Endocrine, *vol. 30, no. 1, 3–11, August 2006* 0969–711X/06/30:3–11/$30.00
ENDO (Online) ISSN 1559-0100 © 2006 by Humana Press Inc. All rights of any nature whatsoever reserved.

Diagnostic Criteria for Polycystic Ovarian Syndrome

F. J. Broekmans and B. C. J. M. Fauser

Department of Reproductive Medicine and Gynecology, University Medical Center, Utrecht, Heidelberglaan 100, 3584 CX Utrecht

Until recently no universally accepted clinical definition existed for the polycystic ovary syndrome (PCOS). What has emerged from research over the last 30 yr is a profound heterogeneity and ongoing speculation regarding etiology. The various symptoms and signs related to PCOS have now been extensively evaluated as to their possible contribution to the diagnosis. Consensus has been reached for the use of oligomenorrhea or amenorrhea, clinical or biochemical hyperandrogenism, and polycystic ovaries at ultrasound as key diagnostic criteria. Obesity, insulin resistance, and the so-called metabolic syndrome should be recognized as associated conditions that present long-term health risks for diagnosed PCOS cases. The way all these features need to be applied in the work up of the individual index patient is reviewed here.

Key Words: Polycystic ovary syndrome; consensus; ultrasonography; hyperandrogenism; anovulation.

Introduction

The history of the diagnostic challenge of a condition currently referred to as the polycystic ovary syndrome (PCOS) goes back some 70 yr. It was in 1935 that Stein and Leventhal described several cases presenting with oligomenorrhea/amenorrhea combined with the presence at operation of bilateral polycystic ovaries (PCO) *(1)*. Of these seven patients, three also presented with obesity and five showed signs of hirsutism. Only one patient was both obese and showed hirsutism. These findings indicate that in cases with polycystic ovaries proven by morphology not all of the features associated with the PCOS necessarily have to be present *(2,3)*. With the introduction of transvaginal ultrasonography it also became clear that patients with oligomenorrhea, obesity, and hirsutism do not necessarily have the typical polycystic morphology on ultrasound *(4,5)*. Moreover, as the etiology of PCOS is far from well understood, diagnostic criteria for PCO syndrome have been subject of lengthy debates among clinicians *(6,7)*. Specialty groups may still differ in their use of diagnostic criteria and diagnostic work up, as well in their choice of first- and second-line treatment *(7)*.

At the expert consensus meeting held in 2003 in Rotterdam *(3,8)*, it was agreed that the polycystic ovary syndrome should be diagnosed in cases of WHO II anovulation if at least two of the following three features were present: (1) oligomenorrhea or amenorrhea, (2) clinical or biochemical hyperandrogenism, and (3) polycystic ovaries at ultrasound. The approach of only requiring a certain number of relevant features to diagnose a disease state or clinical condition is not without precedent. For instance, for the diagnosis of the metabolic syndrome it was decided that only three out of five key criteria should be present *(9,10)*. Several commentaries have since emerged continuing the debate on the definition and classification issue and have suggested adaptations in the set of diagnostic criteria *(11–13)*. The Rotterdam consensus, however, is indeed a compromise, which bridges the immense gap between the European and American perspectives with regard to PCOS. It is anticipated that with the use of consensual diagnostic criteria among physicians working in the field of both endocrinology and gynecology the comparability of published research will increase and the search for etiological factors will lead to improved results of patient management. It is therefore recommended that all clinicians and investigators now use this internationally agreed definition to ensure uniformity in research studies and routine clinical management.

In this section much of the background for the use of the so-called Rotterdam criteria will be discussed. Also, associated features will be addressed, such as obesity, elevated serum LH, insulin resistance, and the metabolic syndrome. Those features are frequently present in PCO patients without contributing to the diagnosis per se, and may well have consequences for long-term health and as such should be recognized. Also, risks for cancer development based on unopposed estrogen exposure are briefly discussed. Finally, the necessity for the exclusion of other explaining causes for the phenotypic features will be addressed and a diagnostic work up scheme presented.

In the original description of the syndrome, the histological confirmed polycystic nature of ovarian architecture was the primary abnormality. The association between endocrine

Received December 11, 2005; Accepted December 11, 2005.
Author to whom all correspondence and reprint requests should be addressed: F. J. Broekmans, MD, PhD, Department of Reproductive Medicine, University Medical Center, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. E-mail: f.broekmans@azu.nl

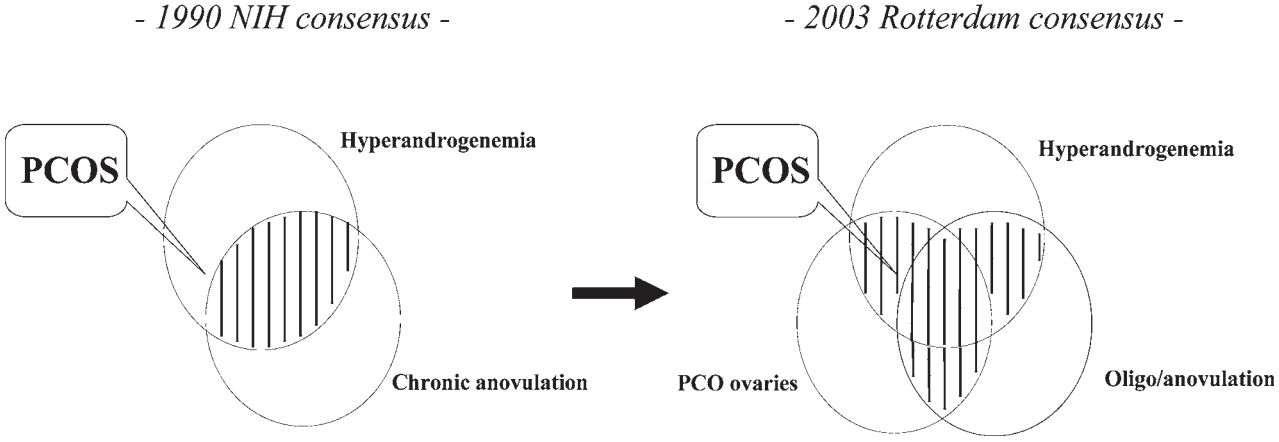

Fig. 1. Shift in criteria for the diagnosis of PCO syndrome.

abnormalities and ovarian morphology in cases with proven polycystic ovaries led to the use of serum LH and serum androgens as endocrine tests for the clinical diagnosis in patients with cycle disturbances with or without obesity *(14, 15)*. The ever presence of a considerable heterogeneity of clinical symptoms and endocrine profiles even implied that some women with polycystic ovaries on ultrasound appeared to have none of the endocrine and clinical features attributed to PCOS. In contrast, at the 1990 National Institute of Health conference on PCOS it was concluded that, for the diagnosis of the syndrome, evidence should be present of both hyperandrogenism and ovarian dysfunction and that presence of PCO morphology was not absolutely required *(16)* (Fig. 1). At the 2003 Rotterdam consensus workshop it was agreed that the polycystic ovary syndrome is principally a syndrome of ovarian dysfunction along with features of hyperandrogenism and PCO morphology *(3,8)* (Fig. 1). The new criteria broaden rather than replace the previous NIH criteria for PCOS diagnosis. Under the new criteria the prevalence of PCOS among the general female population may rise up to 10%. Whether these additional women diagnosed as PCOS under the new criteria truly represent a continuum of the broad and heterogeneous spectrum of PCOS, in terms of pathophysiology, response to ovulation induction treatment or long-term health consequences remains to be established.

Diagnosis: Key Features

Ovarian Dysfunction

Ovarian dysfunction is usually manifested as oligomenorrhea or amenorrhea resulting from chronic oligoovulation/anovulation. However, prolonged anovulation may sometimes lead to dysfunctional uterine bleeding that mimics menstrual bleeding *(17)*. Although the vast majority of diagnosed PCOS patients shows signs of ovarian dysfunction, the present diagnostic criteria *(3,8)* state that women with regular menstrual cycles may well be diagnosed as PCOS patients because of the presence of hyperandrogenism combined with PCO on ultrasound. From large series it has been reported that among women diagnosed with at least one symptom of PCOS approx 70–80% either had oligomenorrhea or amenorrhea *(4)*. In women presenting with oligomenorrhea or amenorrhea it has been shown that approx 80–90% of them eventually will be diagnosed with PCOS, while for those with amenorrhea this figure will amount to only 40% *(18)*, as in this group hypothalamic dysfunction is much more common. In PCOS women history taking will often reveal that menarche occurred at a time point some 1 or 2 yr later than normal *(19,20)*, that cycles are irregular (i.e., oligomenorrhea) from menarche onward, and that this irregularity often becomes camouflaged by the use of oral contraceptives *(17)*. When the use of oral contraceptives is interrupted, the original irregular cycle pattern is resumed. In some PCOS cases bleeds may become very frequent and occasionally very heavy. This is caused by long-term unopposed estrogen exposure leading to endometrial hyperplasia and uncontrolled estrogen-withdrawal bleeding *(17)*. Through the use of the new criteria these cases may still be recognized as PCOS (hyperandrogenism and PCO).

Endocrine features that are associated with the oligomenorrhea/amenorrhea include elevated levels of luteinizing hormone (LH), coexistant with levels of follicle-stimulating hormone (FSH) in the normal range. Both serum estradiol and progesterone levels are usually in the normal range for the early or mid-follicular phase of a normal cycle, unless sporadic dominant follicle growth and ovulation occurs. The reason why follicles remain arrested in the antral stage of 2–6 mm size and selection of one dominant follicle is impaired is one of the great enigmas of the PCOS syndrome. It may suffice to state here that the normal interplay between exposure to a late luteal and early follicular FSH rise and intraovarian regulation of the sensitivity of follicles to this FSH has become disrupted. Factors that contribute to this disrupted balance are the excessive intraovarian production of AMH *(21–23)* related to the increased size of the preantral and early antral follicle cohort, the

Table 1
Ultrasound Criteria and Approach in PCOS Diagnosis

Factor	Cut off	Method of assessment
Volume assessment	One or two ovaries volume > 10 cm^3	(length × width × thickness) × (π/6)
Number assessment	One or two ovaries ≥ 12 follicles sized 2–9 mm in diameter	Whole ovary scanning Follicle size from mean of two diameters
Test Conditions	Transvaginal approach No use of oral contraceptives After progestogen-induced or spontaneous bleed or random in oligomenorrhea/amenorrhea Absence of cysts > 10 mm	

intraovarian hyperandrogenism attributed to altered stimulation of theca cell function by LH and insulin growth factors, as well as alterations in theca and granulosa cell function based on altered enzymatic control of the synthesis of steroids and inhibins *(24–26)*.

Polycystic Ovary and Ovarian Morphology

From the initial publication by Stein and Leventhal, but possibly already in the 18th century, a characteristic ovarian morphology was described from histological examination of the wedges that were resected from the ovaries of women with oligomenorrhea and enlarged, polycystic ovaries at laparotomy. The ovary showed a prominent fibrotic thickening of the tunica albuginea, large numbers of small cystic follicles in the 2–6 mm size range, often showing signs of atresia and granulosa cell degeneration and hypertrophy, and luteinization of the inner theca cell layer *(27, 28)*. Moreover, the ovarian volume observed at laparotomy was clearly increased compared to the size in normal women. Quantitative histological data produced by Hughesdon and Webber indicated a two- to threefold increase in the number of follicles in all stages after the primordial follicle stage *(29,30)*. This implies that, up to the stage that follicles have attained FSH sensitivity, their number has more than doubled. With the use of transabdominal ultrasound, which became available from the late 1970s, reports described the ultrasound appearance of the ovaries in PCOS patients. It was in 1985 that the Adams group proposed to define the polycystic ovary appearance by abdominal ultrasound as the presence in one plane of at least 10 follicles within the size range of 2 × 8 mm arranged peripherally around a dense hyperechogenic core of the ovarian stroma *(31)*. The Adams criteria have been used in many studies for the detection of polycystic ovaries and were often used as a supportive finding in women with clinical signs and symptoms typical for PCO syndrome. Moreover, adequate correlation was found between the PCO ultrasound morphology and histopathological criteria *(27,28)*.

With the advent of the transvaginal ultrasonography, a more accurate view of ovarian structure could be obtained. In the report by Adams, polycystic ovaries as scanned through abdominal ultrasonography were discovered to have a larger volume compared to normal ovaries, although this feature was not incorporated in their classification. Studies using transvaginal sonography confirmed this notion and indicated that the preferred method for the calculation of ovarian volume is the formula for a prolate ellipsoid (π/6 × longitudinal × anteroposterior × transverse diameter) *(32, 33)*. From studies addressing the issue of ovarian volume measurements in PCOS patients, the Rotterdam consensus definition for polycystic ovary included the presence of one or two ovaries with a volume over 10 mL as the first feature. A second feature of ovarian architecture is the number and size of the antral follicles visible at ultrasound. With the use of transvaginal ultrasonography equipment it has become clear that the size range of follicles that contribute to the predominance of antral follicles present in the polycystic ovary tend to be in the size range of 2–5 mm, while larger follicles in the size range of 6–9 mm were not increased in number. According to the available literature *(32–35)* the criteria to define the PCO ovary are 12 or more follicles measuring 2–9 mm in diameter present in one or two ovaries. These findings in a single ovary present are sufficient to provide the diagnosis. The spatial distribution of the follicles and the architecture or echogenicity of the stroma are no longer key features in the ultrasound diagnosis.

Many normal healthy women in the general community will have an ultrasound appearance of polycystic ovaries but no relevant clinical symptoms, and little is known about the natural history and health risks of this group. Therefore, a distinction needs to be made between those women with polycystic ovaries without symptoms and those with symptoms and signs sufficient to warrant the diagnosis of PCOS Currently a woman with a PCOS ovary that has no evidence of ovulation disorders or hyperandrogenism should not be considered as having a PCO syndrome. Full description of the current consensus on ultrasound criteria are found in Table 1.

Hyperandrogenism

The frequent occurrence of clinical and/or biochemical signs of androgen excess in PCOS patients stems from increased synthesis and release of androgens from ovarian theca cells *(36)*. Elevated plasma levels of LH and insulin

synergistically lead to increased stimulation of theca cells to synthesize androgens. Moreover, theca cells in PCOS are believed to have enhanced efficiency for converting precursors into androgenic substances, like androstenedione and testosterone *(37,38)*. Also, high insulin levels tend to reduce production of sex hormone–binding globulin from liver cells, thereby raising the proportion of free circulating testosterone *(39)*. The presence of androgen excess itself may contribute to the presence of increased numbers of follicles in all stages *(36)*, as well in the arrest of FSH-sensitive follicles in their efforts to select a dominant follicle.

Clinical hyperandrogenism includes hirsutism, acne, male pattern hair loss, and, rarely, mild virilization *(40)*. The clinical signs of androgen excess result from the increased exposure to dihydrotestosterone, which is synthesized in the skin from circulating androgens and affects both hair follicles and sebaceous glands.

Hirsutism can be defined as the occurrence in females of male-type terminal hair growth and distribution. PCO syndrome is a very common cause of hirsutism, while the occurrence of hirsutism in PCOS patients is high (approx 60%). The frequency of occurrence of hirsutism may however vary with the race of the woman. For instance, the incidence in Japanese PCOS women is half of that in Caucasian *(41)*. The assessment of hirsutism should preferably be done using a standardized scoring system, as described by Ferriman and Gallwey *(42)*. In addition, the use of hormonal treatment for hirsutism should be avoided before true assessment of the body hair pattern.

Acne is present in one of three PCOS cases, while in young women with severe acne, a high percentage will be diagnosed with PCOS.

Male pattern hair loss (androgenic alopecia) is not frequently seen in PCOS cases, as it also requires a familial predisposition *(43)*. In this condition there is a progressive loss of terminal scalp hair over the crown area, while the frontal area is initially preserved. Widening of the hair parting ("geheimratsecken") may be the first sign of this type of hair loss.

Mild virilization, especially present as clitoromegaly, has been described as a possible feature in PCOS patients in the older literature *(40)*. It may well reflect more classic and thus severe cases of the syndrome. Frank virilization, especially of rapid onset, should urge the exclusion of a possible adrenal or ovarian androgen secreting tumor.

Biochemical hyperandrogenism is present in most patients with PCOS *(4,44)*. Assessment of circulating androgens as a tool for diagnosis in PCOS is, however, limited by the lack of normative ranges corrected for body mass index, race, and age *(45)*. Also, there is a wide array of androgenic substances circulating of which some may be considered more valuable than others *(46)*. From the Rotterdam consensus meeting it was advised to measure free testosterone or the free (testosterone) androgen index (FAI) by applying either equilibrium dialysis *(47,48)*, or calculating free testosterone from SHBG (sex hormone binding globulin) measurement and total testosterone, or by the ammonium sulfate precipitation technique *(49)*. The use of total testosterone assays as well as the measurement of dehydroepiandrosteronesulphate and androstenedione are currently considered as having no additional value *(3,8)*.

Diagnosis: Associated Features

Obesity

Obesity has been one of the features for the diagnosis of PCOS in the classical description by Stein and Leventhal *(1)*. Indeed, in many cases of PCOS, body mass index (BMI) is increased above or may even greatly exceed the limit of normality (≥25 kg/m^2 being considered as overweight, ≥27 kg/m^2 as obese). However, the BMI also may be in the normal or even subnormal range (<19 kg/m^2, lean PCO). Even more important is the notion that fat distribution often follows the abdominal pattern, with increased waist-to-hip ratio or waist circumference (central obesity). As this pattern is typically associated with increased risk of cardiovascular disease, in the diagnostic criteria for the metabolic syndrome (see below) obesity is defined as a waist circumference of more than 88 cm (35 in.).

Although the cause for the occurrence of obesity in PCOS patients remains largely unknown, androgen excess and insulin resistance are considered as the main independent factors that contribute to the development of central obesity in PCOS cases, while the role of leptin remains to be further elucidated. Obesity induces, through the path of insulin resistance, the presence of oligoovulation/anovulation, and caloric restriction, even with mild body weight reduction will frequently lead to restoration of ovarian function *(50–52)*. Also, obesity increases the risk of developing type II diabetes and cardiovascular disease like hypertension and cerebral/coronary artery disease. Both obesity and the long-term sequela in the field of glucose tolerance and vascular compromise are considered part of the so-called metabolic syndrome, which will be discussed below.

Elevated LH

Elevated LH, in the presence of normal levels of FSH, has long been one of the basic features of the diagnosis. Increased frequency of LH pulses in the peripheral blood, resulting from a presumed altered GnRH pulse frequency, is the cause of the rise in serum LH *(53,54)*. Increased pulse frequency may be caused by continued low progesterone levels or be a consequence of an intrinsic abnormality of the pulse generator. Elevated LH is found in over 60% of PCOS cases and is thought to be one of the actors in the increased theca cell production of androgens. Alternatively, elevated LH may play a role in the lower rates of ongoing pregnancies obtained in PCOS patients, but definite proof for such contention, as well as for the benefits of LH manipulation, has not been provided to date *(107)*. According to

Table 2
Tests for Assessment of Insulin Sensitivity

Test	Correlation with clamp test	Calculation	Cut off for insulin resistance in PCOS	Note
Hyperinsulinemic-euglycemic clamp	Gold standard	—	—	—
Oral glucose tolerance test	Good	G_{120}/I_{120}	≤1.0 mg/dL/μU/mL	Various modifications exist
Fasting insulin	Good	I_0	≥20 μU/mL (White) ≥23 μU/mL (Hispanic)	No standard assay Not accurate in hyperglycemia Race differences
Fasting glucose/insulin ratio[a]	Good	G_0/I_0	≤4.5 mg/dL/μU/mL (White) ≤7.2 mg/dL/μU/mL (White) ≤4.0 mg/dL/μU/mL (Hispanic)	No standard assay Not accurate in hyperglycemia Race differences

Adapted from Legro *(73)*.

[a]The Homeostatic Model Assessment (HOMA) and Quantitative Insulin Sensitivity Check Index (QUICKI) both apply the results of the fasting glucose and insulin levels in an adapted fashion and are applicable to cases with fasting hyperglycemia. For calculation and reference values see Legro *(73)*.

the Rotterdam consensus, LH measurements are not essential for the diagnosis of PCOS, but may be useful in lean women with oligoamenorrhea that do not otherwise fulfil the new criteria.

Insulin Resistance

As already stated, there is an increased risk for the development of type II diabetes and gestational diabetes in PCOS women *(55–58)*. This seems especially true for PCOS women with obesity or overweight *(57,59)*, although normal weight PCOS women still have increased incidence of diabetes. In longitudinal studies on PCOS women with either normal or impaired glucose tolerance, a high number of cases developed either impaired tolerance, or overt diabetes type II *(60)*. The disturbance in carbohydrate metabolism is clearly associated with the increased presence of insulin resistance in PCOS cases, with an estimated risk of between 50 and 70% *(61)*. Resistance to insulin in fat and skeletal tissue cells stems from defects in the insulin signaling pathways that may typically be present in PCOS cases *(62–64)*. Overt glucose intolerance, however, will only develop in those PCOS cases where, in addition to the insulin resistance, pancreatic β cell capacity to respond to the increased demand is insufficient *(65–67)*. Apart from being a key factor in the development of glucose intolerance, high levels of insulin-related growth factors will stimulate theca cells to produce excess amounts of androgens. Therefore, insulin resistance is one of the targets for therapy in PCOS, both for the control of glucose tolerance as well as for the restoration of ovarian function *(68–72)*. For this purpose both life style changes (caloric restriction and weight loss) and the use of insulin sensitizers has shown to be effective. Therefore, PCOS women are advised to be screened for the presence of insulin resistance and glucose intolerance.

Table 3
Consensus Criteria
for the Metabolic Syndrome in Women with PCOS[a]

Risk Factor	Abnormal result
1. Abdominal Obesity (waist circumference)	>88 cm or > 35 inch
2. Triglycerides	≥150 mg/dL
3. HDL-C (high density lipoprotein-cholesterol)	<50 mg/dL
4. Blood pressure	≥130/≥ 85 mmHg
5. Fasting and/or	>110–126 mg/dL
2 h glucose level after 75 g oral glucose	140–199 mg/dL

[a]At least three out of the five criteria have to be met for the diagnosis *(76)*.

Assessment of insulin tolerance may be difficult *(73)* (see Table 2). The ratio of fasting levels of insulin and the glucose/insulin ratio both correlate well with the results of more laborious tests like the euglycemic clamp test, but there is lack of a standardized insulin assay. Also, insulin levels show physiological fluctuations and β cell function may become altered in PCOS cases, changing the sensitivity of the test. Therefore, to date, specific screening for insulin resistance is not recommended. Instead, it was agreed to apply the criteria for the presence of the so-called metabolic syndrome, which comprises factors related to insulin resistance and cardiovascular disease, as will be listed below (Table 3). In this set of criteria oral glucose tolerance testing is incorporated to identify cases with impaired glucose tolerance based solely on the 2 h glucose. Oral glucose tolerance testing using both fasting and 2 h glucose levels especially is advised in obese PCOS women *(9,10,57,60,73,74)*.

Acanthosis nigricans is a skin eruption clearly associated with the presence of insulin resistance in PCOS *(75)*. It is found as areas of increased pigmentation and papillomatosis of the skin of the backside of the neck, and in skin flexures, preferably the axilla region. Its presence is found in 1–3% of PCOS cases.

Metabolic Syndrome

Apart from the criteria for the presence of impaired glucose intolerance, the metabolic syndrome as defined in Table 3 represents risk factors for the development of cardiovascular disease. The criteria used for the metabolic syndrome are based on the third report of the National Cholesterol Education Program (NCEP) *(76)*, which was recently adjusted as for the treatment approach in cases that were diagnosed based on this definition *(77)*. Although debates upon the preferred definition of the metabolic syndrome are still ongoing, it is crucial to apply a consented definition within the field of PCOS to be able to evaluate the role of this condition as for the long-term health risks in PCOS. With the current definition (three out of five criteria as listed in the table), the incidence of the metabolic syndrome in PCOS is not well established, although recent observations suggest it to be around 40–50% *(78–80)*. The increased presence of dyslipidemia, however, has been more clearly established *(81–83)*. This disturbance itself may be related to or even manifested by the presence of obesity, hyper-androgenism, and hyperinsulinemia.

The question whether PCOS women do have an increased risk for the development of cardiovascular disease, based on the increased incidence of hyperlipidemia and insulin resistance, remains to be answered. Studies on true outcome variables like cardiovascular morbidity and mortality rates show a trend toward a higher incidence of hypertension only *(84–88)*. If biochemical and histological markers for vascular damage are taken as measure, PCOS patients show alterations in platelet and endothelium function, as well as clear changes in vascular architecture associated with arterial disease *(89–95)*. All this seems to be truer for the obese PCOS case and argues for the longitudinal follow up of PCOS patients to assess the true risk for cardiovascular disease. At present, assessment of the presence of the metabolic syndrome is advised for obese PCOS cases, as well as for non-obese PCOS with insulin resistance and a family history of type II diabetes *(3,8)*.

Cancer Risk

Unopposed exposure to estrogens has been known as an important risk factor for the development of endometrial hyperplasia and eventually endometrial carcinoma. Women with PCOS do have an increased life time risk for endometrial carcinoma, as has been suggested by several studies *(96–98)*. Whether this is caused by unopposed estrogen exposure due to ovarian dysfunction alone or also by the presence of diabetes and obesity, which in itself are risk factors for endometrial carcinoma, is difficult to assess. Currently, it is advised to perform endometrial histological evaluation through directed biopsy at hysteroscopy, endometrial brush, or curettage in cases with heavy prolonged bleeding or sustained increased endometrial thickness at transvaginal ultrasound *(99)*. Risks for the development of cancers of the breast, ovary or uterine cervix have shown to be not increased.

Differential Diagnosis

In the consensus meeting on the diagnosis PCO syndrome it was decided to use three key criteria, of which at least 2 should be present, while exclusion of other aetiologies was mandatory. In the following other possible explanations for two of the key features of PCOS are briefly summarised.

Other Causes of Oligomenorrhea/Amenorrhea

1. Hypogonadotropic (WHO I)
   - Stress, weight or exercise related: Plasma levels for both gonadotropins and estrogens are typically low.
   - Hyperprolactinemia: Galactorrhea is often present and prolactin levels are elevated. Further work-up directed toward pituitary adenoma, history on central nervous system drug use, evaluation of thyroid function *(100,101)*.
2. Hypergonadotropic (WHO III)
   - Plasma levels for both gonadotropins are typically elevated and levels for estrogens low.
3. Normogonadotropic (WHO II)
   - Levels for both gonadotropins are in the normal range and only one or none of the criteria for PCOS present. These cases should be categorized as WHO II non PCOS.

Other Causes of Hyperandrogenism

1. Congenital adrenal hyperplasia (see Fig. 2). This disorder comprises several possible enzymatic defects, of which the 21-hydroxylase deficiency is by far the most common *(102)*. It is the non-classic, late onset type in which the enzymatic defect is partial, that has to be excluded in a suspected PCOS case. Levels of 17-hydroxy-progesterone are elevated in the follicular or anovulation state of ovarian function. Also, the increased production of androstenedione and testosterone, which results from the pooling of 17-OH-progesterone, leads to clinical hyperandrogenism, which may be indistinguishable from that in PCOS women. However, hirsutism may be more severe and, more frequently, signs of virilization are present. Inheritance is autosomal-recessive and explains a family tendency. The ovaries on ultrasound may show the same appearance as is typical for PCOS patients. Cases with partial 11-β-hydroxylase deficiency largely show the same features as the much more common partial 21-hydroxylase deficiency, but in addition have elevated levels of 11-deoxycortisol and an accompanying arterial hypertension *(103)*.
2. Cushing's syndrome. This rare entity results from excessive cortisol production based on the presence of an adrenal neoplasm or driven by enhanced ACTH release, which is almost invariably due to a pituitary tumor and seldom

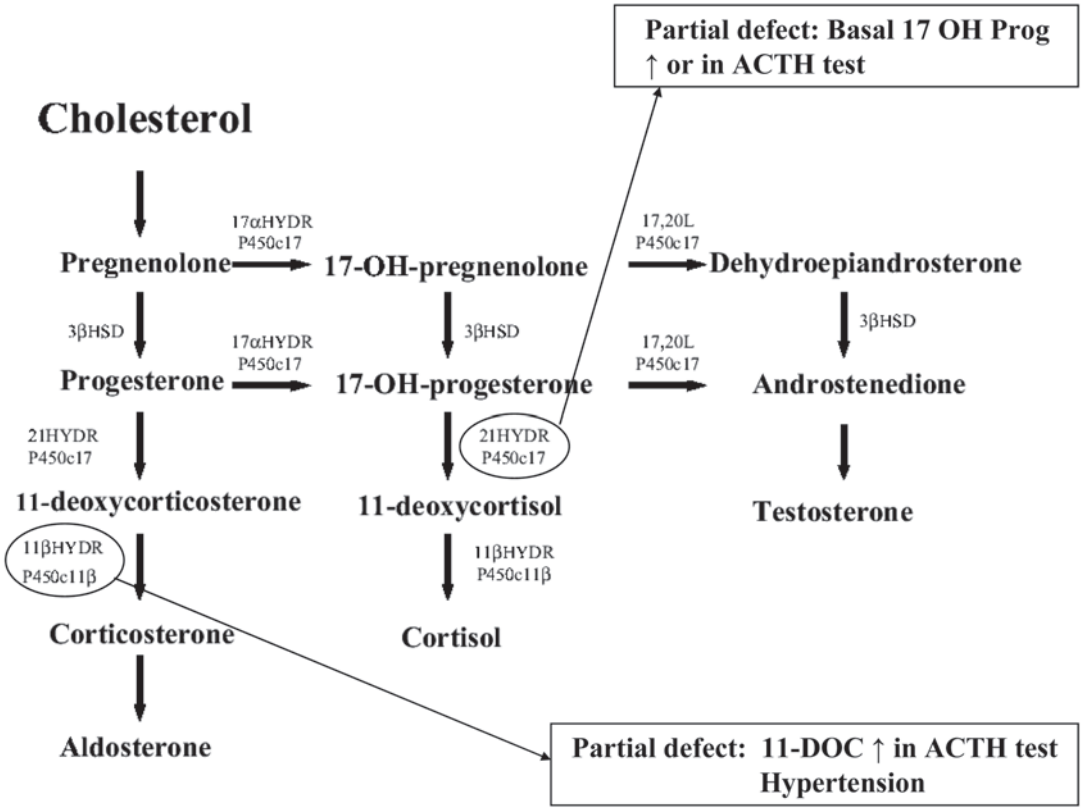

Fig. 2. Scheme of steroid synthesis pathways in the adrenals, showing effects of partial enzymatic failure of 21-hydroxylase and 11-β-hydroxylase.

from ectopic origin. The presence of obesity, hirsutism, acne, and oligomenorrhea may create confusion with the PCOS but the finding of signs like moon face, muscle waisting, abdominal striae, and hypertension point toward hypercortisolism. Fasting cortisol levels may be elevated and diurnal rhythm absent. Failure to suppress cortisol levels in an overnight dexamethasone suppression test is the final clue for diagnosis *(104)*.

3. Androgen-producing neoplasms. These rare tumors may arise in the ovary or adrenal gland. The clinician should be alerted to their possible presence in cases with rapid development of severe hirsutism, acne, and virilization, with clitoromegaly, deepening of the voice and a male body shape. Secondary to raised androgen levels, PCO-like morphology of the ovaries may develop, as well as oligomenorrhea/amenorrhea. Levels of testosterone and androstenedione may be elevated far more above upper limits for normality and may urge to apply imaging techniques of the adrenals and ovaries like MRI or CT *(105,106)*.

References

1. Stein, I. and Leventhal, M. (1935). *Am. J. Obstet. Gynecol.* **29,** 181.
2. Goudas, V. T. and Dumesic, D. A. (1997). *Endocrinol. Metab. Clin. North Am.* **26,** 893–912.
3. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). (2004). *Hum. Reprod.* **19,** 41–47.
4. Balen, A. H., Conway, G. S., Kaltsas, G., et al. (1995). *Hum. Reprod.* **10,** 2107–2111.
5. van Santbrink, E. J., Hop, W. C., and Fauser, B. C. (1997). *Fertil. Steril.* **67,** 452–458.
6. Balen, A. and Michelmore, K. (2002). *Hum. Reprod.* **17,** 2219–2227.
7. Cussons, A. J., Stuckey, B. G., Walsh, J. P., Burke, V., and Norman, R. J. (2005). *Clin. Endocrinol. (Oxf.)* **62,** 289–295.
8. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. (2004). *Fertil. Steril.* **81,** 19–25.
9. Bloomgarden, Z. T. (2004). *Diabetes Care* **27,** 824–830.
10. Bloomgarden, Z. T. (2003). *Diabetes Care* **26,** 1297–1303.
11. Azziz, R. (2005). *Fertil. Steril.* **83,** 1343–1346.
12. Geisthovel, F. (2003). *Reprod. Biomed. Online* **7,** 602–605.
13. Jonard, S., Robert, Y., and Dewailly, D. (2005). *Hum. Reprod.* **20,** 2893–2898.
14. Franks, S. (1995). *N. Engl. J. Med.* **333,** 853–861.
15. Balen, A. (1999). *Lancet* **354,** 966–967.
16. Zawadski, J. K. and Dunaif, A. (1992). In: *Polycystic ovary syndrome*. Dunaif, A., Givens, J. R., and Haseltine, F. (eds.), Blackwell Scientific, Boston, pp. 377–384.
17. Fraser, I. S. and Kovacs, G. (2004). *Best Pract. Res. Clin. Obstet. Gynaecol.* **18,** 813–823.
18. Goldzieher, J. W. and Green, J. A. (1962). *J. Clin. Endocrinol. Metab.* **22,** 325–338.
19. Sadrzadeh, S., Klip, W. A., Broekmans, F. J., et al. (2003). *Hum. Reprod.* **18,** 2225–2230.
20. Helm, P., Munster, K., and Schmidt, L. (1995). *Acta Obstet. Gynecol. Scand.* **74,** 718–722.
21. Stubbs, S. A., Hardy, K., Silva-Buttkus, P., et al. (2005). *J. Clin. Endocrinol. Metab.* **90,** 5536–5543.

22. Piltonen, T., Morin-Papunen, L., Koivunen, R., Perheentupa, A., Ruokonen, A., and Tapanainen, J. S. (2005). *Hum. Reprod.* **20,** 1820–1826.
23. Pigny, P., Merlen, E., Robert, Y., et al. (2003). *J. Clin. Endocrinol. Metab.* **88,** 5957–5962.
24. Strauss, J. F. III. (2003). *Ann. NY Acad. Sci.* **997,** 42–48.
25. Welt, C. K., Taylor, A. E., Fox, J., Messerlian, G. M., Adams, J. M., and Schneyer, A. L. (2005). *J. Clin. Endocrinol. Metab.* **90,** 5582–5587.
26. Welt, C. K., Taylor, A. E., Martin, K. A., and Hall, J. E. (2002). *J. Clin. Endocrinol. Metab.* **87,** 5559–5565.
27. Saxton, D. W., Farquhar, C. M., Rae, T., Beard, R. W., Anderson, M. C., and Wadsworth, J. (1990). *Br. J. Obstet. Gynaecol.* **97,** 695–699.
28. Takahashi, K., Eda, Y., Abu-Musa, A., Okada, S., Yoshino, K., and Kitao, M. (1994). *Hum. Reprod.* **9,** 1231–1236.
29. Hughesdon, P. E. (1982). *Obstet. Gynecol. Surv.* **37,** 59–77.
30. Webber, L. J., Stubbs, S., Stark, J., et al. (2003). *Lancet* **362,** 1017–1021.
31. Adams, J., Franks, S., Polson, D. W., et al. (1985). *Lancet* **2,** 1375–1379.
32. Jonard, S., Robert, Y., and Dewailly, D. (2005). *Hum. Reprod.* **20,** 2893–2898.
33. Balen, A. H., Laven, J. S., Tan, S. L., and Dewailly, D. (2003). *Hum. Reprod. Update* **9,** 505–514.
34. Pache, T. D., de Jong, F. H., Hop, W. C., and Fauser, B. C. (1993). *Fertil. Steril.* **59,** 544–549.
35. Pache, T. D., Wladimiroff, J. W., Hop, W. C., and Fauser, B. C. (1992). *Radiology* **183,** 421–423.
36. Jonard, S. and Dewailly, D. (2004). *Hum. Reprod. Update* **10,** 107–117.
37. Nelson, V. L., Qin, K. N., Rosenfield, R. L., et al. (2001). *J. Clin. Endocrinol. Metab.* **86,** 5925–5933.
38. Nelson, V. L., Legro, R. S., Strauss, J. F. III, and McAllister, J. M. (1999). *Mol. Endocrinol.* **13,** 946–957.
39. Pugeat, M., Ducluzeau, P. H., and Mallion-Donadieu, M. (2000). *Horm. Res.* **54,** 322–326.
40. Goldzieher, J. W. and Axelrod, L. R. (1963). *Fertil. Steril.* **14,** 631–653.
41. Carmina, E. and Lobo, R. A. (1993). *J. Clin. Endocrinol. Metab.* **76,** 1111–1114.
42. Ferriman, D. and Gallwey, J. D. (1961). *J. Clin. Endocrinol. Metab.* **21,** 1440–1447.
43. Hart, R., Hickey, M., and Franks, S. (2004). *Best Pract. Res. Clin. Obstet. Gynaecol.* **18,** 671–683.
44. Laven, J. S., Imani, B., Eijkemans, M. J., and Fauser, B. C. (2002). *Obstet. Gynecol. Surv.* **57,** 755–767.
45. Bili, H., Laven, J., Imani, B., Eijkemans, M. J., and Fauser, B. C. (2001). *Eur. J. Endocrinol.* **145,** 749–755.
46. Rittmaster, R. S. (1993). *Endocr. Rev.* **14,** 121–132.
47. Imani, B., Eijkemans, M. J., de Jong, F. H., et al. (2000). *J. Clin. Endocrinol. Metab.* **85,** 676–682.
48. Vermeulen, A., Verdonck, L., and Kaufman, J. M. (1999). *J. Clin. Endocrinol. Metab.* **84,** 3666–3672.
49. Tremblay, R. R. and Dube, J. Y. (1974). *Contraception* **10,** 599–605.
50. Kiddy, D. S., Hamilton Fairley, D., Bush, A., et al. (1992). *Clin. Endocrinol. (Oxf.)* **36,** 105–111.
51. Hoeger, K. M., Kochman, L., Wixom, N., Craig, K., Miller, R. K., and Guzick, D. S. (2004). *Fertil. Steril.* **82,** 421–429.
52. Hoeger, K. (2001). *Obstet. Gynecol. Clin. North Am.* **28,** 85–97, vi–vii.
53. Burger, C. W., Korsen, T., Van Kessel, H., van Dop, P. A., Caron, F. J., and Schoemaker, J. (1985). *J. Clin. Endocrinol. Metab.* **61,** 1126–1132.
54. Waldstreicher, J., Santoro, N. F., Hall, J. E., Filicori, M., and Crowley, W. F. J. (1988). *J. Clin. Endocrinol. Metab.* **66,** 165–172.
55. Elting, M. W., Korsen, T. J., Bezemer, P. D., and Schoemaker, J. (2001). *Hum. Reprod.* **16,** 556–560.
56. Dahlgren, E., Johansson, S., Lindstedt, G., et al. (1992). *Fertil. Steril.* **57,** 505–513.
57. Legro, R. S., Kunselman, A. R., Dodson, W. C., and Dunaif, A. (1999). *J. Clin. Endocrinol. Metab.* **84,** 165–169.
58. Lesse, K. B. and Garcia, F. A. (1997). *J. Matern. Fetal Med.* **6,** 303–307.
59. Legro, R. S., Driscoll, D., Strauss, J. F. III, Fox, J., and Dunaif, A. (1998). *Proc. Natl. Acad. Sci. USA* **95,** 14956–14960.
60. Norman, R. J., Masters, L., Milner, C. R., Wang, J. X., and Davies, M. J. (2001). *Hum. Reprod.* **16,** 1995–1998.
61. Hanson, R. L., Imperatore, G., Bennett, P. H., and Knowler, W. C. (2002). *Diabetes* **51,** 3120–3127.
62. Dunaif, A., Segal, K. R., Futterweit, W., and Dobrjansky, A. (1989). *Diabetes* **38,** 1165–1174.
63. Dunaif, A. (1997). *Endocr. Rev.* **18,** 774–800.
64. Dunaif, A., Wu, X., Lee, A., and Diamanti-Kandarakis, E. (2001). *Am. J. Physiol. Endocrinol. Metab.* **281,** E392–E399.
65. Ehrmann, D. A., Sturis, J., Byrne, M. M., Karrison, T., Rosenfield, R. L., and Polonsky, K. S. (1995). *J. Clin. Invest.* **96,** 520–527.
66. Ehrmann, D. A. (2004). *Reprod. Biomed. Online* **9,** 28–34.
67. O'Meara, N. M., Blackman, J. D., Ehrmann, D. A., et al. (1993). *J. Clin. Endocrinol. Metab.* **76,** 1241–1247.
68. Diamanti-Kandarakis, E., Alexandraki, K., Protogerou, A., et al. (2005). *Eur. J. Endocrinol.* **152,** 749–756.
69. Fleming, R., Harborne, L., MacLaughlin, D. T., et al. (2005). *Fertil. Steril.* **83,** 130–136.
70. Harborne, L. R., Sattar, N., Norman, J. E., and Fleming, R. (2005). *J. Clin. Endocrinol. Metab.* **90,** 4593–4598.
71. Ibanez, L., Ferrer, A., Ong, K., Amin, R., Dunger, D., and de Zegher, F. (2004). *J. Pediatr.* **144,** 23–29.
72. Knowler, W. C., Barrett-Connor, E., Fowler, S. E., et al. (2002). *N. Engl. J. Med.* **346,** 393–403.
73. Legro, R. S., Castracane, V. D., and Kauffman, R. P. (2004). *Obstet. Gynecol. Surv.* **59,** 141–154.
74. Ehrmann, D. A., Barnes, R. B., Rosenfield, R. L., Cavaghan, M. K., and Imperial, J. (1999). *Diabetes Care* **22,** 141–146.
75. Conway, G. S. and Jacobs, H. S. (1993). *Clin. Endocrinol. (Oxf.)* **39,** 623–632.
76. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). (2001). *JAMA* **285,** 2486–2497.
77. Stone, N. J., Bilek, S., and Rosenbaum, S. (2005). *Am. J. Cardiol.* **96,** 53E–59E.
78. Dokras, A., Bochner, M., Hollinrake, E., Markham, S., Vanvoorhis, B., and Jagasia, D. H. (2005). *Obstet. Gynecol.* **106,** 131–137.
79. Apridonidze, T., Essah, P. A., Iuorno, M. J., and Nestler, J. E. (2005). *J. Clin. Endocrinol. Metab.* **90,** 1929–1935.
80. Ehrmann, D. A., Liljenquist, D. R., Kasza, K., Azziz, R., Legro, R. S., and Ghazzi, M. N. (2005). *J. Clin. Endocrinol. Metab.* **91,** 48–53.
81. Wild, R. A. (2002). *Am. J. Obstet. Gynecol.* **186,** 35–43.
82. Wild, R. A. (2002). *Hum. Reprod. Update* **8,** 231–241.
83. Legro, R. S., Kunselman, A. R., and Dunaif, A. (2001). *Am. J. Med.* **111,** 607–613.
84. Dahlgren, E., Janson, P. O., Johansson, S., Lapidus, L., and Oden, A. (1992). *Acta Obstet. Gynecol. Scand.* **71,** 599–604.
85. Pierpoint, T., McKeigue, P. M., Isaacs, A. J., Wild, S. H., and Jacobs, H. S. (1998). *J. Clin. Epidemiol.* **51,** 581–586.
86. Wild, S., Pierpoint, T., Jacobs, H., and McKeigue, P. (2000). *Hum. Fertil. (Camb.)* **3,** 101–105.
87. Wild, S., Pierpoint, T., McKeigue, P., and Jacobs, H. (2000). *Clin. Endocrinol. (Oxf.)* **52,** 595–600.

88. Elting, M. W., Korsen, T. J., Bezemer, P. D., and Schoemaker, J. (2001). *Hum. Reprod.* **16,** 556–560.
89. Dereli, D., Ozgen, G., Buyukkececi, F., Guney, E., and Yilmaz, C. (2003). *J. Clin. Endocrinol. Metab.* **88,** 2263–2268.
90. Meyer, C., McGrath, B. P., and Teede, H. J. (2005). *J. Clin. Endocrinol. Metab.* **90,** 5711–5716.
91. Meyer, C., McGrath, B. P., Cameron, J., Kotsopoulos, D., and Teede, H. J. (2005). *J. Clin. Endocrinol. Metab.* **90,** 4630–4635.
92. Paradisi, G., Steinberg, H. O., Hempfling, A., et al. (2001). *Circulation* **103,** 1410–1415.
93. Orio, F. Jr., Palomba, S., Cascella, T., et al. (2004). *Reprod. Biomed. Online* **9,** 505–510.
94. Orio, F. Jr., Palomba, S., Cascella, T., et al. (2004). *J. Clin. Endocrinol. Metab.* **89,** 4588–4593.
95. Carmina, E., Chu, M. C., Longo, R. A., Rini, G. B., and Lobo, R. A. (2005). *J. Clin. Endocrinol. Metab.* **90,** 2545–2549.
96. Hardiman, P., Pillay, O. C., and Atiomo, W. (2003). *Lancet* **361,** 1810–1812.
97. Dahlgren, E., Friberg, L. G., Johansson, S., et al. (1991). *Eur. J. Obstet. Gynecol. Reprod. Biol.* **41,** 143–150.
98. Chamlian, D. L. and Taylor, H. B. (1970). *Obstet. Gynecol.* **36,** 659–666.
99. Schmeler, K. M., Soliman, P. T., Sun, C. C., Slomovitz, B. M., Gershenson, D. M., and Lu, K. H. (2005). *Gynecol. Oncol.* **99,** 388–392.
100. Raber, W., Gessl, A., Nowotny, P., and Vierhapper, H. (2003). *Clin. Endocrinol. (Oxf.)* **58,** 185–191.
101. Biller, B. M. (1999). *J. Reprod. Med.* **44,** 1095–1099.
102. Azziz, R., Hincapie, L. A., Knochenhauer, E. S., Dewailly, D., Fox, L., and Boots, L. R. (1999). *Fertil. Steril.* **72,** 915–925.
104. Azziz, R., Boots, L. R., Parker, C. R. Jr., Bradley, E. Jr., and Zacur, H. A. (1991). *Fertil. Steril.* **55,** 733–741.
105. Lindsay, J. R. and Nieman, L. K. (2005). *Endocrinol. Metab. Clin. North Am.* **34,** 403–421, x.
106. Waggoner, W., Boots, L. R., and Azziz, R. (1999). *Gynecol. Endocrinol.* **13,** 394–400.
106. Danilowicz, K., Albiger, N., Vanegas, M., Gomez, R. M., Cross, G., and Bruno, O. D. (2002). *Obstet. Gynecol.* **100,** 1099–1102.
107. Hamburg, R. (2006). *Clin. Endocrinol. Metab.* **20,** 281–292.