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REVIEW

Ovulation induction in polycystic ovary syndrome

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Abstract

The objective of this narrative review was to suggest a rational order of treatment choices in anovulatory women with polycystic ovary syndrome (PCOS), for whom a multitude of treatment options exist. In obese/overweight women with PCOS the importance of weight reduction should be stressed. Inositol, a dietary supplement with a documented effect on ovulation and without adverse effects in the doses recommended, may be suggested. Additional first-line medical alternatives include insulin sensitizers, selective estrogen receptor modulators, and aromatase inhibitors. Of these, the aromatase inhibitor letrozole and the combination of clomiphene citrate and metformin have the highest rates of ovulation and live birth. Second-line treatments are ovarian electrocautery and low-dose follicle-stimulating hormone stimulation. Controlled ovarian stimulation with in vitro fertilization should be considered the last option as it carries a significant risk of ovarian hyperstimulation syndrome in patients with PCOS.

KEYWORDS

aromatase inhibitors, follicle-stimulating hormone, in vitro fertilization, inositol, metformin, polycystic ovary syndrome, selective estrogen modulators, surgery

1 | INTRODUCTION

Disorders of ovulation are common causes of infertility, and polycystic ovary syndrome (PCOS) is by far the most frequent condition. In the general population, PCOS has a prevalence of 5%-15% depending on the phenotype, ethnicity, and classification system used.[1] Several classification systems for PCOS exist, but the most commonly used is the Rotterdam criteria from 2003, where 2 out of 3 criteria are to be met: oligo/anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound examination.[2] Later, it was suggested to focus more on the sonographic appearance of the polycystic ovaries, particularly the number of antral follicles in each ovary and anti-Müllerian hormone (AMH).[3]

The association between hyperandrogenism and anovulation is complex. Women with PCOS often have an increased pulsatility of gonadotropin-releasing hormone (GnRH), resulting in increased pituitary release of luteinizing hormone (LH) and an elevated LH/follicle-stimulating hormone (FSH) ratio.[4] LH stimulates androgen synthesis by theca cells, while FSH stimulates aromatization of androgens to estrogen by granulosa cells, and follicle maturation. Intraovarian androgens stimulate the growth of preantral and early antral follicle stages, thereby promoting initial follicle recruitment, while elevated androgen levels induce atresia in later antral stages.[5] This pro-atretic effect of androgens commences when folliculogenesis switches from the gonadotropin-independent, initial phase to the FSH-dependent cyclic recruitment phase at a follicular diameter of approximately 2-5 mm.[6] In women with PCOS, the serum FSH levels are slightly lower than during the follicular phase, therefore aromatization of excessive androgens is insufficient and the follicles will not undergo the final FSH-dependent maturation, resulting in a dominant follicle.[7] Furthermore, granulosa cells in follicles from patients who are

Abbreviations: AMH, anti-Müllerian hormone; CC, clomiphene citrate; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; IVF, in vitro fertilization; LH, luteinizing hormone; LOD, laparoscopic ovarian diathermy; PCOS, polycystic ovary syndrome; SERM, selective estrogen receptor modulators.

anovulatory with PCOS synthesize AMH in concentrations several times higher than in ovulatory women and higher than in ovulatory women with polycystic-appearing ovaries; consequently the serum level of AMH is elevated in individuals with PCOS. AMH counteracts the FSH-driven aromatase complex activity, so high AMH levels will inhibit granulosa cell conversion of androgens to estrogens, and also have a detrimental effect on final follicular maturation.[8] Therefore, in women with PCOS, a large number of small antral follicles are present, as observed on ultrasound scan. However, these are not cysts according to a conventional understanding, so the name polycystic ovary syndrome is a misnomer.

Polycystic ovary syndrome is often associated with overweight/obesity. Obesity may result in insulin resistance and a compensatory hyperinsulinemia, which will exacerbate hyperandrogenism by stimulation of theca cell androgen synthesis.[9] In addition, adipose tissue produces leptin, which in animal studies has been found to have a synergistic effect on insulin-driven theca cell androgen synthesis and a direct effect on ovarian function.[10]

Mainstream treatments of PCOS-related anovulatory infertility therefore aim to tilt the balance of intraovarian steroid synthesis away from an LH-insulin-leptin-driven excessive androgen synthesis resulting in follicular atresia, toward FSH-driven final development of a dominant follicle. Many treatment options exist (Table 1).[11] In this paper the various possibilities are reviewed, with a suggested ranking of the various alternatives based on documented effects, simplicity, and adverse effects.

2 | MATERIAL AND METHODS

We performed a literature search in PubMed, MEDLINE, Embase, and the Cochrane Library through January 2018 using the keywords and MeSH terms polycystic ovary syndrome, hyperandrogenism, anovulation, infertility, obesity, antiestrogens, estrogen receptor modulators, clomiphene citrate, tamoxifen, aromatase inhibitors, letrozole, metformin, gonadotropins, inositol, ovarian wedge resection, ovarian electrocautery, and in vitro fertilization (IVF). We also searched relevant clinical guidelines. The search was restricted to sources in the English language. Preferably, randomized controlled trials and systematic reviews including randomized controlled trials and/or cohort studies were included.

TABLE 1 Ovulation induction treatments in polycystic ovary syndrome

Lifestyle intervention and weight reduction
Selective estrogen receptor modulators (clomiphene citrate, tamoxifen)
Metformin
Aromatase inhibitors (letrozole)
Inositol
Laparoscopic ovarian diathermy
Low dose follicle-stimulating hormone stimulation
Controlled ovarian stimulation and in vitro fertilization

KEY MESSAGE

Polycystic ovary syndrome is a common cause of anovulatory infertility and many treatment alternatives exist. We review the various treatment options and suggest a ranking of these based on simplicity, efficacy, and adverse effects.

3 | RESULTS

3.1 | Weight reduction and lifestyle change

As PCOS is often associated with obesity, concomitant insulin resistance, and hyperinsulinemia, weight reduction and lifestyle change are considered important in overweight women with PCOS with anovulatory infertility.[12] Weight reduction reduces hyperinsulinemia and insulin resistance, and increased physical activity increases insulin sensitivity.[13,14] This improves the hormonal imbalance in the ovary and reduces androgen dominance.[15] The effect of weight reduction on AMH levels is, however, equivocal.[16,17] In a systematic review (17 studies, 533 patients) the effect of a hypocaloric diet on ovulation in obese women with anovulatory PCOS was studied. The conclusion was that in most studies sporadic ovulation occurred after weight loss, and some patients had regular ovulations.[18] A steady decrease in weight seems to be more important than the actual amount of weight lost, and even moderate exercise without concomitant weight loss seems to improve ovulation rate.[19] Weight loss medication may have an additive effect, resulting in ovulation and conception.[20] Dramatic weight loss, such as seen after bariatric surgery, has a substantial effect on metabolic and endocrine disturbances in PCOS, and has in addition a beneficial effect on PCOS-related anovulatory infertility.[21] On the other hand, there is a risk for nutritional deficiencies after such surgery, and during pregnancy the risk of small-for-gestational-age offspring and possibly perinatal death are increased while the risk of gestational diabetes and large-for-gestational-age offspring decrease.[22]

3.2 | Inositol

Inositol is a naturally occurring sugar alcohol consisting of several stereoisomers serving among others as intracellular signaling molecules. Myo-inositol promotes glucose uptake and FSH activity, while D-chiro-inositol ameliorates insulin-stimulated androgen synthesis in the ovary. Both of these effects may positively affect the ovarian function in PCOS.[23] A number of studies have investigated possible clinical effects of inositol in PCOS, and in a systematic review including four randomized controlled trials and 100 patients, it was found that inositol treatment significantly increased the likelihood

of spontaneous ovulation compared with placebo (risk ratio 2.32, 95% CI 1.14-4.73).[24] Inositol is available as a nonprescription dietary supplement in health food stores. Doses used are for myo-inositol 2 g and for chiro-inositol 0.6 g both taken twice daily, and treatment duration is reported to be between 2 and 6 months. Adverse effects seem to be negligible and limited to mild abdominal discomfort, even with doses six times higher than usually described for myo-inositol.[25] Due to the insulin-sensitizing effect, myo-inositol supplementation during pregnancy has been shown to reduce the risk of gestational diabetes; however, no effect on fetal outcomes often associated with gestational diabetes, such as macrosomia, neonatal hypoglycemia and shoulder dystocia, have so far been found[26]

3.3 | Metformin

Metformin is an insulin sensitizer that lowers fasting levels of plasma insulin, C-peptide, and proinsulin-like molecules, increases binding of insulin to its receptor, increases peripheral utilization of glucose, and decreases hepatic glucose production. It also lowers theca cell androgen synthesis in vitro.[27] Metformin has a positive effect on metabolic disturbances and bleeding disorders in women with PCOS,[28] and has a significant ovulation stimulatory effect compared with placebo, the effect being either comparable to or slightly inferior to clomiphene.[29] Doses used are in the range of 1500-2500 mg per day divided into 2 or 3 doses. Patients must be informed that treatment with metformin may cause significant gastrointestinal adverse effects, especially at start-up, and treatment should last for several weeks. Another beneficial effect is that treatment with metformin before or during controlled ovarian stimulation for IVF in women with PCOS, has been shown to reduce the risk of subsequent ovarian hyperstimulation syndrome.[30]

3.4 | Selective estrogen receptor modulators

Clomiphene citrate (CC) is a selective estrogen receptor modulator (SERM) consisting of 2 isomers, zu- and en-clompihene, of which the former is the most biologically active one. Blocking the estrogen receptors at the level of the hypothalamus and the pituitary results in an increased output of gonadotropins from the anterior pituitary, thereby stimulating the final maturation of follicles.[31] Standard treatment for ovulation induction with CC in women with PCOS has been doses of 50-150 mg per day for 5 days starting on day 3-5 after the onset of a withdrawal bleeding. With increasing dose of CC, the probability of ovulation rises from approximately 45% to 90%, therefore a stair-step protocol to rapidly increase probability of ovulation has been suggested.[32,33] The multiple pregnancy rate is almost 10 times higher than in spontaneous conceptions, therefore monitoring with ultrasound to detect multifollicular development and to advise the couple when to have intercourse should be performed.[34] The antiestrogenic effect of CC may adversely affect the development of the endometrium, but the importance of this relative to implantation is uncertain.[35] In a recent meta-analysis, CC increased the odds of achieving clinical pregnancy compared with placebo, but the included studies were considered to be of low quality.[36] Transient side effects like hot flushes and blurred vision are common. Tamoxifen is another SERM and is chemically very similar to CC. Although its primary indication is in adjuvant treatment of breast cancer, it has also been used for ovulation induction. Ovulation and pregnancy rates appear to be comparable to CC.[37] As an ovulation induction agent, tamoxifen should, at least in theory, have an advantage over CC, because it does not seem to have the possible adverse effect on the endometrium as observed with CC. As a substitute for CC, tamoxifen may be used in doses of 20-40 mg and administered in the same way.[38]

3.5 | Aromatase inhibitors

Aromatase inhibitors prevent the conversion of androgens to estrogens. Low serum concentrations of estrogen inhibit negative feedback on the pituitary/hypothalamus and increase FSH secretion from the pituitary gland.[39] The aromatase inhibitor that has been most used for ovulation induction is letrozole, which is administered in much the same way as SERMs, 2.5-5 mg for 5 days after a withdrawal bleeding. Letrozole provides an ovulation rate per cycle of 70%-84% with a pregnancy rate of 20%-27%.[40] Although hot flushes may occur, these are infrequent due to the short half-life of letrozole.

A problem with the prescription of letrozole is that according to the manufacturer it is contraindicated in the treatment of premenopausal women. This label is a consequence of an abstract presentation at the annual meeting of the American Society for Reproductive Medicine in 2005, suggesting an increased risk of fetal cardiac and skeletal malformations, but no overall increase following ovulation induction with letrozole.[41] The study was of poor scientific quality and has never been published in full in a peer review journal. Subsequent studies on the use of letrozole for ovulation induction have not shown such increased risk of malformations,[42-44] although none of them have sufficient statistical power. Nonetheless, prescription of letrozole as an ovulation induction drug has been prohibited in some countries; therefore, treatment with letrozole requires that the patients are well informed.

3.6 | Gonadotropin stimulation

Low-dose FSH stimulation may be indicated in women who fail to ovulate upon treatment with SERM and/or aromatase inhibitor. Treatment requires experience with gonadotropin stimulation, careful follow up and the possibility of converting to IVF in case of multifollicular development. The usual starting dose is 50-75 IU for 2 weeks with an increase of 25-37.5 IU weekly in case of no response. If follicle development occurs, the same dose is maintained until follicle size reaches 18-20 mm, followed by induction of final follicular maturation with human chorionic gonadotropin or LH. In most patients, ovulation is achieved, but some cycles must be interrupted or converted to IVF because of multifollicular development.[45,46]

3.7 | Surgery

Surgery was the first treatment option for PCOS-related infertility. Wedge resection of the ovaries was a recognized intervention for many decades,[47] but due to fear of injury to the ovaries and pelvic adhesion formation, the procedure was gradually abandoned. A long-term follow up, however, proved it to be very effective.[48] Laparoscopic ovarian diathermy (LOD) is a further development of the wedge resection procedure and was introduced by Gjønnaess in the early 1980s.[49] A Cochrane review concluded that LOD was as effective as other treatment options in CC-resistant PCOS,[50] and long-term follow-up studies have shown that the method is cost-effective compared with other ovulation induction procedures and has a low risk of multiple pregnancies.[51,52] Although the effect of ovarian surgery for PCOS is not fully understood, a decrease in the levels of testosterone, androstenedione, estradiol, and LH has been shown, while FSH in some cases increases, possibly due to a reduced negative feedback from estradiol.[31,53] Follow ups on the effect of LOD on AMH levels have shown a significant decline after 6 months, but whether this is caused by damage to the ovaries or rather from a normalization of the endocrine dysfunction is currently unknown as there are no long-term follow-up studies.[54]

3.8 | In vitro fertilization

In treatment-resistant PCOS-related infertility, or when PCOS is seen in combination with tubal factor infertility or significantly reduced sperm quality, IVF may be the preferred treatment option. IVF in patients with PCOS produces as good results as in tubal factor infertility,[55,56] but the risk of developing ovarian hyperstimulation syndrome is significantly increased, even with the use of GnRH-antagonist protocols.[57,58]

4 | DISCUSSION

What is the relative efficacy of these treatment options and in which order should they be prescribed?

In overweight/obese women, weight loss and lifestyle change are the first treatment choices, and bariatric surgery can be considered in the case of extreme overweight. Inositol in the doses used does not seem to have any serious adverse effects and might be a low-threshold treatment option.

Among the drugs used for ovulation induction, the first choice since the 1960s has been CC. Previous studies on ovulation and pregnancy rates with tamoxifen and letrozole indicate success rates in the same range as CC; however, these are not approved for ovulation induction and must therefore be prescribed off-label. Metformin alone results in lower ovulation rates than the other drugs; however, it is a cheap drug, and if started with a low dose of 500 mg and increased weekly to a maximum dose of 1500 mg after 3 weeks, then the risk of gastrointestinal adverse effects is low. It can also be used in combination with inositol for some months because none of them requires monitoring during treatment. Metformin also seems to have a synergistic effect in combination with CC. Low-dose FSH stimulation and LOD are mostly used in CC-resistant PCOS.

Recently, a network meta-analysis was published comparing a variety of different treatment options for anovulatory infertility, World Health Organization group II, mostly PCOS (57 trials reporting on 8082 women).[59] Network meta-analyses evaluate the efficacy of different treatment alternatives against each other.[60] Compared with gonadotropin stimulation, treatment with letrozole or SERM + metformin resulted in similar live birth rates and the risk of multiple pregnancies was low (Table 2). Compared with ovulation induction with CC only, letrozole treatment resulted in higher ovulation, pregnancy, and live birth rates with a lower multiple pregnancy rate. This network meta-analysis only included 1 study on the effect of LOD, whereas in a previous Cochrane study comparing the effect of LOD against other ovulation-inducing treatments in PCOS, a total of 25 randomized controlled trials were included.[50] In the latter study, LOD had similar results with regard to clinical pregnancy rate and live birth rate (eight studies, 525 patients) in CC-resistant PCOS compared with other medical treatments. Although being a minimal invasive procedure, the complications are very few. There is no need for monitoring afterwards as the incidence of multiple pregnancy is the same as in spontaneous conceptions in ovulatory women, and there is no risk of ovarian hyperstimulation.

TABLE 2 Success rates (%) of various ovulation induction treatments compared with an imaginary best treatment[58]

Treatment type	Ovulation rate (%)	Pregnancy rate (%)	Live birth rate (%)	Multiple pregnancy rate (%)
CC	51	46	36	70
Metformin	26	50	30	14
CC + metformin	75	90	71	44
Letrozole	86	80	81	34
Tamoxifen	36	36	48	46
FSH	88	82	74	93
Electrocautery	39	22	—	—
Placebo	1	3	10	50

CC, clomiphene citrate; FSH, follicle-stimulating hormone.

Controlled ovarian stimulation with IVF should only be offered to women with PCOS if other treatments have failed or in the case of multifactorial infertility. The risk of excessive response to FSH stimulation and hence subsequent development of ovarian hyperstimulation syndrome is high. For all forms of ovarian stimulation with FSH in PCOS, follicular development must be carefully monitored by experienced staff, and strategies for handling an excessive response must exist.

5 | CONCLUSION

The treatment possibilities for anovulatory infertility in women with PCOS are many. Based on the success rate, complexity, and adverse effects of different treatment options, a suggestion in which order the various treatment options should be offered is: (i) lifestyle intervention and weight reduction in the obese, (ii) inositol and/or metformin for some months, (iii) ovulation induction with letrozole or SERM without or with the addition of metformin, (iv) LOD or low-dose FSH stimulation in case of SERM and/or letrozole resistance, and (v) IVF in case of combined infertility or resistance to other treatments.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

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