Health and fertility in World Health Organization group 2 anovulatory women

ESHRE Capri Workshop Group*

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BACKGROUND: Disruption of ovulation occurs in different types of clinical infertility. The World Health Organization (WHO) has provided a classification of ovulation disorders. This review focuses on WHO group 2 anovulation.

METHODS: Searches were performed in Medline/PubMed and EMBASE. Each subject summary was presented to the European Society of Human Reproduction and Embryology (ESHRE) Workshop Group, where omissions or disagreements were resolved by discussion.

RESULTS: Disorders resulting in ovulatory disturbances are a relatively common cause of infertility. They occur most frequently in the context of WHO group 2 anovulation as reflected, for example, in the polycystic ovary syndrome (PCOS). The aetiology of PCOS remains unclear but evidence exists for a multifactorial origin with a genetic predisposition. Women with PCOS show an increased time to pregnancy but their eventual family size is not necessarily reduced. Also their frequency of miscarriage does not appear increased. Clomiphene citrate is still the first-line treatment in subfertile anovulatory patients with PCOS, with gonadotrophins and laparoscopic ovarian surgery as second-line options. Aromatase inhibitors show promising results.

CONCLUSIONS: Long-term health risks in patients with WHO group 2 anovulation demand their general health be monitored, even after their reproductive needs have been fulfilled. Metabolic and cardiovascular risk prevention in women with PCOS should start as early as

* The list of ESHRE Capri Workshop Group participants is given as an appendix.

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Introduction

Although reproduction is of pivotal importance for the survival of the species, for individuals it is an expendable function that can be deferred in times of stress. Physiological mechanisms for postponing reproduction by avoiding ovulation are available and disruption of ovulation occurs in different types of clinical infertility. Ovulation is the process by which the maternal genetic material can be transferred, by the oocyte, to the next generation. Hence it would be expected that the selection pressures on women to evolve a robust mechanism of gamete transfer would be enormous. However, although reproduction is important for survival of the species, in times of stress it is a dispensable that can be deferred until conditions are better (ESHRE Capri Workshop Group, 2006). In women, in contrast to men, the physiological mechanisms for postponing reproduction (by avoiding ovulation) are readily available.

Regular menstrual cycles are usually the outward manifestation of cyclical ovarian activity and ovulation (Baird, 1997). The establishment of regular ovulatory cycles at puberty depends on a complex series of interactions involving the hypothalamus, anterior pituitary and ovary (the HPO axis; Marshall, 2006).

With these series of complex interrelated events it is hardly surprising that disorders of ovulation are relatively common causes of infertility and irregular menstrual cycles.

Methods

Searches were performed in Medline/PubMed and EMBASE by individual participants in the workshop. Selection criteria included high-quality studies relevant to clinical reproductive medicine. Each subject summary was presented to the Workshop Group where omissions or disagreements were resolved by discussion.

Results and Discussion

Ovarian function in anovulatory patients

(a) Primary ovarian insufficiency

Any condition where there is an absence or severely reduced complement of primordial oocytes will result in anovulation (De Vos et al., 2010). Primary ovarian insufficiency, characterized by amenorrhoea and elevated levels of FSH and LH (hypergonadotrophic hypogonadism) can be caused by failure of ovarian development or an antenatal reduction in the numbers of normal primordial follicles or their accelerated depletion, as in Turner syndrome. Acquired ovarian insufficiency can occur because of a range of conditions that result in the destruction or loss of ovarian tissue (e.g. endometriosis, ovarian surgery, chemo- or radiotherapy). Where there is a reduction in the number rather than a total absence of oocytes, the levels of FSH may fluctuate from month to month. Episodes of periodic bleeding coinciding with the development of antral follicles may alternate with prolonged periods of amenorrhoea. The factors determining the availability of the few remaining follicles for development are unclear. Measurement of anti-Mullerian hormone (AMH) in addition to FSH, LH and inhibin is useful in the clinical assessment (Knauff et al., 2009). AMH is produced by the granulosa cells of pre-antral, as well as small antral follicles. Thus its concentration in serum reflects the total follicle population rather than that of estradiol ($E_2$) which is principally derived from the large antral follicle(s) or the corpus luteum.

(b) Secondary ovarian insufficiency

Lack of the appropriate gonadotrophic stimulation of the ovaries is a common cause of anovulation (Baird, 1997). It is helpful for diagnostic and therapeutic purposes to classify anovulation by the level of gonadotrophins.

In hypogonadotrophic hypogonadism (the WHO group 1). The levels of LH and FSH are below the range necessary to stimulate follicle development and hence the levels of $E_2$ are low. This may be caused by primary pituitary disease (tumour or destruction) or more commonly to hypothalamic suppression reflected in a marked reduction in the frequency and amplitude of LH pulses. In this respect, endocrinologically many of these women resemble the prepubertal state. Hypothalamic suppression is a very common cause of secondary amenorrhoea and occurs in association with weight loss and negative energy balance, such as occurs in anorexia nervosa and endurance athletes. There is a relative shortage of freely available oxidizable substrate and levels of leptin are low. Infusion of leptin may restore LH levels in some women with this condition but the relationship between body weight, fat and gonadotrophins is complex. Many women remain amenorrhoeic for several months after they have regained their ideal body weight (ESHRE Capri Workshop Group, 2006).

The hypogonadism in hyperprolactinaemia. It is related to the low levels of LH in association with raised levels of prolactin which disrupt or arrest normal functioning of the hypothalamic GnRH pulse generator.

Normogonadotrophic anovulation (WHO group 2). There are different aetiologies and clinical presentations (Table I). About 30% of women presenting with secondary amenorrhoea have concentrations of gonadotrophins within the normal range (Baird et al., 1977). Careful analysis of the pattern of LH secretion may reveal subtle abnormalities, such as frequent high-amplitude pulses, as in polycystic ovary syndrome (PCOS), or failure of an LH surge. Many women with these disorders present with irregularities in the pattern of menstrual bleeding (dysfunctional uterine bleeding) rather than with secondary amenorrhoea. Follicular development and estrogen production continue but are arrested at some stage short of full maturation of an ovulatory follicle. Thus, these women, although anovulatory, show no signs of...
Table 1 Mechanisms of normogonadotrophic anovulation (WHO group 2).

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine: hypothalamic–pituitary–ovarian axis</td>
<td>Inability to generate LH surge in response to an estrogen challenge</td>
</tr>
<tr>
<td></td>
<td>Lack of maturation at puberty (failure of positive feedback)</td>
</tr>
<tr>
<td></td>
<td>Interference by ‘ectopic’ steroids (e.g. adrenal androgens, progestogens)</td>
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<tr>
<td></td>
<td>(e.g. Congenital Adrenal Hyperplasia)</td>
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<tr>
<td></td>
<td>Dysfunction of follicle maturation</td>
</tr>
<tr>
<td></td>
<td>Premature acquisition of LH receptors by a small antral follicle</td>
</tr>
<tr>
<td></td>
<td>Relative lack of FSH at the critical point when follicles are selected for</td>
</tr>
<tr>
<td></td>
<td>final ovulatory maturation</td>
</tr>
<tr>
<td></td>
<td>Failure of follicle rupture</td>
</tr>
<tr>
<td></td>
<td>Inappropriate LH surge</td>
</tr>
<tr>
<td></td>
<td>Drugs (non-steroidal anti-inflammatory drugs, clomiphene citrate,</td>
</tr>
<tr>
<td></td>
<td>progestrone antagonists</td>
</tr>
</tbody>
</table>

PCOS, polycystic ovary syndrome.

The health of WHO group 2 anovulatory patients at young age

(a) Prevalence, aetiology and clinical presentation

The WHO group 2 classification of anovulatory infertility applies almost exclusively to women with PCOS. A report from a large specialist centre showed that 91% of women categorized as having WHO group 2 anovulation met the broader diagnostic criteria for PCOS (Broekmans et al., 2006). PCOS is the commonest endocrine disorder in women and is the major cause of anovulation. The prevalence of PCOS in the population depends on the criteria used for diagnosis, as well as the ethnic background of the population studied. Nevertheless, even if we use the classic ‘NIH’ definition of PCOS (i.e. the combination of anovulation and hyperandrogenism), the prevalence of the syndrome is in excess of 5% (Knochenhauer et al., 1998; Diamanti-Kandarakis et al., 1999; Asuncion et al., 2000). The prevalence of the characteristic polycystic ovary (PCO) morphology, e.g. at ultrasound, is around 20% (Polson et al., 1988), and may be even higher in certain ethnic groups. For example, both PCO and PCOS (i.e. the morphological ovarian appearance plus at least one characteristic clinical symptom) are more common in women from the Indian subcontinent than in those from northern Europe. Increased age is accompanied by a decrease in the prevalence of both clinical and biochemical hyperandrogenism in women (Liang et al., 2011). Hyperandrogenism is the important factor for young women with PCOS; however, abdominal obesity and certain metabolic disturbances became major concerns for older women with PCOS (Liang et al., 2011). Obesity amplifies the symptoms and biochemical abnormalities of PCOS. The current obesity ‘pandemic’ results in a greater proportion of the population with polycystic ovaries becoming symptomatic, or in the case of those who already have symptoms, development of a more severe clinical picture (Barber et al., 2006).

The aetiology of PCOS remains unclear but there is compelling evidence for a major genetic predisposition to the syndrome (Escobar-Morreale et al., 2005a). This may appear paradoxical given that one would have expected an inherited cause of infertility to result in a dwindling population of women with PCOS. The answer to this conundrum may lie in the study of PCOS in the general population in which a wider spectrum of presentation of women with symptoms of PCOS can be observed compared with the selected population that typically presents in endocrine or fertility clinics. Results from the North Finland Birth Cohort 1966 study show that although there may be a delay in conceiving in patients with PCOS symptoms, the family size is not significantly compromised in the end (Koivunen et al., 2008). This key epidemiological study has followed a cohort of over 4000 women born in 1966 whose reproductive history was reviewed at the age of 31 years. Women with symptoms of PCOS (oligomenorrhea and hirsutism) were identified within this cohort and their reproductive history was compared with that of the remaining women in the cohort (reference group). In total, 1103 of 4535 (24%) had symptoms of PCOS. These women suffered more frequently from subfertility (26 versus 17%) and had reduced fecundability (i.e. the time to first pregnancy was increased). However, the percentage of women conceiving overall was similar in those with and without PCOS symptoms (78 versus 76%), and their eventual family size (number of children) was not reduced.

These observations suggest that, in the context of the population as a whole, women with PCOS may take longer than expected to conceive (i.e. have reduced fecundability by virtue of having fewer ovulatory cycles per year than normal) but their ‘lifetime fertility’ is not significantly impaired. The women with WHO group 2/PCOS who are seen in specialist infertility clinics are usually overweight and represent the more severe end of the spectrum of presentation of oligo-anovulatory infertility.

The origin of PCOS is multifactorial but the importance of genetic factors in its aetiology is intriguing. Looking at the reproductive history of women with symptoms of PCOS in the general population gives us a new insight into its high prevalence despite its link with anovulation. PCOS clearly does not mean infertility in every patient. Indeed it has been hypothesized that there may be a reproductive advantage in having polycystic ovaries and the attendant predisposition to insulin resistance in PCOS represents a thrifty reproductive phenotype, ensuring, especially in times of famine, its survival in the population as a whole (Escobar-Morreale et al., 2005a; Corbett et al., 2009).

(b) Cycle and skin problems

Women who are not ovulating commonly present with complaints of irregular or absent menses or with one of a number of skin conditions
related to hyperandrogenism. Unless the woman wishes to conceive, in which case she should be referred to a reproductive endocrinologist or infertility specialist, most women can be treated by generalists. Long-term risks in patients with WHO group 2 anovulation, however, dictate that their general health be monitored at regular intervals, even (especially) after their reproductive needs have been fulfilled.

**Menstrual dysfunction.** The degree of ovarian dysfunction, the amount of follicular activity and circulating concentration of estrogens stimulating endometrial development will determine whether women have amenorrhea or oligomenorrhea (Burgers et al., 2010). Sporadic anovulatory cycles do occur among all regularly menstruating women (Mumford et al., 2011); however, this does not present a clinical problem.

The approach to management will depend on the type of menstrual dysfunction and the life stage, medical history and preferences of the woman concerned. All women should be examined and investigated in order to establish the underlying cause of the menstrual dysfunction—to confirm or exclude, for example, PCOS, hyperprolactinaemia, hypogonadotrophic hypogonadism or other endocrine or gynaecological disorders.

Oligomenorrhoea in adolescents does not usually require active treatment but simple reassurance that menstrual cycles will become regular with time and regular follow-up to ensure that this does in fact happen. Approximately 4–5% of young women experience secondary amenorrhoea (Table II). For other women with oligoamenorrhoea, treatment is usually required to prevent the consequences of either hypo- or hyperestrogenism and/or because the woman prefers menstrual regularity. Management will depend on the need for contraception. For sexually active women combined oral contraception (COC) given cyclically will provide estrogen replacement and confer regular monthly withdrawal bleeds. Some women, even those who are not sexually active, may prefer to bleed less frequently and there is no contraindication to tailored COC regimes allowing a bleed, for example every 3 months, or even no bleeding at all. For women who are not hypoestrogenic and who prefer amenorrhoea, the levonorgestrel-releasing intrauterine system will provide contraception and protect the endometrium from unopposed estrogens.

Skin problems. Dermatological sequelae of hyperandrogenaemic anovulation include acne vulgaris, hirsutism, androgenic alopecia and acanthosis nigricans. Among 115 consecutive Turkish women newly diagnosed with PCOS and evaluated for cutaneous features, the prevalence of acne, hirsutism, seborrhoea, androgenetic alopecia and acanthosis nigricans was 53, 73.9, 34.8, 34.8 and 5.2%, respectively (Ozdemir et al., 2010).

Acanthosis nigricans is characterized by dark brown thickened cutaneous plaques commonly in the neck and axillae formed by the proliferation of epidermal keratinocytes and fibroblasts. Treatment involves management of the underlying disorder, laser or surgical excision. Topical tretinoin and calcipotriol have also been used with some, although limited, success (Kapoor, 2010). Hair loss is a clinical problem that is common in hyperandrogenic women (Camacho-Martinez, 2009). Typically alopecia begins with a specific diffuse loss of hair from the parietal or fronto-temporal areas with an intact frontal hairline. Topical treatment of hair loss is with minoxidil, 2–5% twice daily. When hair loss is associated with high levels of androgens, systemic anti-androgenic therapy may be beneficial (Paradisi et al., 2011; Escobar-Morreale et al., 2012). Some women with hirsutism respond to topical treatment with eflornithine or local hair removal techniques.

Acne can similarly be treated with topical products or systematically with isotretinoin (Ehrmann et al., 2006). For women with hyperandrogenism, the general treatment is focused on reducing androgen production, decreasing the fraction of circulating free testosterone, and limiting androgen bioactivity at the target tissue level (e.g. the hair follicle). COC has been shown to be of benefit in the treatment of acne and hirsutism (Escobar-Morreale et al., 2012). The additional anti-androgenic effects of cyproterone acetate are well known, however, the benefit of drospirenone is less clear, as the dose contained in the COC is rather low (Arowojolu et al., 2009). Both cyproterone acetate and drospirenone have been implicated in increased risks of venous thromboembolism (Van Vliet et al., 2004). Other drugs that have been used, some in combination with a COC, are spironolactone (Brown et al., 2009a), flutamide (Ehrmann et al., 2006), finasteride (Chuan and Chang, 2010) and insulin-sensitizing agents, such as metformin and thiazolidinediones (Costello et al., 2007). Whereas weight loss usually improves skin problems, in overweight patients with an excess of androgen the PCOS Society advises against using insulin sensitizers for hirsutism. There is not enough evidence supporting their use for this indication (Escobar-Morreale et al., 2012).

The choice of therapy for the treatment of acne and hirsutism will depend on the degree of severity of the condition, the desire for fertility or need for effective contraception and the balance of the safety profile and side effect profile in relation to individual patients (Fig. 1).

(c) Early prevention of metabolic risks

Metabolic disturbances are frequent in adolescent and adult women with PCOS and may include abdominal adiposity, disorders of glucose tolerance, dyslipidaemia and the metabolic syndrome (Escobar-Morreale and San Millan, 2007). Despite the fact that even morbid obesity may not lead to PCOS, novel metabolomic data indicate that it plays a major role in the development of metabolic dysfunction in women with the syndrome (Escobar-Morreale et al., 2005b).

While in non-obese PCOS patients increased insulin concentration may result partly from decreased hepatic clearance, in most patients with PCOS the key metabolic disturbance is a condition of insulin resistance. This metabolic trait is present even before puberty.

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### Table II A cross-sectional study from a Danish county.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>15–24</th>
<th>25–34</th>
<th>35–44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>434</td>
<td>432</td>
<td>655</td>
</tr>
<tr>
<td>All (%)</td>
<td>7.6</td>
<td>3.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–6 months</td>
<td>5.8</td>
<td>2.3</td>
<td>1.7</td>
</tr>
<tr>
<td>7–12 months</td>
<td>1.4</td>
<td>0.2</td>
<td>1.1</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>0.4</td>
<td>1.5</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Prevalence (%) of secondary amenorrhoea by age (Münster et al., 1992).
and contributes to androgen excess because insulin acts as a co-gonadotrophin at the level of the ovaries. However, accumulating evidence suggests that an excess of androgen, beginning as early as fetal life in affected women, might also contribute to insulin resistance in women with PCOS by favouring a predominantly abdominal distribution of body fat and visceral adipose tissue dysfunction (Escobar-Morreale and San Millan, 2007). According to this view, abdominal adiposity and adipose tissue dysfunction may induce insulin resistance, and compensatory hyperinsulinaemia favours further androgen excess closing a vicious circle that contributes to metabolic and cardiovascular risk in affected women.

Metabolic and cardiovascular risk prevention in women with PCOS should start as early as possible, and that usually means at diagnosis. But considering that PCOS shows significant familial aggregation (Escobar-Morreale et al., 2005a), by extending preventive strategies to the relatives of patients with PCOS, these preventive strategies may prove useful for the affected daughters of women with PCOS even before these girls are diagnosed with the syndrome. A screening strategy for PCOS is summarized in Table III.

Among preventive strategies, those promoting a healthy lifestyle based on a correct diet, regular exercise and smoking cessation are possibly the most effective but at the same time the most difficult to comply with (Wild et al., 2010; Teede et al., 2011). Every effort should be made to avoid weight gain and obesity, given the deleterious impact that obesity exerts on the metabolic and cardiovascular associations of PCOS and the other known cardiovascular risk factors (Table IV).

Most of the pharmacological strategies used for PCOS may also contribute to metabolic and cardiovascular prevention (Fauser and Bouchard, 2011; The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group, 2012). In particular, modern low-dose oral contraceptives and anti-androgens not only improve the signs and symptoms of the androgen excess but are metabolically safe and ameliorate several cardiovascular risk markers and surrogates of early cardiovascular disease (CVD), such as carotid intima-media thickness (Table V; Luque-Ramirez et al., 2007, 2009). Insulin sensitizers ameliorate insulin resistance and secondarily improve the androgen excess and menstrual dysfunction. Finally, in selected cases, bariatric surgery in severely obese women may resolve the signs and

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**Table III** PCOS: screening for metabolic and cardiovascular risk factors (Wild et al., 2010).

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure BMI and waist circumference at every visit</td>
</tr>
<tr>
<td>Obtain a complete lipid profile and repeat every 2 years if normal</td>
</tr>
<tr>
<td>2-h 75 g OGTT in obese women, or in non-obese if older than 40 years, previous gestational diabetes, or a family history of diabetes, and repeat every 2 years if normal. Consider using HbA1c</td>
</tr>
<tr>
<td>Measure the clinical blood pressure at each visit</td>
</tr>
<tr>
<td>Suggestion Assess for depression, anxiety and quality of life</td>
</tr>
</tbody>
</table>

OGTT, oral glucose tolerance test.

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**Table IV** Patients with PCOS who are at risk of metabolic and CVD (Wild et al., 2010).

**At risk if:**
- Obesity (especially abdominal)
- Cigarette smoking
- Hypertension
- Dyslipidaemia
- Subclinical cardiovascular disease
- Impaired glucose tolerance
- Family history of premature CVD

**At high risk if:**
- Metabolic syndrome
- Type 2 diabetes
- Overt vascular or renal disease
symptoms of PCOS, thereby restoring insulin sensitivity and fertility (Escobar-Morreale et al., 2005b).

**Spontaneous and treatment-related fecundity**

(a) **Reduced fecundability**

As already mentioned, a recent Finnish study showed that women with PCOS may take longer to conceive but their lifetime fertility is not impaired. Only women suffering from both obesity and PCOS experienced lower fertility (Koivunen et al., 2008). Interestingly, women with PCOS show sustained fertility with advancing age when compared with infertile eumenorrhoeic women (Mellembakken et al., 2011).

(b) **Management and first-line profertility strategies**

Several studies have shown that a modest weight loss (5–10%) in overweight patients restores normal fecundity (Clark et al., 1998; Huber-Buchholz et al., 1999; Crosignani et al., 2003; NICE, 2004; Escobar-Morreale et al., 2005b; Thomson et al., 2008; Kuchenbecker et al., 2011). Lifestyle management targeting weight loss in overweight and obese patients with PCO and prevention of weight gain in lean patients with PCO should include both reduced dietary energy (caloric) intake in the setting of healthy food choices and exercise, and should be first-line therapy for all women with PCO (Teede et al., 2011).

In case of failure of weight loss, clomiphene citrate at incremental daily oral doses of 50–150 mg has been the medication of choice for the first-line treatment of anovulatory PCOS for 50 years. It induces ovulation in about 75% of women, pregnancy in 35%, with about 20% miscarriages and 8–10% multiple pregnancies, so that in the end 25% of clomiphene citrate starters will have a singleton live birth (Homburg, 2005; Brown et al., 2009b). Ultrasound-monitored clomiphene citrate-treated cycles produce better pregnancy rates compared with non-monitored cycles (König et al., 2009). The discrepancy between ovulation and pregnancy rates is explained by the anti-estrogenic effects of clomiphene citrate on the endometrium or undiagnosed LUF (Homburg et al., 2006).

A novel alternative to clomiphene citrate is letrozole, an aromatase inhibitor (AI). AIs are potent compounds that suppress estrogen biosynthesis by blocking the action of aromatase, an enzyme that converts androgens to estrogens. The efficient estrogen-lowering properties of AIs temporarily release the hypothalamus from the negative feedback effect of estrogens. This in turn results in an increased discharge of FSH. The differences in the mode of action of AIs and clomiphene citrate confer several theoretical advantages to AIs for ovulation induction: AIs have no effect on estrogen receptors and therefore no deleterious effect on the cervical mucus or endometrium. They do not block hypothalamic estrogen receptors and, therefore, the negative feedback mechanism remains intact, enabling the regulation of the FSH discharge when estrogen starts to be produced again, theoretically reducing the occurrence of multiple follicle development and multiple pregnancies when compared with clomiphene citrate. The half-life of the AIs is about 2 days, shorter than that of clomiphene (Casper and Mitwally, 2006). Letrozole is given in a dose of 2.5–5 mg/day for 5 days starting on Days 2–5 of the cycle, similar to clomiphene citrate. The optimal dose for letrozole seems to be 5 mg/day. A randomized controlled trial (RCT) comparing results of ovulation induction for treatment-naïve women with PCOS has shown a superiority for letrozole over clomiphene citrate. Both the number of mature follicles and estrogen levels were lower with letrozole (Polyzos et al., 2008). The multiple pregnancy rate with letrozole in an uncontrolled series was 0.2% (Aghassa et al., 2007). Some recent studies, however, found anastrozole treatment less effective compared with clomiphene (Tredway et al., 2011a, b).

Hyperinsulinaemia, a common feature of PCOS especially in obese patients, hinders ovulation induction, increases FSH requirements and decreases pregnancy rates. Insulin-sensitizing agents, such as metformin, are capable of restoring ovulation but birth rates and miscarriage rates are inferior to those with clomiphene citrate. The use of insulin sensitizers, such as metformin, is not recommended for first-line treatment in preference to clomiphene citrate (Tang et al., 2009) although it may be useful as an adjunctive in clomiphene citrate-resistant subjects (Legro et al., 2007; Palomba et al., 2009; Zain et al., 2009).

A study examining the feasibility of low-dose FSH for first-line treatment showed a superiority of FSH over clomiphene citrate (Homburg et al., 2012). Pregnancies and live births were achieved faster with low-dose FSH than with clomiphene citrate. This result has to be balanced by convenience and cost in favour of clomiphene citrate, but FSH may be an appropriate first-line treatment for some women with PCOS and anovulatory infertility.

(c) **Second-line infertility treatments**

Infertile women who fail to conceive following clomiphene citrate or AIs require an alternative, second-line approach.

Exogenous gonadotrophins. With conventional high-dose protocols applied in the 1960s and 1970s, ovulation rates were excellent but at the price of unacceptably high rates of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy. During the 1980s, low-dose regimens were introduced, with the current standard of care being the so-called low-dose step-up protocol, with initial daily doses of 75 or even 37.5 IU/day for 2 weeks. The dose then can be increased by half the starting dose in case of an absent ovarian response. Close monitoring of the ovarian response by ultrasound is required.

Cumulative ovulation rates are as high as 90%, with pregnancy rates of 50–70%, multiple pregnancy rates up to 15% and OHSS 2% (The Thessaloniki ESHRE/ASRM sponsored PCOS consensus workshop group, 2008).

The chances of a live birth in women resistant to clomiphene citrate undergoing ovulation induction with gonadotrophins is highly influenced by the menstrual cycle pattern, duration of infertility and...
concentration of FSH (within the normal range) before the start of stimulation (Nyboe Andersen et al., 2010).

Cumulative singleton live birth rates as high as 71% after 24 months of ovulation-induction treatment with clomiphene citrate as first line, followed by gonadotrophins as second-line treatment, have been described (Eijkemans et al., 2003).

A mild ovarian stimulation with a low risk of twins is also frequently used in connection with intrauterine insemination (ESHRE Capri Workshop Group, 2003; Crosignani and Somigliana, 2007).

**Laparoscopic ovarian surgery.** Laparoscopic ovarian surgery (LOS) represents a single surgical procedure (under general anaesthesia) which may replace months of daily hormone injections and frequent hospital visits. Multiple ovarian punctures, either by diathermy or laser, are performed at laparoscopy. LOS is usually effective in generating ovulatory cycles in around 50% of women, and additional ovulation-induction agents are successful in a part of the remainder. The mechanism of action remains unknown. Predictors of persistent anovulation following cauterity are the LH/FSH ratio, age at menarche and glucose levels (Van Wely et al., 2005).

The risk of multiple pregnancy and OHSS is low for LOS. However, concerns remain in relation to long-term effects on intra-abdominal adhesions and ovarian function.

An RCT comparing LOS with 6 months of FSH ovarian stimulation showed that the latter group of patients had twice the pregnancy rate: 67 versus 34%, the latter increasing to 49% after additional clomiphene (Bayram et al., 2004).

A meta-analysis involving nine studies (Farquhar et al., 2010) comparing LOS with gonadotrophins concluded that no difference exists in live birth rates [odds ratio (OR) 1.04; 95% confidence interval (CI): 0.59–1.85], or miscarriage rates (OR 0.81; 95% CI: 0.36–1.86), but multiple pregnancy rates are lower after LOS [1 versus 16%; OR 0.13 (95% CI: 0.03–0.52)].

In vitro fertilization. According to the Canadian Society of Obstetricians and Gynecologists, IVF should be reserved for women with PCOS who fail gonadotrophin therapy or who have another indication for IVF treatment (Vause et al., 2010).

There is still a remarkable lack of studies concerning specifically outcomes of IVF in women with PCOS. It is generally estimated that around 20% of all IVF patients are diagnosed with PCOS, and that these women are difficult to hyperstimulate in a controlled manner, giving rise to increased chances of either under-response or hyperstimulation and OHSS. Owing to the prevalence of obesity among PCOS women, the detrimental effect of overweight on the success rate must also be taken in account (Luke et al., 2011).

Many questions remain in relation to the preferred ovarian hyperstimulation protocol (including type and dose of gonadotrophin, and GnRH agonist or antagonist co-treatment).

A meta-analysis involving nine studies (458 patients with PCOS versus 694 controls) reported higher cancellation rates in patients with PCOS (OR 0.5; 95% CI: 0.2–1.0), as well as significantly more oocytes per retrieval (OR 3.4; 95% CI: 1.7–5.1) and similar clinical pregnancy rates (OR 1.0; 95% CI: 0.8–1.3; Heijnen et al., 2006). Insufficient data were collected to reliably compare the incidence of OHSS; however, increased OHSS rates in PCOS as high as 15% have been reported in single-centre studies (Swanton et al., 2010).

**Is recurrent miscarriage more common?**

In the Finnish epidemiological birth cohort study (Koivunen et al., 2008) the rate of miscarriage was not higher in women with PCOS-associated symptoms than in the reference population. This is an important observation since the data indicating increased risk of miscarriage in women with PCOS refer almost exclusively to those with elevated BMI (Hamilton-Fairley et al., 1992; Lashen et al., 2004) or who have undergone induction of ovulation (Wang et al., 2000).

Several other epidemiological studies suggest an increased risk of miscarriage in patients with PCOS, however, the exact mechanism by which this syndrome would be able to affect a (spontaneous or induced) pregnancy remains unclear. Hyperandrogenism, hypersecretion of LH, hyperinsulinaemia, insulin resistance and abnormal (elevated as well as decreased) serum leptin levels are but a few of the many putative endocrine factors that have been proposed as causative agents in patients with PCO who miscarry, by affecting oocyte quality, early embryo development, the endometrium and hypothalamic function. An increased prevalence of insulin resistance—as often found in PCOS patients— has been found in women with a history of recurrent pregnancy loss (Craig et al., 2002), as has an increased free androgen index (Cocksedge et al., 2008). The latter authors, in a related study (Cocksedge et al., 2009), investigated 300 women with recurrent miscarriage (RM). A diagnosis of PCOS was established via a measurement of the cycle length and the Day 21 serum progesterone, determination of the free androgen index and pelvic ultrasound, applying the Rotterdam criteria: 25–30 (8.3–10%) patients had PCOS. Cocksedge et al. (2009) concluded that the prevalence of PCOS in patients with recurrent early pregnancy loss is considerably lower than had been thought previously (Tulppala et al., 1993; Clifford et al., 1994; Liddell et al., 1997; Rai et al., 2000). The fact that PCOS does not occur more frequently in patients with repeated early pregnancy loss, however, does not rule out that RM is more common in PCOS patients.

Metwally et al. (2010) reported a retrospective analysis of prospectively collected data from 844 pregnancies in 491 patients with RM. All pregnancies that occurred before referral were excluded. Logistic regression analysis showed that an advanced maternal age (P = 0.02) and increased BMI (P = 0.04) predicted the occurrence of another miscarriage in a subsequent pregnancy with 60% accuracy. After these two factors had been taken into account, neither the presence of PCOS nor the number of previous miscarriages contributed significantly to the predictive power of the model.

Rai et al. (2000) found a similar live birth rate among RM patients with PCO morphology (142/233; 60.9%) and RM patients with normal ovaries (148/253; 58.5%). These authors conclude that PCO morphology is not predictive of future pregnancy loss among women with RM, and neither are elevated serum LH levels or elevated serum testosterone concentrations.

Why is it so hard to establish the prevalence of RM in patients with PCOS more reliably? Homburg (2010) addressed this issue and mentioned several reasons: Ovulation induction is required to make PCOS patients ovulate, and both treatment with anti-estrogens and with gonadotrophins themselves are associated with a higher incidence of RM; for women with PCOS who conceive spontaneously the incidence of early pregnancy loss is unknown; observer bias exists in
fertility clinic patients: they receive closer scrutiny and because of this, very early miscarriages—that otherwise might have remained undetected—are more likely to be picked up; obesity, often associated with PCOS, is an important cause of spontaneous miscarriage in its own right (Rittenberg et al., 2011); PCOS is a very heterogeneous syndrome and the use of various definitions has greatly confused the issue. Particular subgroups may exist that are more prone to miscarriage but these remain to be identified. Until a means of recognizing these groups becomes available, they may get lost in the large group of ‘regular PCOS patients’.

Heijnjen et al. (2006) performed a meta-analysis of the outcomes of IVF in women with PCOS when compared with (predominantly) patients with tubal factor. Overall, patients with PCOS and controls had similar miscarriage rates per biochemical pregnancy (OR 1.0; 95% CI: 0.5–1.8; Heijnjen et al., 2006). Kim et al. (2010) studied miscarriage rates after IVF in patients with the complete PCO syndrome and those with ultrasound evidence of PCO only, and found no difference between the two subtypes.

**Ovulation induction: risks for the offspring**

Congenital anomaly risk related to drugs used in ovulation induction. Over the years, a number of reports have suggested the possibility of an association between clomiphene citrate exposure and neural tube defects, although a pooled analysis reported a risk ratio (RR) of 1.08 (95% CI: 0.76–1.51) (Greenland and Ackerman, 1995). A more recent study included spina bifida occulta and reported an RR of 1.17 (95% CI: 2.0–44.8) (Wu et al., 2006). There have also been reports of an increased risk of hypospadias (Sorensen et al., 2005). The National Birth Defects Prevention Study of North America examined 19,059 women with babies affected by at least one birth defect compared with 6,500 controls, of whom 94 (1.4%) had used clomiphene citrate (Reefhuis et al., 2011). The use of clomiphene citrate was not associated with hypospadias in this study but there was a significant association with other anomalies, such as cloacal extrophy (OR 5.4), ventricular septum heart defects (OR 4.9), Dandy–Walker syndrome (OR 4.4), as well as, to a smaller degree, with anencephaly, craniosynostosis, aorta coarctation, oesophageal atresia and omphalolele (Reefhuis et al., 2011).

A problem with the Reefhuis et al. (2011) study, as with all others of this nature, is its inability to clearly determine the reason for clomiphene citrate use—in other words, it is likely that not all women had PCOS and, furthermore, it is difficult to match cases with controls and to adjust for the various components or characteristics of women with subfertility and/or any influence their partners may have on congenital anomaly risk. The use of AIs became off-label for ovulation induction after an abstract presentation at the 2005 ASRM meeting, which was never published and has been widely criticized (see Section “Spontaneous and treatment-related fecundity”). In a subsequent attempt to assess the safety of letrozole, a multicentre study was performed to assess 514 babies of mothers who conceived with letrozole treatment and 397 babies of women who conceived with clomiphene citrate (Tulandi et al., 2006). In the letrozole group, 252 babies were born following the treatment with letrozole alone and 262 after a combination of letrozole and FSH treatment. In the clomiphene citrate group, 293 were born after clomiphene citrate alone and 104 after clomiphene citrate and FSH treatment. Congenital malformations or chromosomal abnormalities were found in 14 of 514 newborns in the letrozole group (2.4%) and in 19 of 397 newborns in the clomiphene citrate group (4.8%). The major malformation rate in the letrozole group was 1.2% (6/514) compared with 3.0% (12/397) in the clomiphene citrate group. One newborn in the letrozole group was found to have a ventricular septum defect (0.2%) compared with four in the clomiphene citrate group (1.0%). In addition, the rate of all congenital cardiac anomalies was significantly higher (P = 0.02) in the clomiphene citrate group (1.8%) compared with the letrozole group (0.2%). The rates of minor congenital malformations were similar (letrozole: 1.6%, clomiphene citrate: 1.8%).

**Multiple pregnancy.** Multiple pregnancies used to be a common result of ovulation induction in patients with PCOS. It has been shown that there is an increased risk of neonatal mortality in women who take a long time to conceive naturally, compared with those who conceive quickly (Basso and Olsen, 2005). Poorly monitored ovulation induction, whether by clomiphene citrate or gonadotrophin therapy, is still an important cause of multiple births, especially in PCOS patients (Bardis et al., 2005).

Multiple pregnancies carry significantly increased risks for the fetus and the mother. Premature delivery is three times more common with twins than with singleton pregnancies and the risk of all other obstetrical complications is increased (pre-eclampsia, abnormal bleeding). Triplet and quadruplet pregnancies further magnify these risks, with mean gestation at delivery of 33.5 and 31.5 weeks, respectively, and neonatal morbidity increased at least 20-fold (Bryan, 2003). Cerebral palsy rates have been reported as 2.3/1000 singletons, 12.6/1000 surviving twins and 44.8/1000 triplets (Pharoah and Cooke, 1996). While in IVF single embryo transfer is becoming more and more accepted, risking multiple pregnancies in other assisted reproduction techniques no longer reflects responsible practice.

**Pregnancy and health of children of women with PCOS.** In addition to ovulation there may be other factors that contribute to subfertility in women with PCOS including the direct and indirect effects of obesity and of metabolic, inflammatory and endocrine abnormalities on oocyte quality and early embryonic and fetal development. Rittenberg et al. (2011) pointed at the independent effect of obesity on the miscarriage rate after a single blastocyst transfer. Ovarian hyperandrogenism and hyperinsulinaemia may promote premature granulosa cell luteinisation; furthermore, paracrine dysregulation of growth factors may disrupt the intrafollicular environment, alter granulosa cell–oocyte interactions and impair cytoplasmic and/or nuclear maturation of oocytes (Dumesic et al., 2008). There is variability in these changes, however, and oocyte quality, fertilization and implantation rates in women with PCOS may also be normal (Weghofer et al., 2007).

PCOS is associated with metabolic disturbances that include impaired insulin signalling and glucose metabolism in ovarian follicles (Rice et al., 2005). It is possible that an altered metabolic milieu throughout the period of oogenesis has downstream consequences for oocyte energy generation. This may lead to reduced expression of genes involved in oxidative phosphorylation (Skov et al., 2007). Altered expression of key genes associated with chromosome alignment and segregation has also been attributed to hyperandrogenaemia (Wood et al., 2007). Indeed, it has been shown that differences in metabolism exist in
oocytes derived from women with PCOS and this is associated with chromosomal pre-division: premature separation of sister chromatids (Harris et al., 2010). During early pregnancy in patients with PCOS the embryo may be exposed to androgen excess in utero, which may have long-term effects, particularly on female offspring.

Fetal hyperandrogenism may disturb epigenetic programming, in particular, of the genes regulating reproduction and metabolism (Hickey et al., 2006; Li and Huang, 2008).

In a meta-analysis in which pregnancy outcomes in women with PCOS were compared with controls, women with PCOS demonstrated a significantly higher risk of developing gestational diabetes mellitus (GDM) (OR 2.94; 95% CI: 1.70–5.08), pregnancy-induced hypertension (OR 3.67; 95% CI: 1.98–6.81), pre-eclampsia (OR 3.47; 95% CI: 1.95–6.17) and preterm birth (OR 1.75; 95% CI: 1.16–2.62). Their babies had a significantly higher risk of admission to a neonatal intensive care unit (OR 2.31; 95% CI: 1.25–4.26) and a higher perinatal mortality (OR 3.07; 95% CI: 1.03–9.21), unrelated to multiple births (Boomsma et al., 2006). In addition GDM may also result in fetal macrosomia. Obesity in its own right is associated with several adverse pregnancy outcomes, including spontaneous miscarriage, pre-eclampsia, gestational diabetes, congenital anomalies (e.g. cardiac malformations and spina bifida) and, again, fetal macrosomia (Wax, 2009), and for the newborn, heritability of the risk of obesity at adult age (Herrera et al., 2011).

**Cancer and cardiovascular risk later in life**

Most cancers, and almost all CVDs, in women occur after the menopause. Nonetheless, anovulation and infertility have an impact on the risk of selected cancers and perhaps of CVD too.

Breast cancer. Early menarche and late menopause increase the risk of breast cancer. Endogenous progesterone, together with estrogens, may be related to the risk of breast cancer, as is the combination of estrogens and progestins in menopausal hormone replacement therapy (Chlebowski et al., 2010). In fact, besides a role of a longer duration of menstrual activity, there are also indications that regular menstrual cycles increase the breast cancer risk, as indicated by case–control (La Vecchia et al., 1985) and cohort studies (Terry et al., 2005) showing a reduced breast cancer risk among women with irregular, long menstrual cycles, at least for premenopausal breast cancer (Terry et al., 2005; Table VI).

These observational studies cannot identify the irregular cycles caused by a defective ovarian estrogen production (Table I) and, moreover, a PCOS condition coexisting with underlying hypogonadotrophic hypogonadism has been documented (Sum and Warren, 2009).

Ovarian cancer. Ovulation has also been related to the risk of ovarian cancer (Fathalla, 1971; Casagrande et al., 1979). In a combined analysis of two Italian case–control studies including 1822 cases and 4631 controls (Pelucchi et al., 2007), compared with the lowest quartile of the number of ovulatory cycles, the RRs were 1.6 (95% CI: 1.3–1.9), 1.7 (95% CI: 1.3–2.0) and 1.8 (95% CI: 1.5–2.2) for subsequent quartiles. The protection of pregnancy and COC use, however, was stronger than that of late menarche and early menopause, confirming that the association between menstrual cycle patterns and ovarian cancer risk is more complex than defined by the number of ovulations only (La Vecchia et al., 1983). In a study from Hawaii, the effect of ovulation on the ovarian cancer risk was stronger in pre-menopause (Tung et al., 2003).

Endometrial cancer. In contrast, the risk of endometrial cancer is increased not only in nulliparae but also in women with a history of infertility and PCOS (Zucchetto et al., 2009), particularly in pre-menopause. This is likely due to anovulation, which leads to a more prolonged exposure to estrogens, insufficiently counterbalanced by progesterone (Klip et al., 2000). Anovulation and PCOS are also related to obesity, which is a recognized risk factor for endometrial cancer (Parazzini et al., 1991). It is therefore not easy to disentangle the role of obesity from that of hormonal imbalance on the endometrial cancer risk (Norman, 2001).

**Cardiovascular risks.** It is even more complex to understand a possible role of PCOS, independent of overweight, insulin resistance, diabetes and hence metabolic syndrome on the risk of CVD, particularly as the incidence of CVD is low in the premenopause and apparently not every woman with PCOS is at risk of CVD (Wild et al., 2010). Consequently, the few earlier studies do not show a consistent association of PCOS and the risk of CVD, independent of overweight, hypertension, diabetes and their respective implications on CVD (Teede et al., 2006; de Groot et al., 2011). Recent studies, however, indicate that impaired glucose metabolism, enhanced ovarian

<table>
<thead>
<tr>
<th>Menstrual cycle length (day)</th>
<th>Number Of cases</th>
<th>Age-adjusted HR (95% CI)</th>
<th>Covariate-adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;26</td>
<td>108</td>
<td>0.92 (0.75–1.12)</td>
<td>0.91 (0.74–1.12)</td>
</tr>
<tr>
<td>26–31</td>
<td>743</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>32–39</td>
<td>167</td>
<td>0.95 (0.80–1.12)</td>
<td>0.94 (0.80–1.12)</td>
</tr>
<tr>
<td>&gt;40 or too irregular to estimate</td>
<td>78</td>
<td>0.87 (0.69–1.10)</td>
<td>0.87 (0.69–1.10)</td>
</tr>
<tr>
<td>Total</td>
<td>1096</td>
<td></td>
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</tr>
</tbody>
</table>

p$_{trend}$ 0.38

CI, confidence interval.

*Adjusted for age, a family history of breast cancer, history of benign breast disease, height, current BMI, BMI at age 18 years, age at menarche, age at first birth, parity, alcohol use, physical activity, and current and past oral contraceptive use.
androgen secretion and chronic inflammation observed in premenopausal women with PCOS persist after menopausal transition, emphasizing life-long health risks related to this syndrome (Markopoulos et al., 2011; Puurunen et al., 2011). There are some data suggesting that irregular menstrual cycles and early age at first and subsequent births are associated with an increased risk of myocardial infarction in young women (La Vecchia et al., 1987); however, residual confounding by socioeconomic status or other correlates of the CVD risk cannot be excluded. The association between infertility, anovulation and CVD risk is moderate and hence of limited, if any, relevance for an individual risk assessment.

Conclusions

WHO group 2 (normogonadotrophic) anovulation is the most common category of anovulatory infertility and within this group PCOS is by far the most prevalent cause. For an excellent recent systematic review of the literature the interested reader is referred to Teede et al. (2011). Anovulation in PCOS impairs fecundity only if associated with overweight and its mechanism remains unclear. Nevertheless, a relative deficiency of FSH is a specific feature of anovulatory women with PCOS and treatments that elevate serum FSH—anti-estrogens, AIs and exogenous FSH—are effective in inducing ovulation. Multiple follicle development and its adverse consequences—OHSS and multiple pregnancy—are particular concerns with respect to gonadotrophin treatment of patients with WHO group 2 anovulation. The impact of WHO group 2 infertility (and PCOS in particular) on the outcome of pregnancy requires further study. There are conflicting data regarding miscarriage rates, which may be explained, at least in part, by the confounding effects of factors such as obesity and induced multiple follicle development. Gestational diabetes and pregnancy-induced hypertension appear to be more common in PCOS pregnancies but more extensive prospective data are needed to establish the magnitude of this problem. Little is known about the impact of maternal PCOS on the offspring. There are now plentiful data that draw attention to the long-term health implications of PCOS. Endometrial cancer is more prevalent and Type 2 diabetes is 3–4-fold more common in women with a history of PCOS than in the general population. Cardiovascular risk markers are also more common in PCOS than in matched controls but, interestingly, there is little evidence to date of an increased frequency of cardiovascular events. In conclusion, the management of WHO group 2 anovulatory women involves not only great care in the induction of ovulation but vigilance with respect to long-term health.

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Authors’ roles

All lecturers and discussants contributed to the preparation of the first draft and to the subsequent changes suggested by the Reviewers.


Lasuncion MA, Escobar-Morreale HF. Comparison of ethinyl-estradiol plus progesterone and 40.


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