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REPRODUCTIVE MEDICINE

Clomiphene citrate alternatives for the initial management of polycystic ovary syndrome: an evidence-based approach

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Abstract Polycystic ovary syndrome (PCOS) is a prevalent and heterogeneous condition affecting 4–8% of reproductive age women. It is the most common cause of chronic anovulation and is associated with hyperandrogenemia. Clomiphene citrate (CC) is considered as the first-line therapy for ovulation induction in these patients. Despite progress in understanding the pathophysiology of PCOS over the past 20 years, many questions persist to the extent that PCOS was described as "A Riddle Wrapped in a Mystery inside an Enigma". On the other hand, a recent publication from the Centers for Disease Control suggested that CC may be associated with an increased risk of birth defects. The purpose of this review is to critically evaluate and summarize the current literature regarding CC alternatives for the initial management of PCOS focusing specifically on the roles of weight loss and other approaches to ovulation induction as insulin-sensitizing drugs, aromatase inhibitors, minimal stimulation protocol, gonadotrophins and surgery (laparoscopic ovarian drilling). Finally, the efficacy of intrauterine insemination with CC for the initial management of PCOS will be evaluated.

Keywords Polycystic ovary syndrome · Ovulation induction · Clomiphene citrate · Laparoscopic ovarian diathermy · Gonadotrophins · Metformin · Aromatase inhibitors · Intrauterine insemination

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Introduction

World Health Organization (WHO) type II anovulation is defined as normogonadotrophic normoestrogenic anovulation and occurs in ~85% of anovulatory patients. Polycystic ovary syndrome (PCOS) is the most common form of WHO type II anovulatory infertility and is associated with hyperandrogenemia [1, 2]. Moreover, PCOS is the most common endocrine abnormality in reproductive age women. The prevalence of PCOS is traditionally estimated at 4–8% from studies performed in Greece, Spain and the USA [3–6]. The prevalence of PCOS has increased with the use of different diagnostic criteria and has recently been shown to be 11.9 ± 2.4–$17.8 \pm 2.8\%$ in the first community-based prevalence study based on the current Rotterdam diagnostic criteria compared with 10.2 ± 2.2–$12.0 \pm 2.4\%$ and $8.7 \pm 2.0\%$ using National Institutes of Health criteria and Androgen Excess Society recommendations, respectively [7]. Importantly, 70% of women in this recent study were undiagnosed [7].

Clomiphene citrate (CC) represents the first-line therapy for ovulation induction in PCOS patients [2, 8, 9]. Standard practice is to administer CC for 5 days from the second or third day of the menstrual cycle, starting with 50 mg/day and increasing to 250 mg/day [10]. However, managed care studies have shown that the most effective dosage is 100–150 mg/day and over 75% of ovulations occur within these dosages [11]. CC induces ovulation in almost 75–80% of selected women with PCOS-related infertility [12]. After six to nine cycles of treatment with CC, cumulative pregnancy rates reach 70–75% [11]. Life table analysis of the most reliable studies indicated a conception rate up to 22% per cycle in women ovulating on CC [8]. The NICE clinical guideline 2004, recommended the use of CC for up to 12 cycles as cumulative pregnancy rates continue to rise after 6 treatment

cycles [13]. However, its use longer than 12 months is not recommended due to the possible increased risk of ovarian cancer together with decreased pregnancy chances after this period [13]. Clomiphene-resistant patients are those who did not ovulate in response to doses of CC up to 150 mg for at least three successive cycles, meanwhile clomiphene failure includes patients who failed to conceive with CC despite successful regular ovulation on CC for six to nine cycles [14]. In a large randomized trial, Legro et al. [15] compared the effects of CC, metformin and combination therapy for up to six cycles in 626 infertile women with PCOS. They reported an ovulation rate and clinical pregnancy rate per woman of 75.1 and 23.9%, respectively after CC treatment up to 150 mg/day. This discrepancy between ovulation and pregnancy rates may be explained by the peripheral anti-estrogenic effects of CC at the level of the endometrium and cervical mucus or by hypersecretion of LH [10, 16–21]. Clomiphene resistance is common and occurs in ~15–40% in women with PCOS [2, 13]. Insulin resistance, hyperandrogenemia and obesity represent the major factors involved in CC resistance; it prevent the ovaries from responding to raised endogenous follicle-stimulating hormone (FSH) levels following CC therapy [22–24]. Moreover, a genetic predisposition was suggested [25].

Despite progress in understanding the pathophysiology of PCOS over the past 20 years, many questions persist to the extent that PCOS was described as "A Riddle Wrapped in a Mystery inside an Enigma" [26]. On the other hand, a recent publication from the Centers for Disease Control suggested that CC may be associated with an increased risk of birth defects [27]. The purpose of this review is to critically evaluate and summarize the current literature regarding CC alternatives for the initial management of PCOS focusing specifically on the roles of weight loss and other approaches to ovulation induction as insulin-sensitizing drugs, aromatase Inhibitors, minimal stimulation protocol, gonadotrophins and surgery (laparoscopic ovarian drilling). Finally, the efficacy of intrauterine insemination with clomiphene citrate for the initial management of PCOS will be evaluated.

Materials and methods

Publication search

PubMed was searched using the above mentioned key words (the last search update was on July 25, 2011). The relevant evidence was identified, assessed for quality and selected for inclusion, such as systematic reviews, meta-analyses, different guidelines, randomized controlled trials (RCTs) and prospective cohort studies followed by other observational studies. Additional studies were identified by a manual search of the references of original studies.

Weight loss and lifestyle modifications

Obesity is strongly associated with PCOS and may be present in up to 50% of cases [28–32]. Obese women with PCOS are more likely than thin women with PCOS to suffer from anovulation [28]. 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 [32]. Lifestyle modification is the first-line treatment in an evidence-based approach for the management of the majority of PCOS women who are overweight [8, 9, 13, 33–35]. The NICE clinical guideline 2004 [13] recommended weight loss for anovulatory PCOS women who have a BMI >29 kg/m^2 before starting ovulation induction therapy. In these women, weight loss of even 5–10% of body weight often restores ovulatory cycles [9, 29, 31]. Studies also showed that overweight women are less likely to respond to pharmacologic ovulation induction methods. In a cohort of 270 women with PCOS who received either CC or gonadotrophins for ovulation induction, almost 80% with a BMI of 18–24 kg/m^2 ovulated at 6 months compared with only 12% of women with a BMI ≥35 kg/m^2 [28]. Moreover, overweight women require higher doses of CC and gonadotrophins [29].

The current recommendation is to reduce weight gradually to increase the chances of maintaining the weight loss [9]. Preferential diet composition has been evaluated in two small studies [36, 37]. 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. Routine exercise is also very important in the reproductive health of PCOS women. Exercise increases insulin sensitivity and helps achieve and maintain weight loss [9, 35]. Incorporating simple moderate physical activity including structured exercise (at least 30 min/day) and incidental exercise increases weight loss and improves clinical outcomes in PCOS, compared to diet alone [38]. Also, a recent study reported that a 6-week intervention of structured exercise training and a hypocaloric diet was effective in increasing the probability of ovulation under CC treatment in overweight and obese PCOS patients [39]. Other lifestyle factors such as excessive caffeine intake, alcohol consumption and smoking should also be addressed [13, 30].

Otta et al. [40] in a randomized, double-blind and placebo control trial compared lifestyle modification and 1,500 mg of metformin or placebo for 4 months in 30 women with insulin resistance PCOS. They reported that

metformin has an additive effect to diet and exercise to improve parameters of hyperandrogenism and insulin resistance. However, a small decrease in body weight through lifestyle changes could be enough to improve menstrual cycles in these women. Karimzadeh and Javedani [41] in another randomized double-blind study compared lifestyle modification with medical treatment plans, such as CC, metformin and CC with metformin in 343 overweight infertile women with PCOS. They showed that metformin or metformin with CC does not cause a significant weight loss or an improvement in the endocrine status of PCOS women. However, lifestyle modification to reduce waist circumference and body weight could improve their menstrual cycles, hormonal status and was an effective treatment for ovulation induction in those patients with an ovulation and pregnancy rates of 66.6 and 20%, respectively.

In morbidly obese women, the PCOS phenotype appears to be very frequent [42]. Importantly, this disorder has been found to improve markedly after sustained weight loss following bariatric surgery [43]. Anti-obesity pharmacological agents have been used in obese women with PCOS. Both orlistat, which blocks intestinal absorption of fat [44], and sibutramine, an appetite suppressant [45], have displayed a weight loss-independent effect on androgens and insulin resistance. It should be noted that these treatments should not be considered as first-line therapy for obesity in women with PCOS [8].

Insulin-sensitizing drugs

Approximately 50–70% of all women with PCOS have some degree of insulin resistance [46]. Hyperinsulinemia probably contributes to the hyperandrogenism which is responsible for the signs and symptoms of PCOS [46]. Metformin, a biguanide, is now the most widely used insulin sensitizer for ovulation induction in women with PCOS [47, 48]. There are differences in opinion as to whether metformin should play a role in the primary treatment of anovulatory infertility for women with PCOS. At 2008, Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group [8] reported that the use of metformin in PCOS should be restricted to those patients with glucose intolerance. Metformin alone is less effective than CC in inducing ovulation in women with PCOS, and there seems to be no advantage to adding metformin to CC in those women. A recent meta-analysis of RCTs showed no significant difference in effectiveness of metformin versus CC as a first-line treatment for ovulation induction in non-obese women with anovulatory PCOS [49]. Another recent review reported that metformin is not a useful fertility agent on its own, and the treatment of first choice for overweight or obese women with PCOS is modification of diet and lifestyle [48]. Also, a recent Cochrane review reported that metformin is still of benefit in improving clinical pregnancy and ovulation rates. However, there is no evidence that it improves live birth rates whether it is used alone or in combination with CC or when compared with CC. Therefore, the use of metformin as a first-line treatment in improving reproductive outcomes in women with PCOS appears to be limited [50].

Third-generation aromatase inhibitors

Third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) are the approved adjuvants for the treatment of estrogen receptor-positive breast cancer [51] that were first used in ovulation induction in anovulatory women in 2001 [52]. Evidence suggests that nonsteroidal aromatase inhibitors (AIs), specifically letrozole and anastrozole, have ovulation-inducing effects by inhibiting androgen-to-estrogen conversion. Centrally, this effect releases the hypothalamic/pituitary axis from estrogenic negative feedback, increases gonadotrophin secretion, and results in stimulation of ovarian follicle maturity. Moreover, peripherally, AIs may increase follicular sensitivity to FSH [53]. AIs have relatively short half-lives (~2 days) compared with CC (~2 weeks), so estrogen target tissues (e.g., endometrium and cervix) are spared adverse effects. Because of these mechanisms, it was postulated that AIs may have superior ovulation induction properties in terms of follicular growth and endometrium development, which is important for embryo implantation [53].

Letrozole has the potential to be the first-line treatment option for ovulation induction in PCOS women being at least as effective as CC for inducing ovulation and achieving pregnancy in these patients. Potential advantages of letrozole include reduced multiple pregnancies, absence of anti-estrogenic adverse effects and the subsequent need for less intensive monitoring [54–56]. A recent meta-analysis included six RCTs involving 841 patients concluded that letrozole is as effective as CC for ovulation induction in patients with PCOS [57]. Letrozole was associated with a number of lower mature follicles per cycle [standardized mean difference (SMD) −1.41; 95% confidence intervals (CI) −1.54 to −1.28; $P < 0.00001$] compared with CC. There were no significant differences in pregnancy rate (relative risk (RR) 0.97; 95% CI 0.79–1.18), abortion rate (RR 1.38; 95% CI 0.48 to −3.96) and multiple pregnancy rate (RR 0.34; 95% CI 0.07 to −1.72) between the two groups. The evidence from ovulation rates was not enough to support either letrozole or CC [57]. Different doses of letrozole ranging from 2.5 to 7.5 mg/day were utilized. However, the optimal doses are still unclear. In a study of Yang et al. [58]

on 76 PCOS patients comparing 2.5 mg with 5 mg letrozole for 5 days stating from day 3 of the cycle, the total number of mature follicles and pregnancy rate was higher in the 5 mg group. In their study, there was no difference regarding days to reach mature follicle between groups. A recent RCT by Ramezanzadeh et al. [59] on 67 PCOS patients did not show any advantage to the use of 7.5 mg/day over 5 mg/day dose of letrozole as the first-line treatment for ovulation induction in PCOS women.

Anastrozole has also been proposed as the first-line treatment option for ovulation induction in PCOS women. However, recently, based upon the results of the phase 1 and 2 trials, it was reported that although anastrozole may be viewed as an alternative oral therapeutic agent in the induction of ovulation, it should not be viewed as a replacement for CC in the majority of PCOS patients. Patients with androgenization may not respond predictably to anastrozole; meanwhile those without androgenization and with irregular menses may have a better response to the single-dose rather than the multiple-dose regimen. A benefit could not be demonstrated for multiple treatment cycles with anastrozole [60].

The safety of letrozole has elaborated a hot discussion. According to an abstract published by the American Society for Reproductive Medicine (ASRM) in 2005 [61], the use of letrozole for ovulation induction has been discouraged, since there was a significant increase in congenital cardiac and bone malformations in newborns in letrozole-treated pregnancies compared with controls. However, there were numerous concerns regarding the methodology of this study: firstly, the small size of the letrozole group ($n = 171$ babies) of women who received letrozole with or without gonadotrophins. Moreover, 21 babies were lost in follow-up; Secondly, the choice of a control group from a database of normal deliveries containing 36,050 deliveries that would have a lower risk of pregnancy complications and congenital malformations than an infertile population; finally the under-representation of congenital anomalies in the control group (noting that any babies identified as abnormal on prenatal ultrasound would be delivered at a tertiary care hospital rather than a community hospital) [62].

Subsequently, two retrospective studies did not support the concern that letrozole use for ovulation induction could be teratogenic [62, 63]. A review of 911 newborns conceived after infertility treatment found that the rate of congenital malformations and chromosomal abnormalities was not significantly different, but slightly higher, in newborns from CC-treated compared with letrozole-treated women (4.8 vs. 2.4%, respectively). Moreover, the major cardiac congenital abnormality rate (e.g., ventricular septal defect, transposition of great vessels, right ventricle atresia, pulmonary valve atresia) was significantly higher with CC than with letrozole (1.8 vs. 0.2%, $P = 0.02$, respectively) [63]. Another retrospective study of 477 newborns revealed fewer malformations with letrozole (0%) than with CC (2.6%) or spontaneous pregnancy (3.2%) [62]. Importantly, positive results for the safety for newborns from these two retrospective studies have been replicated by a recent randomized trial assessing pregnancy outcomes after treatment with AIs in 796 infertile women [64]. Accordingly, the previous concerns for the safety of AIs appear to be fading. In fact, letrozole may well be teratogenically safer than CC. The shorter half-life virtually assures elimination from the body prior to implantation, whereas this is not the case with the relatively slowly eliminated CC [55].

Laparoscopic ovarian diathermy (LOD)

Laparoscopic ovarian diathermy is currently accepted as a successful second line treatment for ovulation induction in CC-resistant PCOS being as effective as gonadotrophin treatment, and is not associated with an increased risk of multiple pregnancy or ovarian hyperstimulation syndrome (OHSS) [8, 9, 13, 14]. The main shortcomings of LOD are the need for general anesthesia and the risk of postoperative adhesions [65, 66]. The claim that it might affect the ovarian reserve is not more than a theoretical concern, since a recent report concluded that LOD, when applied properly, does not seem to compromise the ovarian reserve in PCOS women [67].

Only two studies in the literature addressed the use of LOD as a first line of treatment for ovulation induction in PCOS patients. Cleemann et al. [68] in a prospective case series reported a pregnancy rate of 61% among 57 infertile women with PCOS in whom LOD was performed as a first line of treatment. Out of 35 (61%) women who became pregnant after LOD, pregnancy was achieved with LOD only in 18 cases, while the remaining 17 had ovulation induction after LOD. The median time to pregnancy after LOD was 135 days. They proposed that a strategy with diagnostic laparoscopy and LOD as the first line of treatment of infertility in women with PCOS will shorten the time to pregnancy for many women, reduce the need for medical ovulation induction and enable diagnosis of those women with anatomic infertility, who can achieve pregnancy only by in vitro fertilization treatment [68]. A recent RCT by Amer et al. [69] compared LOD with CC as a first-line treatment for anovulatory infertility in 72 women with PCOS. No significant difference was reported regarding the ovulation rate per woman and per cycle; 64 versus 76% and 70 versus 66% after LOD and CC treatment, respectively. Also, no significant difference was reported regarding the pregnancy rate per woman and the cumulative pregnancy rate at 12 months follow up; 27 versus 44% and 52 versus

63% after LOD and CC treatment, respectively. Live birth rate was comparable between both groups (46 vs. 56% after LOD and CC treatment, respectively). The authors concluded that LOD is not superior to CC as a first-line treatment of ovulation induction in women with PCOS [69]. Moreover, in a recent RCT, we compared the efficacy of LOD versus continuation of CC for up to six further cycles in 176 infertile PCOS patients who failed to achieve pregnancy despite previous successful CC induced ovulation [70]. The clinical pregnancy rate per patient and the cumulative pregnancy rate after six cycles were comparable in both groups (39 vs. 33.7% and 47 vs. 39.2%, respectively). Four twin pregnancies occurred in CC group and none in LOD group and the difference was statistically significant. Miscarriage and live birth rates were comparable in both groups. Accordingly, we concluded that LOD during the 6 months follow up period and CC for up to six further cycles are equally effective for achieving pregnancy in CC failure PCOS patients [70].

Gonadotrophins

Traditionally, ovulation induction with gonadotrophins has been used as a second-line treatment for CC-resistant PCOS women; however, it is expensive requires extensive monitoring and associated with significantly increased risk for OHSS and multiple pregnancy [8, 9, 13]. Furthermore, a significant and consistent relationship between PCOS and OHSS was reported in a systematic review [71]. The high sensitivity of the PCOS to gonadotrophic stimulation is probably related to the fact that they contain twice the number of available FSH-sensitive antral follicles in their cohort than the normal ovary [72]. A low-dose, step-up gonadotrophin therapy should be preferred to the now outdated conventional protocol for patients with PCOS and the strong justification seems to be the achievement of high rate of monofollicular development, which is ~69% (54–88%) [73, 74] with nearly complete elimination of OHSS (0–2.4%) and a multiple pregnancy rate of ~6% [73, 75]. The recommended approach is to begin with a low dose of gonadotrophin, typically 25–75 IU/day, increasing after 7 days or more if no follicle >10 mm has yet emerged, in small increments, at intervals, until evidence of progressive follicular development is observed. The maximum required daily dose of FSH/hMG seldom exceeds 225 IU/day [76, 77].

Only a single centre RCT was undertaken to compare the efficacy and safety of CC and low-dose recombinant FSH as first-line pharmacological therapy for anovulatory infertility associated with PCOS [78]. Seventy-six infertile patients with PCOS were randomized to receive CC (50–150 mg/day for 5 days, $n = 38$) or recombinant human FSH ($n = 38$) in a chronic, low dose, step-up protocol (daily starting dose 75 IU) for up to three consecutive cycles. No significant differences were reported regarding the ovulation rate per woman and per cycle; 79 versus 92% and 53 versus 74% after CC and FSH treatment, respectively. Also, no significant differences were reported regarding the pregnancy rate per woman and per cycle as well as the cumulative pregnancy rate after three treatment cycles; 24 versus 42%, 9 versus 18% and 24 versus 43% after CC and FSH treatment, respectively. Live birth rate was comparable between both groups (16 vs. 29% after CC and FSH treatment, respectively). There was one twin pregnancy in the CC group (11%) and three in the FSH group (19%) ($P = 1.0$). There were two cases of mild OHSS in the FSH group and none in CC group. This RCT suggested that low-dose recombinant FSH may be an effective alternative to CC in first-line treatment for anovulatory PCOS patients. However, being underpowered, the authors admitted that further studies are warranted to confirm these results [78].

Minimal stimulation protocol

Corfman et al. [79] previously have described a novel ovarian stimulation protocol consisted of 5 days of CC (100 mg/day) followed by a single dose of menopausal gonadotrophin (hMG, 150 IU) on cycle day 9, termed 'minimal stimulation' which was less expensive, easy to administer, required minimal monitoring with comparable pregnancy rates to conventional hMG stimulation in cases undergoing in vitro fertilization procedures. Lu et al. [80] in a retrospective study reported that minimal stimulation was as effective as the hMG alone protocol for non-ART treatment of infertility. Their published description of this protocol (61 women, 106 cycles) showed a favorable clinical pregnancy rate (20.8% per cycle) in a relatively young population (mean age 31.9) with a high rate of ovulatory dysfunction (40%). This might be related to better quality oocytes and more receptive endometrium expected with minimal stimulation protocol due to the effect of the injected exogenous gonadotrophin resulting in further help in late follicular growth of dominant follicles recruited with CC. Accordingly, minimal stimulation protocol is logistically more challenging.

Recently, in a well designed adequately powered RCT, we compared the efficacy of minimal stimulation protocol and CC as a first-line treatment in 113 women with PCOS [81]. Patients received minimal stimulation protocol consisted of 5 days CC (100 mg/day) then 150 IU of highly purified urinary FSH (uFSH) on cycle day 9 ($n = 58$, 159 cycles) or CC only ($n = 55$, 153 cycles) for up to three cycles. There were no differences between both groups regarding the clinical pregnancy rate per cycle and per woman (8.8 vs. 7.8% and 24.1 vs. 21.8%, respectively). One twin pregnancy occurred in each group. Miscarriage

rate was comparable (14.3 vs. 16.7%). No differences were found regarding the number of follicles, serum P, ovulation rate, E2 and endometrial thickness at the hCG day (7.8 ± 0.5 vs. 7.6 ± 0.6 mm). Accordingly, we concluded that ovulation induction with minimal stimulation is not more effective than CC alone for achieving pregnancy when used as initial treatment in PCOS patients [81].

Day 3 uFSH protocol

A recent large prospective clinical trial was conducted to compare the efficacy of single dose uFSH (75 IU) on day 3 of menstrual cycle along with CC versus CC alone as a first-line treatment in 1,527 infertile women (4,381 cycles), including PCOS ($n = 911$; 2,573 cycles) and unexplained infertility ($n = 616$; 1,808 cycles) [82]. Pregnancy and miscarriage rates were compared between groups. A significantly higher pregnancy rate was found in PCOS women who received day 3 uFSH compared with CC only group (22 vs. 9.3%, respectively). However, there was no significant difference in pregnancy rate between both groups in women with unexplained infertility. Miscarriage rates were comparable in both groups in PCOS women as well as women with unexplained infertility (8.8 vs. 9.5% and 14 vs. 13%, respectively). The improved pregnancy rate observed in PCOS women may be related to the addition of uFSH on day 3 of menstrual cycle with CC, which could negate the detrimental effect of the elevated basal LH levels on pregnancy and miscarriage in those women. The authors concluded that the addition of single dose of uFSH improves pregnancy outcome particularly in anovulatory infertility (WHO II) compared with CC alone. However, they admitted the need for more RCTs to confirm the possibility of replacing CC as the first-line therapy for PCOS with CC + uFSH [82].

Intrauterine insemination with clomiphene citrate as first-line treatment in women with PCOS

Currently, intrauterine insemination (IUI) with or without ovarian stimulation is widely used to treat male infertility, unexplained infertility and for couples with minimal and mild endometriosis [83, 84]. The rationale of IUI treatment is to increase the pregnancy rate by increasing the chance that maximum number of healthy sperm reaches the site of fertilization. However, in couples with abnormal cervical mucus, the rationale might be to bypass a possible cervical factor [83]. The first RCT comparing the addition of IUI to CC for the initial management of women with PCOS and normal semen analysis was reported recently by Abu Hashim et al. [85]. In this study, a total of 525 cycles were studied in 188 patients, 259 cycles in 93 patients who had CC/IUI and 266 cycles in 95 patients in the control group who underwent CC with timed intercourse (TI). In this study, we found that performing IUI did not translate into a significantly higher clinical pregnancy rates as the clinical pregnancy rate per cycle as well as per woman did not differ significantly in both groups (8.49 vs. 7.89% and 23.6 vs. 22.1%, respectively). Also, in cycles in which ovulation occurred, the pregnancy rate per cycle was 16.3% with CC/IUI and 15.3% with CC/TI and the difference was not statistically significant. This might be related to reduced endometrial thickness at the time of hCG administration (7.7 ± 0.4 mm) rather than depression of cervical mucus. Our findings match with those reported by other investigators who found thinner endometrial thickness with the use of CC when measured on late proliferative days [10, 16–19]. Accordingly, we concluded that ovulation induction with CC and TI is as effective as that with CC and IUI for achieving pregnancy in PCOS and can represent the initial treatment option being less invasive and less expensive than IUI.

Conclusion

In PCOS, the first treatment choice for induction of ovulation is CC. Selection of patients for CC treatment should take into account body weight/BMI, female age and the presence of other infertility factors. With this drug, in properly selected patients, the cumulative pregnancy rate approaches that of normal women. However, in obese women with PCOS, weight loss and exercise should be recommended as the first line of therapy. Ovulation induction with minimal stimulation protocol is not more effective than CC alone for achieving pregnancy when used as initial treatment in PCOS patients. Low-dose protocols of FSH are the second line of treatment effective in inducing monofollicular development in clomiphene-resistant patients. LOD can be an alternative second-line treatment in clomiphene-resistant patients but not as a first choice treatment. Metformin is still of benefit in improving ovulation and clinical pregnancy rates. However, there is no evidence that it improves live birth rates whether it is used alone or in combination with CC or when compared with CC. Therefore, the use of metformin as a first-line treatment in improving reproductive outcomes in women with PCOS appears to be limited. Up till now, the evidence is not enough to support either letrozole or anastrozole as a replacement for CC in the initial management of PCOS patients. Ovulation induction with CC and TI is as effective as that with CC and IUI for achieving pregnancy in PCOS.

Conflict of interest We declare that we have no conflict of interest.

References

1. Overbeek A, Lambalk CB (2009) Phenotypic and pharmacogenetic aspects of ovulation induction in WHO II anovulatory women. Gynecol Endocrinol 25:222–234. doi:10.1080/09513590802571118
2. Brown J, Farquhar C, Beck J, Boothroyd C, Hughes E (2009) Clomiphene and anti-oestrogens for ovulation induction in PCOS. Cochrane Database Syst Rev (4):CD002249. doi:10.1002/14651858.CD002249.pub4
3. Diamanti-Kandarakis E, Kouli CR, Bergiele AT et al (1999) A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. J Clin Endocrinol Metab 84:4006–4011. doi:10.1210/jc.84.11.4006
4. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R (1998) Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 83:3078–3082. doi:10.1210/jc.83.9.3078
5. Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF (2000) A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab 85:2434–2438. doi:10.1210/jc.85.7.2434
6. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO (2004) The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 89:2745–2749. doi:10.1210/jc.2003-032046
7. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ (2010) The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod 25:544–551. doi:10.1093/humrep/dep399
8. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2008) Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril 89:505–522. doi:10.1016/j.fertnstert.2007.09.041
9. Vause TD, Cheung AP, Sierra S, Society of Obstetricians and Gynaecologists of Canada et al (2010) Ovulation induction in polycystic ovary syndrome: no. 242, May 2010. Int J Gynaecol Obstet 111:95–100. doi:10.1016/j.ijgo.2010.07.001
10. Homburg R (2005) Clomiphene citrate-end of an era? A mini-review. Hum Reprod 20:2043–2051. doi:10.1093/humrep/dei042
11. Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC (2002) A nomogram to predict the probability of live birth after clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. Fertil Steril 77:91–97. doi:10.1016/S0015-0282(01)02929-6
12. Messinis IE (2005) Ovulation induction: a mini review. Hum Reprod 20:2688–2697. doi:10.1093/humrep/dei128
13. National Collaborating Centre for Women's and Children's Health/National Institute for Clinical Excellence (2004) Fertility: assessment and treatment for people with fertility problems. Clinical Guideline No. 11. RCOG Press, London. http://www.nice.org.uk/nicemedia/pdf/CG011niceguideline.pdf
14. Amer SAK (2008) Laparoscopic ovarian surgery for polycystic ovarian syndrome. In: Dunlop W, Ledger WL (eds) Recent advances in obstetrics and gynaecology, 24th edn. Royal Society of Medicine Press Ltd, London, pp 227–243
15. Legro RS, Barnhart HX, Schlaff WD, Cooperative Multicenter Reproductive Medicine Network et al (2007) Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med 356:551–566
16. Gonen Y, Casper RF (1990) Sonographic determination of a possible adverse effect of clomiphene citrate on endometrial growth. Hum Reprod 5:670–674
17. Opsahl MS, Robins ED, O'Connor DM, Scott RT, Fritz MA (1996) Characteristics of gonadotropin response, follicular development, and endometrial growth and maturation across consecutive cycles of clomiphene citrate treatment. Fertil Steril 66:533–539
18. Nakamura Y, Ono M, Yoshida Y, Sugino N, Ueda K, Kato H (1997) Effects of CC on the endometrial thickness and echogenic pattern of the endometrium. Fertil Steril 67:256–260. doi:10.1016/S0015-0282(97)81907-3
19. Dehbashi S, Parsanezhad ME, Alborzi S, Zarei A (2003) Effect of clomiphene citrate on endometrium thickness and echogenic patterns. Int J Gynecol Obstet 80:49–53. doi:10.1016/S0020-7292(02)00341-7
20. Randall JM, Templeton A (1991) Cervical mucus score and in vitro sperm mucus interaction in spontaneous and CC citrate cycles. Fertil Steril 56:465–468
21. Shoham Z, Borenstein R, Lunenfeld B, Pariente C (1990) Hormonal profiles following clomiphene citrate therapy in conception and nonconception cycles. Clin Endocrinol (Oxf) 33:271–278. doi:10.1111/j.1365-2265.1990.tb00491.x
22. Imani B, Eijkemans MJC, te Velde ER, Habbema JD, Fauser BC (1998) Predictors of patients remaining anovulatory during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. J Clin Endocrinol Metab 83:2361–2365. doi:10.1210/jc.83.7.2361
23. Imani B, Eijkemans MJ, de Jong FH, Payne NN, Bouchard P, Giudice LC, Fauser BC (2000) Free androgen index and leptin are the most prominent endocrine predictors of ovarian response during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. J Clin Endocrinol Metab 85:676–682. doi:10.1210/jc.85.2.676
24. Parsanezhad ME, Alborzi S, Zarei A, Dehbashi S, Omrani G (2001) Insulin resistance in clomiphene responders and nonresponders with polycystic ovarian disease and therapeutic effects of metformin. Int J Gynaecol Obstet 75:43–50. doi:10.1016/S0020-7292(01)00470-2
25. Overbeek A, Kuijper EA, Hendriks ML et al (2009) Clomiphene citrate resistance in relation to follicle-stimulating hormone receptor Ser680Ser-polymorphism in polycystic ovary syndrome. Hum Reprod 24:2007–2013. doi:10.1093/humrep/dep114
26. Padmanabhan V (2009) Polycystic ovary syndrome—"A Riddle Wrapped in a Mystery inside an Enigma". J Clin Endocrinol Metab 94:1883–1885. doi:10.1210/jc.2009-0492
27. Reefhuis J, Honein MA, Schieve LA, Rasmussen SA, National Birth Defects Prevention Study (2011) Use of clomiphene citrate and birth defects, National Birth Defects Prevention Study, 1997–2005. Hum Reprod 26:451–457. doi:10.1093/humrep/deq313
28. Al-Azemi M, Omu FE, Omu AE (2004) The effect of obesity on the outcome of infertility management in women with polycystic ovary syndrome. Arch Gynecol Obstet 270:205–210. doi:10.1007/s00404-003-0537-2
29. Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX (2004) Improving reproductive performance in overweight/obese women with effective weight management. Hum Reprod Update 10:267–280. doi:10.1093/humupd/dmh018
30. Norman RJ, Davies MJ, Lord J, Moran LJ (2002) The role of lifestyle modification in polycystic ovary syndrome. Trends Endocrinol Metab 13:251–257. doi:10.1016/S1043-2760(02)00612-4
31. Hoeger KM (2007) Obesity and lifestyle management in polycystic ovary syndrome. Clin Obstet Gynecol 50:277–294. doi:10.1097/GRF.0b013e31802f54c8
32. Pasquali R, Gambineri A, Pagotto U (2006) The impact of obesity on reproduction in women with polycystic ovary syndrome. BJOG 113:1148–1159. doi:10.1111/j.1471-0528.2006.00990.x
33. Tolino A, Gambardella V, Caccavale C et al (2005) Evaluation of ovarian functionality after a dietary treatment in obese women

with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 119:87–93. doi:10.1016/j.ejogrb.2004.06.043
34. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ (2009) Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril 92:1966–1982. doi:10.1016/j.fertnstert.2008.09.018
35. Moran LJ, Hutchison SK, Norman RJ, Teede HJ (2011) Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev (2):CD007506. doi:10.1002/14651858.CD007506.pub2
36. Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkman CL, Legro RS (2004) A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. Fertil Steril 81:630–637. doi:10.1016/j.fertnstert.2003.08.023
37. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Galletly C, Norman RJ (2003) Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab 88:812–819. doi:10.1210/jc.2002-020815
38. Poehlman ET, Dvorak RV, DeNino WF, Brochu M, Ades PA (2000) Effects of resistance training and endurance training on insulin sensitivity in nonobese, young women: a controlled randomized trial. J Clin Endocrinol Metab 85:2463–2468. doi:10.1210/jc.85.7.2463
39. Palomba S, Falbo A, Giallauria F et al (2010) Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome: a randomized controlled trial. Hum Reprod 25:2783–2791. doi:10.1093/humrep/deq254
40. Otta CF, Wior M, Iraci GS et al (2010) Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: a randomized, double-blind, and placebo control trial. Gynecol Endocrinol 26:173–178. doi:10.3109/09513590903215581
41. Karimzadeh MA, Javedani M (2010) An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome. Fertil Steril 94:216–220. doi:10.1016/j.fertnstert.2009.02.078
42. Alvarez-Blasco F, Botella-Carretero JI, San Millán JL, Escobar-Morreale HF (2006) Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. Arch Intern Med 166:2081–2086
43. Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millán JL (2005) The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. J Clin Endocrinol Metab 90:6364–6369. doi:10.1210/jc.2005-1490
44. Jayagopal V, Kilpatrick ES, Holding S, Jennings PE, Atkin SL (2005) Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. J Clin Endocrinol Metab 90:729–733. doi:10.1210/jc.2004-0176
45. Sabuncu T, Harma M, Harma M, Nazligul Y, Kilic F (2003) Sibutramine has a positive effect on clinical and metabolic parameters in obese patients with polycystic ovary syndrome. Fertil Steril 80:1199–1204. doi:10.1016/S0015-0282(03)02162-9
46. Legro RS, Castracane VD, Kauffman RP (2004) Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. Obstet Gynecol Surv 59:141–154
47. Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Economou FN (2010) Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur J Endocrinol 162:193–212. doi:10.1530/EJE-09-0733
48. Franks S (2011) When should an insulin sensitizing agent be used in the treatment of polycystic ovary syndrome? Clin Endocrinol (Oxf) 74:148–151. doi:10.1111/j.1365-2265.2010.03934.x
49. Johnson N (2011) Metformin is a reasonable first-line treatment option for non-obese women with infertility related to anovulatory polycystic ovary syndrome—a meta-analysis of randomised trials. Aust N Z J Obstet Gynaecol 51:125–129. doi:10.1111/j.1479-828X.2010.01274.x
50. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH (2010) Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev (1):CD003053. doi:10.1002/14651858.CD003053.pub4
51. Mauri D, Pavlidis N, Polyzos NP, Ioannidis JP (2006) Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. J Natl Cancer Inst 98:1285–1291. doi:10.1093/jnci/djj357
52. Mitwally FM, Casper RF (2001) Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 75:305–309. doi:10.1016/S0015-0282(00)01705-2
53. Casper RF, Mitwally MF (2006) Review: aromatase inhibitors for ovulation induction. J Clin Endocrinol Metab 91:760–771. doi:10.1210/jc.2005-1923
54. Casper RF (2009) Letrozole versus clomiphene citrate: which is better for ovulation induction? Fertil Steril 92:858–859. doi:10.1016/j.fertnstert.2007.03.094
55. Pritts EA (2010) Letrozole for ovulation induction and controlled ovarian hyperstimulation. Curr Opin Obstet Gynecol 22:289–294. doi:10.1097/GCO.0b013e32833beebf
56. Lee VC, Ledger W (2011) Aromatase inhibitors for ovulation induction and ovarian stimulation. Clin Endocrinol (Oxf) 74:537–546. doi:10.1111/j.1365-2265.2011.04006.x
57. He D, Jiang F (2011) Meta-analysis of letrozole versus clomiphene citrate in polycystic ovary syndrome. Reprod Biomed Online 23:91–96. doi:10.1016/j.rbmo.2011.03.024
58. Yang MQ, Quan S, Li H, Song YL, Xing FQ (2008) Effect of two different doses of letrozole in promoting ovulation in infertile women with polycystic ovarian syndrome. Nan Fang Yi Ke Da Xue Xue Bao 28:2060–2061
59. Ramezanzadeh F, Nasiri R, Sarafraz Yazdi M, Baghrei M (2011) A randomized trial of ovulation induction with two different doses of letrozole in women with PCOS. Arch Gynecol Obstet 284:1029–1034. doi:10.1007/s00404-011-1951-5
60. Tredway DR, Schertz JC (2011) Anastrozole versus clomiphene citrate: which is better for ovulation induction? Fertil Steril 95:1549–1551. doi:10.1016/j.fertnstert.2010.07.1094
61. Biljan MM, Hemmings R, Brassard N (2005) The outcome of 150 babies following the treatment with letrozole or letrozole and gonadotropins. Fertil Steril 84(suppl 1):S95
62. Forman R, Gill S, Moretti M, Tulandi T, Koren G, Casper R (2007) Fetal safety of letrozole and clomiphene citrate for ovulation induction. J Obstet Gynaecol Can 29:668–671
63. Tulandi T, Martin J, Al-Fadhli R et al (2006) Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. Fertil Steril 85:1761–1765. doi:10.1016/j.fertnstert.2006.03.014
64. Badawy A, Shokeir T, Allam AF, Abdelhady H (2009) Pregnancy outcome after ovulation induction with aromatase inhibitors or clomiphene citrate in unexplained infertility. Acta Obstet Gynecol Scand 88:187–191. doi:10.1080/00016340802638199
65. Felemban A, Lin Tan S, Tulandi T (2000) Laparoscopic treatment of polycystic ovaries with insulated needle cautery: a reappraisal. Fertil Steril 73:266–269. doi:10.1016/S0015-0282(99)00534-8
66. Mercorio F, Mercorio A, Di Spiezio Sardo A, Barba GV, Pellicano M, Nappi C (2008) Evaluation of ovarian adhesion formation after

laparoscopic ovarian drilling by second-look minilaparoscopy. Fertil Steril 89:1229–1233. doi:10.1016/j.fertnstert.2007.05.009
67. Api M (2009) Is ovarian reserve diminished after laparoscopic ovarian drilling? Gynecol Endocrinol 25:159–165. doi:10.1080/09513590802585605
68. Cleemann L, Lauszus FF, Trolle B (2004) Laparoscopic ovarian drilling as first line of treatment in infertile women with polycystic ovary syndrome. Gynecol Endocrinol 18:138–143. doi:10.1080/09513590410001667869
69. Amer SA, Li TC, Metwally M, Emarh M, Ledger WL (2009) Randomized controlled trial comparing laparoscopic ovarian diathermy with clomiphene citrate as a first-line method of ovulation induction in women with polycystic ovary syndrome. Hum Reprod 24:219–225. doi:10.1093/humrep/den325
70. Abu Hashim H, Foda O, Ghayaty E, Elawa A (2011) Laparoscopic ovarian diathermy after clomiphene failure in polycystic ovary syndrome: is it worthwhile? A randomized controlled trial. Arch Gynecol Obstet 284:1303–1309. doi:10.1007/s00404-011-1983-x
71. Tummon I, Gavrilova-Jordan L, Allemand MC, Session D (2005) Polycystic ovaries and ovarian hyperstimulation syndrome: a systematic review. Acta Obstet Gynecol Scand 84:611–616. doi:10.1111/j.0001-6349.2005.00788.x
72. Van Der Meer M, Hompes PG, De Boer JA, Schats R, Schoemaker J (1998) Cohort size rather than follicle-stimulating hormone threshold level determines ovarian sensitivity in polycystic ovary syndrome. J Clin Endocrinol Metab 83:423–426. doi:10.1210/jc.83.2.423
73. Cristello F, Cela V, Artini PG, Genazzani AR (2005) Therapeutic strategies for ovulation induction in infertile women with polycystic ovary syndrome. Gynecol Endocrinol 21:340–352. doi:10.1080/09513590500463360
74. Homburg R, Insler V (2002) Ovulation induction in perspective. Hum Reprod Update 8:449–462. doi:10.1093/humupd/8.5.449
75. Homburg R, Howles CM (1999) Low-dose FSH therapy for anovulatory infertility associated with polycystic ovary syndrome: rationale, reflections and refinements. Hum Reprod Update 5:493–499. doi:10.1093/humupd/5.5.493
76. White DM, Polson DW, Kiddy D, Sagle P, Watson H, Gilling-Smith C, Hamilton-Fairley D, Franks S (1996) Induction of ovulation with low-dose gonadotropins in polycystic ovary syndrome: an analysis of 109 pregnancies in 225 women. J Clin Endocrinol Metab 81:3821–3824. doi:10.1210/jc.81.11.3821
77. Yarali H, Zeyneloglu HB (2004) Gonadotrophin treatment in patients with polycystic ovary syndrome. Reprod Biomed Online 8:528–537. doi:10.1016/S1472-6483(10)61099-1
78. López E, Gunby J, Daya S, Parrilla JJ, Abad L, Balasch J (2004) Ovulation induction in women with polycystic ovary syndrome: randomized trial of clomiphene citrate versus low-dose recombinant FSH as first line therapy. Reprod Biomed Online 9:382–390. doi:10.1016/S1472-6483(10)61273-4
79. Corfman RS, Ory SJ, Milad MP, Erickson LD, Bellevance TL, Ball GD (1993) A novel ovarian stimulation protocol for use with assisted reproductive technologies. Fertil Steril 60:864–870
80. Lu PY, Lee SH, Chen ALJ, Erickson LD, Atkinson EJ, Ory SJ (1996) Minimal stimulation achieves pregnancy rates comparable to human menopausal gonadotropins in the treatment of infertility. Fertil Steril 65:583–587
81. Abu Hashim H, Bazeed M, Abd Elaal I (2012) Minimal stimulation or clomiphene citrate as first line therapy in women with polycystic ovary syndrome: a randomized controlled trial. Gynecol Endocrinol. 28:87–90. doi:10.3109/09513590.2011.589924
82. Mukherjee S, Sharma S, Chakravarty BN (2010) Comparative evaluation of pregnancy outcome in gonadotrophin-clomiphene combination vs clomiphene alone in polycystic ovarian syndrome and unexplained infertility—a prospective clinical trial. J Hum Reprod Sci 3:80–84. doi:10.4103/0974-1208.69341
83. Aboulghar M, Baird DT, Collins J, ESHRE Capri Workshop Group et al (2009) Intrauterine insemination. Hum Reprod Update 15:265–277. doi:10.1093/humupd/dmp003
84. Abdelkader AM, Yeh J (2009) The potential use of intrauterine insemination as a basic option for infertility: a review for technology-limited medical settings. Obstet Gynecol Int 2009:584837. doi:10.1155/2009/584837
85. Abu Hashim H, Ombar O, Abd Elaal I (2011) Intrauterine insemination versus timed intercourse with clomiphene citrate in polycystic ovary syndrome: a randomized controlled trial. Acta Obstet Gynecol Scand 90:344–350. doi:10.1111/j.1600-0412.2010.01063.x