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CONSENSUS STATEMENT

Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome

The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group

Rotterdam, The Netherlands

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May 1–3, 2003, Rotterdam, The Netherlands.
Congress chairmen: Tarlatzis (Gr), Fauser (Nl).
Scientific committee: J. Chang (USA), R. Azziz (USA), R. Legro (USA), D. Dewailly (Fr), S. Franks (UK), R. Tarlatzis (Gr), B. Fauser (Nl).
Invited discussants: A. Balen (UK), Ph. Bouchard (Fr), E. Dahlgren (Sw), L. Devoto (Chi), E. Diamanti (Gr), A. Dunaif (USA), M. Filicori (It), R. Homburg (Is), L. Ibanez (Sp), J. Laven (Nl), D. Magoffin (USA), J. Nestler (USA), R. Norman (Aus), R. Pasquali (It), M. Pugeat (Fr), J. Strauss (USA), S. Tan (Can), A. Taylor (USA), R. Wild (USA), S. Wild (UK).
Invited discussants not present during the meeting: J. Chang (USA), D. Guzick (USA), D. Ehrmann (USA), R. Lobo (USA).
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Reprint requests: Bart C. J. M. Fauser, M.D., Ph.D., Center of Reproductive Medicine, Erasmus Medical Center, 3015 GD Rotterdam, The Netherlands (FAX: 31-10-4367306; E-mail: b.fauser@erasmusmc.nl).

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Since the 1990 National Institutes of Health–sponsored conference on polycystic ovary syndrome (PCOS), it has become appreciated that the syndrome encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria. The 2003 Rotterdam consensus workshop concluded that PCOS is a syndrome of ovarian dysfunction along with the cardinal features hyperandrogenism and polycystic ovary (PCO) morphology. PCOS remains a syndrome, and as such no single diagnostic criterion (such as hyperandrogenism or PCO) is sufficient for clinical diagnosis. Its clinical manifestations may include menstrual irregularities, signs of androgen excess, and obesity. Insulin resistance and elevated serum LH levels are also common features in PCOS. PCOS is associated with an increased risk of type 2 diabetes and cardiovascular events. (Fertil Steril® 2004;81:19–25. ©2004 by American Society for Reproductive Medicine.)

Nearly 15 years have passed since the first international conference on polycystic ovary syndrome (PCOS) was held. During that initial meeting at the National Institutes of Health (NIH) in Bethesda, Maryland, there was considerable discussion with little consensus, although a questionnaire led to the current diagnostic criteria that stand today (see Table 1). Based on the majority opinion rather than clinical trial evidence, the following diagnostic criteria were put forth: clinical or biochemical evidence of hyperandrogenism, chronic anovulation, and exclusion of other known disorders (1). These criteria were an important first step toward standardizing diagnosis and led to a number of landmark randomized multicenter clinical trials in PCOS (2, 3). Since that time and as outlined during a number of subsequent international conferences (4), there has been a gradually increasing awareness that the clinical expression of PCOS may be broader than that defined by the 1990 NIH criteria.

Rotterdam Consensus on Diagnostic Criteria for PCOS

PCOS is a syndrome of ovarian dysfunction. Its cardinal features are hyperandrogenism and polycystic ovary morphology (5). Its clinical manifestations may include menstrual irregularities, signs of androgen excess, and obesity. PCOS is associated with an increased risk of type 2 diabetes (6, 7). Since the 1990 NIH-sponsored conference on PCOS, it has become appreciated that the syndrome encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria (Table 1). It is now recognized that women with regular cycles and hyperandrogenism and/or polycystic ovaries (PCO) may have the syndrome (8–10). It has also been recognized that some women with the syndrome will have PCO without clinical evidence of androgen excess but will display evidence of ovarian dysfunction.

PCOS remains a syndrome and as such no single diagnostic criterion (such as hyperandrogenism or PCO) is sufficient for clinical diagnosis. PCOS also remains a diagnosis of exclusion. Known disorders that mimic the PCOS phenotype should be excluded.

Diagnostic Criteria for Clinical Trials and Familial Studies

The above-mentioned diagnostic criteria may not be suitable for trials focusing on clinical outcomes in women with PCOS. For instance, trials focusing on pregnancy as an outcome may place greater emphasis on anovulation as the identifying symptom, rather

TABLE 1

Revised diagnostic criteria of polycystic ovary syndrome.

1990 Criteria (both 1 and 2)
1. Chronic anovulation and
2. Clinical and/or biochemical signs of hyperandrogenism and exclusion of other etiologies.

Revised 2003 criteria (2 out of 3)
1. Oligo- or anovulation,
2. Clinical and/or biochemical signs of hyperandrogenism,
3. Polycystic ovaries

and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome)

Note: Thorough documentation of applied diagnostic criteria should be done (and described in research papers) for future evaluation.

2003 Rotterdam PCOS consensus. Fertil Steril 2004.

than the presence of PCO or clinical hyperandrogenism. Similarly, trials seeking an improvement in hirsutism may deemphasize baseline ovulatory function and require some pathological terminal hair growth for entry. Moreover, women with chronic anovulation and hyperandrogenism and/or PCO appear to be at substantially greater risk for insulin resistance than those with hyperandrogenism and regular cycles (11, 12). Accordingly, it is essential that studies of the metabolic features of PCOS stratify affected women according to ovulatory function (i.e., chronic oligo-/amenorrhea vs. regular cycles).

Family studies are critical for understanding the spectrum of phenotypes and for identifying susceptibility genes for PCOS. More narrow diagnostic criteria may be used in family studies to identify affected individuals, such as the presence of PCO alone (13) or hyperandrogenemia per se (14). A rigid definition of PCOS based on the present or past proposed diagnostic criteria may hamper our understanding of this heterogeneous disorder.

Exclusion of Related Disorders

To establish the diagnosis of PCOS, it is important to exclude other disorders with a similar clinical presentation, such as congenital adrenal hyperplasia, Cushing's syndrome, and androgen-secreting tumors. Exclusion of 21-hydroxylase deficient nonclassic adrenal hyperplasia (NCAH) can be performed using a basal morning 17-hydroxyprogesterone level, with cutoff values ranging between 2 and 3 ng/mL (15). Some participants felt that the routine screening of hyperandrogenic patients for NCAH should take into account the prevalence of this autosomal recessive disorder in the population under study.

The routine exclusion of thyroid dysfunction in patients deemed to be hyperandrogenic was felt to have limited value, as the incidence of this disorder among these patients is no higher than that in normal women of reproductive age. However, because screening for thyroid disorders may be advisable in all women of reproductive age, the routine measurement of TSH in the hyperandrogenic patient need not be discouraged.

The initial workup in women presenting with oligo/anovulation may also include the assessment of serum FSH and E_2 levels to exclude hypogonadotropic hypogonadism (i.e., central origin of ovarian dysfunction) or premature ovarian failure characterized by low E_2 and high FSH concentrations, according to World Health Organization (WHO) classification (16, 17). PCOS is part of the spectrum of normogonadotropic normoestrogenic anovulation (WHO 2) (5, 18). It should be emphasized, however, that serum LH concentrations are frequently elevated in these patients, as will be discussed later.

Most participants felt that the routine measurement of PRL in the evaluation of hyperandrogenic patients should be performed to exclude hyperprolactinemia, with a caveat that many hyperandrogenic patients may have PRL levels in the upper normal limit or slightly above normal.

Finally, syndromes of severe insulin resistance (e.g., for the diagnosis of the hyperandrogenic-insulin resistant-acanthosis nigricans, or HAIRAN, syndrome) (19), Cushing's syndrome (20), androgen-secreting neoplasms (20, 21), or high-dose exogenous androgens (22) should be excluded if clinically suspected.

Hyperandrogenism

Clinical phenotyping of PCOS involves determining the presence of clinical and/or biochemical androgen excess (hyperandrogenism), while excluding related disorders.

Clinical Hyperandrogenism: Most participants felt that the primary clinical indicator of androgen excess is the presence of hirsutism (23). However, the following issues should be emphasized:

- Normative data in large populations are still lacking.
- The assessment of hirsutism is relatively subjective.
- Few physicians in clinical practice actually use standardized scoring methods.
- Hirsutism is often treated well before the patient is ever evaluated endocrinologically.
- Hirsutism may be significantly less prevalent in hyperandrogenic women of East Asian origin (24) or in adolescence (25).

The sole presence of acne was also felt to be a potential marker for hyperandrogenism, although studies are somewhat conflicting regarding the exact prevalence of androgen excess in these patients (26). The sole presence of androgenic alopecia as an indicator of hyperandrogenism has been less well studied. However, it appears to be a relatively poor marker of androgen excess, unless present in the oligo-ovulatory patient (27). Overall, the clinical evidence of hyperandrogenism is an important feature of patients with PCOS, notwithstanding the above-mentioned limitations.

Biochemical Hyperandrogenism: Most patients with PCOS have evidence of hyperandrogenemia, and recent ob-

servations suggest that circulating androgen levels may also represent an inherited marker for androgen excess (14). However, it was clearly denoted that a proportion of patients with PCOS may not demonstrate an overt abnormality in circulating androgens (5, 28–31).

The limitations of defining androgen excess by the measurement of circulating androgen levels were felt to be due in part to the inaccuracy and variability of the laboratory methods of measurement that are often used (32–34):

- There are multiple androgens that may not be considered (35).
- There is wide variability in the normal population.
- Normative ranges have not been well-established using well-characterized control populations.
- Age and body mass index (BMI) have not been considered when establishing normative values for androgen levels (36, 37).
- Little normative data are present on adolescent and older women.
- Androgens are suppressed more rapidly by hormonal suppression than other clinical features and may remain suppressed even after discontinuation of hormonal treatment.

Notwithstanding these limitations, it was felt that the measurement of free T or the free T (free androgen) index (34) were the more sensitive methods of assessing hyperandrogenemia (38, 39). Recommended methods for the assessment of free T included equilibrium dialysis (33, 34), calculation of free T from the measurement of sex hormone–binding globulin and total T, or ammonium sulfate precipitation (40). It was the uniform impression that currently available direct assays for free T have limited value, particularly in the evaluation of the hyperandrogenic woman.

It was noted that measurement of total T only may not be a very sensitive marker of androgen excess. A small fraction of patients with PCOS may have isolated elevations in dehydroepiandrosteronesulphate (DHEAS) levels. Some felt that the measurement of total T and DHEAS had some value in detecting a patient with an androgen-secreting tumor (41), although more recent data suggest that the best predictor of these neoplasms is the clinical presentation (42).

Finally, little data are available on the value of routinely measuring androstenedione in hyperandrogenic patients (5), although it was noted that it might be somewhat more elevated in patients with 21-hydroxylase–deficient nonclassic adrenal hyperplasia than in patients with PCOS. Nonetheless, the paucity of normative and clinical data with androstenedione precluded its recommendation for the routine assessment of hyperandrogenemia.

Polycystic Ovaries (PCO)

Workshop participants felt that PCO should now be considered as one of the possible criteria for PCOS (see Table 1). According to the available literature (18, 43, 44), the criteria having sufficient specificity and sensitivity to define PCO are the following: "Presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume (>10 mL)" (for a review, see 45). The subjective appearance of PCO should not be substituted for this definition. The follicle distribution should be omitted as well as the increase in stromal echogenicity and volume. Although increased stromal volume is a feature of PCO (46), it has been shown that the measurement of the ovarian volume is a good surrogate for the quantification of stromal volume in clinical practice (47). This definition does not apply to women taking the oral contraceptive pill, since its use modifies ovarian morphology in normal women and putatively in women with PCO (48). Only one ovary fitting this definition is sufficient to define PCO. If there is evidence of a dominant follicle (>10 mm) or a corpus luteum, the scan should be repeated during the next cycle. The presence of an abnormal cyst or ovarian asymmetry (which may suggest a homogeneous cyst) necessitates further investigation.

A woman having PCO in the absence of an ovulatory disorder or hyperandrogenism ("asymptomatic" PCO) should not be considered as having PCOS until more is known regarding the clinical presentation (49). In addition to its role in the definition of PCOS, ultrasound is helpful to predict fertility outcome of clomiphene citrate (50) and the risk of ovarian hyperstimulation syndrome (OHSS) and to assist in deciding whether the in vitro maturation of oocytes is desirable (51).

It is recognized that the appearance of PCO may be seen in women before undergoing ovarian stimulation for IVF in the absence of overt signs of the PCOS. These ovaries, when stimulated, behave like the ovaries of women with PCOS and are at increased risk for hyperstimulation and OHSS (52).

In addition, ultrasound provides the opportunity to screen for endometrial hyperplasia in these patients. The following technical recommendations should be highlighted:

- State-of-the-art equipment is required and should be operated by appropriately trained personnel.
- Whenever possible, the transvaginal approach should be used, particularly in obese patients.
- Regularly menstruating women should be scanned in the early follicular phase (cycle days 3–5). Oligo-/amenorrhoeic women should be scanned either at random or between days 3 and 5 after a progestin-induced withdrawal bleeding.
- Calculation of ovarian volume is performed using the simplified formula for a prolate ellipsoid (0.5 × length × width × thickness) (53).
- Follicle number should be estimated both in longitudinal and antero-posterior cross-sections of the ovaries. The size of follicles <10 mm should be expressed as the mean of the diameters measured on the two sections.

TABLE 2

Summary of 2003 polycystic ovary syndrome (PCOS) consensus regarding screening for metabolic disorders.

Summary of consensus
1. No tests of insulin resistance are necessary to make the diagnosis of PCOS, nor are they needed to select treatments.
2. Obese women with PCOS should be screened for the metabolic syndrome, including glucose intolerance with an oral glucose tolerance test.
3. Further studies are necessary in nonobese women with PCOS to determine the utility of these tests, although they may be considered if additional risk factors for insulin resistance, such as a family history of diabetes, are present.

2003 Rotterdam PCOS consensus. Fertil Steril 2004.

TABLE 3

Criteria for the metabolic syndrome in women with polycystic ovary syndrome. (Three of five qualify for the syndrome.)

Risk factor	Cutoff
1. Abdominal obesity (waist circumference)	>88 cm (>35 inch)
2. Triglycerides	≥150 mg/dL
3. HDL-C	<50 mg/dL
4. Blood pressure	≥130/≥85
5. Fasting and 2-h glucose from oral glucose tolerance test	110–126 mg/dL and/or 2-h glucose 140–199 mg/dL

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Insulin Resistance

Insulin resistance is associated with reproductive abnormalities in women with PCOS (see also Table 2). Improving insulin sensitivity through both lifestyle and pharmacological intervention can ameliorate these abnormalities. Insulin resistance, defined as decreased insulin-mediated glucose utilization, is commonly found in the larger population (10%–25%) when sophisticated dynamic studies of insulin action are performed (54). However, the criteria for selecting an abnormal cutoff point vary. Insulin resistance in women with PCOS appears even more common (up to 50%), both in obese and nonobese women (55). Reports of the prevalence on insulin resistance in women with PCOS vary depending on the sensitivity and specificity of the tests employed and the heterogeneity of PCOS.

There is currently no validated clinical test for detecting insulin resistance in the general population. Dynamic invasive tests such as the euglycemic clamp and frequently sampled glucose tolerance test are research procedures because of their intensive use of time and resources. Calculated indices based on fasting levels of insulin and glucose correlate well with dynamic tests of insulin action. However, there are multiple flaws that limit their widespread clinical use, including changes in beta-cell function with the development of diabetes (which alters the sensitivity of the tests), normal physiologic fluctuation in insulin levels, and the lack of a standardized universal insulin assay.

Other consensus conferences also recommended against screening for insulin resistance in both the general population and in high-risk populations because of these concerns and concerns regarding the value of these tests to predict clinical events (56). Instead, criteria have been developed for defining a metabolic syndrome, which includes components associated with the insulin resistance syndrome, including centripetal obesity, hypertension, fasting hyperglycemia, and dyslipidemia (Table 3) (57).

Other groups have recommended adding an oral glucose tolerance test (OGTT) to these fasting blood tests to evaluate the 2-hour glucose level after a 75-g oral glucose challenge for glucose intolerance (WHO criteria, impaired glucose tolerance [IGT] >140 mg/dL to 199 mg/dL) (58, 59). IGT has long been recognized as a major risk factor for diabetes (60), and recent studies have shown that progression to diabetes in individuals with IGT can be delayed by lifestyle changes and pharmacological intervention (61, 62). Additionally, IGT identifies individuals at risk for excess mortality, especially women (63, 64). Given the high prevalence of IGT and type 2 diabetes as diagnosed by the OGTT among obese women with PCOS, it is prudent to screen obese women (BMI >27 kg/m^2) with PCOS with an OGTT (6, 65). Further studies of the prevalence of features of the metabolic syndrome are necessary in both lean and obese women with PCOS.

Currently, there are scant data to indicate that markers of insulin resistance predict responses to treatment (3, 39, 66). Therefore, the role of these markers in the diagnosis of PCOS, as well as in selecting specific treatments, is uncertain. Tests of insulin sensitivity are of greatest interest in research studies of [1] the pathophysiology of PCOS, [2] young adolescents with a combined history of low birth weight and excessive postnatal catch-up, [3] mechanisms of response to therapy, and [4] family phenotypes. Further studies to identify predictive factors or early response factors to treatments of PCOS are needed.

Luteinizing Hormone

Both the absolute level of circulating LH as well as its relation to FSH levels are significantly elevated in women with PCOS as compared with controls (67, 68). This is due to an increased amplitude and frequency of LH pulses (69). Elevated LH concentrations (above the 95th percentile of normal) can be observed in approximately 60% of women with PCOS (5, 18), whereas the LH/FSH ratio may be elevated in up to 95% of subjects (68) if women who have recently ovulated are excluded. LH levels may be influenced by the temporal relation to ovulation, which transiently nor-

malizes LH, by BMI (being higher in lean women with PCOS), as well as by the assay system used.

The potential negative actions of LH on human reproduction are highly controversial. Some investigators have suggested that high LH levels could have detrimental effects on oocyte maturity and fertilization (70), as well as result in lower pregnancy and higher miscarriage rates (71). However, other studies have shown no untoward actions of LH on oocyte and embryo quality or on fertilization, implantation, and pregnancy rates (72, 73). Reduction of endogenous LH levels with GnRH agonists also provided conflicting results as some studies have suggested that this maneuver could reduce miscarriage rates (74), while others have questioned this therapeutic effect (75, 76). LH levels or the administration of exogenous LH activity were not found to affect the chances of ovulation or achievement of pregnancy using clomiphene citrate (39, 49) or exogenous gonadotropins (77, 78).

Based on the aforementioned data, the panel felt that measurement of serum LH levels should not be considered necessary for the clinical diagnosis of PCOS. LH levels could be useful as a secondary parameter (especially in lean women with amenorrhea or in research). Additional research is needed to further clarify the clinical relevance of LH in PCOS and the potential effects of LH suppression with GnRH analogs or its enhancement through LH activity administration at different stages of follicular maturation.

Long-Term Health Risks

Women with PCOS have multiple risk factors for diabetes including obesity, a family history of type 2 diabetes, and abnormalities in insulin action (both insulin resistance and beta-cell dysfunction). There is now clear evidence that women with PCOS are at increased (3–7 times) risk of developing type 2 diabetes (6, 7, 11, 79, 80). There are several lines of evidence suggesting that women with PCOS are also at increased risk of cardiovascular disease (81). Insulin-resistant states are associated with greater than normal susceptibility to coronary heart disease, and women with PCOS have evidence of dyslipidemia (82–85) and markers of abnormal vascular function (86–88). However, limited epidemiological studies have shown no direct evidence of an increased incidence of coronary heart disease in middle-aged women with a history of PCOS (although the incidence of stroke is slightly increased) (89).

Women with PCOS are also thought to be at increased risk for endometrial cancer through chronic anovulation with unopposed estrogen exposure of the endometrium. However, epidemiological evidence to support this hypothesis is limited (90).

Currently, no firm conclusions can be drawn, but the following statements represent the consensus view that PCOS is associated with an increased risk of type 2 diabetes:

- The risk is greater in anovulatory women with PCO, in obese subjects, and in those with a family history of type 2 diabetes.
- The risk of cardiovascular disease is uncertain at present (89, 91). Limited epidemiological data have shown no increase in cardiovascular events, but two factors need to be borne in mind: The young age of the cohorts studied so far (around 55 years) and the possibility that unknown factors(s) may be present in PCOS that protect the heart in the face of other risk factors.

More research is required to [1] assess the level of risk, [2] enable identification of patients at risk, [3] provide longitudinal follow-up of PCOS cohorts into their sixties and beyond, and [4] determine the place, timing, and efficacy of interventional measures.

Although many questions remain to be answered, lifestyle changes (diet and exercise) should be strongly encouraged to reduce the risk of both type 2 diabetes and cardiovascular disease (37, 92–95).

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Consensus on infertility treatment related to polycystic ovary syndrome

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group March 2–3, 2007, Thessaloniki, Greece*

The treatment of infertile women with polycystic ovary syndrome (PCOS) is surrounded by many controversies. On the basis of the currently available evidence, a group of experts reached a consensus regarding the therapeutic challenges raised in these women. Before any intervention is initiated, preconceptional counseling should be provided emphasizing the importance of lifestyle, especially weight reduction and exercise in overweight women, smoking, and alcohol consumption. The recommended first-line treatment for ovulation induction remains the anti-estrogen clomiphene citrate (CC). Recommended second-line intervention, should CC fail to result in pregnancy, is either exogenous gonadotropins or laparoscopic ovarian surgery (LOS). The use of exogenous gonadotropins is associated with increased chances for multiple pregnancy, and, therefore, intense monitoring of ovarian response is required. Laparoscopic ovarian surgery alone is usually effective in less than 50% of women, and additional ovulation induction medication is required under those circumstances. Overall, ovulation induction (representing the CC–gonadotropin paradigm) is reported to be highly effective with a cumulative singleton live-birth rate of 72%. Recommended third-line treatment is in vitro fertilization (IVF). More patient-tailored approaches should be developed for ovulation induction based on initial screening characteristics of women with PCOS. Such approaches may result in deviation from the above mentioned first-line, second-line, or third-line ovulation strategies in well-defined subsets of patients. Metformin use in PCOS should be restricted to women with glucose intolerance. Based on recent data available in the literature, the routine use of this drug in ovulation induction is not recommended. Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction. Even singleton pregnancies in PCOS are associated with increased health risk for both the mother and the fetus. (Fertil Steril® 2008;89:505–22. ©2008 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, infertility treatment, 2007 consensus

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies, affecting 5% to 10% of women of reproductive age. The syndrome is surrounded by controversies regarding both its diagnosis and treatment. The need to establish universally accepted diagnostic criteria led to the Rotterdam meeting in 2003, during which experts in PCOS from all over the world arrived at a consensus regarding the diagnosis of the syndrome. That meeting was endorsed by both the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), and its proceedings were published in *Fertility and Sterility* and in *Human Reproduction* (1, 2).

Criteria proposed for the diagnosis of PCOS in the Rotterdam meeting were set to allow the performance of properly designed trials with good external validity in PCOS patients. These trials would assist in defining the various phenotypes of the syndrome, in discovering its genetic origins, in evaluating its long-term consequences, and in describing its optimal treatment. Advantages and disadvantages of these criteria, and especially the various phenotypes, were discussed in subsequent publications (3, 4).

Although significant progress has been made toward the development of universally accepted diagnostic criteria for PCOS (1, 2), the optimal treatment for infertile women with PCOS has not yet been defined. Various interventions have been proposed ranging from lifestyle modifications

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Reprint requests: Basil C. Tarlatzis, Unit for Human Reproduction, First Department of Obstetrics and Gynaecology Aristotle University of Thessaloniki, Greece, Papageorgiou General Hospital, Nea Efkarpia Peripheral Road, Thessaloniki 54603, Greece (FAX: +30-2310-989161; E-mail: tarlatzis@hol.gr).

* *Group members:* B. C. Tarlatzis (Gr), B. C. J. M. Fauser (NL), R. S. Legro (USA), R. J. Norman (Aus), K. Hoeger (USA), R. Pasquali (It), S. Franks (UK), I. E. Messinis (Gr), R. F. Casper (Can), R. Homburg (Is), R. Lobo (USA), R. W. Rebar (USA), R. Fleming (UK), B. R. Carr (USA), Ph. Bouchard (Fr), J. Chang (USA), J. N. Hugues (Fr), R. Azziz (USA), E. M. Kolibianakis (Gr), G. Griesinger (Ger), K. Diedrich (G), A. Balen (UK), C. Farquhar (NZ), P. Devroey (B), P.C. Ho (HK), J. Collins (Can), D.G. Goulis (Gr), R. Eijkemans (NL), P. G. Crosignani (It), A. DeCherney (USA), A. van Steirteghem (B).

and administration of pharmaceutical agents such as clomiphene citrate (CC), insulin-sensitizing agents, gonadotropins, and gonadotropin-releasing hormone (GnRH) analogues to the use of laparoscopic ovarian drilling and the application of assisted reproduction techniques (ART).

The recognition of the controversies surrounding the treatment of this enigmatic syndrome led to a second international workshop endorsed by ESHRE and ASRM held in Thessaloniki, Greece, in 2007, to address the therapeutic challenges raised in women with infertility and PCOS and to answer important questions regarding the value of various treatments available for these women and their efficacy as well as their safety. As with the Rotterdam meeting, a panel of international experts was invited to discuss the treatment of women with PCOS and infertility to arrive at a consensus regarding therapy. The reader should note that the vast majority of the available studies used variable criteria for PCOS definition. Nevertheless, the discussants overall felt that the reviewed and cited data were pertinent to the disorder of PCOS, independent of the specific criteria used.

LIFESTYLE MODIFICATIONS

Preconceptional counseling in women with PCOS should identify risk factors for reproductive failure and correct them before treatment initiation. In this respect, it is imperative to recognize the presence of obesity and its centripetal distribution, which may vary according to ethnicity and geographical area, as well as to recommend folate supplementation in all women and smoking cessation where appropriate. It is well known that obesity is associated with anovulation (5), pregnancy loss (6), and late pregnancy complications (preeclampsia, gestational diabetes, etc.) (7). Obesity is common in women with PCOS and is linked to failure or delayed response to the various treatments proposed, such as administration of CC (8, 9), gonadotropins (10, 11) (Fig. 1), and laparoscopic ovarian diathermy (12). Weight loss is recommended as the first-line therapy in obese women with PCOS seeking pregnancy. This recommendation is based on extrapolation from the benefits of weight loss seen in multiple other conditions, such as diabetes and cardiovascular disease, as well as recognition of obesity's association with poor reproductive outcome.

However, it should be noted that there is a paucity of studies suggesting that weight loss before conception improves the live-birth rate in obese women with or without PCOS (13). On the other hand, multiple observational studies have noted that weight loss is associated with improved spontaneous ovulation rates in women with PCOS (5, 13), and pregnancies have been reported after losing as little as 5% of initial body weight (14). The treatment of obesity is multifaceted and involves behavioral counseling, lifestyle therapy (diet and exercise), pharmacologic treatment, and bariatric surgery (15). However, there are no properly designed studies to guide the choice of such interventions in overcoming infertility in women with PCOS. Generally, a combination of medical and behavioral therapies offers the greatest weight loss (16) though long-term bariatric surgery is associated with the best weight maintenance after weight loss (17). The effects of calorie restriction, increased physical activity, and pharmacologic and weight loss agents in the periconceptional period are unknown and are potentially harmful to the goal of live birth (18, 19). These interventions should be conducted before pregnancy, not concurrently with infertility treatment, until the risk–benefit ratio of these therapies on pregnancy is better understood. Table 1 shows randomized trials of lifestyle and pharmacologic weight loss therapy in women with PCOS.

FIGURE 1

Association between obesity and ovulation rate in gonadotropin ovulation induction, with a pooled odds ratio and 95% confidence interval. (Mulders et al., Hum Reprod Update 2003;9:429–49. Used with permission.) Cited Studies: Hamilton-Fairley et al. (154), Strowitzky et al. (155), Vicino et al. (156), Yarali et al. (157).

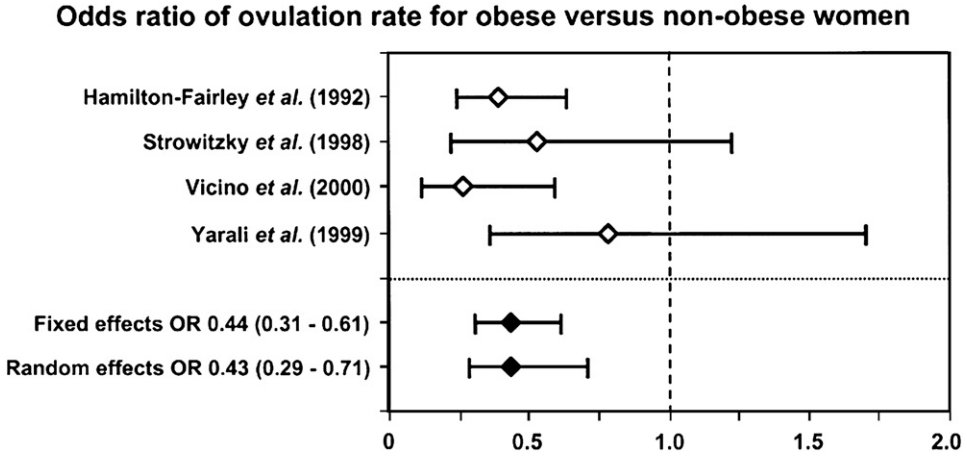

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TABLE 1

Randomized trials of lifestyle and pharmacologic weight-loss therapy in women with polycystic ovary syndrome.

Study	Number of patients	Duration	Intervention	Weight loss (kg)	Reproductive outcome
			Diet		
Moran et al., 2003 (13)	28	16 w	**Diet (RCT):** 6000 KJ/day HP: 40% C, 30% P, 30% F LP: 55% C, 15% P, 30% F	7.7	44% had improvement in ovulation
Moran et al., 2004 (21)	10	16 w	**Diet (RCT):** 6000 KJ/day HP: 40% C, 30% P, 30% F LP: 55% C, 15% P, 30% F	7.1	NA
Stamets et al., 2004 (22)	26	1 m	**Diet (RCT):** 4200 KJ deficit/day HP: 40% C, 30% P, 30% F LP: 55% C, 15% P, 30% F	4.0	Decreased T, increased menstrual bleeding
Moran et al., 2006 (28)	23	8 w 6 m	**Diet (RCT):** 5000 KJ/day 2 meal replacements plus low-fat dinner and snacks fat counting (<50 g/day) or carbohydrate counting (<120 g/day) **Exercise:** 8000 steps/day	4.7	Decreased T, 57% had improved menstrual cyclicity
			Lifestyle		
Hoeger et al., 2004 (163)	38	48 w	**Combined therapy (RCT)** **Diet**: 2100–4200 KJ deficit/day. Individualized healthy meal plan: 50% C, 25% P, 25% F **Exercise:** Group sessions **Behavior:** Group sessions	6.8	NS
Bruner et al., 2006 (26)	12	12 w	**Diet (RCT):** Canadian Food Guide to Healthy Eating **Exercise:** A combination of endurance and resistance activities 3 days/week	NS	NS

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TABLE 1

Continued.

Study	Number of patients	Duration	Intervention	Weight loss (kg)	Reproductive outcome
Tang et al., 2006 (53)	143	6 m	**Diet (RCT):** 500 kcal deficit/day **Exercise:** increase physical activity by 15 minutes a day (unmonitored) Pharmacological	1.5	Improved menstrual frequency (median 1 cycle/6 m)
Sabuncu et al., 2003 (32)	40	6 m	**Medication:** Sibutramine 10 mg/day	5.8	37% decrease in T, 280% increase in SHBG
Jayagopal et al., 2005 (33)	21	3 m	**Diet:** 8-week run in of dietary modification **Medication:** Orlistat 120 mg tid	4.4	8% decrease in T

Note: C: carbohydrate; P: protein; F: fat; HP: high protein; LP: low protein; NA: not available; NS: no statistically significant change from baseline; RCT: randomized, controlled trial; SHBG: sex-hormone–binding globulin; T: testosterone; w: week(s); m: month(s).

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Diet

It is generally agreed that energy restriction is required for weight loss. In fact, early improvements in reproductive function, in the absence of apparent weight loss, were probably due to energy restriction per se. However, there is little agreement on what constitutes the optimal diet for women with PCOS (20). The resurgence of the "Atkins diet" has generated considerable interest in very low calorie diets in recent years, and these can lead to significantly decreased body weight in PCOS (12% in 24 weeks) and can improve reproductive outcome (21). A range of dietary approaches has been shown to be effective in weight loss and in improving reproductive function, but only two randomized controlled trials (RCTs) have compared the effect of different diets in women with PCOS (13, 22). However, these studies did not show that dietary patterns differentially affect weight loss and reproductive outcomes.

Increasing evidence in women without PCOS suggests that diets with reduced glycemic load may be beneficial in alleviating hyperinsulinemia and its metabolic consequences (23). This is of particular relevance to women with PCOS because of the close association between insulin resistance and reproductive health. In the absence of level I evidence, the recommended diet for obese women with PCOS is any hypocaloric diet (with a 500 Kcal/day deficit) with reduced glycemic load and, failing that, any calorie restricted diet with which patients can comply and achieve a 5% weight loss.

Exercise

Insufficient physical activity might explain why women with PCOS have a tendency toward being overweight/obese. Baseline activity levels by self-report were lower in women with PCOS compared with control women (24). In the Nurses' Health Study, vigorous activity was associated with a reduced relative risk of anovulatory infertility (25). Few studies have examined the role of exercise alone in improving reproductive function in PCOS. In a pilot trial examining exercise and nutritional counseling in PCOS, women were assigned to nutritional counseling alone or in combination with exercise. No differences were seen between groups with respect to weight loss or restoration of menstruation (26).

Several studies have examined combination therapy of diet and exercise (27, 28). Most of them, however, were not randomized trials, and exercise was not supervised but rather consisted of lifestyle counseling. Although weight loss alone appeared to improve menstrual frequency, the contribution of exercise alone could not be determined in these studies. It is clear that regular physical activity is an important component of weight loss programs because it is associated with better long-term weight loss maintenance (29). However, its independent role in achieving weight reduction and improved reproductive outcome is less obvious. Increased physical activity is recommended for obese women with PCOS, but always while considering the possible orthopaedic and cardiovascular limitations (28).

Pharmacologic Treatment and Bariatric Surgery

The available literature supports the adjuvant use of bariatric surgery and pharmacologic weight loss for the treatment of obesity in PCOS although large clinical trials are needed. In morbidly obese women, the PCOS phenotype appears to be very frequent (30). Most importantly, this disorder has been

found to improve markedly after sustained weight loss after bariatric surgery (31). Anti-obesity pharmacologic agents have been used in obese women with PCOS although few quality studies have been published (32, 33). Both orlistat, which blocks intestinal absorption of fat (33), and sibutramine, an appetite suppressant (32), have displayed a weight loss–independent effect on androgens and insulin resistance. Currently, there are no studies in women with PCOS regarding the use of rimonabant, which decreases food intake (34). This agent is not approved by the U.S. Food and Drug Administration (FDA), but it is approved in Europe. It should be noted that these treatments should not be considered as first-line therapy for obesity in women with PCOS.

Summary Points

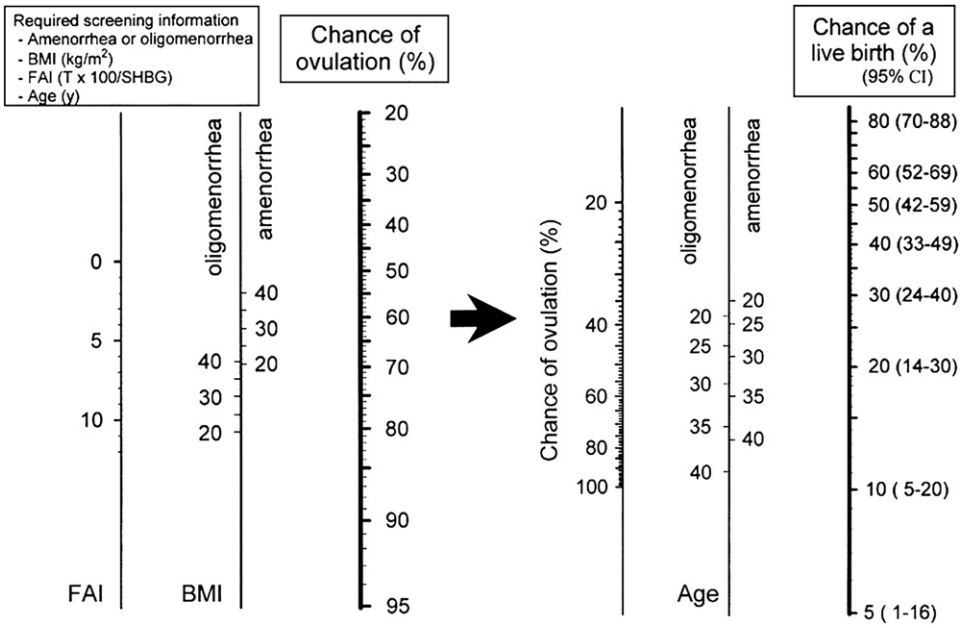
- Obesity adversely affects reproduction and is associated with anovulation, pregnancy loss, and late-pregnancy complications.
- Obesity within PCOS is associated with failure of infertility treatment.
- Weight loss before infertility treatment improves ovulation rates in women with PCOS, but there are limited data that it improves fecundity or lowers pregnancy complications.
- Evidence based schemas to guide the treatment of obesity in women with PCOS have not yet been developed.
- Experience from other areas of medicine suggests lifestyle modifications as the first-line treatment of obesity in PCOS.
- The best diet and exercise regimens are unknown, but caloric restriction and increased physical activity are recommended.
- Caution is recommended about conceiving during the use of hypocaloric diets, excessive physical exertion, pharmacologic intervention, or during the period of rapid weight loss after bariatric surgery because the effects of these interventions on the evolution of early pregnancy are not yet known.
- Treatment of adverse lifestyles, including obesity and physical inactivity, should precede ovulation induction.
- The ideal amount of weight loss is unknown, but a 5% decrease of body weight might be clinically meaningful.

CLOMIPHENE CITRATE

Clomiphene citrate (CC) remains the treatment of first choice for induction of ovulation in anovulatory women with PCOS. The cost of the medication is low, the oral route of administration is patient friendly, there are relatively few adverse effects, little ovarian response monitoring is required, and abundant clinical data are available regarding safety of the drug. The mechanism of action in not entirely known, but it is thought to involve the blockade of the negative feedback mechanism that results in increased secretion of follicle-stimulating hormone (FSH). The main factors that predict outcome of treatment are obesity, hyperandrogenemia, and age (35) (Fig. 2). Ovarian volume and menstrual status are additional factors that help to predict responsiveness to CC (36).

FIGURE 2

Nomogram designed to predict chances for live birth in clomiphene citrate induction of ovulation. Note the two different steps. (Imani et al., Fertil Steril 2002;77:91–7. Used with permission.)



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Selection of Patients

There are no specific exclusion criteria for women with anovulatory PCOS who have normal baseline FSH and estradiol levels, but selection of patients for treatment should take in account body weight/body mass index (BMI), age, and other infertility factors. Poorer outcome in older patients may justify consideration of alternative treatments such as exogenous gonadotropins or in vitro fertilization (IVF).

Dose

The starting dose of CC generally should be 50 mg/day (for 5 days, starting on days 2 to 5 after a spontaneous or progestin-induced withdrawal bleeding). The recommended maximum dose is 150 mg/day as there is no clear evidence of efficacy at higher doses and this is in accord with FDA recommendations of 750 mg per treatment cycle (37).

Monitoring

Although the results of large trials suggest that monitoring by ultrasound is not mandatory to ensure good outcome (38), the practice in many centers is to monitor the first cycle to allow adjustment of the dose in subsequent cycles based on the observed response. In the absence of complete cycle monitoring, a pretreatment ultrasound is often performed to evaluate ovarian and endometrial morphology, which may be followed by serum progesterone measurements (typically one or two samples in the estimated luteal phase). There is no evidence that administration of human chorionic gonadotropin (hCG) in midcycle improves the chances of conception (39).

Efficacy

Approximately 75% to 80% of patients with PCOS will ovulate after CC administration (40, 41). Although there appears to be discrepancy between ovulation and pregnancy rates, life-table analysis of the largest and most reliable studies indicates a conception rate of up to 22% per cycle in those ovulating on CC (36, 42, 43).

Duration of Treatment

Treatment generally should be limited to six (ovulatory) cycles (36, 40). Further cycles (maximum 12 in total) may be considered on an individual basis after discussion with the patient. Normally, however, second-line therapy with FSH or laparoscopic ovarian surgery should be considered at that time (36, 44). Cumulative live-birth rates vary between 50% to 60% for up to six cycles (43).

Adverse Effects

Hot flushes, headaches, and visual complaints are well-recognized side effects during CC treatment, but the drug is generally well tolerated. The multiple pregnancy rate is less than 10%, and ovarian hyperstimulation syndrome (OHSS) is rare (36). Anti-estrogenic effects on endometrium and cervical mucus may occur but appear to represent an idiosyncratic response. There is no clear evidence that the chance of conception is adversely affected in ovulatory cycles (45).

Combination Therapy

There is now clear evidence that the addition of metformin (38, 46) or dexamethasone (47) to CC as primary therapy for induction of ovulation has no beneficial effect.

Alternative Therapies

Anti-estrogens other than clomiphene citrate Tamoxifen appears to be as effective as CC for induction of ovulation but is not licensed for that purpose (48, 49). It may be considered as an alternative to CC in women who suffer intolerable side effects such as hot flushes.

Aromatase inhibitors Initial preliminary studies suggest that letrozole appears to be as effective as CC for induction of ovulation, but the drug is currently not approved for treatment of infertility. Prospective, sufficiently powered studies demonstrating efficacy and safety should be awaited before the widespread use of aromatase inhibitors can be recommended. It may, however, be considered as an off-label option for some patients after appropriate discussion of risks and benefits.

Summary Points

- Clomiphene citrate remains the treatment of first choice for induction of ovulation in most anovulatory women with PCOS.
- Selection of patients for CC treatment should take into account body weight/BMI, female age, and the presence of other infertility factors.
- The starting dose of CC should be 50 mg/day (for 5 days), and the recommended maximum dose is 150 mg/day.
- Results of large trials suggest monitoring by ultrasound or progesterone is not mandatory to ensure good outcome.
- Life-table analysis of the largest and most reliable studies indicates a conception rate of up to 22% per cycle in women ovulating while on CC.
- Further studies should demonstrate efficacy and safety of aromatase inhibitors.

INSULIN-SENSITIZING AGENTS

Insulin-sensitizing agents are currently being used to treat diabetes, and there is considerable interest for their use in the treatment of women with PCOS. Insulin sensitizers available include metformin, a biguanide, and the thiazolidinediones (pioglitazone and rosiglitazone). The primary risk with metformin is lactic acidosis, which is only seen in high-risk patients with renal, liver, or congestive heart failure (50). The major risk with the thiazolidinediones is liver toxicity, and recently there has been concern about increased cardiovascular morbidity with rosiglitazone (51). With regard to the use of these agents use during pregnancy, metformin is a category B drug according to the FDA, which means that either animal-reproduction studies have not shown a fetal risk but there

are no controlled studies in women, or animal studies have shown an adverse effect not confirmed by controlled studies in women. Pioglitazone and rosiglitazone are category C drugs, which means that either studies in animals have shown adverse effects on the fetus and there are no controlled studies in women, or studies in women and animals are not available.

In women with PCOS, metformin appears to lower the fasting insulin level, but it does not appear to result in consistent significant changes in BMI or waist-to-hip ratio (52). Although oligomenorrhea improves in some women with PCOS, significant numbers remain anovulatory and at risk for menorrhagia and endometrial hyperplasia. The degree of improvement in ovulation frequency is the same as is achieved with weight reduction through lifestyle modification, with no difference between metformin and placebo in this regard (53), and has been estimated to represent one extra ovulation every five woman-months (54).

With regard to the use of metformin for induction of ovulation, two RCTs have indicated that metformin does not increase live-birth rates above those observed with CC alone in either obese or normal weight women with PCOS (38, 46). The larger of these two trials (38) demonstrated a selective disadvantage to metformin compared with CC and no apparent advantage to adding metformin to CC, except perhaps in women with BMI >35 kg/m^2 and in those with CC resistance. Results in this trial were the same when subjected to either intention-to-treat analysis or analysis based on adherence: CC resulted in higher ovulation, conception, pregnancy, and live-birth rates compared with metformin, but the combination of both drugs did not result in a significant benefit (Table 2). Addition of metformin did not decrease the incidence of miscarriage, which in fact was higher in the metformin group. Furthermore, metformin treatment conferred no additional advantage when administered to women newly diagnosed with PCOS (46). Thus, insulin sensitizers should not be used as first-choice agents for induction of ovulation in women with PCOS, and their administration does not appear to decrease the incidence of early pregnancy losses. In addition, there are insufficient data to document any advantage to the use of thiazolidinediones over metformin (55, 56).

Although uncontrolled trials and case reports suggest that metformin is safe during pregnancy, it would be prudent to discontinue metformin when pregnancy is confirmed for any woman with PCOS and insulin resistance who has been taking the medication (38). Although there have been suggestions that metformin treatment during pregnancy may be protective against complications (57), currently such use should take place only in a research context (58).

TABLE 2

Randomized trial from the National Institutes of Health Reproductive Medicine Network.

	CC	Metformin	Combination
N	209	208	209
Ovulation	49[a]	29	60[b]
Conception	20[a]	12	38[a]
Pregnancy	24[a]	9	31[a]
Live birth	23[a]	7	27[a]
Multiple	6	0	3

Source: Legro et al., N Engl J Med 2007;356:551–66. Used with permission.

[a] $P<.001$.

[b] $P<.001$ (combination vs. clomiphene citrate [CC]).

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Summary Points

- At present, use of metformin in PCOS should be restricted to those patients with glucose intolerance.
- Decisions about continuing insulin sensitizers during pregnancy in women with glucose intolerance should be left to the obstetricians providing care and should be based on a careful evaluation of risks and benefits.
- Metformin alone is less effective than CC in inducing ovulation in women with PCOS.
- There seems to be no advantage to adding metformin to CC in women with PCOS.

GONADOTROPINS AND GNRH ANALOGUES

The aim of ovulation induction for women with anovulatory PCOS is to restore fertility and achieve a singleton live birth. The method of ovulation induction using gonadotropin therapy is based on the physiologic concept that initiation and maintenance of follicle growth may be achieved by a transient increase in FSH above a threshold dose for sufficient duration to generate a limited number of developing follicles. Application of this concept is essential when ovulation induction is conducted in women with PCOS because they are specifically prone to excessive multiple follicle development (59, 60).

Regimens

The original description of gonadotropin administration for anovulation used a high starting dose of 150 IU a day. In women with PCOS as well as those with multiple follicle formation this "conventional protocol" was associated with an unacceptable rate of excessive follicle development and increased risk of OHSS (61–63). Subsequent efforts to reduce the frequency of ovarian hyperstimulation have resulted in the development of low-dose protocols (37.5–75 IU/day), which have essentially replaced the original conventional protocol (64–67).

Starting doses of daily 150 IU FSH are no longer recommended in women with PCOS (68, 69) and have been replaced by low-dose FSH protocols. Currently, two low-dose regimens are used:

1. *Step-up regimens:* Step-up regimens are based upon the principle of a stepwise increase in FSH supply to

determine the FSH threshold for follicular development. After commencement of gonadotropin administration, if follicle development is not observed on ultrasound after 1 week, an increase in the dose is recommended. Once follicle growth is observed, the same FSH dose is maintained until follicular selection is achieved. To further reduce the risk of ovarian hyperresponsiveness, the duration of the initial dose of FSH was extended (from 7 to 14 days), and the weekly dose increment was reduced (from 100% to 50% of the dose), leading to the so-called chronic low-dose regimen (70–73).

2. *Step-down regimens:* This regimen is designed to achieve the FSH threshold through a loading dose of FSH with a subsequent stepwise reduction as soon as follicular development is observed on ultrasound (74–76). Preliminary studies report that both step-up and step-down regimens achieve similar high rates of monofollicular development (77, 78). However, the largest study published so far has shown that the step-up regimen is safer in terms of monofollicular development (79). Moreover, it is widely accepted that monitoring of a step-down cycle may require more experience and skill compared with a low-dose step-up regimen (80). Alternatively, a combined approach of sequential step-up and step-down regimens has been shown to help reduce the risk of overresponse (81, 82).

Combination of GnRH Analogues and Gonadotropins

It has been suggested that increased luteinizing hormone (LH) secretion in PCOS may interfere with fertility. The mechanisms include premature oocyte maturation through inhibition of oocyte maturation inhibitor (83) and deleterious LH effect on granulosa cell steroidogenesis (84, 85). In addition, elevated LH levels may be associated with an increased pregnancy loss (86–89), although more recent data are not consistent with this assumption (10, 90, 91).

The concomitant use of a GnRH agonist with gonadotropin administration to improve pregnancy rates in patients undergoing ovulation induction has not been firmly established (92–94). Moreover, combined therapy was associated with an increased risk of OHSS (95–99), but there are insufficient data to draw solid conclusions on miscarriage and multiple pregnancy rates (100–102). Therefore, the significantly higher hyperstimulation rate, the associated risk of multiple pregnancies, and the additional inconvenience and cost of concomitant GnRH agonist administration, in the absence of documented increases in pregnancy success, do not justify the routine use of GnRH agonists during ovulation induction with gonadotropins in PCOS patients. The question of whether LH suppression by a GnRH antagonist during gonadotropin-based ovulation induction is of benefit to women with PCOS has not yet been addressed by RCTs.

Monitoring

Ultrasound assessment of the ovary can be performed at baseline before the initiation of each cycle. Serial ovarian ultrasound is an excellent method of determining follicle growth and development in response to gonadotropin stimulation. In particular, documentation of all follicles greater than 10 mm may be helpful to predict the risk of multiple pregnancies. Adherence to the chronic low-dose regimen of FSH administration in women with PCOS should markedly reduce the likelihood of excessive ovarian stimulation and OHSS. However, before ovulation induction with gonadotropins, it is mandatory to counsel the patient about the risks associated with higher-order multiple pregnancies after polyovulation.

In most previous studies, cycle cancellation has been advised when more than three follicles of 16 mm or larger were observed (65, 67, 103) to prevent OHSS and multiple pregnancies. In some studies, the limit was four or more follicles >14 mm (82, 104). Recently, more stringent criteria have been recommended for ovarian stimulation in unexplained infertility: no more than two follicles >14 mm (105) or no more than three or four follicles >10 mm (106, 107). In addition, recent data stress the need for taking into account the overall number of follicles, and cycle cancellation may be considered in the presence of more than three follicles >14 mm. It should be noted that the definition of a monofollicular cycle has usually been a single follicle of $\geq$16 mm without any information on the number of smaller follicles, except in the study by Leader (108), which defined a cycle as monoovulatory when a single follicle of $\geq$16 mm was present with no other follicle $\geq$12 mm. Measurements of circulating estradiol levels have been used to cancel ovulation induction cycles using gonadotropins (due to overresponse or underresponse) or to adjust the dose of gonadotropins used either upward or, more frequently, downward to minimize the risk of multiple pregnancies or OHSS. Although specific normative cut-offs vary, in 2006 the Practice Committee of the ASRM suggested that caution was indicated when a rapidly rising serum estradiol levels or an estradiol concentration in excess of 2500 pg/mL was present during gonadotropin ovulation induction (109). However, in other studies (106, 107), the cut-off estradiol concentration was much lower, below 1000 pg/mL, which seems to be more realistic according to the number of growing follicles.

It would seem prudent to withhold hCG administration in the presence of more than two follicles $\geq$16 mm or more than one follicle $\geq$16 mm and two additional follicles $\geq$14 mm, to minimize the risk of multiple pregnancies in women with PCOS under the age of 38 without any other infertility factors.

Efficacy

Overall, low-dose regimens result in a monofollicular ovulation rate of approximately 70%, a pregnancy rate of 20%, and a multiple live birth rate of 5.7% (103). Correspondingly, there is a low incidence of multiple pregnancies (<6%) and OHSS (<1%) (67, 80, 110, 111). These results compare favorably to the unacceptable high risk of multiple follicular development, multiple pregnancies (36%), and severe OHSS (4.6%) reported for conventional dose protocols (112). For a summary of clinical outcomes, see Table 3 (113).

TABLE 3

Comparison of ovarian response and clinical outcomes in low-dose step-up and step-down protocols for gonadotropin ovulation induction.

	Low-dose step-up			Step-down
	Hamilton-Fairley et al., 1991	Hull et al., 1991	Balen et al., 1994	van Santbrink et al., 1995
Number of patients	100	144	103	82
Number of cycles	401	459	603	234
Duration treatment (days)	14	NR	NR	11
Ampules per cycle	19	NR	NR	14
Ovulation rate (%)	72	74	68	91
Monofollicular cycles				
% of ovulatory cycles	73	NR	NR	62
% of all started cycles	55	NR	NR	56
Pregnancy rate (%)				
Per started cycle	11	11	14	16
Per ovulatory cycle	16	15	20	17
Cumulative pregnancy rate (%)	55	NR	73	47
Multiple pregnancy rate (%)	4	11	18	8
Ongoing singleton pregnancy rate (%)	7	10	9	12
OHSS rate (%)	1	NR	1	2

Note: NR, not recorded. Cited Studies: Hamilton-Fairley et al. (111), Hull et al. (164), Balen et al. (165), Van Santbrink et al. (80).
Source: Fauser and Macklon, in Strauss JF, Barbieri RL, eds. Yen and Jaffe's reproductive endocrinology. Philadelphia: Elsevier Saunders, 2004:965–1012. Used with permission.

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A prospective follow-up study involving 240 women showed a favorable cumulative singleton live-birth rate of 72% after the combined analysis of ovulation induction using CC medication as first-line and exogenous gonadotropins as second-line treatment (36) (Fig. 3).

Summary Points

- The recommended starting dose of gonadotropin is 37.5–50.0 IU/day.
- Adherence to a 14-day starting period at least for the first cycle is less likely to result in excessive stimulation.
- Small FSH dose increments of 50% of the initial or previous FSH dose are less likely to result in excessive stimulation.
- The duration of gonadotropin therapy generally should not exceed six ovulatory cycles.
- Low-dose FSH protocols are effective in achieving ovulation in women with PCOS, but further refinement is needed to better control the safety of these regimens.
- Intense ovarian response monitoring is required to reduce complications and secure efficiency.
- Strict cycle cancellation criteria should be agreed upon with the patient before therapy is started.
- Preventing all multiple pregnancies and OHSS is not possible at this time.
- The significantly higher hyperstimulation rate, the associated risk of multiple pregnancies, and the additional inconvenience and cost of concomitant GnRH agonist administration, in the absence of documented increases in pregnancy success, do not currently justify the routine use of GnRH agonists during ovulation induction with gonadotropins in women with PCOS.

LAPAROSCOPIC OVARIAN SURGERY

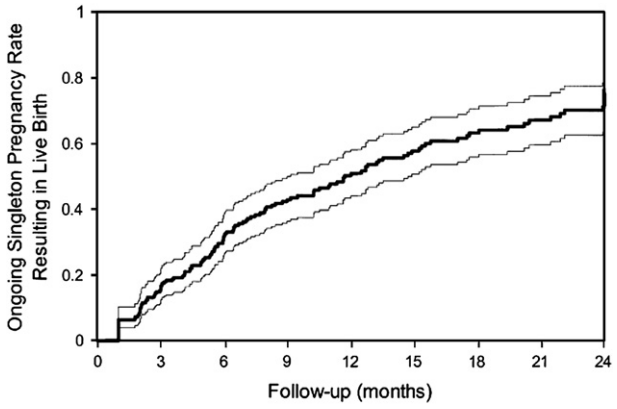
Surgical approaches to ovulation induction have developed from the traditional wedge resection to modern day minimal access techniques, usually employing laparoscopic ovarian diathermy or laser. Multiple ovarian puncture performed either by diathermy or by laser is known as "ovarian drilling" (114).

Indications for Laparoscopic Ovarian Surgery

The main indication for performing laparoscopic ovarian surgery (LOS) is CC resistance in women with anovulatory PCOS. The surgery also may be recommended for patients who persistently hypersecrete LH, either during natural cycles or in response to CC, because it may reduce LH secretion. In addition, LOS may be useful in anovulatory women with PCOS who need laparoscopic assessment of their pelvis

FIGURE 3

Cumulative pregnancy rate resulting in singleton live birth of a consecutive series of 240 normogonadotrophic anovulatory infertile women undergoing classic ovulation induction (clomiphene citrate as first-line, followed by follicle-stimulating hormone as second-line therapy). (Eijkemans et al. Hum Reprod 2003;18:2357–62. Used with permission.)



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or who live too far away from the hospital for the intensive monitoring required during gonadotropin therapy.

Extensive ovarian diathermy is not indicated to prevent hyperresponsiveness to exogenous gonadotropins (115). In addition, ovarian surgery has been suggested for nonfertility indications such as management of menstrual irregularity or hyperandrogenism. Because of the inherent risks of surgery and the lack of long-term evidence from RCTs, surgery cannot be recommended in these circumstances (116).

Methods and Dose

Commonly employed methods for LOS include monopolar electrocautery (diathermy) and laser. There does not appear to be a difference in outcomes between the two modalities (117). Ovarian surgery may also be performed transvaginally by hydrolaparoscopy (118), but no large RCTs are yet available.

There are many variables in the potential for response after LOS, including the anthropometric characteristics of the patients and ovarian morphology. It has been proposed that the degree of thermal stromal damage should be determined by the size of the ovary (119).

There is no evidence that any surgical technique is superior, but as few as four punctures have been shown to be effective. Most investigators use between 4 and 10 punctures; more punctures have been associated with premature ovarian failure (120–122). As in all surgical procedures, an important issue of successful outcome is the expertise of the surgeon. There are no data regarding repeated application of LOS, and such use should not be encouraged.

Efficacy

In approximately 50% of LOS-treated women, adjuvant therapy will be required. In these women, the addition of CC can be considered after 12 weeks if no ovulation is detected (123). The addition of FSH should be considered after 6 months (123). Five RCTs that compared the effectiveness of LOS with that of gonadotropins for women with CC-resistant PCOS did not show a difference in ongoing pregnancy rate or live-birth rate (117, 123–127) (Fig. 4a). In one of these trials (123), if ovulatory cycles were not established 8 weeks after surgery or the woman became anovulatory again, then CC was given in increasing doses. Multiple pregnancy rates were significantly higher in the gonadotropin arms of the five trials compared with LOS (odds ratio [OR]) 0.13; 95% confidence interval [CI], 0.03–0.98) (Fig. 4b). On the other hand, miscarriage rates did not differ between the LOS group and gonadotropin-treated women (OR 0.61; 95% CI, 0.17–2.16). No cases of OHSS were observed in either of the two most recent studies (123, 125).

Economic analyses of two RCTs suggest that LOS treatment of women with CC-resistant PCOS resulted in reduced direct and indirect costs. In the New Zealand study, the cost of a live-birth was one-third lower with surgery; in the Netherlands study, the cost of a term pregnancy was estimated to be 22% lower (128, 129). Predictors of success have included LH level >10 IU/L, normal BMI, and shorter duration of infertility (12, 130, 131).

Safety

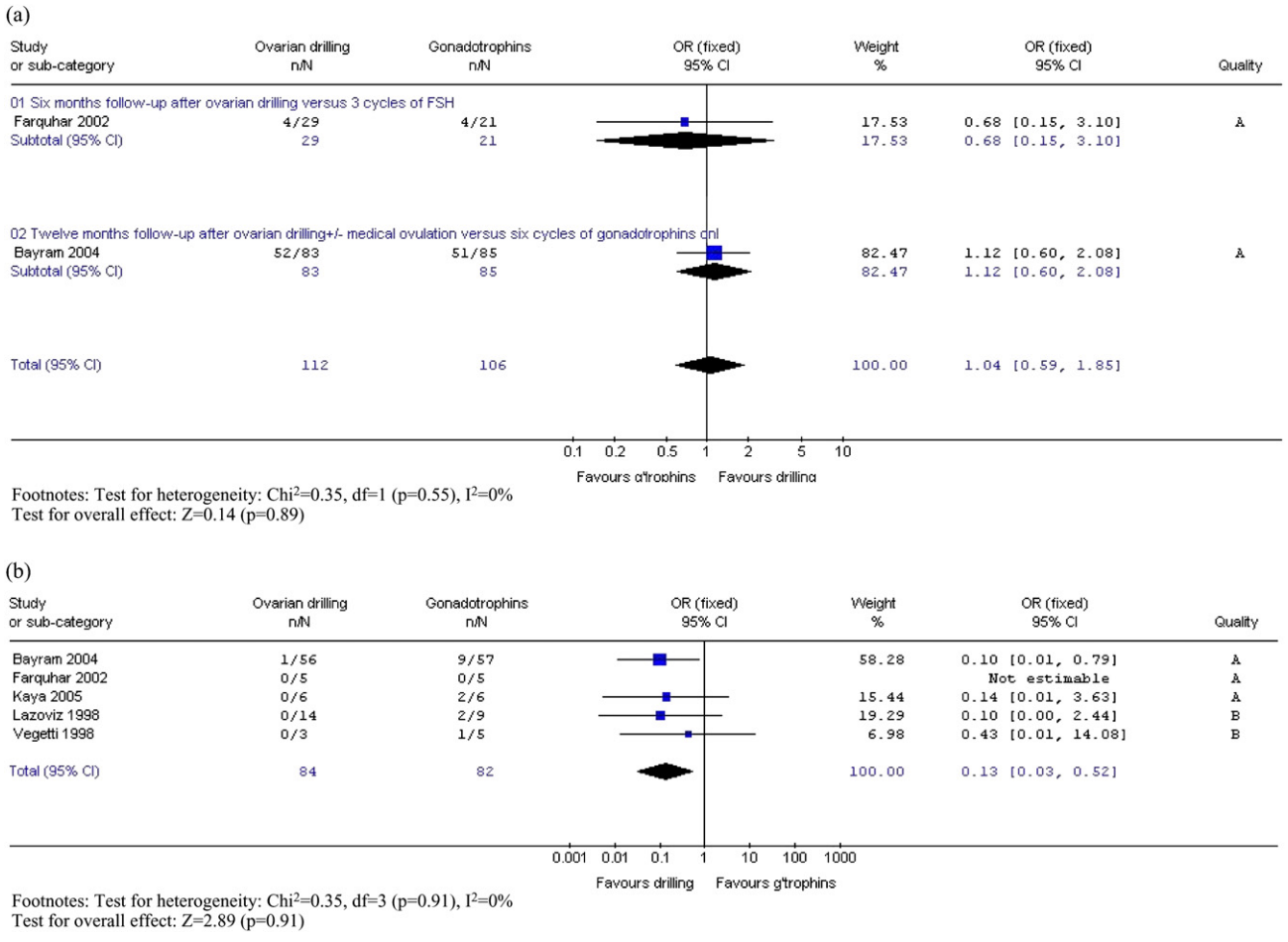
Immediate complications of the surgery are rare. Out of 778 cases of LOS, two cases with hemorrhage requiring laparotomy and one case with bowel perforation have been reported (132). Long-term adverse events potentially include adhesion formation and premature menopause. Only two second-look laparoscopy studies have been done. In one study, out of 17 cases there were two with severe adhesion formation (133). In a second study of eight patients, all of the women had ovarian adhesions on second look after LOS despite the application of an adhesion barrier to one ovary as part of a study protocol (134). Premature ovarian failure is a concern with ovarian drilling, especially when a large number of punctures is used. However, long-term follow-up of women with PCOS treated by LOS has been reassuring in this respect (135, 136).

Summary Points

- Laparoscopic ovarian surgery can achieve unifollicular ovulation with no risk of OHSS or high-order multiples.
- Intensive monitoring of follicular development is not required after LOS.
- Laparoscopic ovarian surgery is an alternative to gonadotropin therapy for CC-resistant anovulatory PCOS.
- The treatment is best suited to those for whom frequent ultrasound monitoring is impractical.

FIGURE 4

Results from the meta-analysis of the randomized, controlled trials of laparoscopic ovarian surgery versus gonadotropins for (**a**) live-birth rate and (**b**) multiple pregnancy rate. Notes: Test for heterogeneity: chi-square = 0.35, df = 1 (*P*=.55), I^2 = 0%. Test for overall effect: Z = 0.14 (*P*=.89). (Farquhar et al., Cochrane Database Syst Rev 2007;3:CD001122. Copyright Cochrane Collaboration, reproduced with permission.)



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- Laparoscopic ovarian surgery is a single treatment using existing equipment.
- The risks of surgery are minimal and include the risks of laparoscopy, adhesion formation, and destruction of normal ovarian tissue. Minimal damage should be caused to the ovaries. Irrigation with an adhesion barrier may be useful, but there is no evidence of efficacy from prospective studies. Surgery should be performed by appropriately trained personnel.
- Laparoscopic ovarian surgery should not be offered for nonfertility indications.

ASSISTED REPRODUCTION TECHNIQUES: IN VITRO FERTILIZATION

In principle, anovulation is not an indication for IVF. The logical therapy for women with PCOS is induction of ovulation, especially by CC administration, and in case of failure by using exogenous gonadotropin therapy. The major complication of ovulation induction is the 10% multiple pregnancy rate, especially after the use of gonadotropin therapy. For this reason use of gonadotropins may be questioned (137).

After failure of weight reduction, anti-estrogen therapy, or LOS, it may be argued that induction of ovulation with exogenous gonadotropin therapy should be omitted and replaced by ovarian stimulation and IVF (138). By using IVF with single embryo transfer, the risk of multiple pregnancies is markedly reduced (139, 140). In women with PCOS who do have associated pathologies, IVF is indicated, such as in cases of tubal damage, severe endometriosis, preimplantation genetic diagnosis, and male factor infertility.

Protocols

Several stimulation protocols have been published for the treatment of patients with PCOS undergoing IVF, including CC associated with human menopausal gonadotropins

(hMG) (141), hMG alone (142), recombinant FSH alone, GnRH-agonist associated with hMG or recombinant FSH (143), and GnRH-antagonist associated with hMG or recombinant FSH (143). Currently, the most standard protocol is a long desensitization protocol associated with FSH.

Efficacy

In a recent meta-analysis (144), it was shown that the cycle cancellation rate is significantly increased in patients with PCOS (12.8% versus 4.1%; OR 0.5; 95% CI, 0.2–1.0). Duration of stimulation is significantly longer in patients with PCOS (1.2 days; 95% CI, 0.9–1.5), even when the daily dose of FSH is similar to that of women without PCOS. Significantly more cumulus–oocyte complexes (2.9; 95% CI, 2.2–3.6) were retrieved in women with PCOS, but the fertilization rates were similar as compared with women without PCOS (Fig. 5).

Regarding the probability of pregnancy, the clinical pregnancy rate per started cycle was similar (≈35%) between PCOS and non-PCOS patients. The same was true for pregnancy rates per oocyte retrieval and embryo transfer. Specific data on the success rates of single-embryo transfer in women with PCOS are still lacking. There is some evidence that the adjuvant use of metformin may enhance ongoing pregnancy rates and reduce the incidence of OHSS (145).

Complications

The most important complication of ovarian stimulation is OHSS. However, currently no solid data are present regarding the occurrence of OHSS in women with PCOS undergoing ovarian stimulation for IVF.

Summary Points

- In vitro fertilization is a reasonable option because the number of multiple pregnancies can be kept to a minimum by transferring fewer embryos.
- The optimal stimulation protocol is still under debate.
- There is a need to perform further RCTs comparing FSH stimulation protocols with use of GnRH agonists versus GnRH antagonists.
- It is reassuring that in the published data the pregnancy rates in women with and without PCOS are similar. This observation suggests that implantation is not compromised in PCOS.
- The increase in the cycle cancellation rate in women with PCOS appears to be due to absent or limited ovarian response or due to increased OHSS.

ASSISTED REPRODUCTION TECHNIQUES: OVULATION INDUCTION AND HOMOLOGOUS ARTIFICIAL INSEMINATION

Indications

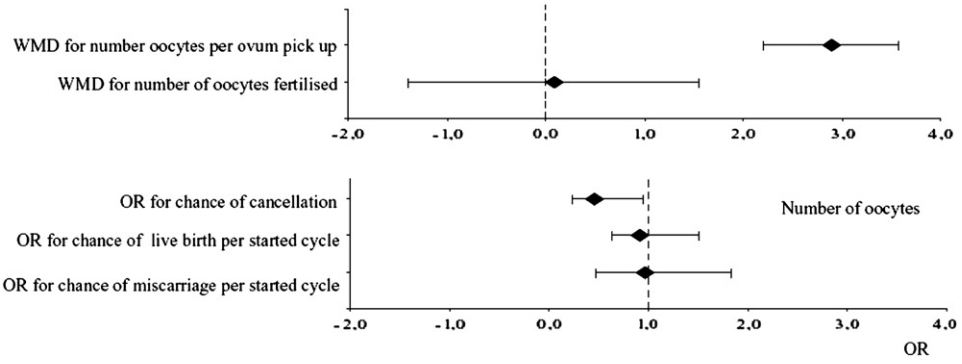
Currently, there are no RCTs conducted in women with PCOS comparing the pregnancy rates of intrauterine insemination (IUI) versus timed intercourse during ovulation induction. Because subfertility in women with PCOS is mainly due to anovulation, induction of ovulation is the main treatment for women with PCOS. Due to the fact that IUI has been shown to significantly improve the probability of conception when compared with timed intercourse in couples with subfertility attributed to male factor infertility (146), it appears reasonable to combine induction of ovulation with IUI in women with PCOS if there is an associated male factor. In women with PCOS who failed to conceive despite successful induction of ovulation, IUI may also be considered.

Protocol

Because many women with PCOS are very sensitive to the use of ovulation induction agents, careful monitoring is essential to reduce the risk of OHSS and multiple pregnancies (147), also in combination with IUI. An additional approach

FIGURE 5

Main findings of clinical IVF outcomes in women with polycystic ovary syndrome compared with matched controls. (Heijnen et al., Hum Reprod Update 2006;12:13–21. Used with permission.)



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is to perform transvaginal ultrasound-guided aspiration of the supernumerary follicles (148).

Semen preparation is necessary before IUI, but there is insufficient evidence to recommend any specific preparation technique. Double insemination did not show any significant benefits in pregnancy rate over single IUI (149).

Efficacy

Only limited studies on the results of ovarian stimulation and IUI in women with PCOS are available (150–152). The clinical pregnancy rates per cycle ranged from 11% to 20% and the multiple pregnancy rates ranged from 11% to 36%. However, there was inadequate information on the singleton live-birth rates or high multiple pregnancy rates.

Complications and Side Effects

The theoretic risk of pelvic infection has not been reported. In view of the paucity of data on the use of ovarian stimulation and IUI in women with PCOS, further studies are necessary in this category of patients.

Summary Points

- Induction of ovulation in combination with IUI is indicated in women with PCOS and associated male factor infertility and may be proposed in women with PCOS who fail to conceive despite successful induction of ovulation.
- Currently, double insemination does not appear to enhance the probability of pregnancy as compared with single IUI.

GENERAL COMMENTS

Initial studies have shown that many features associated with PCOS such as obesity, hyperandrogenemia, and polycystic ovaries predict poor outcome of ovulation induction. Multivariate models have been developed predicting ovulation and pregnancy after CC (35) and chances for success and complications from use of gonadotropins (10, 153) and LOS. These observations need to be confirmed in independent patient populations. These approaches may eventually result in more patient-tailored treatment algorithms in ovulation induction. For instance, CC may not be the drug of first choice in some women previously shown to have poor outcomes after CC medication. Likewise, it may be possible to identify women more suitable for gonadotropins or LOS as second-line treatment. For some older women, IVF may represent the preferred treatment modality certainly under conditions of low chances for multiple pregnancy in case single-embryo transfer is performed.

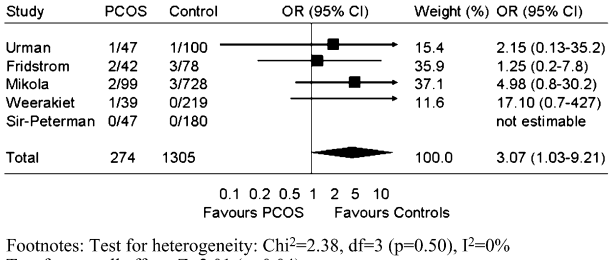
Even singleton pregnancies after ovulation induction in women with PCOS are characterized by more frequent pregnancy complications (such as gestational diabetes, pregnancy-induced hypertension, and preeclampsia) and neonatal complications (such as preterm births and admission to neonatal intensive care units) (7) (Fig. 6). Women should be counseled accordingly.

OVERALL CONCLUSIONS

- Evaluation of women with presumed PCOS desiring pregnancy should exclude any other health issues in the woman or infertility problems in the couple.
- Before any intervention is initiated, preconceptional counseling should be provided emphasizing the importance of lifestyle, especially weight reduction and exercise in overweight women, smoking, and alcohol consumption.
- The recommended first-line treatment for ovulation induction remains the anti-estrogen CC.
- Recommended second-line intervention should CC fail to result in pregnancy is either exogenous gonadotropins or LOS. Both have distinct advantages and drawbacks. The choice should be made on an individual basis. The use of exogenous gonadotropins is associated with increased chances for multiple pregnancy, so intense monitoring of ovarian response is required. Laparoscopic ovarian surgery is usually effective in less than 50% of women, and additional ovulation induction is required under those circumstances.
- Overall, ovulation induction (representing the CC–gonadotropin paradigm) is reported to be highly effective, with a cumulative singleton live-birth rate of 72%.
- Recommended third-line treatment is IVF because this treatment is effective in women with PCOS. Data concerning the use of single-embryo transfer in (young) women with PCOS undergoing IVF, which significantly reduces the chance of multiple pregnancies, are awaited.

FIGURE 6

Odds ratio for the incidence of perinatal mortality in babies from women with polycystic ovary syndrome versus controls. Notes: Test for heterogeneity: chi-square = 2.38, df = 3 (P=.50), I^2 = 0%. Test for overall effect: Z = 2.01 (P=.04). (Boomsma et al., Hum Reprod Update 2006;12:673–83. Used with permission.) Cited Studies: Urman et al. (158), Fridstrom et al. (159), Mikola et al. (160), Weerakiet et al. (161), Sir-Peterman et al. (162).



Footnotes: Test for heterogeneity: Chi²=2.38, df=3 (p=0.50), I²=0%
Test for overall effect: Z=2.01 (p=0.04)

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- More patient-tailored approaches should be developed for ovulation induction based on initial screening characteristics of women with PCOS. Such approaches may result in deviation from the above mentioned first-line, second-line, or third-line ovulation strategies in well-defined subsets of patients.
- Metformin use in PCOS should be restricted to women with glucose intolerance. Based on recent data available in the literature, the routine use of this drug in ovulation induction is not recommended.
- Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction.
- Even singleton pregnancies in PCOS are associated with increased health risk for both the mother and the fetus.

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ESHRE PAGES

Consensus on women's health aspects of polycystic ovary syndrome (PCOS)†

The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group*,‡

*Correspondence address. Prof BCJM Fauser, Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. Tel: +31-88-7557524; Fax: +31-88-755-5433; E-mail: b.c.fauser@umcutrecht.nl

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ABSTRACT: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in females with a high prevalence. The etiology of this heterogeneous condition remains obscure and its phenotype expression varies. Two, widely cited, previous ESHRE/ASRM-sponsored PCOS consensus workshops focused on diagnosis (published in 2004) and infertility management (published in 2008). The present third PCOS consensus paper summarizes current knowledge and identifies knowledge gaps regarding various women's health aspects of PCOS. Relevant topics addressed—all dealt with in a systematic fashion—include adolescence, hirsutism and acne, contraception, menstrual cycle abnormalities, quality of life, ethnicity, pregnancy complications, long-term metabolic and cardiovascular health and finally cancer risk. Additional, comprehensive background information is provided separately in an extended online publication.

Key words: PCOS / hirsutism / contraception / quality of life / pregnancy / type 2 diabetes / cardiovascular disease / insulin resistance / cancer / menopause

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women with a prevalence between 6 and 10% based on the National Institute of Health criteria and as high as 15% when the broader Rotterdam criteria are applied. PCOS is typically first identified during the early reproductive years. The clinical expression varies but commonly includes oligo- or anovulation, hyperandrogenism (either clinical or biochemical) and the presence of polycystic ovaries. The etiology of the syndrome remains obscure, and the variability in phenotype expression continues to render the clinical care and research concerning this heterogeneous condition challenging.

Two ESHRE/ASRM-sponsored PCOS consensus workshops have previously been organized. The first one in Rotterdam, the Netherlands, in 2003, focused on diagnostic criteria for PCOS (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004a,b); the second in Thessaloniki, Greece, in 2007, dealt with infertility management in PCOS (The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008a,b). The conclusions of these meetings have subsequently been jointly published simultaneously in both *Human Reproduction* and *Fertility and Sterility*. These papers are highly cited, suggesting a great interest in this area and underlining the value of such consensus contributions.

A third PCOS consensus workshop—which is the focus of the present paper—took place in Amsterdam, the Netherlands, in October 2010 and attempted to summarize current knowledge and to identify gaps in knowledge regarding various women's health aspects of PCOS. Diverse aspects of care during the reproductive and post-reproductive years were addressed, including adolescence, hirsutism and acne, contraception, menstrual cycle abnormalities, quality of life and sexual health, ethnicity, pregnancy complications, long-term (metabolic) cardiovascular health and cancer risk (Fig. 1). Due to the complexity of the many issues discussed, this contribution will address each topic separately in a fixed format: a brief introduction, concluding statements (where there was agreement), a summary of areas of disagreement (if any) and knowledge gaps with recommended directions for future research. These concluding statements in relation to each specific topic mentioned above are published in the journals (maximum of five references per paragraph). Comprehensive background information will be provided in the initial working document published online.

The hierarchy of the evidence available in the literature assessed for this conference was graded as follows:

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‡ The members of The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group is listed in the Appendix section.

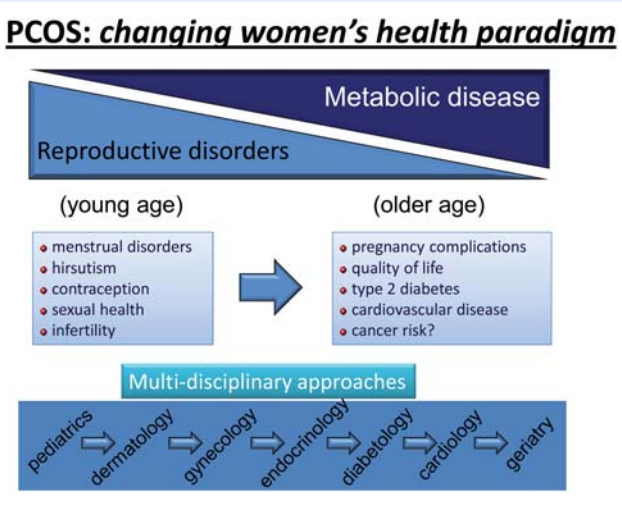

Figure 1 Schematic representation of the change in emphasize from early age reproductive disorders to long-term metabolic and cardiovascular health.

Level A requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation.

Level B requires the availability of well-controlled clinical studies, but no randomized clinical trials on the topics of recommendation.

Level C requires evidence obtained from expert committee reports of opinions and/or clinical experiences of respected authorities indicates an absence of directly applicable clinical studies of good quality.

GPP, good practice points.

Adolescence

There is no overall agreement as to how to diagnose PCOS in adolescence. Acne is common during the adolescent years, whether or not PCOS is present, whereas hirsutism—associated with PCOS—typically develops over time. Hyperandrogenemia may be a more consistent marker for PCOS during the teenage years (Blank *et al.*, 2008). In all young women, irregular menses are common in the years immediately following menarche. As many as 85% of menstrual cycles are anovulatory during the first year after menarche, while up to 59% are still anovulatory during the third year following menarche (Apter, 1998). In one study, persisting oligomenorrhea was not predicted by increased androgens, polycystic ovaries on ultrasound or increased serum LH levels (van Hooff *et al.*, 2004). Increased BMI, however, was the major risk factor for persistent anovulation.

Only around 40% of adolescent women with menstrual irregularity have polycystic ovaries on ultrasound (Venturoli *et al.*, 1995). These considerations have led to the suggestion that all three elements of the Rotterdam criteria should be present in teenagers in order to make the diagnosis of PCOS (Carmina *et al.*, 2010). These investigators suggest that oligomenorrhea or amenorrhea should be present for at least 2 years after menarch (or primary amenorrhea at age 16 years), the diagnosis of polycystic ovaries on ultrasound should include increased ovarian size (>10 cm^3), and hyperandrogenemia rather than just signs of androgen excess should be documented.

Conclusions (agreement)

- Criteria for the diagnosis of PCOS in adolescents differ from those used for older women of reproductive age (Level B).
- Groups at risk (e.g. obese, hirsute, irregular menses) should be identified, but be cautious of overdiagnosing PCOS (Level B).
- Individual PCOS manifestations in adolescents (e.g. obesity, hirsutism, irregular menses) (Level B) should be treated.

Knowledge gaps/recommended future research

- Absence of longitudinal studies through adolescence.
- Absence of specific diagnostic criteria for identifying PCOS early in adolescence.
- Absence of normative values for a number of biochemical markers during adolescence.
- Value of intervention in PCOS early in adolescence should be assessed.
- Unclear if the severity of symptoms during adolescence predicts the extent of the disorder in later life.

Hirsutism/acne/alopecia

Hirsutism is a good marker for hyperandrogenism even when considering ethnic differences and systemic factors such as obesity. Hirsutism is present in ~70% of women with PCOS, but hyperandrogenemia should be evaluated biochemically in all women suspected of having PCOS. By comparison, acne and alopecia are not commonly associated with hyperandrogenemia and therefore should not be regarded as evidence of hyperandrogenemia.

For women with PCOS in whom hirsutism is a major concern, treatment is focused on reduction in androgen production, decreasing the fraction of circulating free testosterone (T) and limiting androgen bioactivity to hair follicles. In those women with PCOS who have acne vulgaris, clinical benefit may be derived from many systemic therapeutic modalities. Because terminal hair turnover occurs slowly, at least 6 months of treatment is generally considered the minimal interval to see a response.

The main therapeutic emphasis has focused on inhibition of ovarian steroid production and decreased bioavailability through augmentation of sex hormone-binding globulin (SHBG) levels with the use of oral contraceptive pills (OCPs). OCPs are often prescribed in combination with an anti-androgen to block androgen action at the hair follicles. Anti-androgens include spironolactone (an aldosterone-antagonist diuretic), flutamide (an androgen receptor antagonist) and finasteride (a 5α-reductase type 2 inhibitor). In general, the addition of an anti-androgen to OCPs has not appeared to increase overall treatment benefit. Each of these agents have been shown to reduce hirsutism and all appear (without head-to-head comparisons) to have equivalent efficacy (O'Brien *et al.*, 1991; Erenus *et al.*, 1997; Moghetti *et al.*, 2000). Notably, anti-androgens should not be used without effective contraception (given potential fetal toxicity). Flutamide is of limited value because of associated hepatotoxicity. In addition, drospirenone in the dose used as a component of some OCPs is not anti-

androgenic. Insulin-sensitizing agents, such as metformin and pioglitazone, have little effect on hirsutism or acne (Harborne *et al.*, 2003; Cosma *et al.*, 2008). Physical approaches, to remove unwanted hair, including electrolysis and laser, may be acceptable to many patients.

In severe acne, isoretinoin can be beneficial, but individual responses vary. It is not effective for hirsutism and occasionally may lead to alopecia. Topical treatment with eflornithine hydrochloride, an inhibitor of ornithine decarboxylase limits cell division, has been shown effective for decreasing the development of new unwanted facial hair (Balfour and McClellan, 2001). No effective pharmacological treatment for alopecia exists.

Conclusions (agreement)

- Hirsutism, considering ethnic differences, is a good marker for hyperandrogenism (Level B).
- Isolated acne and alopecia are not necessarily related to and are not good markers for hyperandrogenism (Level B).
- Hirsutism should be evaluated biochemically (Level B).
- Prolonged (>6 months) medical therapy for hirsutism is necessary to document effectiveness (Level B).
- Many drugs used for the treatment of hirsutism are not FDA approved for this indication (GPP).
- No effective treatment for alopecia is known (Level B).
- Anti-androgens should not be used without effective contraception (Level B).
- Flutamide is of limited value because of its dose-dependent hepatotoxicity (Level B).
- Drospirenone in the dosage used in some OCs is not anti-androgenic (Level B).

Knowledge gaps/recommended future research

- Unclear what is the best medical therapy for hirsutism.
- Unclear how long therapy should be continued.
- Unclear how best to evaluate hirsutism clinically.
- Measurement of serum androgens is fraught with error but is the best estimate we have for hyperandrogenism.

Menstrual irregularity

Although cycle abnormalities are common during the reproductive years, women with PCOS may ovulate spontaneously. How frequently this occurs is unknown (Laven *et al.*, 2002), but ovulations have been reported in up to 32% of 'cycles'. Women with oligo- or amenorrhea have about a 90% chance of being diagnosed with PCOS and up to 95% of affected adults have oligo- or amenorrhea (Kumarapeli *et al.*, 2008). The definition used to establish the diagnosis of PCOS affects the proportion of women included with menstrual irregularities (Vutyavanich *et al.*, 2007).

Amenorrheic women with PCOS usually have the most severe hyperandrogenism and higher antral follicle counts when compared with women presenting with oligomenorrhea or regular menstrual cycles. Menstrual cycles in women with PCOS become more regular as they approach menopause (Dahlgren *et al.*, 1992; Elting *et al.*, 2001). One large study reported that obesity rather than the menstrual cycle pattern or the size of the follicular cohort determines hyperinsulinemia, dyslipidemia and hypertension in aging women with PCOS (Elting *et al.*, 2001).

Conclusions (agreement)

- Both amenorrheic and oligomenorrheic women may occasionally ovulate (Level B).
- Menstrual cycles in women with PCOS may become more regular later in life (Level B).
- Irregular menses are associated with increased metabolic risk (Level B).
- The greater the menstrual irregularity, the more severe the PCOS phenotype (Level B).

Disagreement

- The time needed before regular menstrual cycles occur in young women.
- The extent to which irregular menses (especially amenorrhea) represent a source of psychological morbidity and/or decreased quality of life.

Knowledge gaps/recommended future research

- Unclear to what extent the severity of the menstrual disturbance is associated with the severity of the PCOS phenotype.
- The natural history and progression of menstrual irregularity in PCOS are not well understood.
- It remains unclear whether PCOS patients have a longer reproductive life span.
- How often do oligo- or amenorrheic women ovulate?

Contraception

Women with PCOS who do not desire pregnancy need contraception. No contraceptive methods are contraindicated in PCOS. However, some of the features associated with PCOS [obesity, insulin resistance (IR) etc.] may represent a relative contraindication to the use of combined OCPs. Cycle control is usually achieved by the use of OCPs in women with PCOS.

OCPs suppress LH secretion and lead to a decrease in ovarian androgen production. The estrogenic component increases the levels of SHBG, which, in turn, results in a decrease in circulating free T levels. The progestin in the pill can compete for 5α-reductase at the level of the androgen receptor. Oral contraception also decreases adrenal androgen production by a mechanism yet unclear, possibly due to a decrease in adrenocorticotropin hormone production.

There are few randomized double-blind studies comparing the metabolic effects of a combination of two OCPs, or combined with an insulin sensitizer (Yildiz, 2008). A Cochrane review, based on limited evidence, concluded that OCP use does not increase metabolic risk (Costello *et al.*, 2007). Findings from few small studies suggest that IR worsens during the natural course of PCOS, while long-term OCP use either does not change or improves cardiometabolic risk parameters, including IR, lipoprotein profile and possibly body fat distribution.

Conclusions

- Overall, the benefits of OCPs outweigh the risks in most patients with PCOS (Level B).
- Women with PCOS are more likely to have contraindications for OCP use than normal women (Level C).
- In the absence of other risk factors, there is no evidence that women with PCOS are at increased risk of cardiovascular disease (CVD) with OCP treatment compared with normal women (Level C).
- There is no evidence for differences in effectiveness and risk among the various progestogens and when used in combination with a 20 versus a 30 μg daily dose of estrogen (Level B).
- OCPs do not negatively affect subsequent fertility (Level C).
- There is no definitive evidence that the type of OCP determines efficacy of hirsutism control (Level C).

Knowledge gaps/recommended future research

- Head-to-head blinded trials comparing different OCP strategies are lacking.
- Lack of longitudinal follow-up studies after a course of OCPs.

Quality of life

Patients with PCOS are an at-risk group for psychological and behavioral disorders and reduced quality-of-life (QoL) (*Himelein and Thatcher, 2006*; Jones *et al.*, 2008; Dokras *et al.*, 2011). Studies in this area have been hampered by the existence of only one validated disease-specific questionnaire, the QoL questionnaire for women with PCOS (PCOSQ) (Cronin *et al.*, 1998). A review of generic and specific QoL studies in women with PCOS concluded: (i) PCOS has a significant detrimental effect on QoL compared with controls, (ii) weight issues were most apt to affect QoL, (iii) few studies included an instrument specific for PCOS in their assessment and (iv) very few studies included QoL instruments in their assessment of the benefits of the investigated treatment (Jones *et al.*, 2008).

The PCOSQ cannot be used to evaluate the prevalence of emotional and other disorders (e.g. sexual and eating disorders). However, from other validated measures, it appears that patients with PCOS are at higher risk for developing significant psychological difficulties (i.e. depression, anxiety) compared with healthy and other controls and may also be at risk for eating disorders and sexual and relational dysfunction, though this evidence is inconsistent (Himelein and Thatcher, 2006). It has been suggested that women with PCOS should undergo psychological screening to improve long-term prognosis. However, until it is possible to disentangle potential features of the disorder from reactions to it, recommending psychological screening is premature.

Conclusions (agreement)

- There is evidence of increased prevalence of psychological disorders in women with PCOS (Level B).
- Psychological issues should be considered in all women with PCOS because of evidence suggesting increased prevalence and associated co-morbidities (Level C).
- It is unclear if this increased prevalence is due to the disorder itself or its manifestations (e.g. obesity, hirsutism, irregular menses, infertility etc.) (Level C).
- Based on the consultation and the patient's perception of her problems, appropriate counseling and intervention should be offered (Level C).

Knowledge gaps/recommended future research

- Evaluation of the validity of existing instruments for psychopathology as screening tools in PCOS.
- Determination of the prevalence of psychological disorders using appropriate instruments.
- Appropriate screening instruments and interventions remain to be developed (Level C).
- Determine if it is the disease, its manifestations or consequences that lead to psychological disorders.

Pregnancy

Women with PCOS may be subfertile. This may be explained by the effects of obesity, metabolic, inflammatory and endocrine abnormalities on ovulatory function, oocyte quality and endometrial receptivity. Ovarian hyperandrogenism and hyperinsulinemia may promote premature granulosa cell luteinization and paracrine dysregulation of growth factors may disrupt the intrafollicular environment and impair cytoplasmic and/or nuclear maturation of oocytes (Dumesic *et al.*, 2008). These features are not universal, and oocyte quality, fertilization and implantation rates in an individual woman with PCOS can be normal (Weghofer *et al.*, 2007).

During early pregnancy, the embryo may be exposed to androgen excess *in utero*. This may have long-term effects, particularly on female offspring. Fetal hyperandrogenism may disturb epigenetic programming, in particular those genes regulating reproduction and metabolism. Data in relation to the risk of miscarriage in women with PCOS are conflicting, although miscarriage rates are generally thought to be comparable with other subfertile populations (Tang *et al.*, 2010; Vanky *et al.*, 2010). When pregnancy occurs in women with PCOS, there is a higher incidence of gestational diabetes (GDM) (40–50%) and associated fetal macrosomia, gestational hypertensive disorders (such as pre-eclampsia and pregnancy-induced hypertension) (5%), and birth of small-for-gestational-age babies (10–15%) (Boomsma *et al.*, 2006). The use of metformin for women with anovulatory PCOS has no benefit with respect to enhancing either fertility or live birth rates and its routine use is not recommended.

Conclusions (agreement)

- Women with PCOS who desire a pregnancy may be at increased risk for adverse pregnancy outcomes. This may be exacerbated by obesity and/or IR (Level B).
- Health should be optimized prior to conception, with advice about smoking cessation, lifestyle, diet and appropriate vitamin supplementation (e.g. folic acid) (GPP).
- Miscarriage rates are not increased in natural conceptions in women with PCOS, independent of obesity. Miscarriage rates

after induction of ovulation mirror those found in other infertile populations (Level A).
- Women with PCOS should be followed closely during pregnancy as they may be at increased risk for the development of GDM, gestational hypertension and associated complications (Level B).
- Pregnancy-associated risks are greater in women diagnosed by more classic (NIH) criteria as opposed to non-hyperandrogenic women (Level B).
- Babies born from women with PCOS may have increased morbidity and mortality (Level B).
- There is no evidence for improved live birth rates or decreased pregnancy complications with the use of metformin either before conception or during pregnancy (Level A).

Knowledge gaps/recommended future directions for research

- Is there any value of specific periconceptional diets for women with PCOS?
- Should pregnancies of women with PCOS have increased antenatal monitoring, including earlier screening for GDM, additional Doppler studies etc.?
- Long-term outcome of children born from women with PCOS.
- Long-term outcome for women with PCOS who develop gestational hypertension and GDM, compared with women with PCOS who do no't conceive.

Ethnic differences in the phenotype

There is considerable ethnic variation in the expression of PCOS, including prevalence and severity of obesity, metabolic disturbance and their correlates. There are differences in psycho-social aspects affecting QoL and health-seeking behaviors (Goodarzi *et al.*, 2005). For example, Asian women are generally shorter, have a lower BMI and a milder hyperandrogenic phenotype. South Asians in particular have a high prevalence of the metabolic syndrome (MetS) and risk for type 2 diabetes (T2D), with central obesity more than BMI reflecting metabolic risk (Wijeyaratne *et al.*, 2011). A common clinical indicator of greater metabolic risk is acanthosis nigricans.

African American and Hispanic women are more often obese and more prone to metabolic problems; African descendents are particularly prone to hypertension and CVD, while Hispanic women are more at risk for MetS and T2D (Lo *et al.*, 2006). There is a strikingly high prevalence of hirsutism among women from the Middle East and those of Mediterranean origin. Nevertheless, abnormal glucose tolerance in Southern Europeans and East Europeans is far less common than in South Asians and Hispanics (Kalra *et al.*, 2009; Wijeyaratne *et al.*, 2011). The geographic location, ethnic origin and cultural/social practices are likely contributors to the differing manifestation of PCOS and should be recognized in routine clinical practice.

Conclusions (agreement)

- Ethnic origin and culture contribute to the differing manifestation of PCOS (Level B).
- Ethnically appropriate thresholds are required for identifying anthropometric cut-offs for appropriate metabolic screening in high-risk ethnic groups (Level B).

Knowledge gaps/future directions for research

- Effects of migration and rapid economic development for different ethnic groups for long-term cardiovascular and metabolic risk.
- Population-based prevalence of PCOS in all ethnicities.
- Best managements for manifestations by ethnicity. The role of genetic and environmental factors to explain ethnic variances.
- Effects of insulin sensitizers in different ethnic groups.

Obesity

There is widespread variability in the prevalence of overweight (BMI 25–30 kg/m^2) and obese (BMI $>$ 30 kg/m^2) women in PCOS populations across different countries. The proportion of PCOS women who are overweight but not obese ranges from 10% in Italy to 37% in Kuwait. The highest prevalence of obesity is reported in studies conducted in USA and Australia, with 61–76% of PCOS women considered obese (Glueck *et al.*, 2005; Ching *et al.*, 2007).

PCOS women are more likely to have upper body fat distribution compared with weight-matched controls. Greater abdominal or visceral adiposity is associated with greater IR, which could exacerbate the reproductive and metabolic abnormalities in PCOS (Lord *et al.*, 2006). It is known that obesity is associated with PCOS, but its causal role in this condition has yet to be determined. Very few studies report the associations of BMI with menstrual irregularity. Only a few randomized controlled studies on lifestyle interventions exist, but these suggest substantial reproductive and metabolic benefit (Moran *et al.*, 2009, 2010).

Conclusions (agreement)

- The prevalence of obesity is increasing and has an important bearing on the phenotype of PCOS (Level B).
- Some studies suggest that higher BMI is associated with a greater prevalence of menstrual irregularity, hyperandrogenemia and hirsutism, but more studies are required to confirm this (Level B).
- Increased BMI and visceral adiposity are associated with greater IR as in the general population, but its effect on menstrual irregularity and hirsutism remains unclear (Level B).
- Lifestyle management results in weight loss and improves surrogate markers of metabolic disease/syndrome (Level A).

Knowledge gaps/recommended future directions for research

- Mechanistic studies are necessary to understand the evolution of obesity and PCOS. Does PCOS predispose to obesity and does obesity unmask latent PCOS?
- More studies are required into the type and duration of exercise beneficial to women with PCOS.
- Further research is required on determinants of increasing participation and compliance in lifestyle programs, as well as the

effects of these interventions on primary outcomes such as live birth, perinatal morbidity, diabetes prevention etc.
- Research is required on the role of bariatric surgery for all aspects of PCOS and the off-spring of women with PCOS conceived after such surgery.
- Research is required to optimize lifestyle interventions, maximizing weight loss and minimizing drop-outs of participating women.

IR and MetS

IR is a prevalent finding in women with PCOS (Dunaif, 1997). It is most prevalent and severe in those with the classic NIH PCOS phenotype involving hyperandrogenism and chronic anovulation. Women with PCOS assessed by Rotterdam criteria yet with regular cycles are metabolically less abnormal (*Legro et al., 2005*; Johnstone *et al.*, 2010; Moran *et al.*, 2010).

The cellular and molecular mechanisms of IR in PCOS differ from those in other common IR states such as obesity and T2D. *In vivo* insulin action is profoundly decreased in skeletal muscle secondary to signaling defects, but hepatic IR is present only in obese women with PCOS. There is a synergistic negative effect of having both PCOS and obesity on insulin action. Pancreatic β-cell dysfunction is also present in PCOS but may be more related to T2D risk factors since this dysfunction is most severe in women with a first-degree relative who have T2D (Ehrmann *et al.*, 1995).

Extensive evidence indicates that hyperinsulinemia contributes directly to reproductive dysfunction in PCOS (Dunaif, 1997). Women with classic NIH PCOS have significantly increased rates of the MetS compared with reproductively normal women of similar age and weight.

Conclusions (agreement)

- PCOS-associated metabolic disorders are major predictors of prediabetes, diabetes and MetS in reproductive-age women (Level B).
- Patients with MetS are an important clinical subset of women with PCOS (Level B).
- Not all PCOS phenotypes have similar metabolic risk. The combination of hyperandrogenemia and oligomenorrhea signifies the most at risk group (Level B).
- It is critical for public health and for optimum design of long-term studies to stratify women with PCOS according to metabolic risk. This goal would be greatly facilitated by using a specific name for this high metabolic risk PCOS subset (GPP).

Knowledge gaps/recommended future directions for research

- Long-term prospective studies to define metabolic outcomes and CVD risk in PCOS.
- The role of androgens in the spectrum of MetS risk in women.
- Further, define the importance of adipocyte pathophysiology, in particular in the visceral adipose depot, in the evolution of IR and MetS in PCOS.

Type 2 diabetes

IR is a prominent feature of PCOS. There is now compelling evidence from epidemiological data (Solomon *et al.*, 2001) that PCOS is associated with increased risk of impaired glucose tolerance (IGT), GDM and T2D (Dunaif, 1997; Boomsma *et al.*, 2006; Moran *et al.*, 2010). Biochemical screening, in the form of an oral glucose tolerance test (OGTT), is indicated in obese women with PCOS, and/or those with increased visceral adiposity, as measured by waist circumference. Risk of IGT or diabetes is highest in women who have both oligo/anovulation and hyperandrogenism, and the risk is further amplified by obesity (Barber *et al.*, 2007).

Management of women at risk for T2D should include diet and lifestyle improvement as first-line treatment. Metformin treatment is indicated in those with IGT who do not respond adequately to calorie restriction and lifestyle changes. In those with frank diabetes, metformin is safe and effective, whereas there is concern about the use of thiazolidinediones and glucagon-like peptide-1 analogs in women of reproductive age (Franks, 2011).

Conclusions (agreement)

- PCOS is a major risk factor for developing IGT and T2D (Level A).
- Obesity (by amplifying IR) is an exacerbating factor in the development of IGT and T2D in PCOS (Level A).
- The increasing prevalence of obesity in the population suggests that a further increase in diabetes in PCOS is to be expected (Level B).
- Screening for IGT and T2D should be performed by OGTT (75 g, 0 and 2 h values). There is no utility for measuring insulin in most cases (Level C).
- Screening should be performed in the following conditions: hyperandrogenism with anovulation, acanthosis nigricans, obesity (BMI >30 kg/m^2, or >25 in Asian populations), in women with a family history of T2D or GDM (Level C).
- Diet and lifestyle are first choice in improving fertility and prevention of diabetes (Level B).
- Metformin may be used for IGT and T2D (Level A). Avoid use of other insulin-sensitizing agents, such as thiazolidinediones (GPP).

Knowledge gaps/recommended future research

- Identification of genetic factors contributing to diabetes risk in PCOS.
- Clear definition of the interaction of obesity and body fat distribution with PCOS in the development of IGT and T2D.
- Need to define the prevalence of GDM in a large cohort of women with PCOS.
- Need for collection of good longitudinal data on progression from IGT to T2D.
- Need to gather data on efficacy and safety of newer drugs for treatment of T2D in PCOS (including GLP-1 agonists).
- Need to better assess the efficacy of bariatric surgery and its long-term effect.

CVD markers

Metabolic dysfunction in women with PCOS leads to exaggerated risk for CVD with aging. Markers for CVD risk reflect the metabolic dysfunction. Changes can occur without obesity and are magnified with obesity. More android central obesity occurs in non-obese women with PCOS. Severity of IR is related to the amount of abdominal obesity even in women with normal BMI. This is likely to contribute to the abnormalities in the classic markers for CVD risk (IGT, MetS and T2DM and dyslipidemia).

The odds for these CVD risk indicators are ~3 times higher in women with PCOS compared with those without PCOS, and in BMI-matched studies, the odds are approximately double. The prevalence of these increased CVD risk markers differs by geographical region (Chen *et al.*, 2010). The more severe PCOS phenotypes are associated with greater magnitude of CVD risk and this has been found in obese and non-obese women (Zhao *et al.*, 2010; Dokras *et al.*, 2011).

Triglyceride, low-density lipoprotein (LDL) and non-high-density lipoprotein (HDL) cholesterol changes are higher compared with non-PCOS women. This reflects more atherogenic ApoB/ApoA ratios. Differences are greater when PCOS is diagnosed using NIH rather than Rotterdam criteria. Assessing waist circumference and non-HDL-cholesterol appear to be the most useful clinical indicators of this metabolic disturbance. Systemic inflammation associated with endothelial vascular dysfunction and metabolic disturbance is commonly present in women with PCOS. Numerous biochemical inflammatory and thrombotic markers of CVD risk circulate in excess in women with PCOS. Some of these markers correlate with IR. It remains unclear if increased levels of markers of inflammation and thrombotic risk CVD risk provide additional predictive power beyond assessment using classic CVD risk factor estimates for estimating individual of CVD.

Conclusions (agreement)

- PCOS at any age is characterized by greater odds for elevated CVD risk markers. Elevated markers occur without obesity, and are magnified with obesity (Level B).
- Dyslipidemia, IGT and T2D (classic risk indicators of atherosclerosis and CVD) are more prevalent in women with PCOS, even when weight matched with normal control women (Level B).
- Altered levels of triglycerides, HDL, LDL and non-HDL (reflecting altered ApoB/ApoA metabolism) are prevalent in women with PCOS and are more severe in hyperandrogenic women (Level B).
- Non-HDL cholesterol and waist measurement appear to be the best clinical indicators of elevated CVD risk (Level C).
- All markers reflect a greater magnitude of risk when women are diagnosed using NIH criteria (including hyperandrogenism) compared with the Rotterdam criteria (Level B).
- Depression and anxiety, major risk factors for CVD, are common in women with PCOS (Level B).
- Recommended CVD risk assessment at any age: assessment for psychosocial stress, blood pressure, glucose, lipid profile (cholesterol, triglycerides, HDL, LDL and non-HDL cholesterol), waist circumference, physical activity, nutrition and smoking (Level C).
- Because CVD risk increases with age and accompanying additive environmental insults, periodic reassessment for CVD risk is recommended (GPP).

Knowledge gaps/recommended future research

- How often should CVD risk assessment be repeated in women with PCOS with or without elevated risk indicators?
- What are optimal specific recommendations in various races or ethnicities?
- Which novel CVD risk markers provide added benefit beyond the classic CVD risk indicators?
- Longitudinal studies associating surrogate markers with CVD events are needed for precise CVD risk prediction.

CVD outcomes

Life-long metabolic dysfunction in women with PCOS exaggerates the risk for CVD with aging, particularly after menopause. This metabolic dysfunction is based upon IR, which occurs in most women with PCOS, being independent and additive with that of obesity. Consequently, beginning in adolescence, IGT and T2D are highly prevalent in PCOS [odds ratio (OR) of ~4:1] and occur in ~40% of PCOS women by the fourth decade of life, with age and weight gain worsening glycemic control. Insulin-resistant women with PCOS have vascular dysfunction, which is associated with total and abdominal adiposity. Women with PCOS also have more subclinical vascular disease than normal women. The severity of carotid intima-media thickening, coronary artery calcification and to a lesser extent aortic calcification is greater in women with PCOS (by NIH criteria) than controls, independent of age and BMI.

Nevertheless, evidence for increased CVD morbidity and mortality in women with PCOS, based upon Rotterdam and/or NIH criteria, remains inconclusive (*Pierpoint et al., 1998*; Cibula *et al.*, 2000; Wild *et al.*, 2000; Elting *et al.*, 2001). It is not possible to properly diagnose PCOS after menopause. Nevertheless, post-menopausal women with existent hyperandrogenemia and premenopausal menstrual irregularity have a larger number of cardiovascular events than controls, despite technical challenges in accurately measuring low circulating androgen levels in this age group (Shaw *et al.*, 2008). Among non-diabetic post-menopausal women with intact ovaries, moreover, atherosclerotic CVD is associated with features of PCOS, including premenopausal menstrual irregularity, hirsutism and post-menopausal biochemical hyperandrogenism (Krentz *et al.*, 2007).

Conclusions (agreement)

- Life-long metabolic dysfunction in women with PCOS exaggerates CVD risk, causing a possible increase in CVD events with age, especially after menopause (Level B).
- All surrogate markers of cardiovascular risk are higher in PCOS (adjusted for age and BMI), but the association of these markers with CV events in PCOS remains unclear (Level B).
- Endothelial dysfunction in PCOS is related to abdominal obesity and IR (Level B).

- Coronary artery calcification and carotid intima-media wall thickness are also increased in women with PCOS compared with matched controls (Level B).
- Amongst non-diabetic post-menopausal women with intact ovaries, atherosclerotic CVD is associated with features of PCOS, such as relative androgen excess and a recalled history of irregular menses (Level B).

Disagreement

- Uncertainty exists as to whether PCOS status *per se* increases CV mortality.

Knowledge gaps/recommended future research

- Data are lacking regarding ethnic and racial differences in the set point for vascular damage associated with PCOS.
- Precision of CV surrogate markers is unknown.
- Association between CV surrogate markers and CV events is unclear.
- Longitudinal studies are needed to associate CV markers with vascular events.
- Longitudinal studies are lacking regarding the effects of various PCOS phenotypes on CVD events.
- The role of sex steroids on regional adipogenesis and its impact on total and abdominal obesity is uncertain.
- Does PCOS phenotypic expression vary over lifetime and modulate CV risk?
- Does hyperandrogenemia *per se* have its own independent effects on atherosclerosis?
- Determine the optimum multi-faceted approach to PCOS women that reduces and prevents CVD.

Cancer risk

PCOS disrupts normal reproductive physiology. The condition may be associated with increased risk of the development of cancer of the endometrium, ovary and/or breast, either directly or mediated by its associated reproductive-metabolic alterations. There is a small to moderate amount of literature assessing the association of PCOS with the development of cancer of the reproductive organs.

Estimates of the strength of association are likely to be sensitive to a number of factors, including limitations in the definition of PCOS, limitations in comparison with various populations and the small number of studies assessing each cancer type (*Schildkraut et al., 1996*; Pierpoint *et al.*, 1998; Wild *et al.*, 2000; Chittenden *et al.*, 2009).

Conclusions (agreement)

- There are moderate quality data to support that women with PCOS have a 2.7-fold (95% confidence interval 1.0–7.3) increased risk for endometrial cancer. Most endometrial cancers are well differentiated and have a good prognosis (Level B).
- Limited data suggest that PCOS women are not at increased risk for ovarian cancer (Level B).
- Limited data suggest that PCOS women are not at increased risk for breast cancer (Level B).

Disagreement

- There is no agreement on the optimal modality or timing of how to monitor women for the presence of endometrial cancer or precursor endometrial changes using ultrasound and/or endometrial biopsy. The decision to assess for the presence of endometrial cancer should be based on clinical factors, including length of amenorrhea, presence of abnormal uterine bleeding, thickness and appearance of the endometrium on imaging and the age of the patient (GPP).

Knowledge gaps/recommended future research

- Insufficient evidence to evaluate any association of PCOS with vaginal, vulvar or cervical cancer.
- Difficulty in separating PCOS cancer risk from other recognized risk factors such as nulliparity, infertility and its treatment, anovulation and obesity.
- Lack of precision in the estimate of the risk of endometrial cancer in PCOS, especially in subgroups with and without risk factors.
- Limited confidence in the association of PCOS and ovarian cancer.
- Cancer studies in PCOS should involve more subjects, with more clarity on the phenotypic variation in the diagnosis of PCOS.
- Comparison population studies should be conducted and improved.

Menopause, general health

The transition of women with PCOS into menopause and whether there is a specific phenotype for PCOS after menopause is poorly understood. There is evidence that women with PCOS have a larger cohort of primary follicles than age-matched control women before menopause. Serum T levels decrease as women age from the third to fifth decades. Additionally, women with PCOS often develop improved menstrual regularity with age. These factors may all contribute to improvement in reproductive functioning with age prior to menopause. Menopausal PCOS phenotype is poorly defined. The polycystic ovary criterion is likely not useful in post-menopause.

It is not definitively known what the general health status of post-menopausal women with PCOS is, or what are optimum therapies. It is suspected that women with PCOS who have transitioned through menopause will have increased rates of obesity, diabetes and cardiovascular events. Most reports tend to show normal or increased bone mineral density in women with PCOS. The natural history of hirsutism and/or alopecia in post-menopausal women with PCOS is unknown. It is difficult from the existing data to know whether the mortality rate is different in women with PCOS. Retrospective data in women with polycystic ovaries suggest mortality occurs at a similar rate as in the general population and presumably at the same age (*Dahlgren et al., 1992*; Mulders *et al.*, 2004; Davison *et al.*, 2005; Alsamarai *et al.*, 2009; Hudecova *et al.*, 2009; Tehrani *et al.*, 2010).

Alternative data suggest that they have higher rates of stroke and CVD.

Conclusions (agreement)

- Age may improve many manifestations of PCOS, including normalizing ovarian size and morphology, T levels and oligo-ovulation prior to menopause (Level B).

Knowledge gaps/recommended future research

- There are little data on long-term fecundity and precise age of menopause in women with PCOS.
- Long-term risk for morbidity and mortality among post-menopausal women with a history of PCOS is uncertain.
- There is no established phenotype for PCOS after menopause.
- Most clinical assays are not precise for determining T levels in post-menopausal women
- Long-term, multi-center cohort studies are needed where the following issues should be assessed: menopausal phenotype, cardiovascular events, cancer and other causes of morbidity/mortality.
- Utilize genome-wide association studies to identify new genes/pathways involved in ovarian dysfunction related to age of menopause and polycystic ovaries.

Supplementary Information

An extended supplementary document containing comprehensive background information is provided online at http://humrep.oxfordjournals.org/.

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Appendix

B.C.J.M. Fauser: University Medical Center, Utrecht, The Netherlands; B.C. Tarlatzis: Medical School of Thessaloniki, Greece (congress chairs); R.W. Rebar: University of Alabama at Birmingham, USA; R.S. Legro: Penn State College of Medicine, Hershey, USA; A.H. Balen: Leeds Teaching Hospitals, Leeds, UK; R. Lobo: Columbia University, New York, USA (scientific committee members); H. Carmina: University of Palermo, Palermo, Italy; R.J. Chang: University of California, San Diego, USA; B.O. Yildiz: Hacettepe University School of Medicine, Ankara, Turkey; J.S.E. Laven: Erasmus University Medical Center, Rotterdam, The Netherlands; J. Boivin: Cardiff University, Cardiff, UK; F. Petraglia: University of Siena, Siena, Italy; C.N. Wijeyeratne: University of Colombo, Sri Lanka; R.J. Norman: Robinson Institute, University of Adelaide, Australia; A. Dunaif: Northwestern University, Chicago, USA; S. Franks: Imperial College London, UK; R.A. Wild: Oklahoma University, Oklahoma, USA; D. Dumesic: University of California, Los Angeles, USA; and K. Barnhart: University of Pennsylvania, USA (workshop participants).