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Fertility Treatment for Women with PCOS

Fiona Langdon, Jennifer Pontre and Roger J. Hart

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Abstract

Polycystic ovarian syndrome is the commonest cause of anovulatory infertility. This chapter will explore fertility treatment options for this condition including the risks, benefits and success rates for different treatment methods. The importance of close patient monitoring with hormone levels and pelvic ultrasounds to ensure mono-ovulation and to avoid ovarian hyperstimulation syndrome will be highlighted.

Keywords: polycystic ovary syndrome, anovulation, obesity, ovulation induction, ovarian hyperstimulation, gonadotrophins

1. Introduction

Polycystic ovarian syndrome (PCOS) is the commonest cause of anovulatory infertility [1]. Depending on the population studied between 5 and 18% of women of reproductive age suffer from PCOS, however not all of them are anovulatory or experience subfertility [2–4].

The aim of fertility treatment in women with subfertility and PCOS is to safely induce mono-follicular ovulation resulting in the birth of a singleton child. Women undergoing fertility treatment with PCOS are at significant risk of both multi-follicular development and ovarian hyper-stimulation syndrome (OHSS), so they must be carefully counselled and monitored during fertility treatment. It is imperative that prior to embarking on fertility treatment a patient's health and weight is optimised. This chapter will explore the latest evidence for fertility treatments for women with PCOS.

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2. Definition and diagnosis of PCOS

The current diagnosis for PCOS surrounds the cluster of signs and symptoms that the syndrome encompasses, namely anovulation, hyperandrogenaemia, insulin resistance and polycystic ovaries. The Rotterdam Criteria for diagnosis of PCOS requires two of the three diagnostic criteria, namely oligo- or anovulation, clinical or biochemical signs of hyperandrogenism and polycystic ovarian morphology (**Table 1**) [1].

There is discussion that the Rotterdam criteria is too broad and may be resulting in over diagnosis of the syndrome [5], especially in young women, prone to clinical signs of hyperandrogenism and who are more likely to have morphological features of polycystic ovaries on USS. Furthermore, when investigating a patient for possible PCOS, age, ethnicity and weight should be factored in.

Hyperandrogenic features, either biochemical or chemical, are seen in 60–80% of patients with PCOS [6]. Clinical features of hyperandrogenism correlate poorly with blood androgen levels, especially in some ethnic groups, particularly South East Asian, with increased sebaceous gland susceptibility to circulating androgens. Serum androgen concentrations must be measured in the setting of more severe clinical findings to ensure other causes of hirsutism are excluded such as adrenal tumours or non-classical congenital adrenal hyperplasia (CAH).

Polycystic ovarian morphology definition is predominantly based on findings from a paper by Sonnard in 2003 comparing 214 ovaries of PCOS patients with 112 normal women's ovaries to conclude that a diagnosis of polycystic ovaries should be more than 12 follicles measuring between 2 and 9 mm per ovary or an ovarian volume of more than 10cm^3. This diagnostic criterion is now largely seen to be too broad with further studies and improvement in ultrasound techniques suggesting that either the diagnostic follicle number should be increased [7] or raised AMH levels should be included in the diagnostic criteria.

Oligo-ovulation or anovulation is suggested by either irregular cycles or a sup-optimal mid-luteal phase progesterone. Cycles that are either shorter than 21 days or longer than 35 days are highly suggestive of anovulation, although It is recognised that even in adolescents with very short or protracted cycles ovulation can still occur, with obvious implications should pregnancy avoidance be required [8].

Two out of the following three criteria
1. Oligo- and/or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries on ultrasound after exclusion of other aetiologies (congenital adrenal hyperplasia, androgen secreting tumours, Cushing's syndrome)

Table 1. Revised ESHRE/ASRM Rotterdam consensus diagnostic criteria for PCOS.

3. Lifestyle modifications and weight loss

The first line of treatment and advice to women with PCOS seeking fertility treatment should be to optimise health. This is true for all women considering pregnancy but imperative for women with PCOS due to the commonly seen associations of obesity and metabolic disorders. Furthermore, as with any woman about to start to try to conceive, her doctor must stabilise any co-existing morbidities, and any medication prescribed must be safe for pregnancy.

While 9–18% of the female reproductive age population meet the criteria for PCOS, up to 70% of obese women do [9]. Obese patients with PCOS have an associated increase in severity of the disease, not just from a fertility perspective but for all metabolic and psychological sequelae of the disorder, when compared with non-obese PCOS patients. Obesity is associated with an increased risk of anovulation, increased androgen production and decreased response to follicular stimulating hormone (FSH) equating to decreased fecundity both in natural conception and assisted reproductive techniques [10]. Risks to the foetus if conception does occur include increased rates of congenital anomalies (neural tube defects, omphalocele and cardiac defects) [11], increased rates of hypoglycaemia of the newborn and other complications of gestational diabetes and long-term greater risks of metabolic disease for life. Risks to the pregnant obese patient include greater incidence of hypertensive disorders in pregnancy, increased incidence of thromboembolic events, increased incidence of gestational diabetes, increased risks of operative delivery and increased risks of perineal trauma [11]. For all these reasons, it is imperative that patients embarking on fertility treatment are first counselled and advised to optimise their weight and aim for a body mass index (BMI) in the healthy range.

With a 5–10% weight reduction in patients with PCOS significant benefits are seen in all aspects of health, including reproductive health. Spontaneous ovulation is more likely and patient's response to fertility treatment is more likely to be successful [12, 13]. Caloric restriction, increased physical activity and weight loss medication can all play a role in helping patients achieve the necessary weight loss to either conceive spontaneously or have greater success with fertility treatments. There is limited data on live birth rates, however a loss of weight from an unhealthy weight range in PCOS patients is associated with an improved waist to hip ratio measurement, improved clinical and biochemical signs of hyperandrogenism and improved insulin resistance [14].

A recent randomised control trial of 149 patients with PCOS and body mass index (BMI) between 27 and 41 kg/m^2 compared 16 weeks of lifestyle modification (caloric restriction, weight loss medication and increased levels of physical activity), the combined oral contraceptive pill (COCP) or both interventions followed by 4 cycles of clomiphene citrate and timed intercourse. The researchers found significant weight loss in the lifestyle modification group (mean weight loss −6.2%) and the combined group (mean weight loss −6.4%) when compared to the COCP only group. Superior cumulative ovulation rates were seen in the lifestyle group (60%) and the combined group (67%) compared with the COCP group (46%) after 4 cycles of clomiphene citrate. Live birth rates were not significantly

increased, although the study was not adequately powered for livebirth as an outcome, but were higher in the lifestyle (26%) and combined (24%) group compared with the COCP group (12%) [12].

Bariatric surgery can be considered in women with a BMI over 35 and who have had a failed attempt at weight loss with lifestyle modifications. Bariatric surgery improves markers of PCOS influencing fertility, namely anovulatory cycles, hormonal ratios and insulin resistance, but comes with the increased risk of a malabsorptive state and disordered eating as well as psychological issues [15–17]. There are limited trials powered to confirm an absolute improvement in live birth rates following bariatric surgery. Pregnancy and fertility treatments should be avoided for a minimum of 12 months after such surgery to reduce the pregnancy complications associated with bariatric surgery, such as; preterm birth and being small for gestational age. This is due to the profound catabolic state existing after surgery and the depletion of micro-nutrients from the diet [18]. Due to this enforced time delay, in the setting of an older woman with falling ovarian reserve, time for substantial weight loss or bariatric surgery may not be feasible to ensure a successful pregnancy. In these cases, with proper counselling, more leniency may be given to cut off levels of BMI to commence fertility treatment.

4. Metformin

Metformin is a biguanide antihyperglycaemic medication used in Type 2 diabetes mellitus. It acts by decreasing glucose levels through reducing hepatic glucose production and reducing intestinal absorption of glucose, overall reducing the level of insulin secretion. As PCOS has a strong association with hyperinsulinaemia and insulin resistance many patients with PCOS have been treated with metformin, and there is a substantial amount of research showing the beneficial effects of metformin on reproductive outcomes. There is strong evidence to show that within 1–3 months of commencing metformin treatment there is improvement in cycle regularity and improved ovulation rates [19]. Up to 50% of anovulatory women with PCOS will ovulate after treatment with metformin [20]. It is thought metformin acts by not only reducing insulin levels systemically, but also by directly acting on the ovary to alter gonadotrophin levels [21]. Metformin use is associated with weight loss, greater than with lifestyle changes alone, and thus is associated with the reproductive benefits outlined in the weight loss effects above [22].

Metformin's influence on reproductive outcomes has demonstrated an improvement in clinical pregnancy rates, without an improvement in overall live birth rates, and does not appear to provide additional benefit when combined with clomiphene citrate, unless used in the profoundly overweight patient. A meta-analysis of 38 trials of nearly 3500 women showed that there was no increase in the live birth rate for women treated with metformin, either as a single agent (OR1.80 CI 0.52–6.16) or as an addition to clomiphene citrate. (OR 1.16, CI 0.85–1.56) [23].

However there is some evidence that metformin may improve live birth rates for women undergoing ovulation induction when combined with gonadotrophins. Two RCTS comparing the use of placebo versus metformin in ovulation induction with gonadotrophins for women with PCOS have shown a higher live birth rate (OR 2.31) in the metformin and gonadotrophin group compared with the placebo and gonadotrophin group, however the numbers studied were small [24, 25]. There was no observed increase in multiple pregnancy rates in these studies or others looking at clinical pregnancy rates only, with the addition of metformin [26].

From the studies outlined above metformin cannot be recommended as a treatment for ovulation induction alone, however in obese or overweight women it can play a role in weight loss which may facilitate spontaneous ovulation in conjunction with clomiphene. There is some limited data that it may improve reproductive outcomes as an adjunct to ovulation induction treatment with gonadotrophins in women with diagnosed PCOS.

5. Clomiphene and anti-oestrogens

Clomiphene citrate is a selective oestrogen receptor modulator (SERM) used to induce ovulation in anovulatory patients for over 50 years [27]. It will induce ovulation in around 75% of patients with PCOS. Increasing doses of clomiphene results in increased rates of ovulation, but not necessarily increased rates of pregnancy. Being a SERM, clomiphene acts on oestrogen receptors in the hypothalamus and pituitary, to increase follicular stimulating hormone (FSH) production, and on receptors in the endometrium and cervix with differing antagonist and agonist qualities depending on dose [28]. Clomiphene, particularly in higher doses, can produce a less receptive endometrial environment and a more hostile cervical mucus, which may negatively affect pregnancy rates.

Ovulation rates were studied at different doses for women with PCOS, with the finding that at a starting dose of 50 mg per day 46% of patients ovulate, 70% ovulate with 100 mg, 76% with 150 mg and up to 90% at doses greater than 150 mg daily for 5 days [29]. As doses increase a lower percentage of the women who have not ovulated previously on the lower dose have success with the higher dose as the proportion of women with true clomiphene resistance increases. Patients are usually deemed clomiphene resistant, thought to affect around 15% of women with PCOS, if no follicle development is seen with 3 cycles of maximal dose (150 mg for 5 days) of clomiphene citrate [30]. Patients are more likely to be clomiphene resistant if they are obese and suffer from significant hyperandrogenism [31].

Evidence suggests women with PCOS undergoing fertility treatment with clomiphene have a cumulative pregnancy rate of around 45% after 4 cycles and 65% after 6 cycles [32], with a live birth rate of around 42% [33]. After 6 cycles of treatment the pregnancy rate falls despite regular ovulation, suggesting other subfertility issues may be present in the couple or the effects of high dose clomiphene is impacting the uterus.

It is essential that clomiphene treatment, as with any ovulation induction treatment, must be monitored with serial transvaginal ultrasound examinations (TVUS) to monitor follicular development, and allow for cycle cancellation if a response with more than one dominant follicle developing is seen. Monitoring treatment in this way keeps the rate of multiple pregnancies to a minimum. The multiple pregnancy rate with clomiphene treatment is between 6.9–9% for twin pregnancies and less than 1% for higher order multiple pregnancy. Congenital malformations have not been shown to be any higher in women taking clomiphene than women who spontaneously ovulated [34].

Clomiphene treatment is for the most part well tolerated with common side effects relating to the effects of hypoestrogenism including hot flushes, abdominal distention, nausea and breast tenderness being seen in 10–20% of patients. Side effects do not appear to be dose dependent, but rather a result of patient response.

The risk of ovarian hyperstimulation syndrome (OHSS) is theoretical with clomiphene use and if occurs is nearly always mild. Treatment dose should always be started low and increased only if ovulation has not occurred to avoid this risk.

Clomiphene has been the first line fertility treatment for women with PCOS for many years, however data is emerging that other treatment modalities have greater success and a move away from using clomiphene citrate in the first instance is being practiced.

6. Letrozole

Letrozole is an aromatase inhibitor inducing a hypo-oestrogen state by inhibiting the enzyme converting androgens to oestrone and oestradiol. A low serum oestradiol concentration results in increased pituitary FSH production, and consequently subsequent follicular development and ovulation. It is licenced for the treatment of oestrogen sensitive breast cancers in postmenopausal women, but is gaining popularity in its currently off label use in producing mono-ovulation in women undergoing fertility treatment with PCOS.

Like clomiphene, letrozole is given in the early follicular phase of the cycle for 5 consecutive days. Dosing is started low, usually at 2.5 mg to ensure response can be monitored and avoid cycle cancellation if an exaggerated follicular response is seen. Higher doses are associated with poorer endometrial thickness, but not at the levels seen with clomiphene citrate [35].

Compared with clomiphene citrate letrozole has been shown in a randomised controlled trial and a meta-analysis of six trials to be superior at inducing ovulation (the RCT showing relative risk (RR)1.28) and live-birth rates (RR 1.44) [36, 37]. These results were particularly evident for patients with a body mass index over 30 kg/m^2, with no significant difference between the two treatment modalities in patients with a BMI of less than 30 kg/m^2. The same study reported lower multiple pregnancy rates with letrozole compared with clomiphene use (3.4% vs. 7.4%), however the study was not powered for this outcome.

Studies looking at foetal safety with letrozole use have found no significant difference in the rates of congenital anomalies in pregnancies conceived using letrozole, compared with clomiphene or spontaneous ovulation [38]. Side effects related to low oestrogen levels with letrozole appear to be less common than those seen with clomiphene use.

Particularly for patients who are obese (BMI over 30 kg/m^2) letrozole can be considered as a first line treatment for mono-ovulation induction. For women with a BMI less than 30 kg/m^2 letrozole may lead to similar pregnancy rates to clomiphene, however the side effect profile and the possible lower multiple pregnancy rates may favour the use of letrozole.

7. Gonadotrophins

Gonadotrophins in the form of injectable recombinant FSH are used in women with PCOS to induce mono-ovulation, historically as a second-line treatment after a patient had failed clomiphene citrate treatment. The perceived risk of ovarian hyper-stimulation and multiple gestation has meant it has been overlooked as a first-line treatment. This view is changing with more evidence to support its use, particularly with low dose, step-up protocols with very close monitoring (Langdon et al. 2017 personal communication).

Patients with PCOS are particularly sensitive to FSH due to the high antral follicle count associated with the condition. It is imperative that the dose threshold to induce ovulation is reached gradually to reduce the risk of multiple follicles being recruited resulting in cycle cancellation, multiple pregnancy or even OHSS, as well as patient disappointment. In therapy naïve patients dosing usually begins at 25 or 37.5 IU/day increasing by small increments (usually 12.5 IUI) at a minimum of 7–10 days, if no response is seen on vaginal ultrasound monitoring or serum oestradiol levels [39]. Requirements for higher doses of FSH are often seen in women with a greater BMI, older age, insulin resistance and amenorrhoea compared with oligomenorrhoea [33].

The success of gonadotrophin ovulation induction is superior to clomiphene. An RCT of therapy naïve women with PCOS compared to treatment with either clomiphene or low dose FSH for up to 3 cycles and found that treatment with FSH had a higher first cycle pregnancy rate (30% vs. 14.6%, 95% CI 5.3–25.8), overall pregnancy rate (58% vs. 44%, 95% CI 1.5–25.8) and live birth rate (47.4% vs. 36.9%.) [42].

Despite the increased success rates associated with gonadotrophin use the therapy has not been embraced as a routine first line fertility treatment for PCOS in many fertility centres due to older studies warning of increased complication rates with its use, and a lack of reimbursement in some jurisdictions. Multiple gestation rates when FSH is used with the purpose of achieving of mono-ovulation are documented to be as low as 6%, comparable to clomiphene use [40]. This is achieved by strictly adhering to a low dose, slow step-up protocol as outlined above. It is further achieved by being wary of patients who may have a greater response to FSH treatment, namely younger patients, those with high AMH levels and those with normal BMI, and ensuring treatment is commenced on the lowest FSH dose possible, and only

increased after a period of up to 14 days with no response. Cancelling cycles when response is excessive is imperative to keeping multiple pregnancy rates down. Having a 5–20% cancellation rate has been shown to be associated with a less than 2% higher order multiple pregnancy rate and no difference in pregnancy rates over 4 cycles, and patients should be thoroughly counselled about this [41].

OHSS is a risk with FSH use but with carefully monitored use as described above in women with PCOS the risk is minimal and almost completely avoidable. The risk is only present if too many follicles are stimulated, thus starting with a low dose of FSH, and making small incremental increases only when no response is seen over an extended period and having a low threshold for cancellation of the cycle, OHSS risk can be completely avoided.

A review of 591 cycles of ovulation induction with gonadotrophins in 268 PCOS patients in our unit demonstrated that adherence to a low dose step up protocol had success rates of 22% for their first cycle, 18% for second cycles and 7% for third cycles. Success rates fell steeply after a third cycle. Success rates were highest for women with normal BMI (<25 kg/m^2) and aged less than 35 years. Our multiple pregnancy rate was 2% with a cancellation rate of 13%. Over 591 cycles there were no cases of OHSS (Langdon et al. 2017, personal communication).

With careful administration and monitoring of a low-dose step up protocol, FSH ovulation induction is more successful and not associated with any greater risk than clomiphene. Many units are moving towards using this method as a first line treatment for PCOS patients. It is worth noting that success rates seem to fall after 3 cycles and consideration should be given to attempting other forms of fertility treatment if pregnancy has not been achieved by this point.

8. Laparoscopic ovarian drilling

Laparoscopic ovarian drilling is a longstanding treatment for anovulation for women with PCOS. It is of value if performed at the time of diagnostic laparoscopy as part of a general infertility investigation after fallopian tube patency has been demonstrated and a normal semen assessment has been documented. It also offers rural patients the ability to undergo ovulation induction treatment without the requirement for frequent blood tests and ultrasound examinations. Laparoscopic ovarian drilling improves ovulation rates likely through destruction of theca cells in the ovary that produce androgens resulting in increased FSH levels and reduced LH levels conducive to normal follicular development. As a first line treatment, randomised trials have shown similar results for ovulation, conception and live birth rates when compared with up to 6 cycles of clomiphene [42] and has a likely ongoing success rate without the risk of multiple pregnancy from clomiphene.

Compared with gonadotrophins, similar rates of pregnancy and live birth rate were seen in a meta-analysis of randomised trials comparing the two methods but with far lower multiple pregnancies and no risk of OHSS [43]. Potential drawbacks of laparoscopic ovarian drilling

include the possibility of pelvic adhesion development and possible reduction in ovarian reserve. Studies looking at repeat laparoscopies following ovarian drilling procedures have shown adhesions in over 30% of patients treated with diathermy and 50% of patients treated with laser [44]. Reduced serum AMH concentrations, antral follicle counts, and ovarian volume as well as raised FSH levels following ovarian drilling support the notion that ovarian drilling has a possible negative impact on ovarian reserve.

9. In vitro fertilisation (IVF) and reducing OHSS rates

In vitro fertilisation (IVF) is usually reserved for women with PCOS who have failed other treatments or with additional issues compromising their fertility. Women with PCOS, as has been discussed previously, are especially at risk of developing OHSS when undergoing IVF, but as a consequence of this often respond very well to IVF stimulation producing many follicles and oocytes. It is a careful balance to ensure a patient responds well to FSH dosing, but not so well that they are at significant risk of OHSS. A patient with PCOS undergoing an IVF stimulation cycle needs to have a well monitored, individualised stimulation regime to reduce the risk of OHSS and minimise the chance of cycle cancellation. Her age, antral follicle count, anti-Mullerian hormone level (AMH) and BMI should all be considered when starting a cycle and planning the starting dose of FSH. Monitoring with transvaginal ultrasound and serum oestradiol concentrations should be very thorough with a low threshold for cancelling a cycle or employing other methods to reduce the risk of OHSS.

Other ways of avoiding OHSS in these high-risk patients is to routinely use GnRH antagonists rather than agonists to prevent the LH surge [45]. Two meta-analyses have shown lower rates of OHSS when GnRH antagonists are used compared to use of an agonist, but possibly at the cost of slightly reduced pregnancy rates as GnRH agonists generally result in enhanced follicle recruitment [46, 47].

Coasting can be a way to prevent cancellation of the cycle if oestrogen levels are rising too rapidly and there is concern the patient may be at risk of OHSS. Coasting involves withholding FSH therapy while continuing LH suppression with a GnRH agonist or antagonist. This is done until oestradiol levels fall to an acceptable level, if they do not a low threshold must be maintained to cancel the cycle. A review employing 3 days of coasting in the event of high oestradiol levels had minimal effect on pregnancy rates and importantly a low OHSS rate (<2%) [48]. If coasting occurred for longer than 3 days pregnancy rates were affected and thus the suggestion is made that after 3 days of coasting if oestradiol levels have not fallen, consideration of cycle cancellation is warranted.

There is growing evidence of the benefits of metformin use prior to IVF cycles in women with PCOS to reduce the risk of OHSS. Two meta-analyses have found similar results with a significant reduction in OHSS rates in patients pre-treated with metformin (OR 0.27, 95%CI 0.16–0.46 and OR 0.29, 95%CI 0.18–0.49) [49, 50], although metformin treatment was not shown to affect the live birth rate compared with placebo treatment in either study.

Selection of patients
IVF only in appropriately selected patients following unsuccessful ovulation induction or other specific fertility issues requiring treatment with IVF
Consideration of in vitro oocyte maturation in very high risk patients
Pre-treatment with Metformin and continue through IVF cycle
Cycle management
Well monitored, individualised stimulation regime
Low threshold for cycle cancellation
GnRH antagonist protocol
Consider cycle coasting for up to 3 days if concern high for OHSS
At time of trigger injection
Use an agonist trigger and adopt a "freeze-all embryos" approach to the cycle
Consideration of the use of a dopamine agonist to reduce OHSS risk
Luteal phase management
Continue ovarian down-regulation into the luteal phase if no embryo transfer is planned
Early consideration of adopting a "freeze-all" approach
If proceeding to a fresh embryo transfer: *the replacement of a single embryo*

Table 2. Methods for reduction of rates of OHSS in women with PCOS undergoing IVF.

In vitro oocyte maturation (IVM) is a new technique that eliminates the risk of OHSS [51] and is well suited to patients with PCOS due to their high antral follicle count. Immature oocytes are collected and matured in culture before undergoing either IVF or ICSI fertilisation techniques. It requires minimal amounts of stimulation prior to antral follicle collection eradicating the risk of OHSS and also reducing medication costs to the patient. Data suggests that the live birth rate may be reduced in comparison with standard IVF cycles, especially in fresh cycles, however for frozen embryo transfer cycles pregnancy, miscarriage and live birth rates are not significantly different [52].

It is imperative that clinicians who put women with PCOS through IVF stimulation cycles are vigilant for the development of OHSS in these patients and monitor and treat accordingly (**Table 2**).

10. Conclusion

PCOS is the most common cause of anovulatory infertility and thus is responsible for a large percentage of women seeking fertility treatment. When implementing a treatment plan for a patient with PCOS their metabolic health and weight are important factors that must be

addressed and managed prior to embarking on assisted reproductive techniques. The risks of OHSS and multi-follicular development in patients with PCOS means that care must be taken with close, careful monitoring to ensure mono-ovulation is achieved and the risks of multiple pregnancy and OHSS is kept to a minimum. If this approach is adopted the infertility treatment for these women is both safe and effective and patients should be reassured of these facts.

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