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REVIEW

Mono-ovulation in women with polycystic ovary syndrome: a clinical review on ovulation induction

Kathrine Birch Petersen [a,*], Nina Gros Pedersen [b], Anette Tønnes Pedersen [c], Mette Petri Lauritsen [d], Nina la Cour Freiesleben [e]

[a] *Fertility Clinic, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark;* [b] *Department of Gynecology/Obstetrics, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark;* [c] *Fertility Clinic and Department of Gynecology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark;* [d] *Department of Gynecology/Obstetrics, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark;* [e] *Fertility Clinic and Department of Gynecology/Obstetrics, Holbæk Hospital, Copenhagen University Hospital, Smedelundsgade 60, 4300 Holbæk, Denmark*

* Corresponding author. *E-mail address:* kathrine.birch.petersen@regionh.dk (K Birch Petersen).

Kathrine Birch Petersen is a specialist in obstetrics and gynaecology. She is affiliated to the Fertility Clinic at Rigshospitalet. Primary research areas are female infertility, Fertility Awareness, preconception counselling and intentions in family formations. She is currently completing a PhD from the University of Copenhagen regarding the Fertility Assessment and Counselling Clinic at Rigshospitalet, the first of its kind in the world.

Abstract Polycystic ovary syndrome (PCOS) affects 5–10% of women of reproductive age and is the most common cause of anovulatory infertility. The treatment approaches to ovulation induction vary in efficacy, treatment duration and patient friendliness. The aim was to determine the most efficient, evidence-based method to achieve mono-ovulation in women diagnosed with PCOS. Publications in English providing information on treatment, efficacy and complication rates were included until September 2015. Systematic reviews, meta-analyses and randomized controlled trials were favoured over cohort and retrospective studies. Clomiphene citrate is recommended as primary treatment for PCOS-related infertility. It induces ovulation in three out of four patients, the risk of multiple pregnancies is modest and the treatment is simple and inexpensive. Gonadotrophins are highly efficient in a low-dose step-up regimen. Ovulation rates are improved by lifestyle interventions in overweight women. Metformin may improve the menstrual cycle within 1–3 months, but does not improve the live birth rate. Letrozole is effective for ovulation induction, but is an off-label drug in many countries. Ovulation induction in women with PCOS should be individualized with regard to weight, treatment efficacy and patient preferences with the aim of achieving mono-ovulation and subsequently the birth of a singleton baby.

KEYWORDS: assisted reproduction, BMI, clomiphene citrate, infertility, PCOS

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Introduction

Polycystic ovary syndrome (PCOS) affects 5–10% of women of reproductive age and is the most common cause of anovulatory infertility (ESHRE Capri Workshop Group, 2012). The prevalence of PCOS depends on the diagnostic criteria used. According to the Rotterdam criteria, PCOS is characterized by at least two of the following three features: oligo- or anovulation (clinical); biochemical hyperandrogenism, or both; and polycystic ovarian morphology (PCOM) (ESHRE REA-SPCWG, 2004). In recent years, the Rotterdam criteria have been challenged by reports of a high prevalence of PCOM among young ovulatory women, partly due to the improvement in ultrasound technology (Duijkers and Klipping, 2010). It has been discussed whether the antral follicle threshold for the definition of PCOM should be changed or whether anti-Müllerian hormone could be used as an alternative marker of PCOM (Dewailly et al., 2011; Kristensen et al., 2010; Lauritsen et al., 2015).

Polycystic ovary syndrome is a heterogeneous disorder, ranging from anovulatory women with polycystic ovaries without signs of hyperandrogenism to women with severe metabolic disturbance. The increased risk of type 2 diabetes and cardiovascular disease is associated with the increased prevalence of obesity in women with PCOS (Domecq et al., 2013; ESHRE Capri Workshop Group, 2012). Moreover, ethnic variations in the presentation of symptoms of PCOS also play a role in the decision of treatment strategy (Alebic et al., 2015; Wijeyaratne et al., 2011).

Several approaches to ovulation induction exist in women with PCOS. These approaches vary in efficacy, treatment duration and patient compliance. Moreover, new treatment strategies are continuously being introduced. A clinical update focusing on the current evidence-based practice is therefore highly warranted.

Materials and methods

Search methods, eligibility criteria and outcomes of interest were specified in advance. Outcomes of interest were chosen based on the following objectives of treatment efficacy: cycle regulation, ovulation, live birth rate, multiple births, patient friendliness and side-effects.

Sources

A systematic search of *MEDLINE*, *EMBASE*, and the *Cochrane Library* was conducted on all articles published up to September 2015. Additional records were identified by reference lists in retrieved articles.

Study selection

Eligible articles were published in peer-reviewed journals and written in English. Articles not reporting on ovulation induction in the title or abstract were not included. Full-text articles were screened and the final inclusion decisions were made according to the following criteria: original studies, systematic reviews or meta-analyses; primary or first-line treatment and, if necessary, secondary treatment described; and treatment success, complications and side-effects described.

In the selected publications, data on treatment modalities were collected by two authors (KBP and NCF) (**Tables 1** and **2**). The treatment modalities were divided into six main subjects: clomiphene citrate; exogenous gonadotrophins; metformin; lifestyle intervention; laparoscopic ovarian drilling (LOD); and letrozole.

Study quality assessment

Two authors (KBP and NCF) assessed the quality of the selected articles (**Tables 1** and **2**). The level of evidence was determined in accordance with the Oxford Centre for Evidence Based Medicine guidelines (Phillips et al., 2009).

Results

Details of the included meta-analyses are presented in **Table 1**. The cited randomized controlled trials (RCTs) are presented in **Table 2**.

Clomiphene citrate

Clomiphene citrate can be used as first-line treatment for women with PCOS. Clomiphene citrate is inexpensive and simple to use, and may lead to ovulation in about 75% of patients. Clomiphene citrate treatment includes only a low risk of multiple gestations.

Clomiphene citrate has been used for ovulation induction for more than 5 decades (Greenblatt et al., 1961). It is administered daily for 5 days after a spontaneous or a progestogen-induced menstrual bleeding. The treatment can be initiated on cycle day 2, 3, 4 or 5 (Wu and Winkel, 1989). About 15–40% of women with PCOS are clomiphene citrate resistant (CCR) with no follicle development after a dose of 150 mg clomiphene citrate per day for 5 days (Abu Hashim et al., 2015). The definition of clomiphene citrate failure varies but is frequently defined as no conception despite ovulation during six cycles (Homburg, 2005; ESHRE, 2008). The clomiphene citrate treatment recommendations are presented in **Figure 1**. The evaluation of clomiphene citrate for ovulation induction in relation to efficacy, advantages and disadvantages is presented in **Figure 2**.

Clomiphene citrate dosing

A meta-analysis reported the following ovulation rates after 5 days of treatment for the following different doses: 46% (50 mg), 70% (100 mg), 76% (150 mg) and 85–90% > 150 mg (Rostami-Hodjegan et al., 2004). Another study showed an ovulation rate of 73% and a pregnancy rate of 36% in a collection of data from 5268 patients (Homburg, 2005). The ovulation rates and the probability of pregnancy are reported to be similar with treatment start on day 2, 3, 4 or 5 of the cycle (Wu and Winkel, 1989). The side-effects are dose-dependent. Doses lower than 50 mg/day may be considered for women