Treatment of infertility in women with polycystic ovary syndrome

Traitement de l’infertilité chez les femmes souffrant d’un syndrome des ovaires polykystiques

P. Bouchard
Endocrinology, Hôpital Saint-Antoine, 184, rue du Faubourg-Saint-Antoine, 75012 Paris, France
Available online 14 April 2010

Résumé
Le traitement de l’infertilité dans le syndrome des ovaires polykystiques (SOPK) associe des modifications du style de vie et l’utilisation de médicaments inducteurs de l’ovulation. Dans cet objectif, le citrate de clomifène (CC) doit être utilisé en première intention, suivi si nécessaire par de faibles doses de gonadotrophines en seconde ligne. Dans de rares cas, en cas d’échec du CC, un « drilling » ovarien, i.e. une chirurgie laparoscopique ovarienne, ou enfin une technique de procréation médicalement assistée peut être utilisée. Finalement, l’induction d’ovulation (représentée par le CC et les gonadotrophines) s’avère très efficace avec un taux cumulé de naissances vivantes uniques de 72 %. L’usage d’insulino-sensibilisateurs c’est-à-dire de metformine dans le SOPK doit être réservé aux femmes présentant une intolérance au glucose et/ou une résistance à l’insuline. Compétu-tenu des récents travaux, l’utilisation en routine de ce médicament de façon isolée pour induire une ovulation n’est pas recommandée.

Mots clés : Infertilité ; Syndrome des ovaires polykystiques ; Citrate de clomifène ; Gonadotrophines ; Drilling ovarien ; Technique de reproduction médicalement assistée ; Metformine

Abstract
The treatment of infertility in polycystic ovary syndrome (PCOS) associates lifestyle measures, and the use of drugs to induce ovulation. In this endeavour, clomifene citrate (CC) should be used as the first line of treatment, followed eventually by low dose gonadotrophin stimulation, as a second line. In rare cases, in case of failure of the CC treatment, ovarian drilling i.e. laparoscopic ovarian surgery (LOS), and finally assisted reproduction techniques can be used, if needed. Overall, ovulation induction (representing the CC–gonadotrophin paradigm) is highly effective with a cumulative singleton live birth rate of 72%. The use of insulin sensitizers i.e. metformin in PCOS should be restricted to women with glucose intolerance and/or insulin resistance. Based on recent data available, the routine use of this drug, alone, in ovulation induction is not recommended.

Keywords: Infertility; Polycystic ovary syndrome; Clomifene citrate; Gonadotrophin; Ovarian drilling; Assisted reproduction techniques; Metformin

Polycystic ovary syndrome is a frequent pathology, which presents as a complex genetic disease, associating a strong familial link, and a modulating role of the environment, in particular of body weight excess. Excess body weight is associated with variable degree of insulin resistance, which influences androgen secretion and the clinical phenotype. It is generally accepted that 5–10% of all women are attained.

This enigmatic syndrome associates dysovulation with oligomenorrhea, hyperandrogenism, and multifollicular development on ovary US scans. According to the Rotterdam Consensus Conference (2003), two of these criteria suffice to characterize the syndrome.

The treatment of infertility associates lifestyle measures, and the use of drugs to induce ovulation [1–3]. In this endeavour, clomifene citrate (CC) should be used as the first line of treatment, followed eventually by low dose gonadotrophin stimulation, as a second line. In rare cases, in case of failure of the CC treatment, ovarian drilling i.e. laparoscopic ovarian surgery (LOS), and finally assisted reproduction techniques can be used, if needed.

Overall, ovulation induction (representing the CC–gonadotrophin paradigm) is highly effective with a cumulative singleton live birth rate of 72%.
The use of insulin sensitizers i.e. metformin in PCOS should be restricted to women with glucose intolerance and/or insulin resistance. Based on recent data available, the routine use of this drug, alone, in ovulation induction is not recommended. Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction. These products are still not approved by drug agencies.

It is noteworthy that once pregnant, women with PCOS are exposed to a high risk of miscarriage, although the mechanisms of these pregnancy interruptions remain poorly understood and may reflect abnormal oocyte development. In addition, complications of pregnancy such as preeclampsia and gestational diabetes can be observed, and women should be carefully informed of these risks and of the need of a strict surveillance of their pregnancy.

1. Lifestyles measures

The treatment of obesity is always mandatory in case of PCOS with excess weight [4–6]. Treatment associates behavioural counselling, lifestyle therapy (diet and exercise), pharmacological treatment, and eventually bariatric surgery. A reduction of 5% of body weight is generally recommended. Although we lack proofs of its efficacy in terms of live birth rate, there is a general agreement that weight reduction is of paramount importance to improve ovulation rate, efficacy of drugs used in ovulation induction, and to reduce the pregnancy complications linked to obesity.

2. Insulin sensitizers

Glitazones are very potent insulin sensitizers; however they cannot be used in women seeking pregnancy because of potential adverse effects since PPARγ, the nuclear receptors to which they bind plays a crucial role during development.

Metformin use in PCOS should be restricted to women with glucose intolerance. However, in terms of induction of ovulation, although many studies have been performed, results remain uncertain, and women should not be treated by metformin alone for more than a few months [6–11]. Randomized controlled trials have been unable to demonstrate a uniform efficacy of metformine in ovulation induction and improvement of pregnancy rate. Further, the risk of spontaneous abortion is not improved by metformin use [12].

3. Clomifene citrate

CC use is the first line of ovulation induction therapy [6]. The starting dose of CC should be 50 mg/day, for five or six days, starting on Day 2 of the cycle, following a spontaneous or progestin-induced withdrawal bleeding. The recommended maximum dose is 100–150 mg/day, as there is no clear evidence of efficacy at higher doses. It is prudent to monitor the first cycle with ovary US scan in order to allow adjustment of the dose in subsequent cycles. A pretreatment ultrasound is also needed. Finally progesterone measurements to demonstrate ovulation are also recommended. There is no evidence that administration of human chorionic gonadotrophin (hCG) in mid-cycle improves the chances of conception.

Approximately, 75–80% of patients with PCOS will ovulate after CC [6]. Although there appears to be discrepancy between ovulation and pregnancy rates, a conception rate of up to 22% per cycle is widely accepted in those ovulating on CC. A maximum of six cycles is generally proposed, with a cumulative pregnancy rate of 50–60%. A normal body weight remains the main prognosis criterion for success.

4. Gonadotrophin therapy (FSH)

In case of anovulation with CC, treatment with gonadotrophin should be used [6,13]. The data available support the use of low dose regimens starting with 50 IU per day. In order to avoid ovarian hyperstimulation, and multiple pregnancies, cycle cancellation is advised when more than three follicles of 16 mm or larger were observed. It would seem prudent to withhold hCG administration in the presence of more than two follicles > 16 mm or more than one follicle > 16 mm and two additional follicles > 14 mm, in order to minimize the risk of multiple pregnancies in women with PCOS under the age of 38 without any other infertility factors.

Low-dose regimens result in a monofollicular ovulation rate of 70%, a pregnancy rate of 20% and a multiple live birth rate of 5.7%. The major complication of ovulation induction is the occurrence of a 10% multiple pregnancy rate unless a strict low dose regimen is used.

5. Laparoscopic ovarian surgery (LOS)

Surgical approaches to ovulation induction have developed from the traditional wedge resection [4,6,13,14]. Multiple ovarian puncture performed either by diathermy or by laser is known as “ovarian drilling”.

The main indication for LOS is CC resistance in women with anovulatory PCOS. As few as four punctures have been shown to be effective. LOS can achieve monofollicular ovulation with no risk of OHSS or multiple pregnancies.

Intensive monitoring of follicular development is not required after LOS.

LOS is an alternative to gonadotrophin therapy for CC-resistant anovulatory PCOS.

Another potential advantage is the lack of need for US surveillance unless additional treatment (CC or FSH) is associated.

6. Assisted reproduction techniques: IVF

In principle, anovulation is not an indication for IVF. Clearly, the logical therapy for women with PCOS is induction of ovulation, especially by CC administration, and in case of failure by using exogenous gonadotrophin therapy. As discussed before, the major complication of ovulation induction is the occurrence of a 10% multiple pregnancy rate after the use of gonadotrophin therapy. For this reason, use of gonadotrophins may be questioned. If IVF is proposed, the cycle cancellation rate is significantly increased in patients with PCOS (12.8 versus
4.1%; OR 0.5, 95% CI 0.2–1.0) [6,15]. Duration of stimulation is significantly longer in patients with PCOS (1.2 days, 95% CI 0.9–1.5), even when the daily dose of FSH is similar to that of women without PCOS [15]. Significantly more cumulus–oocyte complexes (2.9, 95% CI 2.2–3.6) were retrieved in women with PCOS, “but fertilization rates were similar as compared with women without PCOS”.

Overall the results of the treatments of infertility in the polycystic ovary syndrome remain successful. Women need to be carefully informed of the need to reduce the excess weight when it is present, they should also be informed of the risk of spontaneous abortions and of pregnancy complications. A careful collaboration between patient and specialized physician is mandatory to improve the live birth rate and avoid the risk of OHSS.

**Conflict of interest statement**


**References**


