Consensus of the French Endocrine Society on Female Hyperandrogenism

Polycystic ovary syndrome (PCOS)

Le syndrome des ovaires polymicrokystiques

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Available online 22 January 2010

Abstract

1. The Rotterdam classification should be used to define PCOS in the event of: menstrual cycle anomalies; amenorrhoea, oligomenorrhoea or long cycles, clinical and/or biochemical hyperandrogenism and ultrasound appearance of polycystic ovaries.
2. The presence of two of these three criteria is sufficient once all other diagnoses have been ruled out.
3. Diagnosis of hirsutism should not be based on the Ferriman-Gallway score.
4. The ultrasound definition of PCOS contains precise criteria that must be included in the report: presence of at least 12 follicles in each ovary measuring 2–9 mm in diameter, and/or increase in ovary size > 10 ml.
5. Screening for elevated plasma LH no longer necessary. Testing for GnRH serves no purpose.
6. Routine screening for metabolic abnormalities should be carried out systematically based on weight, height and BMI, waist circumference, blood pressure and laboratory parameters: plasma glucose, triglycerides, HDL cholesterol.
7. In the case of obesity (BMI > 30 kg/m\textsuperscript{2}), oral glucose tolerance testing (OGTT) is recommended where fasting serum glucose is normal.
8. Clomiphene citrate (CC) remains the first-line therapy for ovulation induction. In patients with BMI > 30, it should be preceded by improvement of metabolic status through appropriate lifestyle modifications.

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Keywords: Polycystic ovary syndrome; Female hyperandrogenism; French consensus

1. Recommendation No. 1

The Rotterdam classification should be used to define Polycystic ovary syndrome (PCOS) in the event of:

- menstrual cycle anomalies: amenorrhoea, oligomenorrhoea or long cycles;
- clinical and/or biochemical hyperandrogenism;
- ultrasound appearance of polycystic ovaries.

1.1. Comments

PCOS is an ovarian dysfunction syndrome of which the main features are hyperandrogenism and an ultrasound appearance of polycystic ovaries (PCO)\textsuperscript{[1]}. Clinical signs may include: irregular menstruation, signs of androgen excess and obesity. Since the 1990 conference on PCOS under the aegis of the NIH, the syndrome now includes a broader spectrum of signs and symptoms of ovarian dysfunction than that set out in the original criteria\textsuperscript{[2]}. It is now agreed that women with regular menstrual cycles and hyperandrogenism and/or PCO at ultrasound are in fact presenting this syndrome\textsuperscript{[3–5]}. In addition, the majority of
authors now agree that women with this syndrome may present an appearance of PCO at ultrasound without any sign of androgen excess, although with indicators of ovarian dysfunction [6]. However, some authors continue to contest this phenotype [7].

PCOS remains a syndrome and as such, no single diagnostic feature (e.g. hyperandrogenism or appearance of PCO) is sufficient in itself to establish the clinical diagnosis. Similarly, PCOS is diagnosed by exclusion, and disorders having a phenotype related to that of PCOS must be ruled out.

1.2. Exclusion of related disorders

In diagnosing PCOS, it is important to rule out disorders with similar clinical features such as congenital adrenal hyperplasia, Cushing syndrome and virilising tumours. Routine screening for thyroid dysfunction in hyperandrogenic patients is of little value since the incidence of these disorders is not higher in hyperandrogenic patients than in normal women of child-bearing age. However, routine determination of TSH levels in hyperandrogenic patients should not be abandoned because of the importance of detecting thyroid disorders in women of child-bearing potential.

The initial workup for women consulting for oligoovulation should include assay of plasma FSH and oestradiol (E2) in order to rule out hypogonadotrophic hypogonadism (i.e. ovarian dysfunction of central origin) or premature ovarian failure, which is characterised by low E2 levels and elevated FSH based on the WHO classification [8,9]. PCOS is classified as normo-ovestrogenic normogonadotropic anovulation (WHO group 2) [1,10]. It should nevertheless be stressed that serum LH is frequently augmented in these patients, as discussed below.

Routine determination of prolactin should be maintained in the workup for hyperandrogenism, although it must be noted that in many hyperandrogenic patients prolactin levels are either the upper limit of normal or slightly over.

Finally, severe insulin-resistance syndromes (HAIR-AN syndrome) [11], Cushing syndrome [12], androgen-secreting tumours [12,13] and use of high-dose of androgens [14] must be ruled out in the event of clinical suspicion.

2. Recommendation No. 2

Diagnosis of hirsutism should not be based on the Ferriman-Gallway score.

2.1. Comments

Although the main clinical indicator of androgen excess is the presence of hirsutism [15], the following points must be stressed:

- no norms have as yet been established in large populations;
- evaluation of hirsutism is relatively subjective [16]. Very low Ferriman-Gallway scores (less than five) may in fact be associated with patient complaints of hirsutism resulting in biochemical diagnosis of hyperandrogenism in 50% of cases [17];
- few practitioners use standardised scores in reality;
- hirsutism is often treated long before the patient undergoes endocrinological assessment;
- while hirsutism may be significantly less frequent among hyperandrogenic women from the far East [5] and adolescents [18], its prevalence is identical among black women and white women [19].

The presence of acne is in itself a potential marker for hyperandrogenism, although the exact prevalence of androgen excess in acne patients is still debated in the literature [20]. While androgenic alopecia alone has not been satisfactorily validated as an indicator of hyperandrogenism, it nevertheless appears to be a relatively poor marker for androgen excess, except in patients with oligomenorrhea [21].

3. Recommendation No. 3

The ultrasound definition of PCOS contains precise criteria that must be included in the report:

- presence of at least 12 follicles in each ovary measuring 2–9 mm in diameter;
- and/or increase in ovary size greater than 10 ml.

3.1. Comments

Based on data available in the literature [10,22], the following criteria have sufficient specificity and sensitivity for the definition of PCO:

- “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” (for a review see Balen et al. [23]). This definition should not be replaced by a subjective appearance of PCO. Follicle distribution must be omitted, together with increased stromal echogenicity and volume. Although increased stromal volume is a characteristic feature of PCO [24], determination of ovarian size has been shown to be a good replacement for quantitation of stromal volume in clinical practice [25]. 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 [26]. A single ovary meeting the definition forms a sufficient basis for PCO. In the event of a dominant follicle (greater than 10 mm or a corpus luteus), a further examination should be carried out during the subsequent cycle. Additional investigations should be performed if a cyst or ovarian asymmetry is detected (possibly suggesting full formation);
• in the absence of ovulation disorders or hyperandrogenism, women presenting PCO (asymptomatic PCO) should not be considered as presenting PCOS before further data has been collected concerning the clinical condition;
• in addition to its role in defining PCOS, ultrasound is useful for predicting fertility with clomiphene citrate treatment [27] and risk of ovarian hyperstimulation syndrome (OHSS) [23]. It is accepted that the appearance of PCO may be encountered in women prior to ovarian stimulation for IVF, in the absence of overt signs of PCOS. Upon stimulation, such ovaries behave in the same way as those of women with PCOS and there is thus a risk of OHSS [28];
• finally, ultrasound may be used to screen for endometrial hyperplasia in these patients at risk.

The following technical recommendations must be emphasised:
• the necessary equipment must be updated and used by properly trained staff;
• the transvaginal route must be used wherever possible, particularly in obese patients;
• women with regular cycles should undergo investigation at the start of the follicular phase (days 3 to 5 of the cycle). Women presenting oligoamenorrhoea may be investigated either at any time, or between 3 and 5 days after progestin-induced withdrawal bleeding;
• ovarian size is determined using the simplified formula for an ovoid (0.5 × length × breadth × height) [29];
• the number of follicles must be determined in two planes: longitudinal and anteroposterior. Follicle size less than 10 mm must be expressed as the mean of the diameters measured in both planes.

4. Recommendation No. 4

Screening for elevated plasma LH no longer necessary.
Testing for GnRH serves no purpose.

4.1. Comments

Absolute levels of circulating LH as well as the LH/FSH ratio are significantly higher in women with PCOS than in the normal population [30,31]. This is due to the increased amplitude and frequency of LH pulses [32]. High levels of LH (above the 95th percentile of normal women) are seen in around 60% of women with PCOS [1,10], while LH/FSH ratio is higher in up to 95% of subjects [31] when recently ovulating women are excluded. Levels of LH may be affected by the closeness of ovulation (which produces transient normalisation of LH), by BMI (higher levels are seen in thin women with PCOS) [33] and by the assay system used [34]. On the basis of this data, determination of plasma LH should not be regarded as necessary for clinical diagnosis of PCOS. Determination of LH levels could be useful for subsequent investigations, particularly in thin women with amenorrhoea, or for research purposes.

5. Recommendation No. 5

Routine screening for metabolic abnormalities should be carried out systematically based on the following criteria:
• weight, height and BMI;
• waist circumference;
• blood pressure;
• laboratory parameters:
  - plasma glucose,
  - triglycerides,
  - HDL cholesterol.

5.1. Comments

Insulin resistance, defined as decreased insulin-mediated glucose utilisation, is a common finding in the general population (10–25%) when screening is performed by sophisticated tests to evaluate the action of insulin [35]. However, the criteria used to define the threshold of positivity vary. Insulin resistance is more frequent in women with PCOS (up to 50%) and affects both obese and non-obese subjects [36]. The prevalence of insulin resistance among women with PCOS varies according to the sensitivity and specificity of the tests used in different publications, and according to the heterogeneity of PCOS.

There are currently no validated tests to detect insulin resistance in the general population. The main clinical indicator of reduced sensitivity to insulin is excess weight and in particular abdominal obesity, as shown in various studies conducted involving CAT scans. Waist-to-hip ratio, a parameter long used, has now been abandoned in favour of waist circumference, which provides a more accurate indication of visceral fat and is better correlated with insulin resistance. The risk of insulin resistance has been shown to be far higher in women with waist circumferences in excess of 88 cm.

Although euglycaemic hyperinsulinaemic clamp technique is the gold standard for investigating insulin resistance, it is too complicated for clinical care and is used only in medical research. Various mathematical indexes involving fasting serum glucose and insulin levels (e.g. HOMA, QUICKI and others) correlate more or less well with clamp results depending on the study populations. They have been assessed in PCOS and there is some disagreement about their value in this population [37].

The prevalence of metabolic syndrome (NECP ATP-III definition) is greater in overweight subjects with PCOS (30 to 50%) and increases with age [38]. Since metabolic syndrome
is considered an expression of insulin resistance, it is worth seeking clinical and laboratory signs of this condition such as central obesity, hypertension, fasting hyperglycaemia and dyslipidaemia [39]. Waist circumference, blood pressure level, triglycerides and/or HDL cholesterol levels, and fasting plasma glucose should thus all be taken into consideration. In women with PCOS investigated using the reference clamp method, waist circumference parameter is strongly predictive for insulin resistance, as are triglycerides [40].

6. Recommendation No. 6

In the case of obesity (BMI greater than 30 kg/m²), oral glucose tolerance testing (OGTT) is recommended where fasting serum glucose is normal.

6.1. Comments

Most women with PCOS presenting carbohydrate intolerance (CI) or diabetes have normal fasting plasma glucose levels [41]. Given the high prevalence of CI (30 to 35%) and of type II diabetes (7.5 to 10%) diagnosed by OGTT in obese women with PCOS, it is recommended that obese women (BMI greater than 30 kg/m²) with PCOS should undergo OGTT [41,42]. CI is defined in accordance with the WHO criteria as plasma glucose of between 1.40 and 1.99 g/l2 h after an oral glucose load of 75 g [43,44]. It is considered a major risk factor for diabetic patients [2]. The annual conversion rate from impaired glucose tolerance status and CI remains to be determined. If the OGTT is normal, fasting plasma glucose should be monitored annually.

Recent studies have shown that progression from CI to diabetes may be slowed down by lifestyle and pharmacological measures [46,47]. Furthermore, CI serves to identify individuals at excess risk of mortality, particularly women [48,49].

Further studies are needed to assess the value of OGTT in non-obese women. However, it should be contemplated in the presence of additional risk factors such as a familial history of type II diabetes, regardless of the patient’s weight.

7. Recommendation No. 7

Clomiphene citrate (CC) remains the first-line therapy for ovulation induction. In patients with BMI greater than 30, it should be preceded by improvement of metabolic status through appropriate lifestyle modifications.

7.1. Comments

Lifestyle modifications:

- obesity reduces the chances of conception (anovulation, early and late stillbirth) as well as the efficacy of ovulation induction therapy;
- weight loss through caloric restriction and regular exercise is a necessary prerequisite of all treatments. These measures improve the likelihood of spontaneous ovulation as well as the efficacy of induction therapy;
- lifestyle modification must necessarily be introduced prior to treatment for anovulation but it must be reviewed in pregnancy since the consequences on the actual course of pregnancy are not known;
- A 5% reduction in baseline weight improves the chances of both spontaneous and induced pregnancy.

Treatment with clomiphene citrate (CC):

- CC remains the first-line treatment for ovulation induction in the majority of women in whom anovulation is associated with PCOS. Patient selection should take into account weight, age and any associated infertility factors;
- the recommended initial dose is 50 mg/d for 5 days, with a maximum daily dose of 150 mg;
- ultrasonography monitoring and determination of plasma progesterone during the luteal phase are optional. Ultrasound verification of the number of dominant follicles at D10–12 is recommended in order to avoid the risk of multiple pregnancy;
- data from clinical trials in large populations indicate a satisfactory rate of pregnancy, evaluated at 22% per cycle in women with ovulation obtained after CC;
- additional studies are required to demonstrate the efficacy and safety of treatment with aromatase inhibitors;
- association of metformin with CC has not been shown to be effective in all women presenting PCOS (see Duranteau et al. in this issue).

8. French version

A French version of this article is available at doi: 10.1016/j.ando.2009.12.004

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