Management of infertility in the setting of polycystic ovary syndrome

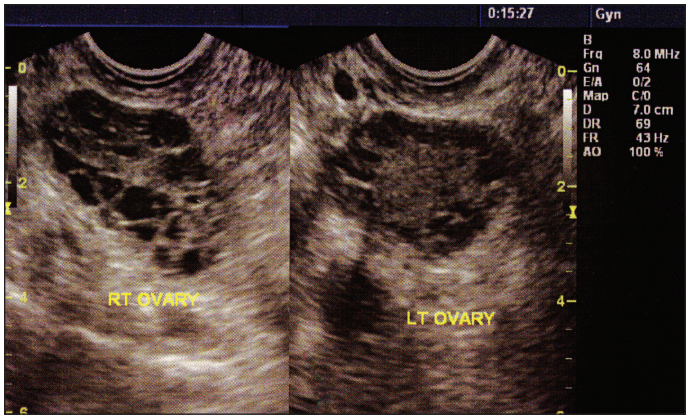
Sophia Wong
Fifth Year Medicine (Undergraduate)
University of New South Wales

Sophia is currently in her fifth year of medicine at the University of New South Wales. Her medical interests include cardiology and cardiothoracic surgery. She was the winner of the Ross Woodham Scholarship in 2006.

Polycystic ovary syndrome (PCOS) is a common endocrine disorder which affects a significant number of premenopausal women in Australia. PCOS has long-term clinical implications which can lead to decreased quality of life and psychological morbidity. A major contributing factor to this is the impact of PCOS on a woman's fertility. However, there are a number of treatment modalities that may be used to treat PCOS-related infertility and with appropriate treatment, a woman's prognosis with regards to PCOS-related infertility can be excellent.

Introduction

Polycystic ovary syndrome (PCOS) is a syndrome of ovarian dysfunction, hyperandrogenism and polycystic ovary morphology. [1] It is the commonest endocrine disorder among women of reproductive age and is thought to affect 5-10% of women in Australia. [2] Indigenous women are affected at a higher rate of 21%. [3] PCOS has significant reproductive implications for women including anovulatory infertility, miscarriage and pregnancy-related complications. [4] Furthermore, the state of unopposed oestrogen arising from chronic anovulation increases the risk of developing endometrial hyperplasia and cancer. [5] The exact pathophysiology of PCOS remains unknown but an underlying genetic predisposition has been suggested. Women with this predisposition are thought to go on to develop the condition in the presence of insulin resistance, which in turn can be related to the amount of adipose tissue present (Figure 1). [5]



A MEDLINE search was conducted using the key words "PCOS" and "infertility" to find the various treatment modalities currently used to treat PCOS-related infertility. The search was then restricted to English language, peer-reviewed, full text documents. The Cochrane Library was also searched using the search term "PCOS" and several articles were found following citations in other documents. This review summarises the current literature on treatment options for PCOS-related infertility, including lifestyle modification, medical therapy, laparoscopic ovarian drilling and in-vitro fertilization (IVF).

Lifestyle modification

Obesity is strongly associated with PCOS and affects 50% of PCOS

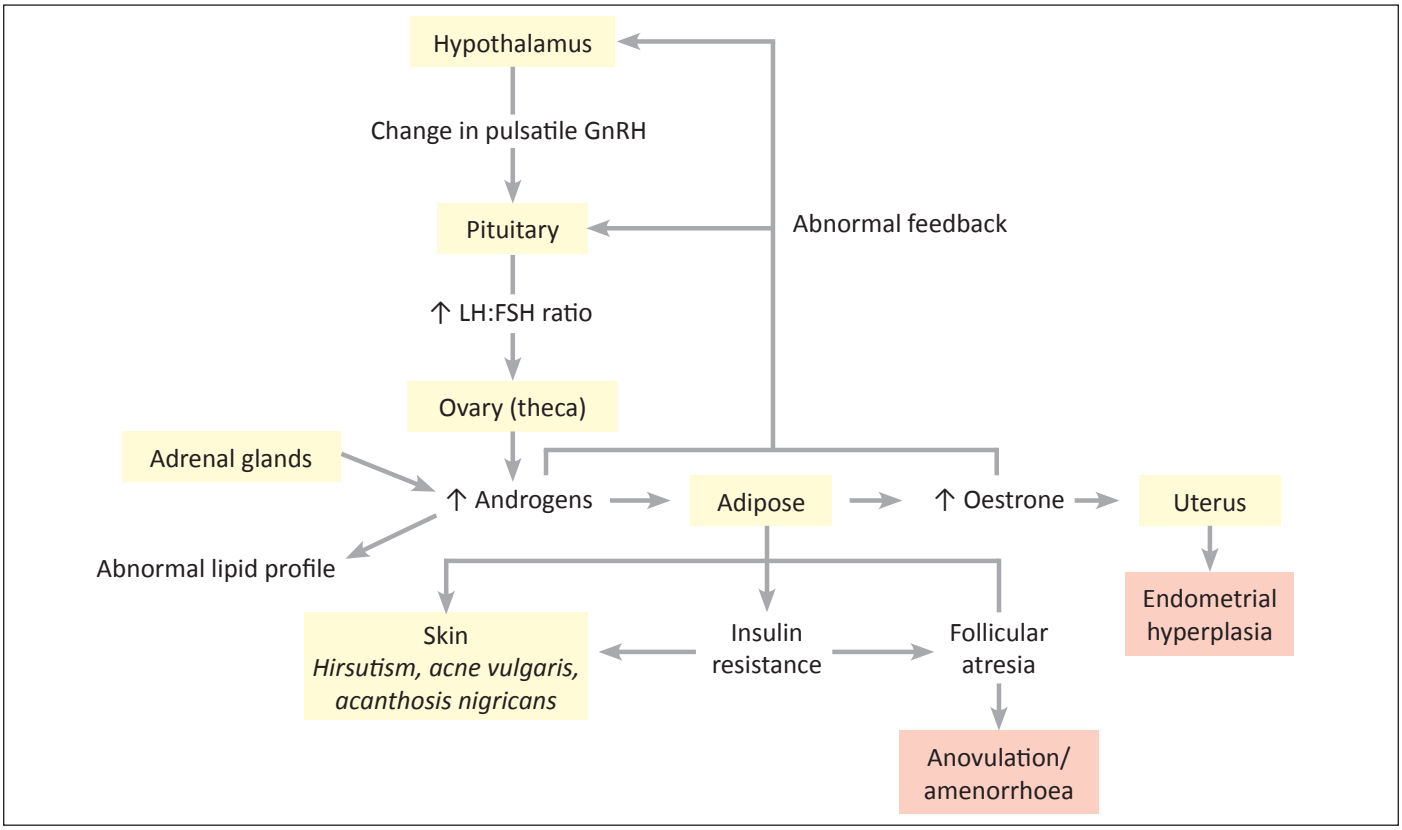


Figure 1. *The flow chart above details the suggested pathophysiology of polycystic ovary syndrome. Endocrine abnormalities are thought to occur at the level of the hypothalamus, pituitary and ovary. PCOS then manifests itself in the presence of insulin resistance due to the presence of excess adipose tissue. Insulin resistance contributes to anovulatory infertility and amenorrhoea in affected women.*

patients. There is now evidence showing that adipose tissue takes part in sex steroid metabolism and that central obesity impairs a woman's reproductive capabilities even in the absence of PCOS. [6] Obese PCOS patients are more likely to experience anovulation as compared to their thinner counterparts. [4,7]

The anovulatory effect is thought to be mediated by insulin resistance which in turn leads to hyperinsulinaemia and stimulation of excess androgen production in the ovaries. The high levels of androgens in the ovaries prevents maturation of ovarian follicles. [4,8] A combination of diet and exercise leading to weight reduction of even just 5-10% has proven effective in restoring menstrual and ovulatory cycles, thus allowing these women to achieve a pregnancy. [2,9] Furthermore, reduction in obesity improves the woman's response to other pharmacological ovulation induction methods. However, many obese women have reported difficulty in maintaining weight loss which may be a reflection of inherent metabolic disturbance in these patients. As such, PCOS patients are currently encouraged to aim for gradual weight reduction which increases the likelihood of maintaining the weight that is lost. [2]

In terms of specific dietary compositions, studies comparing high carbohydrate (55%), low protein (15%), hypocaloric diets and low carbohydrate (40%), high protein (30%), hypocaloric diets have shown similar weight loss and circulating androgen and insulin levels, thus suggesting that patients can follow either dietary composition. [10,11] Later studies have suggested that a high protein, low glycaemic index diet is effective for long-term weight reduction. [12] As a whole, the present consensus is that calorie restriction is essential but specific dietary recommendations still require more evidence. Regular exercise is also essential as it increases insulin sensitivity and resting metabolic rate, thus helping to both achieve and maintain weight loss. [6,13] Finally, other lifestyle factors such as smoking, alcohol intake and excessive caffeine consumption will also need to be addressed.

Medical therapy

Anti-oestrogen therapy

Anti-oestrogens such as clomiphene citrate (CC) are commonly used to induce ovulation. CC is thought to bind with and block oestrogen receptors in the hypothalamus, thus resulting in a perceived drop in the level of endogenous oestrogen. [14] This in turn triggers a rise in gonadotrophin secretion and subsequently, ovulation. In fact, CC has been the first-line agent for ovulation induction for over 40 years. CC has been shown to be six times more effective than a placebo at inducing ovulation and successfully does so in 50-70% of cases. [15,16] About half of these ovulations result in pregnancies and the disparity between the figures can be attributed to the anti-oestrogenic effect of CC on the endometrium and cervical mucus as well as by the resultant hypersecretion of luteinising hormone. [4,17]

Side effects of CC include a 6% chance of having a multiple pregnancy (2% background risk), vasomotor symptoms such as hot flushes and unusual visual disturbance and an increased risk of developing ovarian tumours if the patient is exposed to over twelve cycles in a lifetime. [2] There is also a small increase in the risk of developing Ovarian Hyperstimulation Syndrome (OHSS). [4] At present more evidence is needed to determine the length of treatment and effectiveness of anti-oestrogen therapy in assisted conception cycles. [18]

Gonadotrophins

Gonadotrophins (that is, follicle-stimulating hormone) are considered second-line therapy and are used when CC fails to achieve ovulation or a pregnancy. Gonadotrophins come in the form of daily injections and are particularly useful in controlled ovarian stimulation for assisted reproduction techniques. However, they are very potent and will stimulate multiple follicles simultaneously, thus increasing the risk of OHSS and multiple pregnancies. As such, ovarian response needs to be monitored using ultrasound and serum oestradiol measurements. Ultrasound monitoring alone has been shown to reduce the rate of multiple pregnancies and has a good predictive value for the development of OHSS. [18] In addition, a 'low-dose step-up' protocol has been established in fertility practice to minimise the risk of multiple pregnancies. [19]

Insulin sensitisers

Metformin is a commonly used treatment for type two diabetes mellitus. It suppresses hepatic gluconeogenesis, reduces gastrointestinal glucose absorption thereby enhancing weight loss and increases peripheral insulin sensitivity. [4] Given that insulin resistance and hyperinsulinaemia are important factors in the pathogenesis of PCOS, studies have sought to establish the role of metformin in treating infertility due to PCOS. However, studies comparing metformin with CC have been inconclusive due to the variability of their outcomes.

A randomised control trial (RCT) by Kashyap, Wells and Rosenwaks [20] concluded that metformin was beneficial for induction of ovulation and that addition of metformin to CC might increase rates of ovulation and pregnancy by three to four times. Other RCTs found the addition of metformin to CC to be of no benefit in achieving pregnancy. [21,22] Furthermore, metformin causes gastrointestinal intolerance in 40% of subjects and takes a substantially longer time to achieve a pregnancy when compared to CC. In view of this, some groups have recommended the use of metformin only as an adjunct and in women who have glucose intolerance, CC resistance or a high BMI. [18,23]

Aromatase inhibitors

Third-generation aromatase inhibitors (AI) such as anastrozole and letrozole block the conversion of testosterone and androstenedione to oestradiol and oestrone, thus augmenting pituitary feedback on gonadotrophin secretion. AIs may be used alone or in combination with CC or a gonadotrophin, in which case a lower dose of the latter is required. AIs have been found to be as successful as CC in generating follicles and achieving pregnancies and do not have the anti-oestrogenic effects observed in CC, such as endometrial thinning or cervical mucus changes. [24,25] However, some studies involving rats have raised questions about the safety of AIs in pregnancy as these studies found an increased incidence of cardiac and bone abnormalities in foetuses exposed to letrozole. [26] Therefore, until further research is conducted AIs should be used with caution and only after appropriate counselling due to the potential medico-legal implications of this medication.

Surgery

Laparoscopic ovarian drilling (LOD) is another second-line therapy. Ovarian drilling is thought to trigger resumption of menstrual cycles and ovulation by reducing ovarian theca cells and, by extension, serum androgens and luteinising hormone. [4] Since ovarian drilling has a similar efficacy to gonadotrophin therapy but has significantly less risk of inducing OHSS, the UK National Institute for Health and Clinical Excellence has advised that women resistant to CC should undergo ovarian drilling in order to avoid the risk of multiple pregnancy. [27,28] A recent RCT of five-, ten- or fifteen-puncture ovarian drilling concluded in favour of the fifteen-point puncture to each ovary in order to resume ovulation and pregnancy. However, current data only includes pregnancy rates and there is no data on live birth rates. Furthermore, as with any surgical procedure, there is a risk of complications such as adhesions, anaesthesia risks and other operative morbidities. The long-term effect of such aggressive ovarian insult has also not been established. [29]

In-vitro fertilisation

IVF tends to be reserved for women with PCOS who have failed to become pregnant following gonadotrophin therapy. [2] Women with PCOS who undergo IVF are seven times more likely to develop OHSS. One way of avoiding this is by inducing maturation in vitro after oocytes are collected from the unstimulated ovaries of a woman during a cycle. [30] Women with PCOS respond very well to ovarian stimulation and therefore tend to perform well in IVF cycles. [4]

Management of patients with clomiphene citrate-resistance

The current expert-based recommendation for first-line treatment of infertility due to PCOS is ovulation induction with CC for up to six ovulatory cycles, with the addition of metformin where there is glucose intolerance. [23] CC administration begins on day two or three and comprises a 50mg/day dose with increases of up to 150mg/day with each unsuccessful cycle. If ovulation still has not occurred at the maximum dose, the patient is considered 'clomiphene citrate-resistant' and alternative treatments will be introduced. Table 1 outlines the various traditional and alternative treatment regimes including dosing regimens where a general consensus has been found.

Metformin is the most commonly used adjunct to CC. Other adjuncts such as dexamethasone have been shown to have some benefits but are not commonly used in clinical practice and therefore have not been included in Table 1. [16,31] At present, AIs appear to be one of the more promising treatment alternatives to CC due to their efficacy in achieving ovulation and pregnancy as well as their lack of anti-oestrogenic side effects. However, more research is needed investigating the optimal dose required and the effect of AIs on the foetus.

Conclusion

In conclusion, the prognosis for women with PCOS-related infertility remains excellent due to the various treatment modalities that are currently available. However, there is still a significant level of inconsistency when the effectiveness of each therapeutic modality is evaluated. This inconsistency is partly due to the differences in definition of primary and secondary outcomes as well as the variety of settings in which various therapies are investigated. Furthermore, while most studies have used ovulation and pregnancy rates as the measurable outcome, only a few have actually included the most relevant primary outcome, live birth rates. Finally, more research is needed to determine the dosage regimes and long-term health consequences of the various treatment modalities. Clinicians should also take into account the costs and side effect profile when choosing a suitable treatment for women with infertility due to PCOS.

Conflict of interest

None declared.

Correspondence

S Wong: sophia_wong@hotmail.com

Table 1. *Outline of traditional and non-traditional therapeutic options for women with PCOS-related infertility, with dosing regimens included where there is general consensus on the treatment.*

Therapy	Dosing Regimen	Advantages/Disadvantages
Traditional Therapy		
First-line therapy Clomiphene citrate	Five days starting at day two or three of cycle. 50mg/day at first cycle, dose can be increased to 150mg/day over six cycles.	Very effective. High level of clinician familiarity. Has anti-oestrogenic effects which affect pregnancy rates.
Second-line therapy Gonadotrophin	Daily injection.	High risk of multiple pregnancies and OHSS. High level of monitoring required. Expensive.
Second-line therapy Laparoscopic ovarian drilling (LOD)	Four- to fifteen-puncture LOD followed by three months observation. In patients who are still anovulatory, three further cycles of CC may be considered.	General risks associated with surgical procedures. Cheaper than gonadotrophins. Increases ovarian response to gonadotrophins. Reduced risk of OHSS.
Alternative therapies		
Insulin-sensitising drugs Metformin	Metformin only	Metformin is approximately twenty times cheaper than LOD.
	Metformin or other insulin-sensitisers plus CC	Metformin plus CC may be even more effective than LOD in achieving ovulation and pregnancy.
	Metformin plus gonadotrophin	Some evidence of more orderly follicular growth, reduction in multifollicular development, reduced risk of OHSS.
	Metformin plus letrozole	Similar rates of ovulation, number of mature follicles and pregnancies to metformin plus CC. Significantly higher endometrial thickness and full-term pregnancies than metformin plus CC.
Aromatase inhibitors Letrozole	Five days starting from day three of cycle, 2.5mg/day letrozole. OR Single dose 20mg on day three of cycle.	Ovulation induction without anti-oestrogenic effects. May be embryotoxic. More evidence needed.
Clomiphene citrate combinations	Pre-treatments: Metformin	Thought to sensitise patients to CC. Two months of hypothalamic-pituitary-ovarian axis suppression followed by administration of CC has been shown to be even more effective at inducing ovulation and achieving pregnancy than CC alone.
	Combinations: CC + metformin	Improves insulin sensitivity and decreased hyperandrogenaemia.

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