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Management of Women with Clomifene Citrate Resistant Polycystic Ovary Syndrome – An Evidence Based Approach

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1. Introduction

World Health Organisation (WHO) type II anovulation is defined as normogonadotrophic normoestrogenic anovulation and occurs in approximately 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% to 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 $11.9 \pm 2.4\%$ - $17.8 \pm 2.8\%$ in the first community-based prevalence study based on the current Rotterdam diagnostic criteria compared with $10.2 \pm 2.2\%$ - $12.0 \pm 2.4\%$ 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) is still holding its place as the first-line therapy for ovulation induction in these patients (2,8,9). CC contains an unequal mixture of two isomers as their citrate salts, enclomiphene and zuclomiphene. Zuclomiphene is much the more potent of the two for induction of ovulation, accounts for 38% of the total drug content of one tablet and has a much longer half-life than enclomiphene, being detectable in plasma 1 month following its administration (10). CC is capable of inducing a discharge of FSH from the anterior pituitary and this is often enough to reset the cycle of events leading to ovulation into motion. This is achieved indirectly, through the action of CC, a non-steroidal compound closely resembling an estrogen, in blocking hypothalamic estrogen receptors, signalling a lack of circulating estrogen to the hypothalamus and inducing a change in the pattern of pulsatile release of GnRH(10). Standard practice is to administer CC for 5 days from the second or third day of the menstrual cycle, starting with 50mg/day and increasing to 250mg/day (10). However managed care studies have shown that the most effective dosage is 100-150mg/day and over 75% of ovulations occur within these dosages (11). 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). In a large randomized trial, Legro et al., 2007 (12) compared the

effects of CC, metformin and combination therapy in 626 infertile women with PCOS. They reported an ovulation and clinical pregnancy rates per woman of 75.1% and 23.9% respectively, after CC treatment up to 150mg/day.

Clomiphene resistance defined as failure to ovulate after receiving 150 mg of CC daily for 5 days per cycle, for at least three cycles, is common and occurs in approximately 15 to 40% in women with PCOS (2, 13). Insulin resistance, hyperandrogenemia, and obesity represent the major factors involved in CC resistance; avert the ovaries from responding to raised endogenous FSH levels following CC therapy (14-16). Moreover, a genetic predisposition was suggested (17).

The purpose of this chapter is to review the evidence based treatment strategies for ovulation induction in anovulatory PCOS patients with known CC resistance, both the traditional and new ones. The traditional options include gonadotrophins and surgery (laparoscopic ovarian drilling). New strategies as insulin-sensitizing drugs, aromatase Inhibitors, oral contraceptives, dexamethasone, N-acetyl-cysteine...etc. Moreover, optimizing the body mass index (BMI) firstly before commencing therapy is an important issue to improve the treatment outcome in obese anovulatory women with PCOS. In vitro fertilization (IVF) is the recommended line of treatment after failure of these strategies; however, it is outside the scope of this chapter. Finally an algorithm will be provided to facilitate management of this important clinical issue.

2. Weight loss and lifestyle modifications

Obesity is strongly associated with PCOS and may be present in up to 50% of cases (18-22). Obese women with PCOS are more likely than thin women with PCOS to suffer from anovulation (18). 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 (22). 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, 23-25). The NICE, 2004 (13) recommended weight loss for anovulatory PCOS women who have a BMI > 29 kg/m² before starting ovulation induction therapy. In these women, weight loss of even 5% to 10% of body weight often restores ovulatory cycles (9, 19, 21). 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/m² ovulated at 6 months compared with only 12% of women with a BMI ≥ 35 kg/m² (18). Moreover, overweight women require higher doses of CC and gonadotrophins (19).

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 2 small studies (26, 27). 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, 25). 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 (28). 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 CC-resistant PCOS patients (29). Other lifestyle factors such as excessive caffeine intake, alcohol consumption, and smoking should also be addressed (13,20).

Otta et al., 2010 (30) in a randomized, double-blind, and placebo control trial compared lifestyle modification and 1500 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 & Javedani, 2010 (31) 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 (32). Importantly, this disorder has been found to improve markedly after sustained weight loss following bariatric surgery (33). Anti-obesity pharmacological agents have been used in obese women with PCOS. Both orlistat, which blocks intestinal absorption of fat (34), and sibutramine, an appetite suppressant (35), 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).

3. Gonadotrophins

Ovulation induction for women with anovulatory PCOS using gonadotrophin therapy is based on the physiological concept that initiation and maintenance of follicle growth may be achieved by a transient increase in FSH above a threshold dose for sufficient duration to generate a limited number of developing follicles (8). 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 ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy (8, 9, 13, 36-38). Furthermore, a significant and consistent relationship between PCOS and OHSS was reported in a systematic review (39). The high sensitivity of the PCOS to gonadotrophic stimulation is probably related to the fact that they contain twice the number of available follicle-stimulating hormone (FSH)-sensitive antral follicles in their cohort than the normal ovary (40). A meta-analysis concluded that the outcomes of treatment achieved with hMG and with FSH alone in infertile patients with PCOS were similar except for a reduction in the risk of OHSS with the urinary FSH (uFSH) (41). 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 mono-follicular development which is ~69% (54-88%) (36,42) with nearly complete elimination of OHSS (0-2.4%) and a multiple pregnancy rate of ~6% (36,43). The recommended approach is to begin with a low dose of gonadotrophin, typically 37.5- 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 (38, 44). There is no evidence of a difference between recombinant FSH (rFSH) and uFSH for ovulation induction in CC-resistant PCOS women (45,46). In addition, a randomised trial (RCT) of highly purified uFSH (HP-uFSH) versus rFSH found that the former was non-inferior compared with the latter with respect to ovulation rate (85.2% versus 90.9%) in anovulatory WHO Group II women who failed to ovulate or conceive on CC (47).

4. Laparoscopic Ovarian Diathermy (LOD)

Laparoscopic ovarian diathermy (LOD) 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 OHSS (8, 9,13, 48-51). Bayram et al., 2004 (50) in a RCT compared LOD with rFSH in 168 CC-resistant PCOS women. They reported an ovulation rate of 70% and 69% per cycle and pregnancy and live-birth rates 37%, 75% and 34%, 60% of patients respectively following LOD and FSH therapy. In patients remaining anovulatory 8 weeks after LOD or those who subsequently became anovulatory, adjuvant therapy with CC or gonadotrophins was required to achieve equivalent pregnancy and live-birth rates (50). A Cochrane review found no difference in the rates of miscarriage, ongoing pregnancy or live birth between LOD and gonadotrophins. Multiple pregnancy rates were significantly lower with LOD than with gonadotrophins (1% versus 16%; OR 0.13, 95% CI 0.03 to 0.52) (49). A recent study concluded that LOD for women with CC-resistant PCOS is as effective as ovulation induction with rFSH treatment in terms of live births, but reduces the need for ovulation induction or ART in a significantly higher proportion of women and increases the chance for a second child (52).

The main shortcomings of LOD are the need for general anesthesia and the risk of postoperative adhesions (53, 54). 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 (55). Moreover, an economic evaluation has shown that the cost of a live birth after LOD is approximately one-third lower than the equivalent cost of gonadotrophin treatment (56). The most commonly used energy for LOD is electrocautery. It has been reported that the clinical and endocrine response to LOD is governed by a dose response relationship. Four punctures per ovary using a power setting of 30 W applied for 5s per puncture (i.e. 600 J per ovary) are sufficient to produce an optimal response (67% spontaneous ovulation rate and 67% conception rate). Reducing the thermal energy below that level reduces the chances of spontaneous ovulation and conception (57). Also, different studies argued for unilateral LOD being equally efficacious as bilateral drilling in inducing ovulation and achieving pregnancy in CC resistant PCOS patients and may be regarded as a suitable option with the potential advantage of decreasing the chances of adhesion formation (58-60).

Although it remains unclear as to how LOD induces ovulation, a potential mechanism is that LOD drains the ovarian follicles containing a high concentration of androgens and inhibin, which causes the reduction of blood androgens and blood inhibin resulting in an increase of FSH and recovery of the ovulation function (51,53, 61,62). Surgery may also provoke an increased blood flow to the ovary, allowing increased delivery of

gonadotrophins (53, 62). Women with marked obesity (BMI >35 kg/m²), marked hyperandrogenism (serum testosterone concentration >4.5 nmol/l, free androgen index (FAI) >15) and/or long duration of infertility (>3 years) seem to be poor responders to LOD. On the other hand, high LH levels >10 IU/l in LOD responders appear to predict higher probability of pregnancy (63). van Wely et al., 2005 (64) reported that women who had an age at menarche < 13 years, an LH/FSH ratio < 2 and a glucose level < 4.5 mmol/l, were more likely to remain anovulatory following LOD.

Restoration of consecutive spontaneous ovulations after LOD in some CC-resistant PCOS patients is one of the most important advantages of this approach (65). Another potential advantage is the increased responsiveness of the ovary to oral ovulation induction agents following the procedure. In a recent study, we evaluated whether LOD in CC-resistant PCOS patients led to the restoration of CC-sensitivity. LOD was performed in 234 CC-resistant PCOS patients. In 150 patients ovulation occurred. The remaining 84 anovulatory patients were again treated with CC. Ovulation occurred in 30 /84 patients (35.7%), meanwhile, pregnancy occurred in 13/ 84 patients (15.5%). Hyperandrogenism and insulin resistance were negative predictors (66).

5. Insulin-sensitizing drugs

Approximately 50%-70% of all women with PCOS have some degree of insulin resistance (67). Hyperinsulinemia probably contributes to the hyperandrogenism which is responsible for the signs and symptoms of PCOS (67). Metformin, a biguanide, is now the most widely insulin sensitizer used for ovulation induction in women with PCOS. In these women, it appears to affect ovarian function in a dual mode, through the alleviation of insulin excess acting upon the ovary and through direct ovarian effects. Being an insulin sensitizer, it reduces insulin secretion and, consequently, lowers circulating total and free androgen levels with a resulting improvement of the clinical sequelae of hyperandrogenism. Importantly, it also seems to have a direct action on ovarian theca cells to decrease androgen production (68). 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 (69). 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 (70).

Many investigators have demonstrated an improvement in insulin sensitivity and a significant decrease in serum insulin and free testosterone levels after long term treatment with metformin for 5–8 weeks (71–73). Creanga et al., 2008 (74) in a meta-analysis, confirmed that metformin in combination with CC increased the likelihood of ovulation [OR 4.39, 95% CI 1.94–9.96, number - needed- to-treat (NNT) 3.7] and pregnancy (OR 2.67, 95% CI 1.45–4.94, NNT 4.6) in comparison with CC alone, especially in CC-resistant and obese PCOS patients. Actually, different mechanisms explaining why metformin therapy would facilitate ovulation induction by CC in CC-resistant PCOS patients have been proposed entailing; an intrinsic alteration of follicle steroidogenesis through the IGF-I pathway in granulosa cells (73); direct inhibition of androgen production in ovarian thecal cells (75); reduction in the

adrenal steroidogenesis response to ACTH (76) and recently its central action on the pituitary gland with an LH lowering and prolactin effects in the PCOS women (77). There are unpleasant gastrointestinal side effects including nausea, vomiting, bloating, cramps and diarrhoea. Rare complication includes lactic acidosis. Metformin has been used in increasing doses from 500 to 1500 mg daily for the induction of ovulation in women with PCOS (9).

Recently, the efficacy of the combination of metformin and CC versus other traditional options including gonadotrophins and LOD for treatment of CC-resistant infertile PCOS patients has been reported. Two RCTs compared the combination of metformin and CC with LOD, showing that both are effective approaches to treat CC-resistant infertile PCOS patients (78, 79). In fifty primary infertile patients with CC-resistant PCOS, Palombo et al., 2010 (78) found no significant difference between the 2 groups in pregnancy and live-birth rates per cycle (13.1% vs. 16.3% and 11.2% vs. 14.1% respectively). However, the ovulation rate per cycle was significantly lower in LOD group than in Metformin/CC group (56.5% vs. 72.0%). On the other hand, in a well designed adequately powered RCT comprised of 282 anovulatory women with CC-resistant PCOS, we reported no significant difference between the 2 groups in ovulation and pregnancy rates per cycle (67% vs. 68.2% and 15.4% vs. 17% respectively). However, a significant difference regarding midcycle endometrial thickness was found (9.2 ± 1.2 mm vs. 7.6 ± 1.1 mm, in Metformin/CC and LOD groups respectively) (79). George et al., 2003 (80) in a small trial of limited power compared sequential treatment of metformin and CC with conventional hMG protocol in 60 CC-resistant PCOS patients. In this trial, metformin alone was given as a single pretreatment for 6 months, followed by ovulation induction with CC. There was no significant difference in pregnancy rates between the two groups (16.7 vs. 23.3%). However, in the metformin group, significant improvements in menstrual function and ovulation rate of 46.7% with a significant decrease in fasting insulin levels were reported. The ovulation rate in hMG group was 43.3%, with a high drop-out rate. Recently, in a well designed adequately powered RCT we compared the effects of combined metformin-CC with HP-uFSH using low-dose, step-up regimen for three cycles in 153 anovulatory women with CC-resistant PCOS (81). Actually, combined metformin-CC therapy was not expected to be more effective than gonadotrophins, however, it did result in modest ovulation and pregnancy rates. Ovulation and pregnancy rates per cycle were 62% vs. 83.8% and 11.2% vs. 21.5% in combined metformin-CC group and HP-uFSH groups respectively. HP-uFSH administration had good results, but, the low-dose, step-up regimen requires extensive monitoring and expertise, and has high costs. Accordingly, it is logical to offer combined metformin-CC therapy first in the step-wise treatment protocol for CC-resistant PCOS patients before resorting to more expensive alternatives especially in developing communities where economic aspects of therapy are important (81).

The safety of metformin has sparked a heated debate. Recent evidence that metformin is probably safe during the first trimester of pregnancy and beyond is accumulating (82-85). Moreover, a recent meta-analysis found no effect of pregestational metformin administration on abortion risk in PCOS patients (86). Other insulin sensitizers from the thiazolidinediones family, namely rosiglitazone, have been used effectively in CC-resistant PCOS patients. In a RCT, the combination of rosiglitazone and CC was reported to be more effective than metformin and CC in terms of ovulation rate (64.3 vs. 36.4%, respectively); whereas no statistical significance was observed in pregnancy rate (50 vs. 38.5%) (87). Also, a recent RCT reported no significant difference between combined treatment with

rosiglitazone and CC vs. LOD in 43 CC-resistant PCOS patients in terms of biochemical response, ovulation rate (80.8 vs. 81.5%) and pregnancy rate (50 vs. 42.8%) (88). A retrospective analysis investigated various clinical, biochemical, and ultrasonographic factors that determine clinical response to rosiglitazone as a first-line therapy in a series of PCOS women with newly diagnosed CC-resistance. It showed that marked obesity, marked hyperandrogenism, and long duration of infertility were predictors of resistance to rosiglitazone therapy (89).

6. Third-generation aromatase inhibitors

Third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) are approved adjuvants for treatment of estrogen-receptor-positive breast cancer (90) that were first used in ovulation induction in anovulatory women in 2001 (91). 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 (92). 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 (92).

Recent studies showed that letrozole has better ovulation and pregnancy rates in comparison to CC and placebo in patients with CC-resistant PCOS (93-96). There are 2 prospective studies in the literature comparing the two commercially available third generation AIs, letrozole and anastrozole in CC-resistant infertile women with PCOS. Al-Omari et al., 2004 (97) studied 40 cases who were considered CC-resistant if failed ovulation after 200 mg CC daily for 5 days or were ovulatory with an endometrium thickness less than 5 mm. Ovulation and pregnancy rates per cycle were significantly higher with letrozole compared with anastrozole (84.4% vs. 60% and 18.8% vs. 9.7%, respectively). Endometrium thickness was significantly greater for letrozole compared with anastrozole (8.16 ± 1.32 vs. 6.53 ± 1.55 mm). Multiple pregnancies did not occur. In this small trial, PCOS diagnostic criteria were not stated. Additionally, the dose of CC used to define resistance was very high, possibly suggesting an extremely refractory population. Importantly, a larger RCT compared the efficacy of letrozole and anastrozole in 220 CC-resistant women with PCOS diagnosed with Rotterdam criteria. More growing and mature follicles and greater endometrial thickness in patients receiving anastrozole were demonstrated; however, no significant advantage for anastrozole over letrozole with regard to ovulation, pregnancy or miscarriage rates was observed (63.4 vs. 62% and 15.1 vs. 12.2% and 9.5 vs. 11.1% respectively). Two twin pregnancies occurred with letrozole, while none occurred with anastrozole (98). In the above mentioned 2 studies, a short course (5 days) of letrozole was used. However, a long letrozole protocol (10 days) was also proposed, with proved advantages in terms of more mature follicles and subsequently more pregnancies (99).

One small trial of limited power compared combined metformin-letrozole vs. metformin-CC in 60 CC-resistant PCOS patients reported that combined metformin-letrozole was

associated with significantly more endometrial thickness, E2 levels and full-term pregnancy rate. However, no statistically significant difference was found between the two groups as regards the mean number of mature follicles, ovulation and pregnancy rates. The authors admitted that combined metformin- letrozole is better than letrozole alone, particularly in overweight women and asked for further studies to confirm their hypothesis (100). Recently, in a well designed adequately powered RCT, we compared the effects of letrozole monotherapy (2.5 mg daily for 5 days from D3-7 of the cycle) with combined metformin-CC in 250 anovulatory women (582 cycles) with CC resistant PCOS. Our findings suggested that letrozole monotherapy and combined metformin-CC were equally effective for inducing ovulation and achieving pregnancy in patients with CC-resistant PCOS (64.9% vs.69.6% and 14.7% vs. 14.4% respectively). The total number of follicles was significantly more in the combined metformin-CC group (4.4 ± 0.4 vs. 6.8 ± 0.3). A non significant increase in endometrial thickness on the day of hCG administration was observed in the letrozole group (9.5 ± 0.2 mm vs. 9.1 ± 0.1 mm). Since letrozole was well tolerated, it is considered as an acceptable alternative if CC-resistant PCOS patients cannot tolerate long-term metformin pretreatment (101).

More recently, the efficacy of the AIs vs. other traditional options including gonadotrophins and LOD for treatment of CC-resistant infertile PCOS patients has been reported. 2 RCTs compared the effect of letrozole (2.5mg and 5 mg respectively from day 3 to day 7 of menses for 6 consecutive cycles) with LOD for ovulation induction in CC resistant women with PCOS. Both trials reported that letrozole and LOD are equally effective for inducing ovulation and achieving pregnancy in these patients. Moreover, women in the letrozole group had a significantly thicker endometrium than those in the LOD group. In view of the invasiveness and cost of surgery, it seems plausible that letrozole therapy should be tried first for most of those women before shifting to LOD (102,103). A recent large randomized trial by Ganesh et al., 2009 (104) compared the efficacy of letrozole with that of rFSH and CC/rFSH for ovarian stimulation in IUI cycles in 1387 PCOS women after CC failure. They reported an ovulation rate of 79.30% in letrozole group vs. 56.95% and 89.89% in other groups respectively and pregnancy rate of 23.39% in letrozole group vs. 14.35% and 17.92% in other groups respectively. However, they included not only CC-resistant PCOS patients but also those who failed to conceive with 100 mg/day CC for 6 cycles despite ovulating and those who showed poor endometrial development i.e. endometrial thickness < 7 mm on the day of hCG administration.

Letrozole was evaluated in 44 women with CC-resistant PCOS and both responders and nonresponders were characterized. PCOS was diagnosed by Rotterdam criteria; CC-resistance was defined as failure to ovulate after 6 cycles of 150 mg CC /day for 5 days. Whereas response to CC is less likely with elevated BMI, amenorrhea, and increased age, significant differences between letrozole responders and nonresponders were not noted for any evaluated measure. This apparent lack of predictive factors for letrozole suggests utility in CC-resistant patients since its efficacy is not limited to specific patient characteristics (105). The safety of letrozole has elaborated a vivid discussion. Preliminary data by Biljan et al., 2005 (106) suggested an increased risk of congenital anomalies in letrozole treated babies, whereas recent data from retrospective and prospective trials (107,108) have contested these initial findings and supported the safety of letrozole compared to traditional ovulation induction treatment.

7. Oral contraceptives

Branigan & Estes., 2003 (109) in a RCT showed that the suppression of the hypothalamic pituitary- ovarian axis for 2 months with combined oral contraceptives (COC) (0.03 mg of ethinyl estradiol and 0.15 mg of desogestrel) followed by CC, at dosage of 100 mg/day on days fifth to ninth of the cycle, improved ovulation and pregnancy rates in CC resistant women in comparison with repeated cycles of CC alone. Oral contraceptive administration showed to reduce serum LH, estradiol and androgen levels. These hormonal changes, especially the reduced androgenic milieu, could act improving the ovarian microenvironment, and thus the ovarian response to CC. Kriplani et al., 2010 (110) in a RCT reported that in women with PCOS, a drospirenone containing COC has better outcome in terms of persistent regular cycles, antiandrogenic effect, fall in BMI and BP, better lipid profile, favorable glycemic and hormonal profile than desogestrel-containing COC.

8. N-acetyl-cysteine

N-acetyl-cysteine (NAC) is a mucolytic drug. Fulghesu et al., 2002 (111) demonstrated that long term NAC treatment (1.8 g/d for 5–6 weeks) was associated with significant increase in insulin sensitivity and reduction in insulin levels, testosterone and FAI in hyperinsulinemic PCOS. Rizk et al., 2005 (112) showed that the combination of NAC (1.2 g/d) with CC (100 mg/d) for only 5 days significantly increased both ovulation and pregnancy rates in obese women with CC-resistant PCOS compared with placebo (49.3% vs. 1.3% and 21.3% vs. 0, respectively). Actually, these results supporting the shorter duration (5 days only) of NAC administration in CC-resistant PCOS women have not been replicated by other trials. Recently, in a well designed adequately powered RCT, we reported that the efficacy of metformin-CC combination therapy is higher than that of NAC – CC for inducing ovulation and achieving pregnancy among CC-resistant PCOS patients (113). In our study, the dose and duration of NAC were chosen based on that published by Fulghesu et al., 2002(111). Over a 3-month follow-up period, women in metformin-CC group had significantly higher ovulation and pregnancy rates compared with women in NAC-CC group (69.1% vs. 20.0% and 22.7% vs. 5.3%, respectively). Moreover, the level of serum estrogen, the endometrial thickness on the day of hCG administration and the midluteal serum progesterone level were all significantly higher for women in metformin-CC group than other group. Additionally, a lower miscarriage rate was observed among women in metformin-CC group (113).

9. Dexamethasone therapy

Dexamethasone therapy during the follicular phase has been described without any side effects or serious events (114). Parsanezhad et al., 2002 (115) in a double-blind RCT, showed the safety and the efficacy of a high-dose short course of dexamethasone for inducing ovulation in 230 CC-resistant patients with PCOS and normal DHEAS levels. They reported significantly higher ovulation and pregnancy rates in those who received 200mg of CC (days 5–9) and 2mg of dexamethasone (days 5–14) compared with CC alone (88% vs. 20% and 40.5 vs. 4.2% respectively). In these patients, dexamethasone reduced circulating DHEAS, T, and LH levels and the LH/FSH ratio after 2 weeks of treatment (115). These results were further confirmed in another RCT (116).

10. Bromocriptine

Currently, evidence suggests that PCOS and hyperprolactinaemia are two distinct entities without a patho-physiological link (117-119). Bromocriptine administration provided no benefit in CC-resistant PCOS patients with normal prolactin levels, receiving 150mg CC (days 5–9) and bromocriptin continuously administrated at a dosage of 7.5 mg daily (120). On the contrary, the use of cabergoline, a long-acting ergoline D2 agonist derivative, has been proved to improve ovarian response in hyperprolactinemic patients with PCOS candidates for treatment with gonadaotrophins (121). These data suggested the presence of a dopaminergic component in the control of LH release in PCOS patients (121).

11. Conclusion

Ovulation induction in women with PCOS who present with CC-resistant anovulatory infertility remains a major challenge in gynecologic endocrinology. Traditional alternatives for CC-resistant patients include gonadotrophin therapy and laparoscopic ovarian diathermy. However, because of the cost and risk inherent in these therapies, alternative treatments are attractive. Obese PCOS women should try to attain BMI<30kg/m2 prior to commencing ovulation induction therapy. In view of our experience, combined metformin-CC therapy did result in modest ovulation and pregnancy rates. Accordingly, it is logical to offer combined metformin- CC therapy for CC-resistant PCOS patients before resorting to more expensive alternatives especially in developing communities where economic aspects of therapy are important. Third generation aromatase inhibitors are promising agents for treatment in these patients. Figure 1 shows an algorithm for ovulation induction treatment in anovulatory infertile women with CC-resistant PCOS.

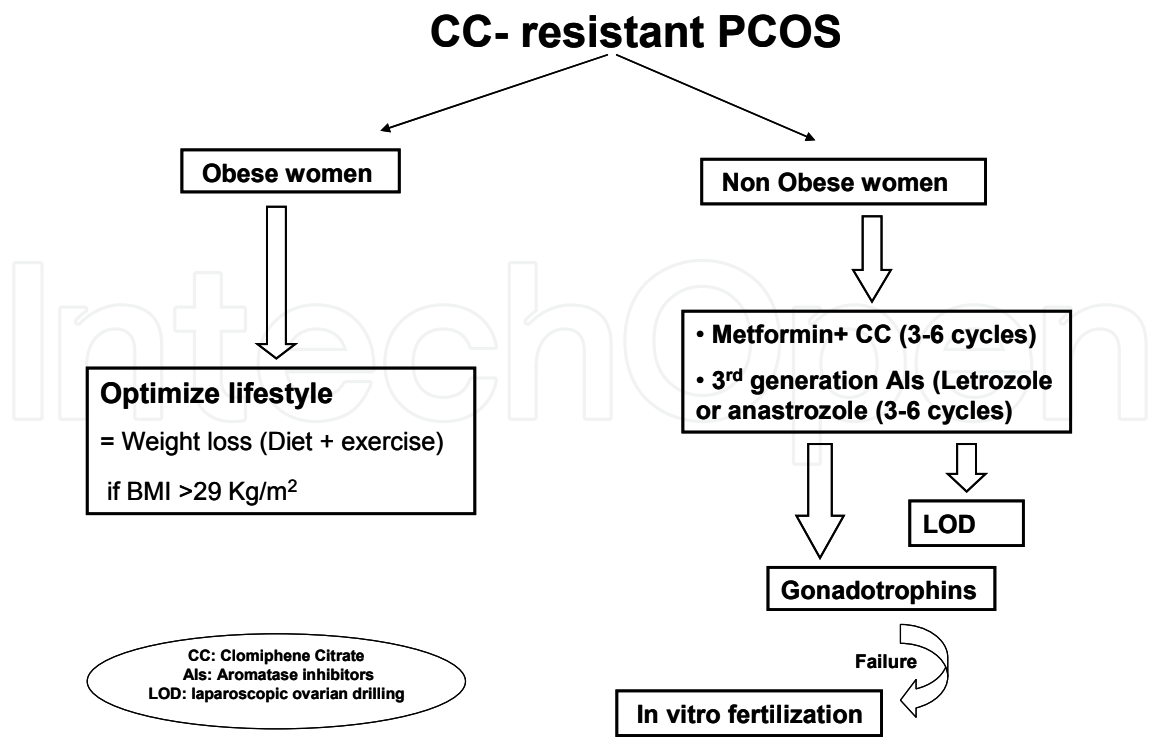


Fig. 1. Algorithm for ovulation induction treatment in anovulatory infertile women with CC-resistant PCOS.

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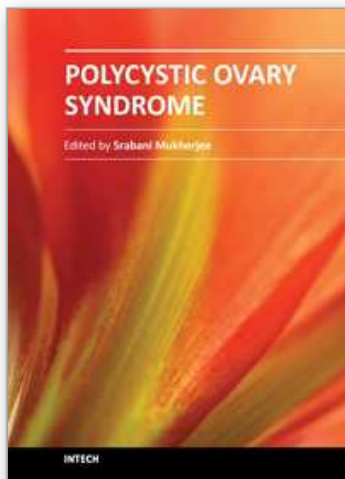
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Brought into the limelight many decades ago, Polycystic Ovary Syndrome (PCOS) is still, to date, surrounded by controversy and mystery. Much attention has been attracted to various topics associated with PCOS research and there has been a healthy advance towards bettering the understanding of the many implications of this complex syndrome. A variety of topics have been dealt with by a panel of authors and compiled in this book. They span methods of diagnosis, reproductive anomalies, metabolic consequences, psychological mindset and ameliorative effects of various lifestyle and medical management options. These books are designed to update all associated professionals on the recent developments in this fast-growing field and to encourage further research into this thought-provoking subject.

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