Polycystic Ovary Syndrome

Introduction:

Polycystic ovary syndrome (**PCOS**) is one of the most common female endocrine disorders. PCOS is a complex, heterogeneous disorder of uncertain etiology, but there is strong evidence that it can to a large degree be classified as a genetic disease ***(Fauser et al., 2011)***.

PCOS produces symptoms in approximately 5% to 10% of women of reproductive age (12–45 years old). It is thought to be one of the leading causes of female subfertility ***(Goldenbrg and Glueck, 2008),*** and the most frequent endocrine problem in women of reproductive age ***(Teede et al., 2010).***

There is considerable heterogeneity of symptoms and signs among women with PCOS and for an individual these may change over time ***(Balen et al., 1995).***

The PCOS is familial and various aspects of the syndrome may be differentially inherited. The PCOS can exist without clinical signs of the syndrome, which may then become expressed in certain circumstances. There are a number of factors that affect expression of PCOS, for example, a gain in weight is associated with a worsening of symptoms while weight loss may ameliorate the endocrine and metabolic profile and symptomatology ***(Clark et al., 1995)***.

Genetic studies have identified a link between PCOS and disordered insulin metabolism, and indicate that the syndrome may be the presentation of a complex genetic trait disorder. The features of obesity, hyperinsulinaemia, and hyper-androgenaemia which are commonly seen in PCOS are also known to be factors which confer an increased risk of

cardiovascular disease and non-insulin dependent diabetes mellitus (NIDDM) ***(Moran et al., 2010).***

There are studies which indicate that women with PCOS have an increased risk for these diseases which pose long-term risks for health, and this evidence has prompted debate as to the need for screening women for PCOS (***RCOG guidelines, 2003).***

Historically the detection of the polycystic ovary required visualization of the ovaries at laparotomy with histological confirmation following biopsy ***(Stein and Leventhal, 1935).***

As further studies identified the association of certain endocrine abnormalities in women with histological evidence of polycystic ovaries, biochemical criteria became the mainstay for diagnosis. Raised serum levels of LH, testosterone, and androstenedione, in association with low or normal levels of follicle stimulating hormone (FSH) and abnormalities of estrogen secretion, described an endocrine profile which many believed to be diagnostic of PCOS ***(Balen et al., 2003)***.

The advent of high resolution ultrasound scanning provided a non-invasive technique for the assessment of ovarian size and morphology. Good correlation has since been shown between ultrasound diagnoses of polycystic morphology and the histopathological criteria for polycystic ovaries by studies examining ovarian tissue obtained at hysterectomy or after wedge resection ***(Takahashi et al., 1994).***

The histopathological criteria have been defined as the observation of: increased numbers of follicles, hypertrophy and luteinization of the inner theca cell layer, and thickened ovarian tunica. Trans-abdominal and/or trans-vaginal ultrasound have since become the most commonly used diagnostic methods for the identification of polycystic ovaries. And an

attempt has been made to provide the ultrasound criteria for the diagnosis of polycystic ovaries. In essence the polycystic ovary should have at least one of the following: either 12 or more follicles measuring 2–9 mm in diameter or increased ovarian volume (> 10 cm3) ***(Balen et al., 2003).***

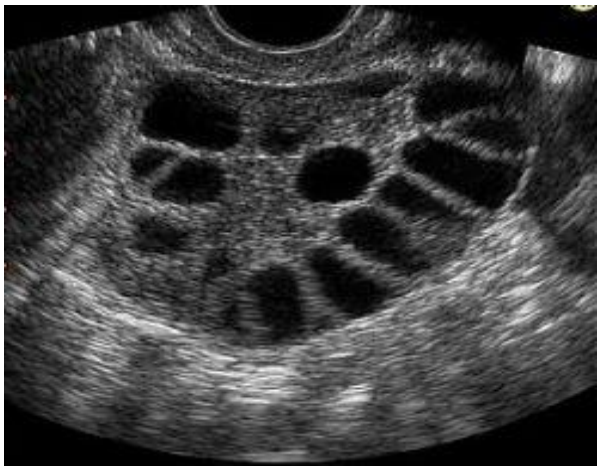

Figure (1): Transvaginal ultrasound scan of a polycystic ovary ***(Balen, 2008).***

The use of magnetic resonance imaging (MRI) for the visualization of the structure of pelvic organs has been claimed to have even greater sensitivity than ultrasound for the detection of polycystic ovaries. However, the substantial cost and practical problems involved with this imaging technique limit its use ***(Faure et al., 1989).***

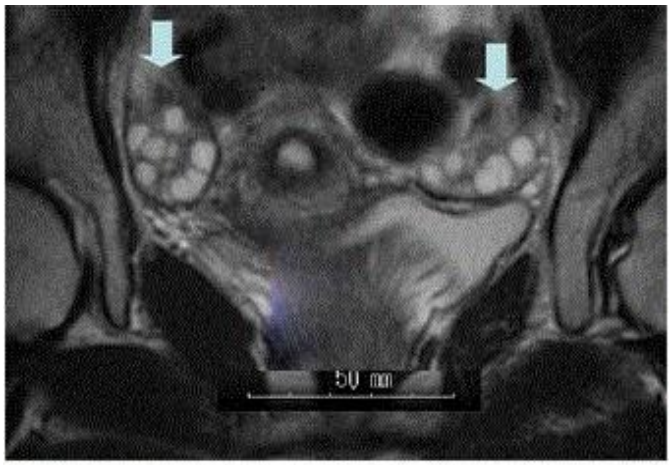

Figure (2): Magnetic resonance imaging (MRI) of a pelvis, demonstrating two polycystic ovaries ***(Balen, 2008).***

The term "polycystic ovary" in some respects adds to the confusion that surrounds its diagnosis. The "cysts" are not cysts in the sense that they do not contain oocytes. So truly it should be called a polyfollicular ovary, to reflect the finding that the "cysts" are actually follicles whose development has been arrested. Indeed the prerequisite of a certain number of cysts may be of less relevance than the volume of ovarian stroma, which has been shown to correlate closely with serum testosterone concentrations ***(Kyei-Mensah et al., 1996).***

Furthermore, it has been suggested recently that an ultrasound assessment of the ratio of ovarian stromal area to total ovarian area gives the greatest sensitivity and specificity for the diagnosis of PCOS ***(Fulghesu et al., 2007)***.

While it is now clear that ultrasound provides an excellent technique for the detection of polycystic ovarian morphology, identification of polycystic ovaries by ultrasound does not automatically conferm a diagnosis of PCOS. Controversy still exists over a precise definition of the ++syndrome and whether or not the diagnosis should require confirmation of polycystic ovarian morphology ***(Fulghesu et al., 2007).***

In North America in 1990 the National Institute of Health conference on PCOS recommended that diagnostic criteria should include evidence of hyperandrogenism and ovulatory dysfunction, in the absence of non-classic adrenal hyperplasia, and that evidence of polycystic ovarian morphology is not essential ***(Zawadski and Dunaif, 1992)***.

This definition results in the mystifying condition of PCOS without polycystic ovaries. However, the more generally accepted theory in the UK and Europe is that a spectrum exists, ranging from women with polycystic ovarian morphology and no overt abnormality at one end, to those with polycystic ovaries associated with severe clinical and biochemical disorders at the other end, hence the ESHRE/ASRM Consensus of 2004 ***(Fauser et al., 2004).***

Although debate on what constitutes PCOS continues, the Rotterdam Consensus on Diagnostic Criteria for PCOS published in 2003 is the most current definition. According to this consensus, a diagnosis of PCOS is based on at least 2 of the following 3 criteria: oligo-ovulation or anovulation, clinical or biochemical evidence of hyperandrogenism, and polycystic ovaries on ultrasound assessment (> 12 small antral follicles in an ovary), with the exclusion of medical conditions such as congenital adrenal hyperplasia, androgen-secreting tumours, or Cushing's syndrome ***(ESHRE/ASRM, 2004).***

Nevertheless, it is widely recognized in the USA that positive ovarian findings predominate and there is considerable overlap between the European and US definitions **(Table 1).** Debate continues regarding the reliability and reproducibility of the various tests that we have at our disposal ***(Barth et al., 2007).***

Table (1): Definitions of PCOS

Definition/year	Diagnostic criteria	Exclusion criteria
NIH/1990	Requires the simultaneous presence of : 1. Clinical (hirsutism, alopecia, acne) and/or biochemical hyperandrogenism. 2. Menstrual dysfunction.	CAH, androgen-secreting tumours, Cushing's syndrome, hyperprolactinaemia .
Rotterdam/ 2003	Requires the presence of at least two criteria: 1. Clincial (hirsutism, acne) and/or biochemical hyperandrogenism. 2. Ovulatory dysfunction. 3. PCOM.	

AES/2006, 2007)	Requires the presence of hyperandorgenism, clinical (hirsutism) and/or biochemical, and either : 1. Oligo-anovulation. 2. PCOM.	CAH, androgen-secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing's syndrome, syndromes of sever insulin resistance, thyroid dysfunction, hyperprolactinaemia .

(Galluzzo et al., 2008)

Using a combination of clinical, ultrasonographic, and biochemical criteria, the diagnosis of PCOS is usually reserved for those women who exhibit an ultrasound picture of polycystic ovaries, and who display one or more of the clinical symptoms (menstrual cycle disturbances, hirsutism, obesity, hyper-androgenism), and/or one or more of the recognized biochemical disturbances (elevated testosterone, androstenedione, LH or insulin). This definition of PCOS requires the exclusion of specific underlying diseases of the adrenal or pituitary glands (e. g. hyperprolactinemia, acromegaly, congenital adrenal hyperplasia, Cushing's syndrome, androgen secreting tumors of the ovary or adrenal gland) which could predispose to similar ultrasound and biochemical features ***(Fauser et al., 2004).***

Clinical manifestations:

PCOS includes a heterogeneous collection of signs and symptoms with varying degree of mildness and severity in affecting the reproductive, endocrine and metabolic functions ***(Edmonds, 2012).***

A few years ago ***Balen (1995)*** reported a large series of women with polycystic ovaries detected by ultrasound scan. All of the 1871 patients had at least one symptom of the PCOS **(see Table 2).**

Thirty-eight percent of the women were overweight (body mass index (BMI) > 25kg/m2). Obesity was significantly associated with an increased risk of hirsutism, menstrual cycle disturbance, and an elevated serum

testosterone concentration. Obesity was also associated with an increased rate of infertility. Twenty-six per cent of patients with primary infertility and 14% of patients with secondary infertility had a BMI of more than 30 kg/m^2 ***(Balen et al., 1995).***

Approximately 30% of the patients had a regular menstrual cycle, 50% had oligomenorrhea, and 20% amenorrhea. In this study the classical endocrine features of raised serum LH and testosterone were found in only 39. 8% and 28. 9% of patients, respectively. Ovarian volume was significantly correlated with serum LH and with testosterone concentrations. Other studies have reported that markers of insulin resistance correlated with ovarian volume and stromal echogenicity, which in turn have been correlated with androgen production. Many other groups have similarly reported heterogeneity in their populations with PCOS ***(Dewailly et al., 1994).***

Table (2): Clinical symptoms and signs of PCOS ***(Barbieri, 2003)***

	Percentage frequency of symptom or sign			
	Balen et al (1995)[1] n = 1741	Franks (1989)[25] n = 300	Goldzieher et al (1981)[24] n = 1079	
Symptom or sign	%	%	%	No. of cases[a]
Menstrual cycle disturbance:	47	52	29[b]	(n = 547)
– oligomenorrhea – amenorrhea	19	28	51	(n = 640)
Hirsutism	66	64	69	(n = 819)
Obesity	38	35	41	(n = 600)
Acne	34	27	–	–
Alopecia	6	3	–	–
Acanthosis nigricans	2	< 1	–	–
Infertility (primary/secondary)	20	42	74	(n = 596)

– Denotes feature not recorded.
[a] In the Goldzieher study clinical details were not available for the entire 1079 women, thus the number of cases which were used to determine the frequency of each symptom is stated.
[b] In this series, any abnormal pattern of uterine bleeding was included.

Franks's series, also from England, related to 300 women recruited from a specialist endocrine clinic ***(Frank, 1989).***

Some years earlier Goldzieher gathered a comprehensive review of 1079 cases of surgically proven polycystic ovaries ***(Goldzieher et al., 1981).***

The frequency of clinical symptoms and signs in these series was similar **(Table 2).** Clinical phenotyping of PCOS involves determining the presence of clinical and/or biochemical androgen excess (hyper-androgenism), while excluding related disorders. The primary clinical sign of androgen excess is the presence of hirsutism. However, at the ESHRE/ASRM consensus meetingit was agreed that normative data in large populations are still lacking ***(Fauser et al., 2004).***

The assessment of hirsutism is relatively subjective and few physicians in clinical practice actually use standardized scoring methods such as

Ferriman Gallwey scoring system to quantify the degree of hirsutism for research purposes ***(Ferriman and Gallwey, 1961).***

The Ferriman Gallwey scoring system was developed in 1961 and later modified in 1981 ***(Hatch et al., 1981).***

Within this system, abnormal hair distribution is assessed in nine body areas and scored from 0 to 4. Increasing numeric scores correspond to greater hair density within a given area. Many investigators define hirsutism as a sore of 8 or greater using the modified version. There are also significant racial differences with hirsutism being significantly less prevalent in hyperandrogenic women of Eastern Asia origin and more so in those from Southern Asia ***(Rodin et al., 1998).***

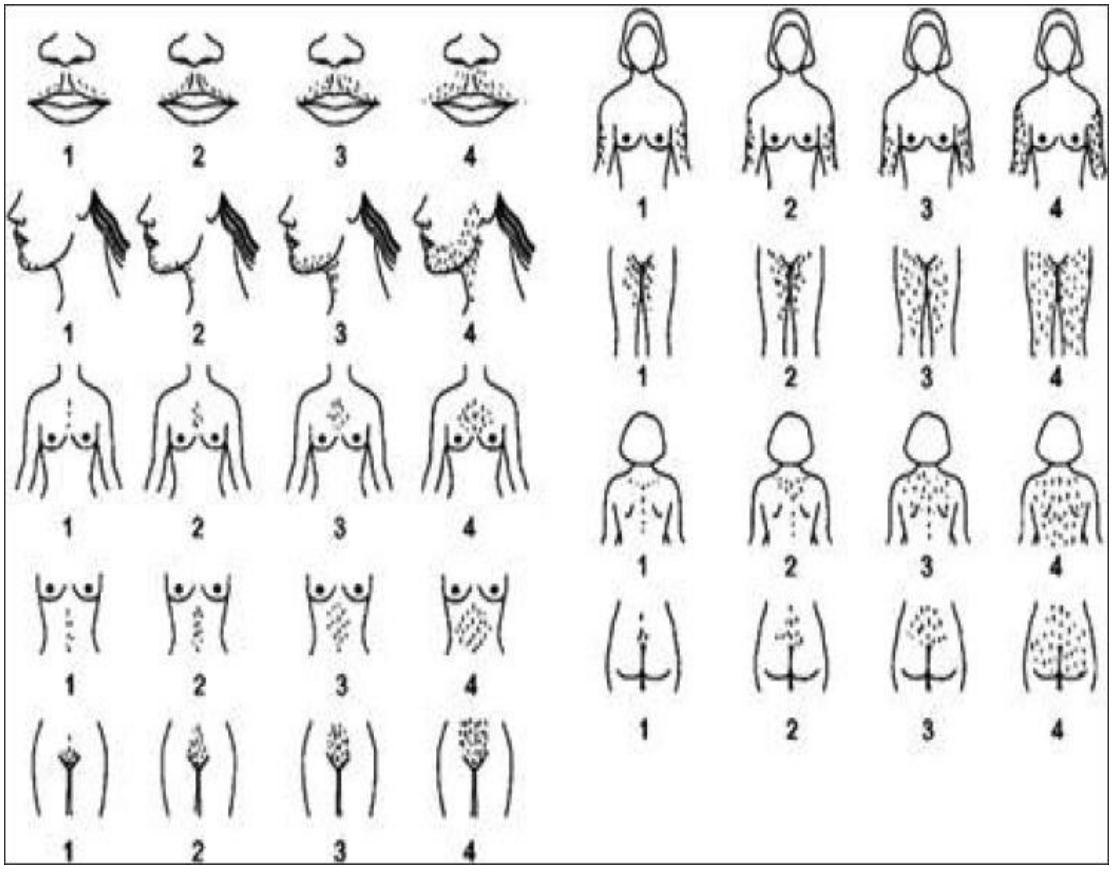

Fig. (3): Depiction of the Ferriman-Gallwey system for scoring hirsutism ***(Hatch et al., 1981).***

Ovarian function in PCOS:

The presence of enlarged polycystic ovaries suggests that the ovary is the primary site of endocrine abnormality, particularly the hyperandrogenism.

This was subsequently confirmed by other workers who assessed the response of the pituitary and ovary to a single dose of the gonadotropin releasing hormone agonist (GnRHa), nafarelin, in hyperandrogenemic women with PCOS in whom adrenal androgen production had been suppressed by administering dexamethasone. The observations were that GnRHa yielded a significant elevation of androstenedione and 17-hydroxyprogesterone ***(White et al., 1995).***

Franks et al., (1996) extended this study to anovulatory and ovulating hyperandrogenemic women, and reported a small but significant increase in androstenedione levels in both groups in response to GnRHa, and a similar response in 17-hydroxyprogesterone, which was significantly higher in the anovulatory women. They also demonstrated that there was no significant rise in these two hormones in response to ACTH injection, which excluded a significant role of adrenal androgen production. These data indicate that hyper-androgenemia, in both ovulatory and anovulatory women with PCOS, is predominantly of ovarian origin. This also confirmed that the primary cause of excess androgen production by the polycystic ovary was not due to hypersecretion of LH alone and it was reasonable to conclude that the intrinsic defect was due to an ovarian theca–interstitial cell dysfunction, or other stimulatory influences such as insulin, IGF-1, etc.

Both *in vivo* and *in vitro* data confirm that the theca cells of PCOS patients have a generalized overactive steroidogenesis. PCOS patients have a tendency to an excess of estradiol at all stages of follicular maturation. This is partly due to availability of excess androgen substrate for aromatase

activity, as well as an excessive response of follicle development and estradiol secretion to FSH. Granulosa cells from PCO *in vitro* have also been reported to lose FSH responsiveness, and produce low amounts of progesterone ***(Mason et al., 1994).***

LH excess is considered the cause of ovarian hyper-androgenism of PCOS, in view of the stimulatory effect of LH on theca cells. Nevertheless, some women with PCOS have normal LH levels whilst being hyperandrogenic, while yet others who had downregulation of LH as secretion with long-term GnRHa displayed hyper-responsiveness of 17-hydroxyprogesterone to human chorionic gonadotropin (HCG) injection (i. e. challenge with LH, as HCG is a surrogate for LH activity). These findings argue against a sole role of LH in the androgen excess of PCOS. They favor the theory that theca cells of PCOS women hyperrespond to gonadotropins and produce excess androgens due to an escape of their normal downregulation to gonadotropins, thereby linking this dysregulation to excess of insulin and IGF1**.**

Prelevic and colleagues supported this theory by demonstrating that suppression of insulin secretion by a somatostatin analog lowers serum LH and androgens in PCOS women ***(Prelevic et al., 1990).***

Indeed insulin acts as a “co-gonadotropin” and also amplifies the effects of testosterone by suppressing SHBG. Inhibin is a FSH inducible factor, which is capable of interfering with the downregulation of steroidogenesis. Plasma inhibin and androstenedione concentrations correlate, and women with PCOS have elevated serum inhibin-B ***(Anderson et al., 1998).***

This helps to explain the relatively low serum concentrations of FSH compared with LH in anovulatory women with PCOS. Since inhibin stimulates androgen production, and androgens in turn stimulate inhibin secretion, there is a potential for the development of a vicious cycle within the ovary that would inhibit follicle development. Alternatively, a defect in the IGF system could cause an alteration of the set point for the response of the granulosa cell to FSH. Mason and co-workers suggested that LH acts on granulosa cells in the presence of insulin, thereby leading to premature luteinization, maturational arrest and excess androgen production ***(Mason et al., 1994).***

In summary, as a consequence of dysregulation of androgen synthesis within the ovary, women with PCOS have ovarian hyperresponsiveness to gonadotropins: that of thecal cells to LH explaining the excess androgens, and that of granulosa cells to FSH leading to increased estrogens.

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