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The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance

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BACKGROUND: Here we describe the consensus guideline methodology, summarise the evidence-based recommendations we provided to the World Health Organisation (WHO) for their consideration in the development of global guidance and present a narrative review on the management of anovulatory infertility in women with polycystic ovary syndrome (PCOS).

OBJECTIVE AND RATIONALE: The aim of this paper was to present an evidence base for the management of anovulatory PCOS.

SEARCH METHODS: The evidence to support providing recommendations involved a collaborative process for: (i) identification of priority questions and critical outcomes, (ii) retrieval of up-to-date evidence and exiting guidelines, (iii) assessment and synthesis of the evidence and (iv) the formulation of draft recommendations to be used for reaching consensus with a wide range of global stakeholders. For

each draft recommendation, the methodologist evaluated the quality of the supporting evidence that was then graded as very low, low, moderate or high for consideration during consensus.

OUTCOMES: Evidence was synthesized and we made recommendations across the definition of PCOS including hyperandrogenism, menstrual cycle regulation and ovarian assessment. Metabolic features and the impact of ethnicity were covered. Management includes lifestyle changes, bariatric surgery, pharmacotherapy (including clomiphene citrate (CC), aromatase inhibitors, metformin and gonadotropins), as well as laparoscopic surgery. *In-vitro* fertilization (IVF) was considered as were the risks of ovulation induction and of pregnancy in PCOS. Approximately 80% of women who suffer from anovulatory infertility have PCOS. Lifestyle intervention is recommended first in women who are obese largely on the basis of general health benefits. Bariatric surgery can be considered where the body mass index (BMI) is $\geq$35 kg/m^2 and lifestyle therapy has failed. Carefully conducted and monitored pharmacological ovulation induction can achieve good cumulative pregnancy rates and multiple pregnancy rates can be minimized with adherence to recommended protocols. CC should be first-line pharmacotherapy for ovulation induction and letrozole can also be used as first-line therapy. Metformin alone has limited benefits in improving live birth rates. Gonadotropins and laparoscopic surgery can be used as second-line treatment. There is no clear evidence for efficacy of acupuncture or herbal mixtures in women with PCOS. For women with PCOS who fail lifestyle and ovulation induction therapy or have additional infertility factors, IVF can be used with the safer gonadotropin releasing hormone (GnRH) antagonist protocol. If a GnRH-agonist protocol is used, metformin as an adjunct may reduce the risk of ovarian hyperstimulation syndrome. Patients should be informed of the potential side effects of ovulation induction agents and of IVF on the foetus, and of the risks of multiple pregnancy. Increased risks for the mother during pregnancy and for the child, including the exacerbating impact of obesity on adverse outcomes, should also be discussed.

WIDER IMPLICATIONS: This guidance generation and evidence-synthesis analysis has been conducted in a manner to be considered for global applicability for the safe administration of ovulation induction for anovulatory women with PCOS.

Key words: polycystic ovary syndrome (PCOS) / anovulatory infertility / ovulation induction / lifestyle / weight management / clomiphene citrate / metformin / aromatase inhibitors / gonadotropin therapy / laparoscopic ovarian diathermy

Introduction

Polycystic ovary syndrome (PCOS) is the most common hormonal disorder in women and accounts for ~80% of women with anovulatory infertility (ESHRE/ASRM, 2008). PCOS prevalence ranges from 9% to 18% in reproductive-aged women depending on definitions and populations studied (March *et al.*, 2010; Yildiz *et al.*, 2012). PCOS is diagnosed based on the Rotterdam criteria with two of three features: anovulation, polycystic ovarian morphology on ultrasound and hyperandrogenism (HA) (clinical or biochemical) (ESHRE/ASRM, 2004). Clinical features are broader and include: reproductive (infertility, pregnancy-related risks), metabolic [obesity, insulin resistance (IR), gestational and type II diabetes (DM2) and cardiovascular risk factors] and psychological features (anxiety and depression, impaired quality of life, body image and eating disorders) (Teede *et al.*, 2011).

In PCOS, various factors influence ovarian function and, additionally, fertility is adversely affected by an individual being overweight, having HA and having an elevated serum concentration of luteinising hormone (LH) (MacDougall *et al.*, 1993; Imani *et al.*, 2002). A Finnish study showed that whilst women with PCOS may take longer to become pregnant their lifetime fertility is not impaired (Koivunen *et al.*, 2008) and they may display sustained fertility with advancing age as compared with infertile ovulatory women (Mellembakken *et al.*, 2011). For those who present with anovulatory infertility, the principles of therapy are first to optimize health before commencing treatment. In those who are obese, weight loss should improve the endocrine profile, the likelihood of ovulation, both naturally and in response to ovulation induction therapy and also the prospects of having a healthy pregnancy (Teede *et al.*, 2011). The aim is then to induce regular unifollicular ovulation, whilst minimizing the risks of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy (Balen, 2013). First-line drug therapy to induce ovulation is the oral anti-oestrogen clomiphene citrate (CC) or the aromatase inhibitor (AI) letrozole, with second-line therapy being parenteral gonadotropin therapy or laparoscopic ovarian diathermy (LOD) (drilling). In some cases, there may be a role for or the insulin sensitizer, metformin (Teede *et al.*, 2011). A large Australian community-based study showed higher rates of ovulation induction, but similar ultimate family sizes for women with PCOS compared to those without (Joham *et al.*, 2015). *In-vitro* fertilization (IVF) may be required for women with anovulatory PCOS who do not become pregnant with ovulation induction or if there are additional fertility factors, for example tubal damage or male subfertility. Women with polycystic ovaries who require IVF are at particular risk of ovarian hyperstimulation and careful strategies are required to minimize risk.

Here we outline the methodology used for evidence synthesis and our recommendations, followed by a narrative review on the assessment and management of women with anovulatory infertility and PCOS. Appropriate pre-treatment assessments are required including fitness to become pregnant, endocrine profile, infection screen and rubella immunity, pelvic ultrasound scan (USS) and, if indicated by previous history, an assessment of tubal patency. A semen analysis is also required from the male partner.

Methods: Evidence synthesis methodology

The methodology used to support the provision of our recommendations involved, as outlined in the WHO Handbook for Guideline

Development (2014): (i) identification of priority questions and critical outcomes, (ii) retrieval of up-to-date evidence and exiting guidelines, (iii) assessment and synthesis of the evidence and (iv) the formulation of draft recommendations to be used for reaching consensus with a wide range of global stakeholders. For each draft recommendation, the methodologist evaluated the quality of the supporting evidence that was then graded as very low, low, moderate or high for consideration during consensus.

We qualified the strength of these recommendations (as strong or weak) by considering the quality of the evidence. These recommendations were then assessed through World Health Organisation (WHO) guideline development processes that are based upon other factors including values and preferences of stakeholders, the magnitude of effect, the balance of benefits versus harms, resource use and the feasibility of implementation.

This document builds upon the work of the PCOS Australian Alliance (Teede *et al.,* 2011; Misso *et al.,* 2012, 2014), which was funded by the Australian government, developed based on international best practice and approved by the National Health and Medical Research Council of Australia. This evidence has significantly informed these current recommendations with the permission of the PCOS Alliance and Jean Hailes for Women's Health and we have expanded upon and updated the evidence-synthesis review in conjunction with the Australian team where required.

The relevant clinical questions were agreed through WHO processes. Evidence-synthesis reviews were conducted for each clinical question and from the evidence reviews, thus the evidence-synthesis team was able to develop recommendations for consideration (WHO, 2014). The PICO (Population, Intervention, Comparison, Outcome) framework was used by the evidence-synthesis team to explore the components of each clinical question. These components were used to include and exclude studies in the evidence review.

Where the clinical question was addressed by the Australian guideline, an update was performed using the same search strategy. Where the clinical question, developed in coordination with the WHO Steering Committee, was not addressed in the Australian guideline, a new search strategy was developed. The broad-ranging systematic search for terms related to PCOS, developed by the Australian guideline evidence team, was used. This PCOS search string was then combined with specific searches tailored for each clinical question according to the PICO developed by the guideline development group. The search terms used to identify studies addressing the population of interest (i.e. women with PCOS) were only limited to PCOS terms. Therefore, studies addressing women with PCOS in all cultural, geographical and socioeconomic backgrounds and settings would be identified by the search. The search strategy was limited to English language articles and abstracts. Searches for clinical questions addressed by the Australian guideline were limited from the year 2010 and there were no limits on year of publication for new clinical questions. For all clinical questions, the literature was searched until February 2014.

The following electronic databases were employed to identify relevant literature: Medline (OVID); Medline in-process and other non-indexed citations (OVID); EMBASE (OVID); all EBM [incorporating Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, NHS Economic Evaluation Database (OVID)]; PsycInfo (OVID); CINAHL and Australasian Medical Index. We also searched the bibliographies of relevant studies identified by the search strategy and relevant reviews/meta-analysis for identification of additional studies, the details of which were provided to the WHO for their guideline development processes.

The methodological quality of the included studies was assessed using criteria developed *a priori* according to study design (i.e. quality appraisal criteria used for a randomized controlled trial is different to that used for a systematic review). Individual quality items were investigated using a descriptive component approach. Each study was allocated a risk of bias rating. Data were presented in summary form and descriptively, in tables or narratively in the evidence reviews for each clinical question. Where appropriate, meta-analyses were conducted. The GRADE framework was applied to the body of evidence for each outcome within each clinical question by a methodologist. The WHO would then use worksheets to summarize the volume and quality of the evidence supporting the recommendations as well as to outline the values, preferences and judgements made about the strength of recommendations. The uniqueness of the WHO process was that these balance worksheets were also to be used to note considerations especially for low and middle-income countries, and to be able to record the reasons for changes made to the default strength of the recommendations generated by the evidence review synthesis team and the GRADE methodologists.

The principles or best practice guidance need to be consensus-based and are also intended to underscore the importance of respect for reproductive rights and dignity as recipients of care, and the need to maintain high ethical and safety standards in clinical practice. These principles, in addition to the strategies for implementation, monitoring and evaluation, are expected to guide end-users in the process of adapting and implementing any recommendation provided by the WHO to consider for a range of global contexts and settings.

This paper presents a narrative summary for management of anovulatory infertility in women with PCOS. The evidence base and detailed analysis, with GRADE tables where possible, for each of the prioritized PICO questions were commissioned by, and provided by the first author to the WHO in support of their guideline processes. A WHO assessment of our evidence-based outcomes is then accomplished with many stakeholders who evaluate other factors including values and preferences of stakeholders, the magnitude of effect, the balance of benefits versus harms, resource use and the feasibility of implementation to better assure global applicability. Once completed, the WHO will be publishing the guidelines together with the detailed evidence base and related products.

Results: Summary of outcomes

PCOS is associated with ~80% of cases of infertility due to anovulation. The specific recommendations formulated for presentation to the WHO on PCOS are included in the text along with an assessment of the quality of supporting evidence and strengths of recommendations based upon our evidence synthesis that we have summarized. A supporting algorithm is presented in Fig. 1 to guide clinicians when managing women with anovulatory infertility in PCOS.

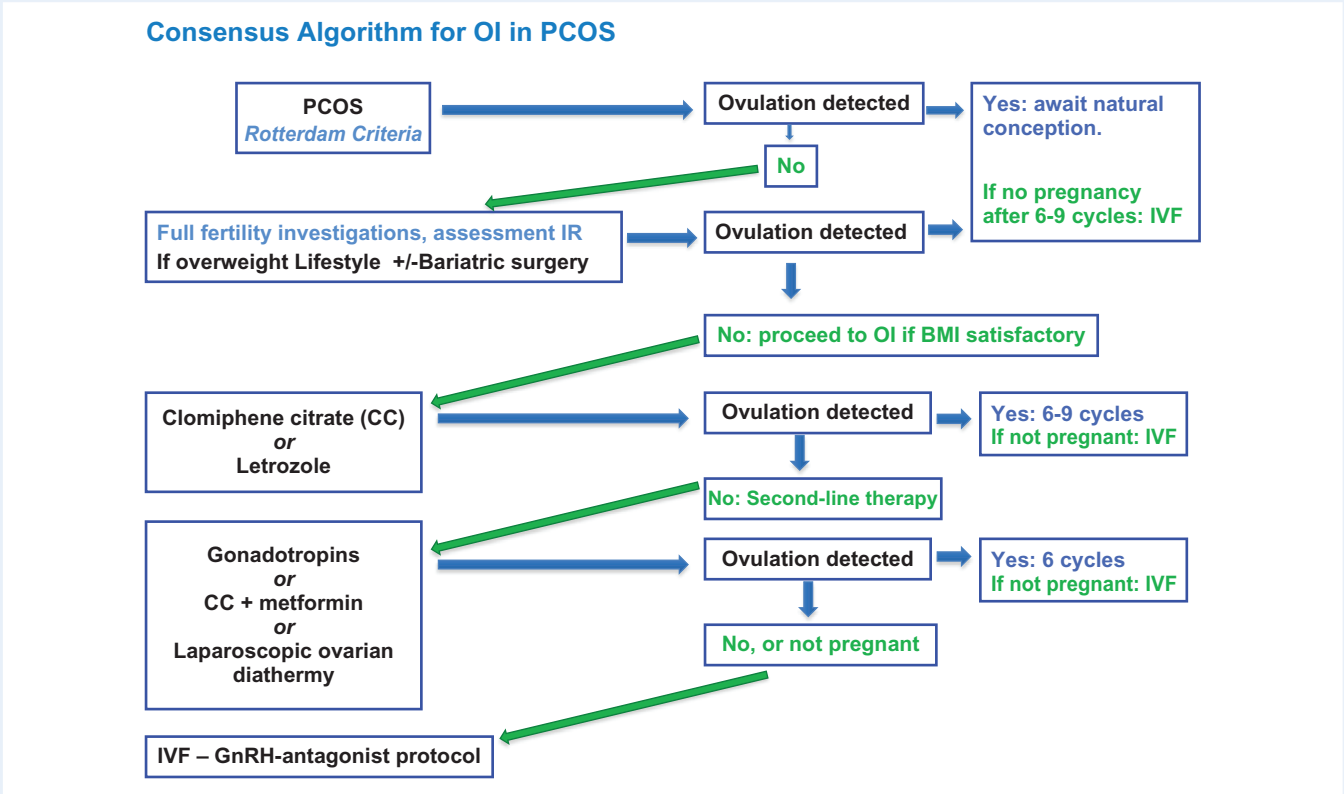

Figure 1 Consensus algorithm.

Narrative review of the assessment and management of anovulatory infertility in PCOS

In Fig. 1, we present an algorithm for the assessment and management of anovulatory infertility in PCOS. Here we aim to provide a narrative review of the evidence that we used to support our specific recommendations.

Definitions of PCOS, the polycystic ovary and anovulatory infertility

PCOS is a condition with a heterogeneous collection of signs and symptoms forming a spectrum of a disorder with a mild presentation in some, whilst in others it causes a severe disturbance of reproductive, endocrine and metabolic function. The American Society for Reproductive Medicine (ASRM) and European Society for Human Reproduction and Embryology (ESHRE) held a joint consensus meeting, which agreed the definition of the PCOS as the presence of two out of the following three criteria (ESHRE/ASRM, 2004): (i) HA (clinical evidence of hirsutism, acne, alopecia and/or biochemical hyperandrogenaemia); (ii) oligo- and/or anovulation (disturbance of the menstrual cycle) and (iii) polycystic ovaries are assessed by USS. Other causes of menstrual cycle disturbance or androgen excess should be excluded.

The diagnosis of PCOS is challenging, as the presenting symptoms and signs are heterogeneous, depending on populations studied, degree of obesity and life stage of the women affected. The symptoms and signs in individual women with PCOS may also change over time (Balen *et al.*, 1995). PCOS is associated with significant adverse effects on quality of life with consequences for psychological morbidity associated with the symptoms and their sequelae, particularly with impaired reproductive function (Jones *et al.*, 2004). The combination of obesity and disordered eating habits further exacerbates reproductive, metabolic and psychological morbidity (Teede *et al.*, 2011).

The precise definition of the 'syndrome' has been controversial for some time (Azziz *et al.*, 2009). Now the generally accepted and an internationally endorsed definition are the Rotterdam criteria. The 'Rotterdam' definition has been endorsed by the Australian Guideline Committee (Teede *et al.*, 2011), the National Institute for Health in the USA (Johnson *et al.*, 2012), the US Endocrine Society Practice Guideline and the European Society for Endocrinology position statement (Legro *et al.*, 2013; Conway *et al.*, 2014). We strongly recommend the use of the Rotterdam diagnostic criteria (Conway *et al.*, 2014).

Although the Rotterdam criteria are accepted, clinically a spectrum exists, ranging from asymptomatic women with polycystic ovarian morphology and biochemical HA to those with severe clinical and biochemical disorders. The recently published statements regarding the diagnosis of PCOS assume that the clinical, laboratory and imaging studies are dichotomous variables, rather than continuous variables and inadequately consider the effect of observer subjectivity of measurement (Dewailly *et al.*, 2014). The current individual diagnostic criteria for PCOS are defined too vaguely to be certain that all affected individuals fit the definition of the syndrome, for example,

there is uncertainty over the definition of 'hyperandrogenaemia' (Teede *et al.*, 2011). Too exclusive a definition would leave many women at the milder end of the PCOS spectrum without diagnosis despite equal rights for medical care. This may impact on the psychological morbidity and negatively impact on quality of life associated with PCOS, whether related to dermatological manifestations, obesity, disturbances in menstrual cycle or subsequent infertility (Jones *et al.*, 2008; Gibson-Helm *et al.*, 2014). A pragmatic approach is therefore required in making the diagnosis and excluding other causes of menstrual cycle disturbance and HA, ensuring that care is taken to explore each individual's symptoms and needs.

In conclusion, it is our strong recommendation that the Rotterdam Consensus definition of PCOS, which satisfies these criteria, will allow for a globally consistent and pragmatic approach for both diagnosis and management. Although profound ethnic variation exists, all women diagnosed with PCOS must fulfil these criteria. In studies of women with PCOS, the phenotypes should be properly defined in detail.

Assessment of HA

HA has both clinical and biochemical manifestations and is detected in around 60–80% of cases with PCOS, yet it is challenging to diagnose. Either clinical evidence of HA or biochemical assessment should suffice to define HA in PCOS. Acne, hirsutism and androgenic alopecia are due to androgenic stimulation of the pilosebaceous unit. Acne occurs in almost all teenagers and a degree of physiological acne occurs in 54% women over 25 years of age with 3% showing clinical acne (Goulden *et al.*, 1999). A study of pregnant women reported that 26% complained of acne prior to pregnancy and a study of PCOS reported that 58% of their control women had acne (Rushton, 1986; Welt *et al.*, 2006). These proportions of unselected populations with acne make the link with PCOS unconvincing, therefore, hirsutism is considered a more specific clinical feature of HA, although this remains subjective and can be difficult to assess given the use of modern cosmetics. However, in East Asian women, who do not express hirsutism, acne is the most definitive cutaneous symptom.

Not all hair growth is induced by hyperandrogenaemia and the degree of hirsutism correlates poorly with circulating androgen concentrations (Barth *et al.*, 2007). There are also significant ethnic differences in the presentation of hirsutism. These may relate to relatively simple issues of hair colour but also the response of the hair follicle to androgens and the amplification of HA by hyperinsulinaemia, which may be more profound in some ethnic groups at lower body mass than others (Wijeyeratne and Balen, 2013). Overall, dermatological manifestations of PCOS (acne, hirsutism and alopecia) should be assessed, understanding that they vary widely between different ethnic groups and correlate poorly with biochemical HA.

Accurate diagnosis of biochemical HA is limited by a lack of methods for accurate measurement (Barth *et al.*, 2007; Teede *et al.*, 2011). Testosterone assays are set up for use in males and so there is poor accuracy at the lower androgen levels seen in women. Measures of androgen status in PCOS include the calculations of bioavailable testosterone and free testosterone (Vermeulen *et al.*, 1999). The free androgen index (FAI) may also be calculated using total testosterone and sex hormone-binding globulin (SHBG) levels (Conway *et al.*, 2014).

The measurement of total testosterone is also a good screening tool for the exclusion of other causes of androgen excess, where it is generally more markedly elevated than in PCOS. The other androgens, such as androstenedione and dehydroepiandrosterone sulphate (DHEAS), can be measured if clinically indicated. Whilst they may be mildly elevated in PCOS, their assessment is primarily indicated in women with rapidly progressive virilization or more severe clinical HA (Teede *et al.*, 2011; Conway *et al.*, 2014). An elevated level of DHEAS elevation is greater in those with androgen-secreting adrenal tumours, whilst in those with non-classical congenital adrenal hyperplasia (CAH), androstenedione levels tend to be high. More recently liquid chromatography mass spectrometry has been adopted by a number of laboratories as the gold standard, although the technology is expensive and normative ranges for different populations are yet to be formulated (Barth *et al.*, 2007; Conway *et al.*, 2014).

Late-onset CAH, although rare, is more common in some populations and needs to be considered before the diagnosis of PCOS (Koskinen *et al.*, 1996). The most common form of CAH is 21-hydroxylase deficiency, which may be excluded by the measurement of serum 17-hydroxyprogesterone in the follicular phase. The additional use of an ACTH-stimulation test may then be required.

The measurement of SHBG assists in calculating FAI and may be useful as a metabolic marker as a surrogate for IR (Moran *et al.*, 2013). SHBG concentrations fall as insulin levels rise and have also been shown to correlate with future risk of gestational diabetes mellitus (GDM; Veltman-Verhulst *et al.*, 2010). Overall SHBG may have a role in metabolic assessment in PCOS; however, there are cost implications, which may preclude its use in some settings.

In summary, it is our strong recommendation, based on high-quality evidence, that either clinical evidence of HA or biochemical assessment should suffice to define HA in PCOS. Dermatological manifestations of PCOS (acne, hirsutism and alopecia) should be assessed but vary widely between different ethnic groups and correlate poorly with biochemical HA.

(i) The measurement of total testosterone is a good screening tool for the exclusion of other causes of androgen excess and will suffice when other testosterone assays are not available.
(ii) Calculated bioavailable testosterone, free testosterone or FAI should be considered the best test at this time for biochemical diagnosis of HA and may be elevated even in the presence of normal total testosterone in PCOS.
(iii) The assay for SHBG is expensive and, in low resource settings, the measurement of total testosterone will suffice.
(iv) If androgen levels are markedly above laboratory reference ranges, or there is rapid onset or progression of signs of HA, secondary causes should be considered such as non-classical CAH and further investigations should be implemented.
(v) Reference ranges for different assays and laboratories vary widely and clinical decisions should be guided by the reference ranges of the laboratory used.

For future research, age and ethnicity-related normative data should be included in order to define androgen profiles for the definition of PCOS. Furthermore, methodological consistency and assay standardization is required for the biochemical evaluation of HA.

Assessment of menstrual cycle disturbance and ovulation

Irregular cycles (>35 or <21 days) continuing for more than 2 years after the onset of menarche are likely to reflect oligo-ovulation or

anovulation (Fauser et al., 2012). Ovulation is assessed by measuring serum progesterone during the mid-luteal phase. The peak value for progesterone only remains for a short time. Indeed, the commonest reason for a low value is that the sample was not taken at the appropriate time. The 'gold standard' would be a combination of ultrasound monitoring of ovarian activity to confirm follicular development and the subsequent evolution of the follicle to a corpus luteum, combined with biochemical evidence of ovulation. In addition, assessment of the endometrium can be helpful during the ultrasound monitoring of ovulation induction therapy.

There is evidence that the endocrine and ovulatory disturbances observed in PCOS exist along a continuum, with a mild phenotype of elevated androgen and follicle number evident in eumenorrheic women having sporadic anovulation, which may occur across a continuum of testosterone concentrations including in eumenorrheic women without clinical HA (Sjaarda et al., 2014).

The measurement of the gonadotropins FSH and LH in the early follicular phase (days 1–5 of the cycle) combined with estradiol will assist in the diagnosis. If the patient has amenorrhoea or oligomenorrhea, a random blood sample should be taken and repeated a week later to form an impression of the underlying pathology. Suppressed gonadotropins and estradiol indicate a hypothalamic or pituitary aetiology, in which case prolactin and thyroid function should be assessed. Elevated gonadotropins with a low estradiol indicate premature ovarian insufficiency (previously known as premature ovarian failure) (Balen, 2014). A useful assessment of estrogenization is the ultrasound measurement of endometrial thickness.

Anti-Müllerian hormone (AMH) levels correlate with the number of antral follicles in the ovary and are a useful measure of ovarian reserve that is not cycle dependent (Dewailly et al., 2011). Furthermore, AMH may be elevated in women with PCOS and has been suggested as a biochemical alternative to the USS, although normative ranges are yet to be agreed (Dewailly et al., 2014).

In summary, we suggest that the following practice points be strongly recommended, despite being based upon ungraded evidence.

(i) FSH, LH and estradiol should be measured on days 1–5 of the cycle, or at random in a woman with amenorrhoea or oligomenorrhoea.
(ii) Assessing ovulation in oligomenorrheic or amenorrheic women with PCOS is difficult.
(iii) A luteal-phase progesterone measurement can be used to assess ovulation.
(iv) Ultrasound monitoring of ovarian activity combined with biochemical assessment of ovulation should be administered to provide more information about timing of ovulation and ovarian function.
(v) AMH may be a biochemical marker for polycystic ovaries, although normative ranges are yet to be agreed and therefore this is a weak recommendation.

For future research, age and ethnicity-related normative data are required when defining AMH values that describe a polycystic ovary or the presence of PCOS.

Assessment of the polycystic ovary

High resolution USS provides a non-invasive technique for the assessment of ovarian size and morphology (Dewailly et al., 2014). Although the ultrasound criteria for the diagnosis of polycystic ovaries have not been universally agreed, the characteristic features are accepted as being an increase in the number of follicles and the amount of stroma as compared with normal ovaries (Dewailly et al., 2014). The Rotterdam consensus definition of the polycystic ovary proposed the presence of >12 follicles of 2–9 mm diameter (as a mean of both ovaries) and/or increased ovarian volume (>10 cm^3) (Balen et al., 2003) and was based largely on a paper, which studied 214 women with PCOS and 112 with normal ovaries to determine the importance of follicle number per ovary (Jonard et al., 2003, 2005). In a 2010 study of community-based screening, up to 68% of 19–21-year-old Danish women had polycystic ovaries according to the Rotterdam criteria (Kristensen et al., 2010). As follicle counts are high at a younger age, the over diagnosis of PCOS needs to be avoided, although this is of less relevance when considering older women with anovulation seeking fertility treatment. Since 2003 there has been further debate about the assessment of the polycystic ovary, with higher resolution ultrasound machines now suggesting that a PCO should contain at least 25 follicles per ovary, although there is still no consensus (Dewailly et al., 2014).

It has been suggested that the measurement of AMH might be a better discriminator of the polycystic ovary than USS, with a value of >35 pmmol/l being suggested as the cut-off value (Laven et al., 2004; Dewailly et al., 2014). AMH may be a biochemical marker for PCO, although normative ranges are yet to be agreed and further research is needed to resolve methodological concerns and clarify the most accurate cut-off measures (Dumesic et al., 2015). In the setting of anovulatory infertility, however, pragmatically, the cost efficacy of methods for both assessing the polycystic ovary and monitoring the response to ovulation induction therapy needs consideration. When combining both these requirements, ultrasound is the only modality that fulfils the role.

Ultrasound assessment of ovarian morphology also allows the detection of other factors pertinent to fertility. These include detection of pathological ovarian cysts, assessment of uterine anatomy (fibroids, polyps, septa, etc.), endometrial thickness (endometrial hyperplasia/adenocarcinoma in anovulatory patients with chronic unopposed estrogenization of the endometrium) and para-ovarian structures (hydrosalpinges, etc.).

In summary, it is our strong recommendation, based on high-quality evidence, that ultrasound of the pelvis should be performed to assess ovarian morphology. The polycystic ovary should contain at least 12 follicles in at least one ovary, 2–9 mm in diameter. With modern-day high resolution scanning, it is appropriate to consider a polycystic ovary to have more than 12 follicles but there is no consensus on the precise number.

For future research, age and ethnicity-related normative data are required when describing the number of follicles required to define a polycystic ovary.

Assessment of IR and glucose tolerance

IR is not part of the diagnostic criteria for PCOS, yet IR and hyperinsulinaemia are central to the pathophysiology for many women with PCOS. IR can be defined as an impaired biological response to exogenous or endogenous insulin, reflecting disturbed metabolic and mitogenic processes (ADA, 2015). Recent research using gold

standard clamp techniques and WHO criteria for IR, noted that 85% of women with PCOS diagnosed by the Rotterdam criteria are affected (75% of lean and 95% of overweight and obese women) (Stepto *et al.*, 2013). Nevertheless, even if IR combined with hyperinsulinaemia is not the initiating cause, it certainly may be an amplifier of HA in those who gain weight (Meyer *et al.*, 2005; Stepto *et al.*, 2013). The measurement of IR requires sensitive measures such as clamp studies or intravenous glucose tolerance tests, as fasting insulin and homeostasis model of assessment for IR are too inaccurate for clinical use in PCOS (Diamanti-Kandarakis and Dunaif, 2012; Dumesic *et al.*, 2015). Therefore, the assessment of IR is not recommended in routine practice (Teede *et al.*, 2011), instead an assessment of glucose tolerance is recommended.

Women with PCOS have higher diabetes risk scores (Moran *et al.*, 2011) as well as increased risk of GDM (Boomsma *et al.*, 2006), prediabetes and DM2 (Moran *et al.*, 2010). Earlier-onset hyperglycaemia and rapid progression to DM2 are also reported in PCOS (Ehrmann *et al.*, 1999). In this context, PCOS is listed by the International Diabetes Federation as a non-modifiable risk factor for DM2 (Alberti *et al.*, 2007).

IR correlates with BMI and is an accurate marker of the metabolic effect of obesity. There are also important ethnic variations in the expression of IR. A BMI > 30 kg/m² is usually considered to confer increased risk in white women, whereas in those, for example, of South Asian origin, a BMI > 25 kg/m² is sufficient to increase the risk of DM2 (Wijeyaratne *et al.*, 2002).

The significantly increased risk of DM2 in PCOS represents a major health and economic burden. The recommendation is therefore to screen all women with PCOS, to enable earlier detection and prevention of DM2 and its complications. Women at high risk of DM2 include women with a BMI > 30 kg/m² and high-risk ethnic groups with a BMI > 25 kg/m² (e.g. South Asian, Hispanic and Polynesian) and these women should therefore be screened when presenting with infertility. Other factors, which confer additional risk of IR, include family history of DM2 and age.

Resource implications of screening for glucose intolerance include the benefits of earlier detection and prevention of sequelae versus the cost of implementing the tests. The Australian evidence-based guidelines recommend that a 75 g oral glucose tolerance test (OGTT) is used to screen and detect abnormal glucose tolerance in PCOS as a high-risk group (Teede *et al.*, 2011). This aligns with the US Endocrine Society Clinical Practice Guidelines, where they also suggest that a serum HbA1c may be performed if the patient is unable to complete the OGTT (Legro *et al.*, 2013). The American Diabetes Association (ADA) defines raised HbA1c as >5.7%, and as diagnostic for DM2 at >6.4%; however, this has not been validated in PCOS. In PCOS, intrinsic IR is primarily at the level of the skeletal muscle, rather than at the liver and fasting glucose and HbA1c may not reflect post-OGTT hyperglycaemia (Diamanti-Kandarakis and Dunaif, 2012). Potential advantages of the HbA1c over the OGTT include the convenience of performing the test at the initial clinic visit with no fasting required, less day-to-day fluctuations in blood glucose level and lack of side effects. However, measuring HbA1c may be costly, especially in areas of the developing world where the validated HPLC test is not widely available. In addition, HbA1c results may be inaccurate if patients are anaemic or have certain haemoglobinopathies, e.g. sickle cell anaemia, haemolytic anaemia and recent blood transfusion (ADA, 2015). However, in PCOS, until larger prospective studies analysing the accuracy and cut-off values for HbA1c are completed and the effect of BMI and ethnicity are understood, the OGTT is still regarded as the 'gold standard' screening tool for IR and DM2 in PCOS (Zhen *et al.*, 2014).

In summary, it is our strong recommendation, based on ungraded evidence that women with PCOS at high risk of diabetes or prediabetes, i.e. women with a BMI > 30 kg/m², and high-risk ethnic groups including South Asian, Hispanic and Polynesisian women with a BMI > 25 kg/m², or with a family history of DM2 should be screened with an OGTT prior to fertility treatment. Furthermore, HbA1c is an alternative marker for metabolic disease.

Ethnic variations in the expression of PCOS

There may be significant ethnic differences in the presentation and spectrum of PCOS, which include variations in normal traits, risk factors for co-morbidities, response to treatment and effects of pharmacologic agents (Wijeyeratne and Balen, 2013). Ethnicity is defined by an individual's history, language, religion and ancestral heritage that are closely linked to geography, geo-politics and culture. This may encompass culture, diet, religion, dress, customs, kinship systems or historical and territorial identity. Socioeconomic differences may also cause health disparities affecting disease manifestation and complications.

Over the past three decades, the main focus of PCOS research has been on the epidemiological, biomedical, genetic and social aspects of predominantly Western women of white European origin. A recent review evaluated the evidence from all published data on PCOS from community-based populations and large clinic-based cohorts of distinct ethnic groups (Wijeyeratne *et al.*, 2010). Variances in the PCOS phenotype have been reported among Caribbean Hispanics, Mexican Americans, Japanese, indigenous Chinese/Taiwanese, migrant and indigenous South Asians, Thai and Malay populations depicting South East Asian groups, Southern Europeans, indigenous Canadians and migrant and indigenous Arabs. Additional data from indigenous South Asians that address the phenotype, metabolic correlates, prevalence of PCO, quality of life (QoL) and health seeking behaviour have shown an ethnic propensity for variation in predominantly the metabolic phenotype of PCOS (obesity, acanthosis nigricans and IR) and to a lesser extent in the androgenic phenotype (Wijeyeratne *et al.*, 2010). For example, one comparative study reports more severe manifestations, including infertility, occurring in younger and more insulin resistant UK-based South Asians of Pakistani origin compared with white Europeans (Wijeyaratne *et al.*, 2002).

A constant feature is that Asian women with PCOS are shorter, have lower BMI, with 'milder' symptoms of HA, but with the highest prevalence of metabolic syndrome, affecting up to 50% of women with PCOS (Lo *et al.*, 2006). In this group, it is their central obesity rather than BMI that correlates with IR and metabolic disorders (Wijeyeratne *et al.*, 2010). Greater awareness and application of ethnic-specific BMI cut-off points are also recommended (Misra *et al.*, 2009). A common clinical indicator of metabolic disturbance is acanthosis nigricans; although not included as a clinical marker in diagnosing PCOS.

Investigating the East Asian population, a study of 883 Chinese women found hyperandrogenaemia, but not hirsutism was

independently associated with the risk of DM2 [odds ratio (OR) 5.7; $P = 0.028$] (Zhao et al., 2010). This reflects the relative absence of hirsutism and the high prevalence of metabolic disturbances in East Asian women with PCOS.

African Americans with PCOS have a higher BMI and blood pressure than US-based Asians (Lo et al., 2006), although their degree of IR does not mirror this difference. Compared with other racial groups, African American women generally carry a disproportionate burden of cardiovascular risk factors, namely hypertension, obesity and metabolic syndrome, reflected by their greater age-adjusted death rates compared with white populations (Shroff et al., 2007). Recent epidemiology studies of DM2 reveal its frequent detection in young adults among American Indians, African Americans and Hispanic/Latino Americans, earlier than among non-Hispanic whites (ADA, 2015).

There are evolving reports of PCOS in Middle Eastern women, that suggest similarity to South Asians, although with greater obesity and hirsutism (Al-Fozan et al., 2005; Al-Ruhaily et al., 2008; Mehrabian et al., 2011). Increased symptomatology in women with PCOS has also been correlated with IR in other 'Latino' populations whether from South America (Soares et al., 2008; Melo et al., 2011) or Mediterranean countries (Carmina et al., 2006).

Practitioners must therefore consider the ethnicity of the woman when diagnosing and managing PCOS. Ethnic-specific BMI cut-off points should include waist circumference measurement to identify those at risk and apply secondary prevention despite a 'lower' BMI in high-risk groups. A policy of training primary healthcare givers in resource-limited countries with high-risk populations should be adopted and should include evaluating women of reproductive age with PCOS using simple low-cost methods, such as measuring BMI, waist circumference, blood pressure and acanthosis nigricans.

In summary, our strong recommendation, based on high-quality evidence, is that practitioners must consider the ethnicity of the woman when diagnosing and managing PCOS. We suggest the following practice points be strongly recommended based upon high-quality evidence.

(i) Ethnic-specific BMI cut-off points should include waist circumference measurement to identify those at risk and apply secondary prevention despite a 'lower' BMI in high-risk groups.
(ii) Family history (of diabetes/PCOS) should be reviewed and baseline 75 g OGTT or measurement of HbA1C should be carried out at initial evaluation of high-risk ethnic groups e.g. South Asian, Hispanic and Polynesian women.

In addition, we suggest the following practice points be strongly recommended based upon ungraded evidence.

(i) Greater awareness is required about the variation in PCOS phenotype linked to IR related to ethnicity e.g. South Asian, Hispanic, Polynesian women.
(ii) A policy of training primary healthcare givers in resource-limited countries with high-risk populations should be adopted and should include evaluating women of reproductive age with PCOS using simple low-cost methods, such as measuring BMI, waist circumference, blood pressure and acanthosis nigricans.

Treatment of women with anovulatory PCOS

The principles of ovulation induction therapy are to optimize health before commencing ovulation induction and then to induce regular unifollicular ovulation, whilst at the same time minimizing the risks of OHSS and multiple pregnancy. For those who are overweight, weight loss may improve the endocrine profile, the likelihood of ovulation and the response to ovulation induction therapy (Balen and Anderson, 2007). Recently, there has been a shift in some clinics away from mono-follicular ovulation induction to IVF treatment, based on a false premise of greater cumulative pregnancy rates, yet ovarian stimulation for IVF presents significant risks for women with PCO, namely the potentially life-threatening complication of OHSS. IVF is therefore only indicated in those who have not responded to first or second-line ovulation induction therapies or in those who require IVF for other indications (e.g. male factor, tubal damage, etc.). Furthermore, there is the additional aspect of significantly increased costs of IVF therapy.

Lifestyle management for women with PCOS

Obesity has a negative impact on naturally becoming pregnant, miscarriage, pregnancy and the long-term health of both mother and child owing to both an increased rate of congenital anomalies and metabolic disease in later life. Women who are obese respond less well to drugs used for ovarian stimulation in the management of both anovulation and assisted reproduction, although this does not always equate with a reduction in pregnancy rates. Furthermore, there are greater risks during pregnancy for those who are obese with increased rates of miscarriage, congenital anomalies [neural tube (OR 3.5), omphalocele (OR 3.3) and cardiac defects (OR 2.0)], gestational diabetes, hypertension, thromboembolic disorders and problems during delivery (Cedergren, 2004). Pregnancy exacerbates underlying IR and women with PCOS and/or obesity have an increased risk of GDM.

Women with PCOS appear to be heavier than women without PCOS, and to gain more weight longitudinally (Glueck et al., 2005; Lim et al., 2012; Teede et al., 2013). Excess weight increases the risk of developing PCOS and increases the severity of reproductive, psychological and metabolic features in PCOS (Balen et al., 1995; Teede et al., 2013) by exacerbating both androgen and insulin levels (Acien et al., 1999). Significant benefits have been demonstrated with 5–10% weight loss in overweight women with PCOS; this may be a feasible initial target (Kiddy et al., 1990; Radon et al., 1999). Whilst fertility rates are lower among obese women, and ovulation is increased with lifestyle intervention, there remains inadequate high-quality evidence on pregnancy outcomes with lifestyle intervention in PCOS (Moran et al., 2011). Pharmacological therapy including CC, metformin and gonadotropins are available and effective in improving fertility in women with PCOS (Tang et al., 2012). However, there are little comparative data on the benefits of lifestyle versus pharmacological therapy in overweight or obese women with PCOS.

The most important determinants of the outcome of ovulation induction therapy are obesity and IR. A positive association was shown in a meta-analysis of 13 studies between the degree of obesity and quantity of gonadotropin required, with a weighted mean difference of an additional 771 iu required [95% confidence interval (CI): 700–842] and a higher rate of cycle cancellation in obese patients (pooled OR 1.86; 95% CI: 1.13–3.06) (Mulders et al., 2003). Obesity also led to a lower rate of ovulation (OR 0.44; 95% CI: 0.31–0.61). There was also a negative association with IR and obesity and pregnancy rate (pooled OR 0.29; 95% CI: 0.10–0.80).

In terms of lifestyle management of PCOS, a large number of small, uncontrolled trials demonstrate that weight loss achieved through lifestyle management decreases abdominal fat, HA and IR and improves lipid profiles, ovulation, menstrual cyclicity, fertility, DM2, cardiovascular risk factors and psychological health in women with PCOS who are overweight (Kiddy *et al.*, 1992; Clark *et al.*, 1998; Moran *et al.*, 2003; Stamets *et al.*, 2004). Given these results and the extensive other health benefits of weight loss in overweight women, lifestyle management is the first-line treatment for a large proportion of women with PCOS. Weight loss [in women with a BMI > 25 kg/m^2 (overweight)] and prevention of weight gain [in women with a BMI < 25 kg/m^2 (lean)] are the joint responsibility of all health professionals and where dietary issues arise (or where obesity is present), referral to a dietitian should be considered (Teede *et al.*, 2011).

Lifestyle management may also improve PCOS independent of weight loss, with exercise intervention improving metabolic risk factors associated with PCOS, including hypertension, IR and elevated blood glucose levels, even when no weight loss occurs (Poehlman *et al.*, 2000; Harrison *et al.*, 2011, 2012). However, it is difficult to definitively ascertain the efficacy of lifestyle interventions in women with PCOS, because available information is based on small uncontrolled trials addressing different outcomes in subgroups of women (Poehlman *et al.*, 2000). Vitamin deficiencies, such as folate and vitamin D, may also impact on fertility and reproductive outcome and may warrant assessment in women with PCOS wishing to become pregnant.

An area under investigation is the macronutrient composition of dietary interventions. Specific approaches including modifying carbohydrate, protein or fat are proposed to have favourable hormonal or metabolic effects or be more sustainable; however, evidence to support this in PCOS is generally lacking (Moran *et al.*, 2013). Caloric (energy) restriction *per se*, rather than changes in macronutrient composition, appears most effective for weight loss and clinical benefits. There is limited research in this area in PCOS; however, a systematic review on existing studies including low glycemic index diets concluded no clear benefit of any specific macronutrient composition and general healthy diets with reduced energy intake were recommended (Moran *et al.*, 2013). Further research is needed in more diverse populations as most studies have recruited Caucasian women and therefore may not be generalizable to other ethnic groups.

Exercise effectively ameliorates IR providing a possible effective intervention for management of PCOS, even in the absence of weight loss (Harrison *et al.*, 2012). Moderate aerobic exercise can be defined as an intensity between 50% and 80% of maximum oxygen consumption or 60% and 90% of maximal heart rate (Pate *et al.*, 1995). A single session of moderate exercise enhances glucose disposal and improves insulin sensitivity (Richter *et al.*, 1989). Ongoing moderate exercise, at least three to five times per week, consistently reduces DM2 and cardiovascular disease risk in general populations (Shephard and Balady, 1999). Similarly, resistance or weight-bearing exercise alone or in combination with aerobic exercise improves health outcomes in high-risk groups (Cuff *et al.*, 2003). It is necessary to tailor exercise levels to the starting BMI in order to achieve optimum effect, but the intensity, type and frequency of optimal exercise in PCOS remain unclear with more research needed.

Therefore, in overweight and obese women with PCOS and with due consideration given to age-related infertility, intensive (frequent multidisciplinary contact) lifestyle modification alone should be first-line therapy for 3–6 months, arbitrarily aiming for a 5–7% weight reduction, to determine if ovulation is induced. To optimize adherence with lifestyle interventions, psychosocial factors should be considered and support provided to infertile women with PCOS. Pharmacological ovulation induction should be discouraged for first-line therapy in women with PCOS who are morbidly obese (BMI > 40 kg/m^2) until weight loss has occurred either through diet, exercise, bariatric surgery or other appropriate means.

Based upon high-quality evidence, general practitioners should be aware that obesity reduces the chance of ovulation and pregnancy and increases risks during pregnancy to both mother and child.

In summary, we strongly recommend the following based upon moderate quality evidence:

(i) Lifestyle management (single or combined approaches of diet, exercise and/or behavioural interventions) for weight loss or prevention of weight gain, or for general health benefits, should be recommended in all women with PCOS.
(ii) Lifestyle management targeting weight loss in overweight women and prevention of weight gain in lean women should include exercise and reduced dietary energy (caloric) intake and should be first-line therapy for all women with PCOS.
(iii) To optimize adherence with lifestyle interventions, psychosocial factors should be considered and support should be provided to infertile women with PCOS, although the evidence for this is weak.

Our following recommendations have a weak strength based upon low-quality evidence:

(i) In overweight and obese women with PCOS and with due consideration given to age-related infertility, intensive (frequent multidisciplinary contact) lifestyle modification alone (and not in combination with pharmacological ovulation induction therapy) should be first-line therapy for 3–6 months, arbitrarily aiming for a 5–7% weight reduction, to determine if ovulation is induced.
(ii) Pharmacological ovulation induction should be discouraged for first-line therapy in women with PCOS who are morbidly obese (BMI > 40 kg/m^2) until weight loss has occurred either through diet, exercise, bariatric surgery, or other appropriate means.

For future research, further methodologically rigorous trials in women with PCOS are important to address the following:

(i) The extent of the benefits of lifestyle management compared with no or minimal therapy for all clinically relevant outcomes.
(ii) The efficacy of types of lifestyle management: diet, exercise, behavioural modification or combinations.
(iii) The effect of lifestyle management for overweight and non-overweight women and specific reproductive outcomes such as menstrual regularity, ovulation, fertility, pregnancy complications and outcomes for children.

Bariatric surgery

It has been suggested that women with a BMI > 35 kg/m^2 after failed attempts at weight loss for more than 1 year may consider bariatric surgery; however, surgical studies are generally poorly designed (Shah and Ginsburg, 2010; Scholtz *et al.*, 2015). Although bariatric surgery has been shown in randomized controlled trials to be beneficial for patients with a BMI above 30 kg/m^2 with DM2 (Busetto *et al.*, 2014),

current guidelines suggest bariatric surgery should be considered for patients with a BMI above 40 kg/m^2 or BMI above 35 kg/m^2 in the presence of obesity-related co-morbidities, which are expected to abate with weight reduction, after failure of a structured lifestyle intervention (SIGN, 2010). Some consider PCOS to be one of these co-morbidities.

A meta-analysis of bariatric surgery in the general population reports weight loss of 38.5 kg or 56% excess weight loss and resolution of DM2 in 78% of patients with DM2 (Picot *et al.*, 2009). Although very few patients attain and maintain normal weight after surgery, several prospective and randomized controlled studies have now confirmed that short-term remission of diabetes can be achieved in 40% of patients (Schauer *et al.*, 2014). Although patients may relapse, they still retain better long-term glycaemic control (Sjostrom *et al.*, 2007; Schauer *et al.*, 2014).

Bariatric surgery may have significant complications, including malabsorptive states, psychological issues and disordered eating (Colquitt *et al.*, 2014). Eating disorders are already relatively common among women with PCOS (Farrell and Antoni, 2010). Also, the nutritional impact in pregnancy is unclear and although supplement use is widely recommended following bariatric surgery, poor compliance may be a problem (Nilsen *et al.*, 2006). Specifically with regards to PCOS, recent guidelines from the American Association of Clinical Endocrinologists and the Obesity Society and the American Society for Metabolic and Bariatric Surgery noted a lack of conclusive clinical PCOS-specific evidence and suggested that patients should be advised that fertility may be improved post-operatively (Mechanick *et al.*, 2009).

Bariatric surgery is known to improve markers of PCOS influencing fertility, including anovulation, hirsutism, hormonal changes, IR, sexual activity and libido (Eid *et al.*, 2005; Teitelman *et al.*, 2006; Malik and Traub, 2012). Whether this translates into improved maternal and foetal outcomes remains an area of debate. Small for gestational age (SGA) and preterm birth have emerged as potential complications associated with births after bariatric surgery. Studies documenting improvement in fertility after bariatric surgery are hampered by a lack of power to determine statistical significance (Dixon *et al.*, 2012). Low-powered studies result in inability to stratify risk according to type of surgery (Sheiner *et al.*, 2011), although preliminary results indicate that weight loss, not the type of surgery, is the mediator for improved fertility (Musella *et al.*, 2012).

Therefore, bariatric surgery could be considered to improve fertility outcomes in women with PCOS who are anovulatory, have a BMI $\geq$ 35 kg/m^2, and who remain infertile despite undertaking an intensive structured lifestyle management programme involving reducing dietary energy intake, exercise and behavioural interventions preferably for a minimum of 6 months. Implementation of these recommendations is likely to have resource implications including the cost of bariatric surgery and specialist care, which may be offset by less use of assisted reproductive technologies and fewer complications in pregnancy and beyond. Additionally, there will be the delay of waiting for surgery and waiting for weight to stabilize after the surgery (usually 6–12 months) (Legro *et al.*, 2012). Studies to date regarding bariatric surgery have primarily addressed Caucasian populations. It is well known that there are ethnic differences in adiposity, weight distribution and disease risk, such that BMI and cut-off points for clinical intervention may be adjusted for ethnicity.

Women with PCOS who become pregnant after bariatric surgery should be considered as having a high-risk pregnancy and they require careful monitoring of foetal growth. The patient should be made aware of the risks of surgery and of post-operative nutritional deficiencies and should be managed in a specialist interdisciplinary care setting, including a dietician and other multidisciplinary staff trained to work with patients who have had bariatric surgery. Pregnancy should be avoided during periods of rapid weight loss and patients should be counselled to avoid pregnancy for at least 6–12 months after bariatric surgery.

In summary, we suggest a weak recommendation based upon low-quality evidence that bariatric surgery could be considered to improve fertility outcomes in women with PCOS who are anovulatory, have a BMI $\geq$ 35 kg/m^2, and who remain infertile despite undertaking an intensive structured lifestyle management programme involving reducing dietary energy intake, exercise and behavioural interventions preferably for a minimum of 6 months.

We suggest that the following practice point be strongly recommended, based upon low-quality evidence, if bariatric surgery is to be prescribed, the following should be considered:

(i) The patient should be made aware of the risks of surgery and of pre- and post-operative nutritional deficiencies and should be managed in a specialist interdisciplinary care setting, including a dietician and other multidisciplinary staff trained to work with patients who have had bariatric surgery.
(ii) Pregnancy should be avoided during periods of rapid weight loss.
(iii) Patients should be counselled to avoid pregnancy for at least 6–12 months after bariatric surgery.
(iv) Foetal growth should be monitored during pregnancy.

For future research, further methodologically rigorous trials are important to address the efficacy, safety and role of bariatric surgery in PCOS including its effect on fertility.

Clomiphene citrate

Anti-oestrogen therapy with CC has traditionally been used as first-line therapy for anovulatory PCOS (Homburg, 2010; Fauser *et al.*, 2012). The anti-oestrogen action of CC blocks estradiol receptors in the hypothalamus, inducing a change in gonadotropin releasing hormone (GnRH) pulse frequency, release of FSH from the anterior pituitary and consequent follicular development. The concomitant release of LH, if chronically elevated during the follicular phase, may be detrimental to the success of the treatment (Shoham *et al.*, 1990). A meta-analysis has confirmed that CC is effective in increasing pregnancy rates when compared with placebo as first-line therapy (fixed OR 5.8, 95% CI: 1.6–21.5; number needed to treat 5.9, 95% CI: 3.6–16.7) (Brown *et al.*, 2009). Nonetheless CC is associated with up to an 11% risk of multiple pregnancy (Kousta *et al.*, 1997) and so careful monitoring with ultrasound to assess ovarian response is recommended. Indeed, all women prescribed CC should be carefully monitored with a combination of endocrine and ultrasound assessments of follicular growth and ovulation and should be ideally managed by specialists in reproductive medicine.

The starting dose of CC is 50 mg/day for 5 days (usually starting day 2 of the cycle). The dose of CC should only be increased if there is no response after two cycles because, of those women who will respond to 50 mg/day, only two-thirds will do so in the first cycle. If

there is an over-response to 50 mg/day, the dose can be decreased to 25 mg/day. The ~20% who are resistant to CC (i.e. remain anovulatory) are usually identified within three cycles. Discontinuation of CC therapy should be considered if the patient is anovulatory after the dose has been increased up to 100 mg/day. Doses of 150 mg/day or more appear not to be of benefit, although doses up to 250 mg have been prescribed by some authors, particularly for those who are obese (Homburg, 2010); doses of >150 mg are off label in some countries (e.g. North America). If the patient is ovulating, pregnancy is expected to occur at a rate determined by factors including the patient's age. An overview of outcomes from CC therapy indicates an overall ovulation rate of 73%, pregnancy rate of 36% and live birth rate of 29% over 6 months (Homburg, 2005).

Ultrasound evaluation of follicular growth and endometrial thickness on days 11–14 of the cycle is justified by the identification of those who are not responding or have an inadequate endometrial thickness, and is helpful in timing natural intercourse or intrauterine insemination. Although this monitoring implies added expense, this is counterbalanced by the prevention of possibly inappropriate or inefficient therapy and the potential to minimize the risk of multiple pregnancy (Homburg, 2010). The addition of an ovulation-triggering dose of human chorionic gonadotropin (hCG) at mid-cycle does not improve pregnancy rates (Agarwal and Buyalos, 1995).

Side effects of CC include visual disturbances (in which case, the drug should be stopped immediately), hot flushes, breast tenderness, dizziness and nausea. Some women who experience troublesome side effects with CC may benefit from tamoxifen (20–40 mg, days 2–6). Monitoring patients on tamoxifen should be the same as for those on CC.

Patients not responding to CC are likely to be more obese, insulin resistant and hyperandrogenic than those who do respond (Imani *et al.*, 1998). Prediction models have been developed, which take these factors into consideration, alongside age and menstrual cycle characteristics (Imani *et al.*, 2002). Approximately 75% of pregnancies that occur with CC do so in the first three cycles of treatment and a few occur following six cycles (Kousta *et al.*, 1997; Homburg, 2010). Therefore, six ovulatory cycles will usually suffice before moving on to more complex treatment. In this context, CC should be first-line pharmacological therapy to improve fertility outcomes in women with PCOS and anovulatory infertility, with no other infertility factors.

Although ovulation is restored in ~80%, pregnancy is achieved in only ~35–40% of patients who are given CC (Homburg, 2010). This may be due to the discharge of LH as well as FSH that occurs with CC, so those with high basal LH levels are less likely to respond and become pregnant, particularly if LH is still elevated after day 8 of the cycle (Shoham *et al.*, 1990). Another factor is the anti-oestrogenic effect of CC on the endometrium and cervical mucus. Suppression of endometrial proliferation, when endometrial thickness remains <8 mm, indicates a poor prognosis for becoming pregnant (Homburg, 2010).

'Clomiphene-resistance' refers to a failure to ovulate rather than failure to become pregnant despite ovulation, which is known as 'clomiphene-failure'. For those resistant to CC the options are AIs, gonadotropin therapy or laparoscopic ovarian surgery. There is some debate as to how many cycles without becoming pregnant constitutes 'failure'. Most pregnancies occur within 6 months of treatment, although the cumulative pregnancy curve rises slowly after this time (Kousta *et al.*, 1997), but if pregnancy has not occurred after 6–9 ovulatory cycles, it is appropriate to offer the couple IVF. Other factors, such as age and resources, will need to be taken into consideration.

In summary, we strongly recommend the following:

(i) Ovulation induction should be carefully monitored by practitioners with appropriate training and expertise to ensure effectiveness and safety, with respect to reducing risk of multiple pregnancy and OHSS (high-quality evidence).
(ii) CC or letrozole (when available and permissible) should be first-line pharmacological therapy to improve fertility outcomes in women with PCOS and anovulatory infertility, with no other infertility factors (high-quality evidence).
(iii) CC-resistant patients could be offered low dose gonadotropin therapy, CC with metformin or laparoscopic ovarian diathermy (LOD) (low quality evidence).

For future research, well-designed prospective cohort studies should measure pregnancy complications and outcomes of children in women with anovulatory PCOS who became pregnant either naturally or as a result of infertility therapy.

Aromatase inhibitors

AIs prevent oestrogen biosynthesis from androgens and through hypothalamic/pituitary feedback, increase FSH secretion (Holzer *et al.*, 2006). These agents theoretically avoid adverse effects of CC, as they do not affect oestrogen receptors centrally or within the endometrium (Holzer *et al.*, 2006). Furthermore, by preserving ovarian/pituitary feedback, there is a reduced risk of multiple follicle development compared with CC (Homburg, 2010).

Adverse effects include gastrointestinal disturbances, asthenia, hot flushes, headache and back pain. The potential for teratogenic effects of letrozole has been raised, with an abstract suggesting higher risk of congenital cardiac and bone malformations in newborns (Biljan, ASRM abstract, 2005); the methodology was highly criticized and a peer-reviewed paper did not result from the presented abstract. Furthermore, subsequent publications indicate that letrozole may not be associated with an increased risk of foetal anomalies (Tulandi *et al.*, 2006; Forman *et al.*, 2007; Legro *et al.*, 2014).

A large, multicentre double-blind RCT (n = 750) demonstrated that letrozole improved pregnancy outcomes compared with CC (Legro *et al.*, 2014). All subjects had anovulatory PCOS, with a mean BMI of 35 kg/m^2, and were randomly assigned to receive letrozole or CC for up to five treatment cycles. The starting doses were 50 mg of CC or 2.5 mg of letrozole; each was increased if there was no response to 100 and 5 mg, respectively, to a maximum of 150 and 7.5 mg. There was a higher cumulative ovulation rate with letrozole, 61.7% versus 48.3% ($P < 0.001$). Live births were achieved in 103 of 374 patients (27.5%) taking letrozole and 72 of 376 (19.1%) in the CC group (rate ratio 1.44, 95% CI: 1.10–1.87). There were no significant between-group differences in pregnancy loss (31.8% in the letrozole group and 29.1% in the CC group) or twin pregnancy (3.4% and 7.4%, respectively). In this study, the number of congenital abnormalities was higher in the letrozole group (4 vs 1) but this was not statistically significant ($P = 0.65$) and lower than expected for either an infertile or normal population (Legro *et al.*, 2014). The anomalies were variable in the letrozole group: (i) imperforate anus and spina bifida; (ii) hemiencephaly and dysgenesis of the left frontal and temporal lobes; (iii) mild cerebral palsy, arrested hydrocephalus,

neutropenia and polycythaemia and (iv) ventricular septal defect (VSD). In the CC group, one baby had an atrial septal defect, VSD and pulmonary stenosis. Whilst the study was not powered to demonstrate a difference in anomaly rates, the low number is reassuring. A more recent study in couples with unexplained infertility randomly assigned 299 women to receive letrozole, 300 to receive clomiphene and 301 to receive gonadotropin therapy. There were no differences in the rate of congenital anomalies, with three in the CC group and two in the letrozole group (Diamond *et al.*, 2015).

In a 2014 Cochrane review, of 26 RCTs (5560 women), letrozole was either compared with placebo, CC or laparoscopic ovarian drilling (Franik *et al.*, 2015). In 15 studies (n = 2816), there was a higher clinical pregnancy rate with letrozole than with CC (OR 1.40, 95% CI: 1.18–1.65). In nine studies comparing letrozole with CC (4783 women), the OR for live birth favoured letrozole (OR 1.64, 95% CI: 1.32–2.04) (Franik *et al.*, 2015). There was a reduction in the rate of multiple pregnancy across 11 studies (n = 2385) when using letrozole, compared with other ovulation inducing drugs (OR 0.38, 95% CI: 0.17–0.84). There was no evidence of a difference in OHSS between letrozole and CC, or letrozole and placebo; however, OHSS was an uncommon complication (Franik *et al.*, 2015). In summary, letrozole (when available and permissible) may be used as first-line therapy and can be used as second-line therapy in CC resistance and/or failure, in women who are anovulatory and infertile, with no other infertility factors.

In summary, we suggest a weak recommendation based upon high-quality evidence, that letrozole can be used as second-line pharmacological therapy in women with PCOS who have CC resistance and/or failure, and are anovulatory, and infertile, with no other infertility factors.

For future research, additional methodologically rigorous trials are important to address the role of AIs for ovulation induction in PCOS, including outcomes in children.

Metformin

Metformin is a synthetically derived biguanide and is the preferred and most cost-effective first-line oral therapy for the treatment of DM2 (Nathan *et al.*, 2009; Inzucchi *et al.*, 2012). The liver is the primary site of action of metformin where it reduces hepatic glucose production, stimulates insulin-mediated glucose uptake by the liver and skeletal muscle and reduces substrate availability for gluconeogenesis by lowering serum lipid levels. It follows that metformin, which reduces serum insulin concentrations, may improve the symptoms of PCOS. Metformin monotherapy, whilst associated with initial gastrointestinal side effects, is usually well tolerated and not complicated by hypoglycaemia. Gastrointestinal side effects are managed by starting at a low dose of 500 mg once daily with gradual titration to 850–1000 mg twice daily. In contrast with most oral hypoglycaemic agents, metformin may support the ability to achieve weight loss, although does not in itself cause weight reduction. However, a recent systematic review has indicated that metformin therapy combined with lifestyle modification in women with PCOS may improve body weight over and above lifestyle alone (Naderpoor *et al.*, 2015).

Early studies of the use of metformin in the management of PCOS suggested an improvement in reproductive function and the possibility of benefits to long-term health; indeed, metformin may act both indirectly by reducing systemic insulin levels and also directly within the ovary itself (Diamanti-Kandarakis *et al.*, 2010). The results of large prospective, randomized studies have, however, largely failed to demonstrate significant benefit. Despite the improvement in biochemical parameters reported in some studies, this does not result in significant improvement of either the dermatological signs of HA (Costello *et al.*, 2007) or in an improvement to fertility (Tang *et al.*, 2012).

A large prospective randomized, double blind, placebo-controlled, multicentre study evaluated the combined effects of lifestyle modification and metformin in obese anovulatory women (BMI > 30 kg/m^2) with PCOS (Tang *et al.*, 2006). All subjects had an individualized assessment by a research dietitian to set a realistic and sustainable goal, aiming for an average reduction of 500 kcal/day. Consequently, both the metformin-treated and placebo groups lost weight although the amount of weight reduction did not differ between groups. Those who lost weight experienced an increase in menstrual cyclicity although there was no difference between the two arms of the study, reinforcing the notion of weight reduction holding the key to improving reproductive function (Tang *et al.*, 2006). Metformin has also been evaluated in combination with CC. In a large Dutch multicentre trial, 228 women with PCOS were randomly allocated to receive either CC plus metformin or CC plus placebo (Mol *et al.*, 2006). There was no difference in the ovulation rate in the metformin group compared with placebo (64% vs 72%), neither was there a difference in the rates of ongoing pregnancy (40% vs 46%) or miscarriage (12% vs 11%). More women who received metformin discontinued therapy because of the gastrointestinal side effects of metformin (16% vs 5%). The pregnancy in PCOS trial enrolled 676 anovulatory women with PCOS and randomized them to three different treatment arms for a total of 6 cycles or 30 weeks: (i) metformin 1000 mg twice daily plus placebo, (ii) CC 50 mg day 3–7 of cycle plus placebo or (iii) combined metformin 1000 mg twice daily plus CC 50 mg/day (days 3–7). The live birth rates were 7.2% (15/208), 22.5% (47/209) and 26.8% (56/209), respectively, and those who received metformin alone fared worse than the other two groups. The rate of miscarriage was also higher in the metformin alone group: 40.0% versus 22.6% and 25.5%, respectively (Legro *et al.*, 2007).

The latest update of the Cochrane review of insulin-sensitizing agents and PCOS included 46 trials with a total of 4227 participants (ranging from 16 to 626 per study). Of these studies, 40 investigated metformin, involving 3848 patients, with a median daily dose of metformin of 1500 mg and durations ranging from 4 to 60 weeks (Morley *et al.*, in press). This systematic review concluded that metformin may improve menstrual frequency and ovulation rate, which may result in a marginal improvement in live birth rate when compared with placebo. However, the negative impact of obesity on pregnancy outcomes remains. Metformin also had no effect on miscarriage rate. Clinical pregnancy rates were improved for metformin versus placebo (OR 1.93., 95% CI: 1.42–2.64, 9 RCTs, 1027 women). This was also reflected in higher live birth rates with metformin versus placebo across two studies [OR 1.64; (1.02, 2.63), 385 women, P = 0.04]. This review update includes a recent large Scandinavian study of 329 women, who received metformin (1500 mg–2000 mg/day) or placebo for 3 months prior to fertility treatment and then for a further 9 months during treatment and up to 12 weeks of gestation. This

study demonstrated an increase in pregnancy rate from 40.4% to 53.6% (OR 1.61, 95% CI: 1.13–2.29), with obese women experiencing the greatest benefit (Morin-Papunen *et al.*, 2012). Furthermore, the live birth rate was increased in those who received metformin (41.9% vs 28.8%, $P = 0.014$).

The clinical pregnancy rate was also improved when adding metformin to CC in women with CC-resistance, in both obese and non-obese patients (OR 1.59, 95% CI: 1.25–2.02, 14 trials, I^2 42%) (Morley *et al.*, in press), although the addition of metformin to CC did not improve live birth rates (OR 1.21, 95% CI: 0.91–1.61, 8 trials, I^2 30%). The few studies, which compare metformin with CC, have conflicting results. A subgroup analysis by BMI, found that metformin was inferior to CC, which improved live birth rate and clinical pregnancy rate in women with a BMI > 30 kg/m^2 (OR 0.3, 95% CI: 0.17–0.52, 2 trials, 500 women; OR 0.34, 95% CI: 0.21–0.55, 2 trials, 500 women, respectively). However at a BMI < 30 kg/m^2, no data for live birth rate were suitable to be pooled, but the clinical pregnancy rate favoured metformin (OR 1.94, 95% CI: 1.19–3.16, 3 trials, 349 women) (Morley *et al.*, in press).

Women with PCOS are at increased risks of pregnancy-related complications including GDM, pregnancy-induced hypertension, pre-eclampsia and neonatal morbidity (Boomsma *et al.*, 2006). In view of the favourable effects of metformin on metabolic, cardiovascular and thrombotic events in the diabetic population, it would seem feasible that microvascular dysfunction and subsequent downstream events could be improved in PCOS pregnancies with metformin. Unfortunately, a large Norwegian multicentre RCT found no improvement in these complications with continued use of metformin throughout pregnancy (Vanky *et al.*, 2010), although there appeared to be a non-significant trend toward reductions in late miscarriage and preterm delivery rates, which is now the subject of a large ongoing RCT. Metformin has a good safety profile, with no evidence of teratogenicity.

Given the varied risk benefit ratio of other insulin-sensitizing agents, metformin remains the main insulin sensitizer therapy in the management of infertility in PCOS and there is insufficient evidence to recommend the use of other insulin sensitizers such as thiazolidinediones, d-chiro-inositol and myo-inositol in the treatment of anovulatory PCOS. Newer insulin-sensitizing agents such as glucagon-like peptide 1 analogues have been studied more recently in women with PCOS (Conway *et al.*, 2014). These agents include exenatide and liraglutide and are currently licensed for the treatment of DM2 and the latter also for obesity. In a study of 60 obese oligo-ovulatory women with PCOS, women were randomized to receive metformin or exenatide or a combination (Elkind-Hirsch *et al.*, 2008). All groups achieved benefit in rates of ovulation, endocrine and metabolic parameters, with the greatest improvement in those treated with the combination. Another study has suggested that liraglutide may additionally help weight loss (Jensterle Sever *et al.*, 2014), although further research is needed.

Metformin has limited value in the management of infertility in anovulatory PCOS but could be used alone to improve ovulation rates and pregnancy rates, if cost and monitoring facilities are a barrier to the use of CC or letrozole therapy (which are more effective). Metformin combined with CC for CC-resistant patients may improve pregnancy rates, but has not been shown to increase live birth rates.

In summary, we suggest as the following weak recommendations:

(i) Metformin could be used alone to improve ovulation rate and pregnancy rate in women with PCOS who are anovulatory and are infertile with no other infertility factors, if facilities are not available for monitoring of CC or letrozole, which are more effective (high-quality evidence).
(ii) Metformin could be combined with CC to improve fertility outcomes rather than persisting with further treatment with CC alone in women with PCOS who are CC resistant, anovulatory and infertile with no other infertility factors effective (high-quality evidence).
(iii) There is insufficient evidence to recommend the use of other insulin sensitizers such as thiazolidionediones, d-chiro-inositol and myo-inositol in the treatment of anovulatory PCOS (ungraded evidence).

For future research, we recommend the following:

(i) Further methodologically rigorous trials are important to address whether the addition of metformin to CC improves live birth rate in anovulatory PCOS women with no other infertility factors.
(ii) Further methodologically rigorous trials are important to address whether there is a difference in effectiveness between CC and metformin in PCOS anovulatory, infertile women with a BMI ≤ 30 kg/m^2 to improve fertility outcomes.
(iii) High-quality studies are required to assess the use of other insulin sensitizers such as myso-inositol for ovulation induction in PCOS, including outcomes in children.

Gonadotropin therapy

Gonadotropin therapy can be used as second-line pharmacological therapy in women with PCOS who have CC resistance and/or failure, are anovulatory and infertile, with no other infertility factors. In order to prevent overstimulation and multiple pregnancy, the traditional standard step-up regimens (Lunenfeld and Insler, 1974) have been replaced by either low-dose step-up regimens (Hamilton-Fairley *et al.*, 1991; White *et al.*, 1996) or step-down regimens (van Santbrink *et al.*, 1995). The low-dose step-up regimen employs a starting dose of 50–75 i.u., which is only increased after 14 days if there is no response and then by only 25–37.5 i.u. every 7 days. Nowadays, with the new gonadotropin pen devices, an ultra-low increment of FSH (8.3–12.5 IU) is possible and widely used (Orvieto and Homburg, 2009).

The low-dose step-up approach may result in lengthy treatment cycles, up to 28–35 days, but with the benefit of a lower risk for multiple follicular growth than with conventional step-up regimens. With the step-down protocol, follicular recruitment is achieved using 150 i.u. daily for 3 or 4 days before decreasing the dose to 50–75 i.u. to maintain follicular development. Gonadotropins are used alone, without a background of pituitary desensitization, which does not confer any advantage. Furthermore, different gonadotropin preparations appear to work equally well and so the most cost-effective preparation should be used (Nugent *et al.*, 2000).

It can be very challenging to stimulate the development of a single dominant follicle and it is difficult determine the required starting dose of gonadotropin. Multiple pregnancy carries increased rates of perinatal morbidity and mortality, and secondary effects due the family pressure to provide care for multiple babies. High-order multiple pregnancies (quadruplets or more) result almost exclusively from ovulation induction therapies. It is essential to carefully monitor follicular development by ultrasound. Ovulation is usually triggered with a single injection of hCG 5000 units when at least one follicle of at

least 17 mm in its largest diameter has developed. To reduce the risks of multiple pregnancy and OHSS, hCG should not be administered if a total of three or more follicles larger than 14 mm in diameter have developed. In overstimulated cycles, hCG is withheld, the patient is counselled about the risks and advised to refrain from sexual intercourse.

Women with PCOS are at an increased risk of developing OHSS. This occurs if many follicles are stimulated, leading to ascites, pleural and, sometimes, pericardial effusions with the symptoms of abdominal distension, discomfort, nausea, vomiting and difficult breathing. Intravenous fluids (colloids preferable to crystalloids), human albumin solution and heparin may need to be given to prevent dehydration and thromboembolism. Although this condition is rare, it is a potentially fatal complication and should be avoidable with appropriate monitoring of treatment.

An ovulation induction strategy applying CC as first-line treatment and gonadotropins as second-line treatment gives singleton live birth rates of around 75–80% (Veltman-Verhulst *et al.*, 2012). If pregnancy has not occurred after six ovulatory cycles in a woman younger than 25 years or after 12 ovulatory cycles in women older than 25, then it can be assumed that anovulation is unlikely to be the cause of the couple's infertility. If no other explanation has been found for their infertility, assisted reproduction (usually IVF) is indicated.

In summary, as general practice points based upon moderate quality evidence we strongly recommend that, where gonadotropins are to be prescribed, the following should be considered:

(i) Cost of the intervention for ovulation induction.
(ii) Expertise required for the use of the intervention for ovulation induction.
(iii) The degree of intensive monitoring that is required.
(iv) Implications of potential multiple pregnancy.
(v) Implications of the potential risk of OHSS.
(vi) The most cost-effective gonadotropin should be used. Review of the evidence indicates no significant difference in effectiveness between preparations.

Furthermore, we strongly recommended the following:

(i) Gonadotropins 'could' be second-line pharmacological therapy in women with PCOS who have CC resistance and/or failure, are anovulatory and infertile, with no other infertility factors (moderate quality evidence).
(ii) In women with PCOS who are anovulatory and infertile, with no other infertility factors, where appropriate to use gonadotropins, consideration should be taken to provide a low-dose protocol and appropriate monitoring that minimizes the risk of multiple pregnancy (high-quality evidence).

Laparoscopic ovarian diathermy

LOD (often referred to as 'ovarian drilling' or laparoscopic electrocautery) is an alternative to gonadotropin therapy for CC-resistant PCOS. This has replaced ovarian wedge resection, which was both more invasive and damaging. Because unifollicular ovulation is induced by laparoscopic ovarian surgery, there is no risk of either multiple pregnancy or OHSS and hence LOD does not require intensive monitoring with ultrasound (Balen, 2013). Laparoscopic ovarian surgery may also be useful for those who fail to respond to CC and persistently hypersecrete LH, those need a laparoscopic assessment of their pelvis or those who are unable to attend for the intensive monitoring required of gonadotropin therapy. Only fully trained laparoscopic surgeons should perform laparoscopic ovarian surgery.

After LOD, with restoration of ovarian activity, serum concentrations of LH and testosterone fall. The response depends on pretreatment characteristics, with those who are slim and with high basal LH concentrations having a better clinical and endocrine response. Commonly employed methods for laparoscopic surgery include monopolar or bipolar electrocautery (diathermy) and laser, whilst multiple biopsy alone is no longer used (Gjonnaess, 1984; Daniell and Miller, 1989). It is self-evident that the greater the amount of damage to the surface of the ovary, the worse will be the risk of peri-ovarian adhesion formation. It is therefore prudent to minimize the amount of diathermy to the lowest effective dose, namely 4 points per ovary for 4 seconds at 40 W (Armar *et al.*, 1990). Wedge resection of the ovaries was well known for resulting in significant adhesion formation, being up to 100% of cases in some series. LOD presents a lower risk of adhesion formation (10–20% of cases) and those that do form are usually fine and of limited clinical significance. The instillation of 500–1000 ml of an isotonic solution into the pouch of Douglas cools the ovaries in order to prevent heat injury to adjacent tissues and reduces the risk of the adhesion formation.

The largest RCT to date is the multicentre study performed in the Netherlands in which 168 CC-resistant patients were randomized to either LOD ($n = 83$) or ovulation induction with recombinant FSH (rFSH, $n = 65$) (Bayram *et al.*, 2004). In those who received LOD, the cumulative pregnancy rate after 6 months was 34% compared with 67% in those who received rFSH. Those who did not ovulate in response to LOD were then treated with additional CC and then, if still anovulatory, they were given rFSH. This resulted in a similar cumulative pregnancy rate by 12 months of 67% in each group. Thus, not only did those treated with LOD take longer to become pregnant, over half (54%) required additional induction of ovulation with medication. The Cochrane database compared gonadotropins with laparoscopic ovarian surgery in women with CC-resistant PCOS and found that there was no difference between the interventions for live birth rate per patient, long-term cost and quality of life; however, laparoscopic ovarian surgery was better than gonadotropins for multiple pregnancy rate [OR 0.13 (0.03, 0.52) $I^2 = 0\%$, $P = 0.0039$; 5 studies, 166 participants] and short-term cost ($P < 0.00001$; 2 studies, 203 participants) (Farquhar *et al.*, 2012).

Overall, LOD could be second-line therapy or a first-line therapy if laparoscopy is indicated for another reason in infertile women with PCOS. The minimum effective (intervention/dose) should be used to achieve ovulation and minimize the risk of ovarian damage including any effect on ovarian reserve and consideration should be given to increased peri-operative risks in women who are overweight or obese.

In summary, we strongly recommend based upon moderate quality evidence that laparoscopic ovarian surgery could be second-line therapy in women with PCOS who are CC resistant, anovulatory, and infertile, with no other infertility factors.

In addition, where laparoscopic ovarian surgery is to be prescribed, the following should be considered:

(i) The minimum effective (intervention/dose) should be used to achieve ovulation and minimize the risk of ovarian damage and potential effect on ovarian reserve (weak recommendation based upon ungraded evidence).
(ii) Laparoscopic surgery in women who are overweight or obese is associated with both intra-operative and post-operative risks (weak recommendation based upon ungraded evidence).

(iii) Where ovulation induction would be considered appropriate, laparoscopic ovarian surgery can be used as first-line therapy if laparoscopy is indicated for another reason in infertile women with PCOS (weak recommendation based upon ungraded evidence).

For future research, the minimum effective (intervention/dose) to achieve ovulation and minimize the risk of ovarian damage when using LOD and the potential effect on ovarian reserve require further investigation.

Complementary and alternative therapies

Western medicine and traditional Chinese medicine (TCM) are to some extent ends of a spectrum, with western medical science working from a basic science and clinical evidence-based perspective while TCM evolves from a holistic and 'macroscopic' perspective. Acupuncture is a method of treatment which dates back at least 3000 years, is an integral part of TCM and over the last decade has become established in Western medicine. The use of acupuncture, herbs and herbal mixtures in the treatment of PCOS-related symptoms have not been well investigated and the few studies that do exist are criticized because of poor design.

Acupuncture may suppress adrenal secretion of cortisol and modulate central β-endorphin secretion, thereby influencing the release of GnRH (Stener-Victorin *et al.*, 2000, 2003, 2006). Although experimental studies in animals indicate that acupuncture has the potential to reduce IR, it is unknown if it has such an effect in women with PCOS. An effect on ovarian function was first demonstrated in an RCT in which low-frequency electroacupuncture (EA) was superior to exercise in improving menstrual frequency and reducing circulating levels of testosterone, AMH and ovarian volume in women with PCOS (Jedel *et al.*, 2011; Leonhardt *et al.*, 2015). The effectiveness of true acupuncture (low-frequency EA) was compared with sham acupuncture in which 12 treatments were given over 14 weeks (Pastore *et al.*, 2011). Both groups improved their menstrual frequency but there was no difference in ovulation rate. In a more recent RCT, the ovulation frequency was found to be higher in women with PCOS during a 3 month long low-frequency EA treatment compared with control treatment (Johansson *et al.*, 2013).

The list of herbs and herbal mixtures used for the relief of symptoms relevant to PCOS is extensive but few have been actually evaluated in women with PCOS. In a placebo-controlled trial in women with undefined irregular menstruation, Vitex agnus-castus restored menstrual cycles and increased pregnancy rates as compared with placebo (Westphal *et al.*, 2006). The effect of this plant has not been tested in women with PCOS. In an uncontrolled trial, 34 women with PCOS were treated with a herbal mixture containing *Glycyrrhiza glabra* and *Paeonia lactiflora* named Shakuyaku-Kanzo-To (TJ-68) for 24 weeks (Takahashi *et al.*, 1988). TJ-68 decreased serum androgens by 35% in women who become pregnant without any negative side effects. *Sairei-to* is a Chinese herbal mixture, which contains 12 active ingredients; in an uncontrolled trial, it has been shown to decrease androgens and induce ovulation (Sakai *et al.*, 1999). The effect of *Mentha spicata Labiatae* (spearmint) teas on hirsute women has also been evaluated in an uncontrolled trial and may decrease free testosterone and LH concentrations (Akdoğan *et al.*, 2007). In a systematic review, it was concluded that there is limited evidence that the addition of Chinese Herbal Medicine to CC is associated with improved clinical pregnancy rate (Zhang *et al.*, 2010).

Overall, there is insufficient evidence to recommend the use of acupuncture, herbs and herbal mixtures in the treatment of anovulatory PCOS.

In summary, there is insufficient evidence to recommend the use of acupuncture, herbs and herbal mixtures in the treatment of anovulatory PCOS (weak recommendation based upon ungraded evidence).

For future research, high-quality studies are required to assess the use of acupuncture, herbs and herbal mixtures in patients with anovulatory PCOS.

IVF and IVM in women with PCO and PCOS

IVF may be required for women with anovulatory PCOS who do not become pregnant with ovulation induction or if there are additional fertility factors, for example tubal damage or male subfertility. Women with polycystic ovaries who require IVF are at particular risk of OHSS and careful strategies are required to minimize risk.

An increased FSH requirement is needed in obese patients to stimulate the ovary but once the threshold has been reached, the subsequent response can be uncontrolled resulting in a risk of OHSS (Dale *et al.*, 1998). Furthermore, whilst more oocytes may be retrieved in women with PCO compared with normal ovaries, there are lower fertilization rates (Dor *et al.*, 1990, MacDougall *et al.*, 1993). Kodama *et al.* (1995) demonstrated a higher incidence of embryo transfer cancellation due to failed fertilization and OHSS (Kodama *et al.*, 1995). A meta-analysis confirmed these findings despite a wide range of demographics and regimens being included (Heijnen *et al.*, 2006). The miscarriage rate in women with PCOS following IVF is high compared with women with normal ovaries (35.8% vs 23.6%, $P = 0.0038$) (Balen *et al.*, 1993). This unwanted outcome is proportional to BMI, increased waist–hip ratio and IR with a relative risk for miscarriage reported as 1.77 for women with a BMI over 25 kg/m^2 (Fedorcsak *et al.*, 2001).

Pituitary desensitization with a GnRH agonist became established in assisted reproduction regimens and was thought to be advantageous for women with PCOS allowing follicular development to occur without the adverse effects of high LH concentrations (Fleming and Coutts, 1988). GnRH antagonist protocols are now in favour due to the significantly reduced risk of OHSS (Griesinger *et al.*, 2006; Lainas *et al.* 2007, 2010). There appears to be no difference in efficacy between urinary-derived or recombinant preparations, or the use of hMG or FSH (Al-Inany and Abou-Setta, 2012).

Regarding the use of metformin for women with PCOS in IVF cycles, the first large RCT investigated 101 consecutive cycles using a conventional long GnRH-agonist protocol and either metformin 850 mg or placebo twice daily prior to oocyte collection (Tang *et al.*, 2006). There were no differences in the total dose of FSH, number of oocytes retrieved or fertilization rate. There was, however, a significant increase in clinical pregnancy rate beyond 12 weeks (38.5% vs 16.3%, $P = 0.023$) alongside a significant reduction in the risk of severe OHSS (3.8% vs 20.4%, $P = 0.023$). Metformin was also shown to attenuate the ovarian secretion of vascular endothelial growth factor, which is known to play a key role in the pathophysiology of OHSS (Tang *et al.*, 2006). Five RCTs have now looked at metformin

in women with PCOS undergoing IVF; four of these used the long protocol with a GnRH agonist for down regulation. The total dose and duration of metformin use were not standardized, ranging from 500 mg twice a day to 850 mg three times a day taken for up to 16 weeks usually up to the hCG trigger. Fleming *et al.* (2002) demonstrated that protracted treatment with metformin over 4 months may decrease the antral follicle count and AMH levels, although this was not shown to improve the number of oocytes retrieved or fertilization rate. In a smaller study, Kjotred *et al.* (2004) corroborated the findings of Tang by suggesting that the live birth rate may be improved in lean women with PCOS (Kjotrod *et al.*, 2004). In a further study of 112 women with a BMI < 28 kg/m, the live birth rate was higher when metformin was given over 12 weeks (48.6% vs 32.0%; 95% CI: 1.1–32.2, $P = 0.0383$) (Kjotrod *et al.*, 2011). Another study looking at 134 women with polycystic ovaries but without the syndrome failed to show an advantage (Swanton *et al.*, 2011).

The main benefit of metformin in the context of IVF therapy for women with PCOS appears to be in the prevention of OHSS in the long GnRH-agonist protocol (OR 0.27 95% CI: 0.16–0.47) (Tso *et al.*, 2014). Furthermore, it has been shown that the use of metformin during a fresh attempt may lead to a significantly increased live birth rate in the subsequent frozen cycle (28.6% vs 12.3%) (Brewer *et al.*, 2010), particularly for those who had all embryos frozen due to OHSS risk, in whom a 9-fold increase in live birth rate was seen (Brewer *et al.*, 2010). In this setting if a long GnRH-agonist IVF protocol is to be used, the addition of metformin should be considered to reduce the risk of OHSS.

In-vitro maturation (IVM) involves the retrieval of immature oocytes from either unstimulated or minimally stimulated ovaries. The oocyte matures *in vitro* in a specially formulated medium for 24–48 hours. The oocyte is then fertilized, usually with ICSI and the selected embryo(s) are transferred 2–3 days later. Although more labour-intensive, the potential clinical advantage is that patients generally require less monitoring and most importantly avoid the risk of OHSS. For those with PCOS, IVM offers a promising alternative to conventional IVF (Chian *et al.*, 2000; Chian, 2004). IVM compared with conventional IVF yields significantly fewer mature oocytes (7.8 vs 12, $P < 0.01$) with significantly lower implantation rates (Le Du *et al.*, 2005). The lower implantation rates may be due to a reduced oocyte potential, higher frequency of abnormal meiotic spindle and chromosomal alignment or reduced endometrial receptivity (Li *et al.*, 2006). It is important to ensure that infants born through such treatment remain healthy in the long term. A prospective observational study on 41 pregnancies showed no increase in preterm birth, birth weight or major structural malformation as compared with those conceived through conventional IVF (Cha *et al.*, 2005).

The maturation rate of oocytes retrieved from patients with PCOS has been lower than those with normal ovaries. Child *et al.* (2002) showed in a prospective observational study that significantly more immature oocytes are retrieved from polycystic ovaries than from normal ovaries (10 ± 5.1 vs 5.1 ± 3.7) (Child *et al.*, 2002). The overall maturation and fertilization rate was comparable but the pregnancy and live birth rates were significantly higher in the PCO/PCOS groups. This is explained in part by the greater number of embryos available to select from but also by the PCOS patients being considerably younger within the study. Research continues into identifying prognostic indicators of developmental potential of the embryos.

Siristatidis *et al.* (2013) conclude in a Cochrane systematic review, that no randomized controlled trials exist to base practice recommendations regarding IVM before IVF or ICSI in women with PCOS (Siristatidis *et al.*, 2013). Larger studies providing robust safety data on this new technology are required, and there are currently insufficient data to recommend the use of IVM in the management of anovulatory PCOS.

In summary, we strongly recommend the following based upon good quality evidence:

(i) In women with PCOS, IVF is indicated in those who have not responded to first or second-line ovulation induction therapies or those who require IVF for other indications.
(ii) Women with PCOS undergoing IVF are at an increased risk of OHSS and should be monitored carefully.
(iii) In women with PCOS undergoing IVF, the GnRH antagonist protocol should be preferred as a safer alternative to the traditional GnRH-agonist protocols because of the reduced risk of OHSS.
(iv) If a long GnRH-agonist protocol is to be used, the addition of metformin reduces the risk of OHSS (high-quality evidence).

In addition, as a practice point, there is insufficient data to recommend the use of IVM in the management of anovulatory PCOS.

For future research, studies are required to directly compare ovulation induction strategies with IVF in women with anovulatory PCOS, reporting on efficacy, health economics and burden. Well-designed prospective cohort studies should measure clinical effectiveness and outcomes of children in women with anovulatory PCOS and undergoing IVM.

Risks for pregnancy in women with anovulatory PCOS

Pregnancy outcomes in women with PCOS have been assessed in a meta-anlysis of 15 studies, involving 720 women with PCOS and 4505 controls (Boomsma *et al.*, 2006). It was found that women with PCOS had a significantly higher risk of developing GDM (OR 2.94; 95% CI: 1.70–5.08), pregnancy-induced hypertension (OR 3.67; 95% CI: 1.98–6.81) or pre-eclampsia (OR 3.47; 95% CI: 1.95–6.17) or having a 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), which was unrelated to multiple births (Boomsma *et al.*, 2006). Furthermore, GDM may also result in foetal macrosomia. There are a number of possible mechanisms for these problems, which include obesity, altered glucose metabolism and disturbances in uterine blood flow. Obesity in its own right is also associated with several adverse pregnancy outcomes, including spontaneous miscarriage, congenital anomalies (e.g. cardiac and spina bifida), pre-eclampsia, GDM, foetal macrosomia, caesarean delivery and post-operative wound complications (Wax, 2009). Women with PCOS should therefore be informed that the risks of pregnancy for both the mother and child are increased, and that these risks are exacerbated by obesity.

In summary, we strongly recommend the following based upon high-quality evidence.

(i) Women with PCOS should be fully informed that the risks of pregnancy are increased; e.g. GDM, pre-eclampsia and hypertension.
(ii) Women with PCOS should be fully informed that obesity both exacerbates the risks outlined above and is associated with an increased risk of miscarriage.

In addition, women with PCOS should be fully informed that the risks for the child are increased; e.g. prematurity, SGA and metabolic dysfunction in later life (high-quality of evidence, weak recommendation).

Summary

PCOS accounts for ~80% of cases of anovulatory infertility in women. Lifestyle intervention is recommended first in women who are obese, largely on the basis of general health benefits. Bariatric surgery could be considered where the BMI is ≥35 kg/m^2 and lifestyle therapy has failed. Ovulation induction therapy can achieve good cumulative pregnancy rates alongside low rates of multiple pregnancy by strictly adhering to the limit of the number of follicles that are allowed to ovulate. CC is recommended as first-line pharmacotherapy and letrozole is an alternative. Metformin has limited benefits in improving live birth rates. Gonadotropins and LOD can be used as second-line treatments. There is no clear evidence for efficacy of acupuncture and herbal mixtures in women with PCOS. For women with PCOS who do not become pregnant with ovulation induction therapy or have additional infertility factors, IVF can be used, with protocols to minimize the risk of OHSS. Patients should be fully informed of the potential side effects of drugs on the developing foetus and of the risks of multiple pregnancy. Women with PCOS should also be informed about the increased risks during pregnancy for both mother and child, including the exacerbating impact of obesity on adverse outcomes.

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Authors' roles

Adam H. Balen (chair of group) wrote the main body of the text, scrutinized the evidence tables and produced the algorithm.

Lara C. Morley was responsible for systematic reviews, evidence tables and grade assessments.

Marie Misso was responsible for systematic reviews, evidence tables and grade assessments.

Stephen Franks provided input on consensus of evidence and input into all sections, especially diagnosis.

Richard S. Legro provided input on consensus of evidence and additional work on manuscript.

Chandrika N. Wijeyaratne provided input on consensus of evidence, and was responsible for section on ethnic variations.

Elisabet Stener-Victorin provided input on consensus of evidence, and was responsible for section on alternative therapies.

Bart C.J.M. Fauser provided input on consensus of evidence and input into all sections.

Robert J. Norman provided input on consensus of evidence and input into all sections, and was a senior author on Australian Guideline, which formed the basis for the initial work.

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