies also confirm that both OV and OA are indeed a good reflection of stromal hypertrophy and follicle excess, which are the anatomical hallmarks of PCOM [Hughesdon, 1982]. While sonohistopathological assessments confirmed a high accuracy in detecting PCOM by transabdominal ultrasonography, these conclusions were based on qualitative assessments of ovarian morphology and not on quantitative measurements such as follicle counts [Saxton et al., 1990]. In fact, there are few data addressing the accuracy of ultrasonographic estimates of follicle counts in polycystic ovaries [Takahashi et al., 1994] demonstrated a good correlation between follicle counts obtained by histopathology and transvaginal ultrasonography. However, the follicle counts were higher when estimated by ultrasound than when measured by histopathology, a result that should not be unexpected because histological assessment was conducted on ovarian wedge resections and did not rely on the examination of whole ovaries.

The first set of most widely adopted criteria, proposed by Adams et al. (1985, 1986) in the 1980s, arbitrarily described PCOM as an ovary containing 10 or more follicles (measuring 2–8 mm in diameter) in one cross section of the ovary by using transabdominal ultrasonography. Since then, transabdominal approaches have been replaced by higher frequency transvaginal approaches which afford a greater likelihood of detecting the ovaries and a much better resolution for imaging small follicles.

Many studies have shown that increased ovarian size represents an important feature of PCOM [Balen et al., 2003]. In fact, ovarian size appears to be increased in the majority of women with PCOS [Carmina et al., 2005] and mean ovarian size is higher in women with PCOS than in normal women matched for age and body weight [Alsamarai et al., 2009]. Less clear is the establishment of an acceptable cut-off for OV between normal and polycystic ovaries [Dewailly et al.]. The Rotterdam consensus statement suggested a threshold of 10 ml based on expert opinion (Balén et al., 2003). Afterwards several groups of researchers have proposed much lower cut-off values including 6.4 ml (Kosuset al., 2011), 6.7 ml (Chen et al., 2008), 7.0 ml (Jonard et al., 2005; Dewailly et al., 2011) and 7.5 ml (Carmina et al., 2005).

In women with PCOS, the mean ovarian size appears to be higher in populations characterised by large prevalence of weight excess, such as those in Canada and the USA [Alsamarai et al., 2009; Lujan et al., 2013], intermediate in European countries [Carmina et al., 2005; Jonard et al., 2005], and lower in East-Asian countries [Chen et al., 2008]. In addition, a positive correlation between ovarian size and circulating insulin levels has been demonstrated by several studies [Carmina et al., 2005; Alsamarai et al., 2009].

By 3D ultrasonography, stromal volume can be measured through calculation and subtraction of total follicular volume from the total OV. The ratio of ovarian stroma to total ovarian size may be a good criterion for diagnosis of PCOS, with a cut-off value of 0.32 indicating an association with hyperandrogenaemia (Fulghesu et al., 2007). However, to date there are few studies corroborating the diagnostic potential of this variable. In general, ovarian stromal volume and total ovarian size are well correlated and hence, there may not be any additional value to including stromal size measurements in clinical practice [Dewailly et al., 2014].

Increased OV has been associated not only with enhanced stromal echogenicity but also with increased vascularity. Even though the introduction of 3D ultrasound has allowed better and more objective assessment of ovarian morphology and vascularisation [Raine-Fenning et al., 2003, 2004], results pertaining to differences in ovarian blood flow in PCOS have been conflicting. Adali et al. (2009) showed higher ovarian stromal blood flow and reduced uterine perfusion in patients with PCOS compared with age-matched women without PCOS. Similarly, Battaglia et al. (2012) reported that assessments of ovarian vascularisation, as judged by 3D power Doppler, were significantly increased in PCOS patients compared with controls. Stromal vascularity may be altered in PCOS through the effects of hyperinsulinaemia on vascular smooth muscle relaxation, increased angiogenesis and dilatation of vessels in ovarian stromal tissue [Steinberget al., 1994].

## CONCLUSION

The definition of PCOS has been controversial and still remains unclear due to the syndrome's heterotrophic nature. The knowledge of developmental changes that take place in the female reproductive organs is essential in the investigation of pelvic conditions. Imaging methods can facilitate the achievement of a correct diagnosis. Ultrasonography (US) remains the most useful modality used in paediatric and adolescent gynaecology and often the only one necessary prior to therapeutic intervention. With ultrasound assessment being an easily available and cost effective test, it definitely has a role in preliminary assessment of female children puberty disorders and expected changes with age.

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