

Ovulation Induction in Polycystic Ovary Syndrome

This Clinical Practice Guideline has been prepared by the Reproductive Endocrinology and Infertility Committee and approved by Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To review current non-pharmacologic and pharmacologic options for ovulation induction in women with polycystic ovary syndrome (PCOS).

Key Words: Polycystic ovary syndrome, ovulation induction, infertility

Options: This guideline reviews the evidence for the various options for ovulation induction in PCOS.

Outcomes: Ovulation, pregnancy and live birth rates, risks, and side effects are the outcomes of interest.

Evidence: Published literature was retrieved through searches of Medline using appropriate controlled vocabulary and key words. Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. Grey (unpublished) literature was identified through searching the websites of health technology assessment and of health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The evidence gathered was reviewed and evaluated by the Reproductive Endocrinology and Infertility Committee of the Society of Obstetricians and Gynaecologists of Canada. The quality of evidence was quantified using the Canadian Task Force on Preventive Health Care.

Benefits, Harms, and Costs: Benefits include weight reduction and improvements in ovulation, pregnancy, and live birth rates. Potential harms include medication side effects and multiple pregnancies.

Validation: These guidelines have been reviewed and approved by the Reproductive Endocrinology and Infertility Committee of the SOGC.

Sponsor: The Society of Obstetricians and Gynaecologists of Canada.

Recommendations

1. Weight loss, exercise, and lifestyle modifications have been proven effective in restoring ovulatory cycles and achieving pregnancy in overweight women with PCOS and should be the first-line option for these women. (I-3A) Morbidly obese women should seek expert advice about pregnancy risk. (III-A)
2. Clomiphene citrate has been proven effective in ovulation induction for women with PCOS and should be considered the first-line therapy. Patients should be informed that there is an increased risk of multiple pregnancy with ovulation induction using clomiphene citrate. (I-A)
3. Metformin combined with clomiphene citrate may increase ovulation rates and pregnancy rates but does not significantly improve the live birth rate over that of clomiphene citrate alone. (I-A) Metformin may be added to clomiphene citrate in women with clomiphene resistance who are older and who have visceral obesity. (I-A)
4. Gonadotropin should be considered second-line therapy for fertility in anovulatory women with PCOS. The treatment requires ultrasound and laboratory monitoring. High costs and the risk of multiple pregnancy and ovarian hyperstimulation syndrome are drawbacks of the treatment. (II-2A)

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Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.⁶⁹

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.⁶⁹

- 5. Laparoscopic ovarian drilling may be considered in women with clomiphene-resistant PCOS, particularly when there are other indications for laparoscopy. (I-A) Surgical risks need to be considered in these patients. (III-A)
- 6. In vitro fertilization should be reserved for women with PCOS who fail gonadotropin therapy or who have other indications for IVF treatment. (II-2A)

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INTRODUCTION

Polycystic ovary syndrome is a heterogeneous endocrine condition that affects approximately 5% to 10% of women in the reproductive age group.^{1–3} Depending on the population being examined, however, prevalence rates as high as 26% have been reported.⁴ Although debate on what constitutes PCOS continues, the Rotterdam Consensus on Diagnostic Criteria for PCOS published in 2003 is the most current definition. According to this consensus, a diagnosis of PCOS is based on at least 2 of the following 3 criteria:

oligo-ovulation or anovulation, clinical or biochemical evidence of hyperandrogenism, and polycystic ovaries on ultrasound assessment (> 12 small antral follicles in an ovary), with the exclusion of medical conditions such as congenital adrenal hyperplasia, androgen-secreting tumours, or Cushing’s syndrome.⁵

Patients who fulfill these criteria are often plagued by infertility secondary to both ovulatory dysfunction and the effects of hyperandrogenism. Several methods have been effective for ovulation induction and fertility treatment in women with PCOS:

- Weight loss, exercise, and lifestyle modifications
- Clomiphene citrate
- Metformin
- Gonadotropins
- Ovarian drilling
- IVF

This guideline addresses the sequential steps that should be undertaken, as well as the pregnancy rates, risks, and benefits of each method.

ABBREVIATIONS

- CC clomiphene citrate
- FSH follicle stimulating hormone
- hCG human chorionic gonadotropin
- LH luteinizing hormone
- LOD laparoscopic ovarian drilling
- PCOS polycystic ovary syndrome

WEIGHT LOSS AND LIFESTYLE MODIFICATIONS

Obesity is strongly associated with PCOS and may be present in up to 50% of cases.^{6–10} Obese women with PCOS are more likely than thin women with PCOS to suffer from anovulation.⁶ This effect on ovulation may be secondary to insulin resistance, which in turn results in hyperinsulinemia and stimulation of excess androgen production from the

ovaries. Intraovarian hyperandrogenism in turn inhibits follicular maturation.¹⁰

Weight loss through exercise and diet has been proven effective in restoring ovulatory cycles and achieving pregnancy for many of these patients.^{11–13} In obese, anovulatory women with PCOS, weight loss of even 5% to 10% of body weight often restores ovulatory cycles.^{7,9,14,15} Studies also show that overweight women are less likely to respond to pharmacologic ovulation induction methods.^{7,16}

Obese women often report difficulty in achieving and maintaining weight loss. The extent to which their obesity reflects an inherent metabolic disturbance, making it more challenging for them to lose weight, remains a question. The current recommendation is to reduce weight gradually to increase the chances of maintaining the weight loss. Preferential diet composition has been evaluated in 2 small studies.^{17,18} These studies compared a high carbohydrate (55%), low protein (15%) hypocaloric diet with a low carbohydrate (40%), high protein (30%) hypocaloric diet and found similar weight loss and decrease in circulating androgen and insulin levels. Although the patient sample size was small, these 2 studies suggest that patients can safely pursue either dietary composition, despite the need for larger confirmatory studies.

Routine exercise is also very important in the reproductive health of women with PCOS. Exercise increases insulin sensitivity and helps achieve and maintain weight loss.¹⁹ Other lifestyle factors such as excessive caffeine intake, alcohol consumption, and smoking should also be addressed.⁸

Once patients have achieved weight loss, they should be encouraged to maintain this in the long term and to have normal weight gain during pregnancy. Obesity contributes to poor obstetric outcome (increased risk of spontaneous abortion and preterm labour) and also increases maternal complications, including gestational hypertension, gestational diabetes mellitus, thromboembolism, and wound infection.⁶ Long-term lifestyle modifications can decrease predisposition to health conditions such as type 2 diabetes mellitus and modify risk factors for cardiovascular disease.⁸

Recommendation

1. Weight loss, exercise, and lifestyle modifications have been proven effective in restoring ovulatory cycles and achieving pregnancy in overweight women with PCOS and should be the first-line option for these women. (II-3A) Morbidly obese women should seek expert advice about pregnancy risk. (III-A)

CLOMIPHENE CITRATE

Clomiphene citrate has been used as a first-line ovulation induction agent for over 40 years.^{20,21} It is a selective estrogen

receptor modulator that stimulates endogenous FSH production and secretion by interrupting estrogen feedback to the hypothalamus and pituitary. PCOS patients can be sensitive to ovulation induction medications because of a large number of antral follicles. This places some women with PCOS at risk of overresponse with multiple follicular development and ovarian hyperstimulation; however, other women have a poor response without development of a dominant follicle, despite using higher doses of CC.

The starting dose of clomiphene citrate is 50 mg per day for 5 days, commencing between day 2 and 5 of menses.²² Menses may be induced with a progestin if required. If this dose produces multiple follicular development, the dose can be lowered to 25 mg. If ovulation is not achieved using 50 mg per day, the dose can be increased in increments of 50 mg. The manufacturer does not recommend exceeding 100 mg per day²³; however, many clinicians use doses up to 150 mg and some even up to 250 mg per day for 5 days,²⁴ taking into account that alternative treatments such as gonadotropins are more costly and have greater risk (see below).

Cycle monitoring should be considered in at least the first cycle and when the treatment dose has to be increased because of failure to ovulate. Common indications of an ovulatory response are a biphasic pattern on basal body temperature charting and a serum progesterone measurement in the expected luteal phase of > 10 nmol/L if tested 6 to 8 days before the onset of menses.²⁵ However, in some circumstances, detection of the pre-ovulatory LH surge with urinary kits, and ovarian follicle and endometrial assessment with transvaginal ultrasound during the late follicular phase can be useful.

If ovulation cannot be achieved with CC, the patient should be offered further options.

Although 60% to 85% of patients will ovulate on CC, only about one half will conceive.^{26,27} Approximately 50% of conceptions will occur on 50 mg, with another 20% to 25% and 10% occurring on 100 mg and 150 mg, respectively.^{15,28} Lack of conception despite evidence of ovulation may be due to anti-estrogenic effects of CC on the endometrium, which may manifest as a thin endometrium on ultrasound.²⁹ In one study, no pregnancies occurred when the endometrium was < 6 mm at midcycle,³⁰ but others have not found a similar association.³¹ Nevertheless, alternatives for ovulation induction should be considered if the periovulatory endometrium is persistently thin on CC therapy. Similarly, if pregnancy does not occur within 6 ovulatory cycles, another ovulation induction method should be considered.

Other drawbacks of CC include an increased rate of twin (7% to 9%) and triplet (0.3%) pregnancy, and side effects such as vasomotor hot flashes.³² Unusual visual symptoms (visual blurring or persistent after-images) are also noted in

1% to 2% of patients taking CC, which are likely due to anti-estrogenic effects of CC on the visual cortex.³³ Although more studies are required, it is best to limit a patient's lifetime exposure to CC to 12 treatment cycles, as additional cycles may place the patient at increased risk of borderline ovarian tumours.³⁴

Recommendation

2. Clomiphene citrate has been proven effective in ovulation induction for women with PCOS and should be considered the first-line therapy. Patients should be informed that there is an increased risk of multiple pregnancy with ovulation induction using clomiphene citrate. (I-A)

INSULIN SENSITIZING AGENTS

The recognition of an association between PCOS and hyperinsulinemia has led to the use of insulin-sensitizing agents in ovulation induction. Metformin, the most widely studied agent used in PCOS, is a biguanide insulin-sensitizing agent that acts by inhibiting hepatic glucose production and increasing peripheral glucose uptake.³⁵ It does not stimulate secretion of insulin or cause hypoglycemia.

Many earlier studies examining the use of metformin alone or in conjunction with CC in ovulation induction showed promising results,^{36–42} but most of these studies had relatively small sample sizes. A meta-analysis of 13 randomized controlled trials by Lord et al.⁴³ in 2003 concluded that metformin is effective in achieving ovulation in women with PCOS, with odds ratios of 3.88 (95% CI 2.25 to 6.69) for metformin compared with placebo and 4.41 (95% CI 2.37 to 8.22) for metformin and CC compared with CC alone. Pregnancy rates were not significantly better with metformin than with placebo (OR 2.76; 95% CI 0.85 to 8.98), but an improvement was seen with metformin plus CC over CC alone (OR 4.4; CI 1.96 to 9.85).⁴³

A more recent meta-analysis published in April 2008⁴⁴ comparing CC and metformin, both alone and in combination, found that metformin alone increased the odds of ovulation compared with placebo (OR 2.94; 95% CI 1.43 to 6.02) but did not result in a statistically significant difference in pregnancy rates (OR 1.56; 95% CI 0.74 to 3.33). When CC and metformin were compared with CC alone, both ovulation and pregnancy rates were statistically increased to 4.39 (95% CI 1.94 to 9.96) and 2.67 (95% CI 1.45 to 4.94), respectively.

This meta-analysis also included studies that reported live birth rates. Ng et al.⁴⁵ in 2001 compared metformin and placebo in 20 women and found that women who received metformin were less likely to achieve a live birth, although this difference did not reach statistical significance (OR 0.44; 95% CI 0.03 to 5.88). Four of the included trials examined

live birth rates with CC and metformin versus CC alone.^{41,46–48} Collectively, the combination of CC and metformin suggested an increase in live birth rate over CC alone, but this increase was not statistically significant (OR 1.74; 95% CI 0.79 to 3.86). The only trial adequately powered to assess live birth rates was the large randomized-controlled trial published by Legro et al. in 2007.⁴⁶ This trial included 626 patients and demonstrated that although the live birth rate following up to 6 months of treatment with metformin and CC was increased (26.8%), it was not significantly different from that with CC alone (22.5%). Live birth rates using CC alone or with metformin were significantly higher than rates with metformin alone (7.2%).

The evidence supports the use of clomiphene citrate over metformin as first-line pharmacologic therapy following lifestyle modification in women with PCOS. However, there may be a role for the addition of metformin to CC in women who are clomiphene-resistant. Siebert et al.⁴⁹ examined 6 trials in which metformin was randomized with either placebo or CC in clomiphene-resistant patients and found an overall statistically significant improvement in ovulation with combination therapy (OR 6.82; 95% CI 3.59 to 12.96). Further, a recent study also suggested that women with PCOS who are older and have increased visceral obesity may benefit from the additional use of metformin.⁵⁰

Patients on metformin often experience unpleasant side effects of nausea, bloating, cramps, and diarrhea, and they should be counselled to start with 250 mg to 500 mg PO daily and increase as tolerated to the optimal daily dose of 500 mg to 750 mg 3 times daily with food. Metformin can also be dosed 850 mg PO twice daily or a long-acting formulation (Glumetza) can be used to improve compliance.

Although some studies have shown that continuing metformin in pregnancy may decrease the spontaneous abortion rate,^{42,51–53} none of these are prospective, randomized trials. Randomized controlled trials are needed in this area before sustained metformin treatment throughout pregnancy can be recommended.

Recommendation

3. Metformin combined with clomiphene citrate may increase ovulation rates and pregnancy rates but does not significantly improve the live birth rate over that of clomiphene citrate alone. (I-A) Metformin may be added to clomiphene citrate in women with clomiphene resistance who are older and who have visceral obesity. (I-A)

GONADOTROPINS

Use of intramuscular gonadotropins began in the 1960s. These preparations, from the purified urine of postmenopausal women, contained both FSH and LH.

Over the last decade, recombinant human FSH has been the main preparation, and it can be self-administered subcutaneously.⁵⁴ Gonadotropins are used when PCOS patients fail either to ovulate or to conceive with oral ovulation inducing medications.

Daily injections of gonadotropins are combined with concurrent blood and ultrasound monitoring with the aim of monofollicular growth and development. However, because of the inherent nature of exogenous gonadotropin treatment, multifollicular development is not uncommon, despite careful dose adjustment and monitoring. Once the dominant follicle has reached the appropriate size, hCG is administered to trigger ovulation.

Injectable gonadotropins are very expensive and require frequent monitoring, with serum estradiol and ultrasound assessments to minimize the risks from excessive follicular growth and development. Because of the high number of antral follicles in women with PCOS, it is not uncommon that treatment is cancelled to minimize the occurrence of multiple pregnancy and also of ovarian hyperstimulation syndrome.⁵⁵ Pregnancy rates with gonadotropins are 20% to 25% per cycle.⁵⁴ Drawbacks to gonadotropin treatment, as mentioned earlier, are requirements for intensive monitoring, cost, multiple pregnancy, and ovarian hyperstimulation. Gonadotropins should be administered by physicians with specific training in reproductive medicine and with ready access to ultrasound monitoring and rapid hormone testing.

Recommendation

4. Gonadotropin should be considered second-line therapy for fertility in anovulatory women with PCOS. The treatment requires ultrasound and laboratory monitoring. High costs and the risk of multiple pregnancy and ovarian hyperstimulation syndrome are drawbacks of the treatment. (II-2A)

OVARIAN DRILLING

Surgical ovarian wedge resection by open laparotomy was one of the first treatments for anovulation due to PCOS.⁵⁶ It was thought to induce ovulation by decreasing the ovarian theca and thus reducing androgen production. Because of the operative morbidity of the procedure and the risk of postoperative adhesions,⁵⁷ ovarian wedge resection by laparotomy has largely been abandoned as more effective medical therapies for ovulation induction have become available. With the popularity of minimally invasive surgery, laparoscopic ovarian drilling is thought to be less destructive to the ovary and has a lower risk of adhesion formation. Laparoscopic ovarian drilling uses either cautery or laser to create approximately 10 superficial perforations per ovary.⁵⁸

A Cochrane review published in 2007 examined 16 randomized controlled trials evaluating ovulation induction in clomiphene-resistant PCOS with LOD. The dose at which clomiphene resistance was defined ranged from 100 mg to 200 mg in the various studies. Approximately 80% of PCOS patients will become ovulatory after LOD. There was no difference found in the rates of miscarriage, ongoing pregnancy, or live birth between patients who underwent LOD and patients treated with gonadotropins for ovulation induction. There were significantly fewer multiple pregnancies in the LOD than in the gonadotropin treatment groups (1% vs. 16%; OR 0.13; 95% CI 0.03 to 0.59).⁵⁸ In one of the included trials, adjuvant therapy with CC or gonadotropins was required to achieve equivalent pregnancy and live birth rates in patients remaining anovulatory 8 weeks after LOD or those who subsequently became anovulatory.⁵⁹

Despite this evidence that LOD may be equivalent to gonadotropins in achieving ovulation, the effects of LOD on postoperative adhesion formation remain a concern,⁶⁰ although it has been shown that in women who respond to this treatment, the rate of cessation of ovulation is low.⁶¹

Recommendation

5. Laparoscopic ovarian drilling may be considered in women with clomiphene-resistant PCOS, particularly when there are other indications for laparoscopy. (I-A)
Surgical risks need to be considered in these patients. (III-A)

AROMATASE INHIBITORS

Aromatase inhibitors have been used for the last decade as adjunctive treatments in breast cancer.⁶² They block the conversion of testosterone and androstenedione to estradiol and estrone, respectively, and hence inhibit the estrogen-negative feedback on the hypothalamic-pituitary axis. This leads to increased gonadotropin secretion, which in turn leads to ovarian follicular growth and development.⁶²

The use of aromatase inhibitors in ovulation induction was first introduced in 2001.⁶³ Ovulation and pregnancy rates with aromatase inhibitors such as letrozole and anastrozole appear to be promising, and these agents appear to have less anti-estrogen effect on the endometrium, but the evidence on endometrial effects is conflicting, and most studies show equivalence with clomiphene citrate.⁶²⁻⁶⁵ In 2005, however, Health Canada and the manufacturing company of letrozole issued a "Physician Warning Letter" on the off-label use of letrozole for fertility and the possibility of embryotoxicity, fetotoxicity, and teratogenicity found in rats.⁶⁶ This followed preliminary research findings by Biljan et al.⁶⁷ comparing congenital malformations in babies conceived with letrozole with or without gonadotropins with those in babies born to a low-risk population of women

without known fertility treatments. These findings reported a higher incidence of both cardiac and bone abnormalities in the letrozole group.⁶⁷ More recently, however, Tulandi et al.⁶⁸ retrospectively evaluated 911 newborns from letrozole and CC pregnancies. They found a 2.4% incidence of congenital malformations and chromosomal abnormalities in the letrozole group versus 4.8% in the CC group.⁶⁸ However, until aromatase inhibitors have been approved for ovulation induction by Health Canada, they should be used with caution, and patients should be carefully counselled, given potential medico-legal implications.

IN VITRO FERTILIZATION

IVF, with or without intracytoplasmic sperm injection, is the next treatment option for women with PCOS who fail to conceive with gonadotropin treatment or in the presence of other indications for advanced reproductive technologies. In IVF, gonadotropins are administered to achieve multifollicular development for oocyte retrieval and generation of embryos for transfer into the uterus. Pregnancy rates can approach 40% to 50% per cycle with IVF, but, as with fertility in general, success is significantly influenced by the women's age.⁵⁴ PCOS patients achieve pregnancy and live birth rates similar to those of non-PCOS patients during conventional IVF cycles. Side effects include multiple pregnancy when multiple embryos are transferred, and a higher risk of ovarian hyperstimulation; however, the risk of multiple pregnancy is more easily controlled with IVF than with ovulation induction with gonadotropins, because the number of embryos transferred into the patient's uterus can be limited and surplus good quality embryos cryopreserved for future transfer.

Recommendation

6. In vitro fertilization should be reserved for women with PCOS who fail gonadotropin therapy or who have other indications for IVF treatment. (II-2A)

SUMMARY

Patients with polycystic ovary syndrome commonly present with a history of infertility due to oligo-ovulation or anovulation. First-line management of infertility should always include weight loss and exercise and lifestyle modifications in the overweight patient. This is beneficial in the patient's overall health, it may lead to spontaneous ovulation, and it will improve response to ovulation-induction medications. Clomiphene citrate has been used for many years and remains the first-line medication despite potential anti-estrogenic effects on the endometrium and cervical mucous. Recent evidence indicates that insulin-sensitizing agents should not be used as a first-line therapy, although they may be beneficial in PCOS patients who are older and

who have increased visceral obesity as assessed by increased waist-to-hip ratios, and in those who have failed to ovulate on clomiphene citrate alone. Laparoscopic ovarian drilling should be considered in women who are resistant to clomiphene citrate because of the lower risk of multifetal gestation compared with gonadotropin therapy. Further trials are needed in the area of aromatase inhibitors if they are to be used routinely for ovulation induction.

Clinicians should always consider a patient's age and duration of infertility as they progress through the different treatment options available. If a patient does not become pregnant in a timely manner, referral to a fertility clinic and appropriate uses of gonadotropins and IVF are effective options.

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