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MINIREVIEW

Up-date Management of Non Responder to Clomiphene Citrate in Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is a heterogeneous disorder in which chronic anovulation is a common feature despite the presence of multiple micro- structures in the ovaries. A growing body of evidence has suggested that serum hyperinsulinemia contributes to the excess ovarian androgen secretion observed in women with PCOS. The standard therapy for anovulatory women with PCOS is oral administration of clomiphene citrate (CC). However, a significant proportion of women with PCOS fail to ovulate with the use of standard dosage of CC and are called CC-resistant PCOS. The recent introduction of the insulin-sensitizing agents as adjuvants to clomiphene citrate and gonadotropins has changed the treatment strategy. This is a comprehensive review of the literature, with an emphasis on the role of hyperinsulinemia in the pathogenesis of PCOS and on randomized controlled trials of the medical and surgical treatment options for women with CC-resistant PCOS. Although both standard and novel treatments were addressed in the present review, special attention was paid to the evidence in support of the recent introduction of insulin-sensitizing agents in the management of anovulatory women with CC-resistant PCOS.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive age, with an incidence of 5 -10% (1). It is also one of the most enigmatic diseases, probably due to the multisystem nature of associated disorders, and the confounding variables associated with diagnosis. The disease is characterized by either oligo- or anovulation leading to oligomenorrhea, hyperandrogenism, reduced fertility, increased rate of miscarriage, dyslipidemia, and frequently insulin resistance, occurring in both lean and obese individuals, most commonly in the latter (2). Anovulatory infertility secondary to PCOS is common (3). Classically clomiphene citrate (CC) is the first approach to induce ovulation in patients with PCOS. Although 70-80% of PCOS women can ovulate by the treatment with CC, only 40% of the PCOS women become pregnant (4). Women who do not ovulate with increasing doses of CC are described as being CC-resistant and remain a major challenge in gynecologic endocrinology (3).

Traditional alternatives for CC-resistant patients include gonadotropin therapy and

laparoscopic ovarian diathermy (5). However, gonadotropin therapy is encrusted with substantial increase in costs and risks of ovarian hyperstimulation syndrome (OHSS) as well as multiple pregnancy compared to ovulation induction with CC (6). Given the importance of hyperinsulinemia in the development of hyperandrogenism and disrupted folliculogenesis, it seems likely that medication that acts as insulin-sensitizing agents may be useful in the restoration of normal endocrinologic and clinical parameters of this condition (7). Moreover, these drugs have allowed us to develop less aggressive therapy that is safer for affected women (8).

In this review, the role of hyperinsulinemia in the pathophysiology of PCOS will be discussed, and both novel and conventional treatment regimens for CC-resistant PCOS will be described.

I. Role of hyperinsulinemia in PCOS

Since the description by Stein and Leventhal (1935) on the syndrome of amenorrhea, infertility and hirsutism associated with sclerotic ovaries, the entity of PCOS has been investigated extensively but its etiology remains to be a subject of much speculation (9). However, insulin resistance with compensatory hyperinsulinemia is a prominent feature of the syndrome and appears to have a pathophysiological role in the hyperandrogenism of the disorder (7). The association between increased insulin resistance and polycystic ovaries is now well recognized (10).

Both lean and obese women with PCOS have showed ample evidence of decreased insulin sensitivity, but insulin resistance accompanied by compensatory hyperinsulinemia is most marked when there is an interaction between obesity and the syndrome (11). Hyperinsulinemia results in increased ovarian androgen biosynthesis in vivo and in vitro and decreased sex hormone-binding globulin (SHBG) synthesis from the liver, leading to increased bioavailability of free androgen (12). The excess in local ovarian androgen augmented by hyperinsulinemia causes premature follicular atresia and anovulation (13).

Chronic hyperinsulinemia and hyperandrogenemia can cause gonadotropin imbalance as an increase in LH and decrease in FSH, which is characteristic of PCOS (14). Early exposure of granulosa cells in small follicles to high concentrations of LH and insulin may prevent the full expression of the potential of these cells for mitotic growth and instead of growing, these granulosa cells may luteinize prematurely and as a result, no large follicles develop and thus ovulation does not occur (15). It is well known that obesity is associated with insulin resistance and approximately 60-70% of woman with PCOS are obese (16). Hyperinsulinemia can inhibit insulin-like growth factor binding protein-1 (IGFBP-1) production by the liver with subsequent increase in the free IGF-I in circulating blood (17). The increased IGF-I in conjunction with increased LH could stimulate androgen production by ovarian thecal cells (18).

There are several mechanisms for insulin resistance which include peripheral target tissue resistance, decreased hepatic clearance or increased pancreatic sensitivity (19). Insulin resistance in at least 50 % of PCOS women appears to be related to excessive serine phosphorylation of the insulin receptor. A factor extrinsic to the insulin receptor, presumably a serine/threonine kinase causes this abnormality and is an example of a new mechanism for human insulin resistance related to factors controlling insulin receptor signaling (20). However, the mechanism of serine/threonine kinase activation still unknown.

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The recently discovered GH secretagogue, ghrelin is intimately involved in control of appetite and weight regulation. Ghrelin levels are decreased in PCOS women and are highly correlated to the degree of insulin resistance, suggesting that ghrelin could be linked to insulin resistance in PCOS women (21). Obese women with PCOS have lower ghrelin levels than obese women without PCOS. Only in obese women with PCOS, ghrelin levels in serum negatively correlates with insulin sensitivity (22). Vascular endothelial growth factor (VEGF) is an endothelial cell mitogen with potent angiogenic property. VEGF originating from the ovarian follicle or corpus luteum seems to be involved not only in the regulation of ovulation and the subsequent corpus luteum formation but also in the development of OHSS (23).

Women with PCOS have higher serum concentrations of VEGF than women with normal ovarian function (24). Insulin is one of the modulators of VEGF expression and increases VEGF mRNA and protein levels in retina (25). The stimulatory effect of insulin on VEGF expression may be related to a high incidence of OHSS in PCOS women treated by gonadotropins.

The following observations provide evidence that insulin resistance associated with PCOS is not the result of hyperandrogenism:

- 1) Hyperinsulinemia is not characteristic of hyperandrogenism in general but is uniquely associated with PCOS (26).
- 2) Treatment with long-acting GnRH agonists does not change insulin levels or insulin resistance (27).
- 3) Oophorectomy in patients with hyperthecosis accompanied by hyperinsulinemia and hyperandrogenemia does not change insulin resistance, despite the decrease in androgen levels (28).

II. Standard medical management of clomiphene-resistant PCOS

1. Adjuvant therapy with CC

Clomiphene resistance was defined as failure to ovulate during the treatment with a total dose of 200 mg of CC for at least four cycles (8). Obesity and insulin resistance are closely implicated in the etiology of PCOS and thus improvement of these conditions should be a central of treatment. Short-term weight loss has been consistently successful in reducing insulin resistance and restoring ovulation and fertility (29). In many patients weight loss was associated with normalization of hormonal disturbances and resumption of regular ovulation (30). Patients with PCOS have a high prevalence of abnormal glucose tolerance which carries a high risk of cardiovascular disease. Weight loss has a beneficial impact on these consequences (31). The only known effective therapy for overweight, hyperandrogenic and hyperinsulinemic anovulation is weight loss. Both hyperinsulinemia and hyperandrogenemia can be attenuated by weight loss which should be at least more than 5% of the initial body weight (32).

Contraceptive pills reduce the high serum LH and androgen levels which contribute to the lack of ovarian response to ovulation inducing agents. When contraceptive pills are used for 6 months followed immediately by resumption of CC administration, a better response might be obtained (33). Several reports have shown that GnRH agonist / oral contraceptive combination is effective in lowering serum LH levels and reducing hyperandrogenism and hirsutism in patients with PCOS. Addition of GnRH agonist to contraceptive pills may be useful particularly in obese patients (34). Since the short-course treatment with dexamethazone during the follicular phase of the menstrual cycle facilitates folliculogenesis, it can enhance the effectiveness of CC on ovulation induction (5). Administration of dexamethazone 0.5mg at bedtime, to blunt the night time peak of ACTH, can decrease the

adrenal contribution to circulating androgens and thus diminish the androgen level in the micro-environment in the ovary. The dexamethazone should be maintained daily until pregnancy is established (35).

Clinical experiences suggest that successful induction of ovulation and achievement of pregnancy with bromocriptine can occur in the absence of galactorrhea and with normal prolactin levels in women who failed to respond to CC (36, 37). The method of administration is to start with a small dose of dopamine agonist to build up tolerance. Once the optimum dose is reached, therapy is pursued for 2 months (38).

2. Gonadotropin therapy

Gonadotropin therapy is widely used for ovulation induction in CC-resistant PCOS patients (39). Human menopausal gonadotropin (hMG) is a gonadotropin preparation extracted from the urine of postmenopausal women. The commercial preparation contains 75 units of FSH and 75 units LH (Pergonal, Serono and Humegon, Organon) (40). The use of urofollitropin, a purified FSH preparation virtually free of LH activity, appears to be a recommendable treatment, since there is evidence that pure FSH may significantly reduce tonic LH levels, favorably alter the intraovarian hormonal milieu, and promote the initial follicular development with minimal risk of multiple follicular growth or ovarian hyperstimulation (41).

The conventional dose protocol starts with a daily dose of 150 IU of hMG for 14 day starting from 3rd-5th day of the menstrual cycle or at the commencement of withdrawal bleeding induced by progesterone. If necessary the dose is increased by 75 IU for another 7 days but the daily dose should not exceed 225 IU (42-43). Since the medical and social implications of the rising rate of multiple pregnancy have emerged, the need to re-evaluate the use of gonadotropin therapy for ovulation induction in PCOS patients has become imperative, thus leading to the implementation of low-dose treatment regimen (44).

The step-down regimen starts with the daily dose of 225 IU of hMG for the first two day then the daily dose is reduced to 75 IU from the 3rd day. When the follicular diameter does not show progressive growth the dose of hMG is increased to 150 IU after the 7 days (41). On the other hand, the low dose step-up regimen consists of 75 IU hMG per day for the first 7 days and if the follicular diameter did not exceed 9 mm the dose is increased by increments of 37.5 IU every 7 days (45). This low-dose step-up regimen is based on the concept that a substantial level of FSH is needed to reach the threshold for ovarian response to occur (46). There is a narrow range for mono-follicular growth between the FSH threshold and ceiling FSH level (47). Many reports have indicated that the rate of monofollicular cycle reached nearly 50-70 % and the incidences of OHSS and multiple pregnancy were extremely low in PCOS patients who received the low dose step-up regimen (45).

Through the application of recombinant DNA technology, it has been possible to produce recombinant FSH for therapeutic use without the need of extraction from postmenopausal urine. Recombinant FSH was prepared by transfecting Chinese hamster ovary cell line with both FSH subunit genes (48). Low dose recombinant FSH is as effective as low dose hMG in producing reasonable ovulation and pregnancy in women with PCOS and past history of severe OHSS (49).

Anovulatory women with PCOS are at greater risk for OHSS (10). Two thirds of the cases of OHSS occur early in the conception cycle. The basic disturbance in hyperstimulation is a shift of fluid from the intravascular space into the abdominal cavity creating a massive third space. A growing body of evidence implicates VEGF in the pathophysiology of OHSS (50). The increased serum concentrations of VEGF in women with PCOS may not only be due to an increased number of actively secreting granulosa cells

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but also due to increased secretory capacity of each granulosa cell (51).

Withholding hCG is most commonly used for the prevention of OHSS in patients predicted to be at high risk of developing OHSS, but it is at an expense of losing the cycle. However, serum estradiol (E2) levels above which hCG administration should be withheld vary widely among different centers. It is suggested to withhold hCG if serum E2 levels > 2000 pg/ml in non-in vitro fertilization (IVF) cycles and >6000 pg/ml in IVF cycles (52).

Cycles overstimulated with gonadotropins can be managed with a controlled drift period as an alternative to cancellation. The duration of the pause in treatment ranges from 2 to 10 days. Gonadotropins should be withheld in patients whose serum E2 exceeded 6000 pg/ml and GnRH agonist administration is continued until E2 levels fall below 3000 pg/ml and then 10000 IU hCG is administered to trigger ovulation (53). In patients at risk of OHSS, intranasal GnRH agonist (buserelin 200 µg, three times daily at 8-hourly interval) is used to trigger ovulation as an alternative to hCG (54).

The incidence of multiple births after gonadotropin therapy is high ranging from 11- 44% (55). As recently shown in long-term follow-up studies, multiple pregnancies have a large adverse impact on perinatal morbidity and mortality (56). Therefore, the need for appropriate stimulation protocols, careful cycle monitoring, and strict criteria for the cancellation of treatment to avoid multiple implantations have been advocated (57).

Studies from various infertility programs have demonstrated that pregnancy after OHSS has an associated increased incidence of preterm delivery that is because relaxin can soften and ripen the uterine cervix. Serum relaxin levels of 7 ng/ml can predict a risk of preterm delivery in 50% of patients (58).

III. Novel medical treatment of CC-resistant PCOS

A novel therapeutic approach has recently emerged from the observation that most women with PCOS suffer from insulin resistance and compensatory hyperinsulinemia. It is now evident that the elevated circulating insulin concentrations impede ovulation (59). Studies with insulin-sensitizing drugs in PCOS patients have suggested that the use of metformin, troglitazone or D-Chiro-inositol will be effective in the treatment of PCOS.

1. Metformin

The biguanide metformin is a drug commonly used for increasing insulin sensitivity in noninsulin-dependent diabetes mellitus (NIDDM) without producing hypoglycemia although the precise mechanisms by which metformin ameliorates insulin sensitivity are incompletely understood (60). Metformin therapy in women with PCOS is associated with a reduction in aromatase activity in response to FSH (61). Metformin therapy in PCOS patients reduced hyperinsulinemia and hyperandrogenemia while facilitating normal menses and pregnancy. Associated with decreasing insulin levels, a decrease in androgen levels seen during a short-term metformin administration in PCOS obese patients, has been associated with a decrease in ovarian cytochrome P450c 17 α activity (62). Moreover, insulin reduction with metformin increases serum glyodelin levels in the luteal phase and enhances uterine vascular blood flow (63). These changes reflect an improved endometrial milieu for establishment and maintenance of pregnancy. A supervised incremental dosage protocol of metformin therapy has been commonly used. During the first week, PCOS patients take 500 mg metformin once daily with meals and this introductory phase can be extended to 14 days. For those women who tolerate metformin poorly, the dose is subsequently increased to 500 mg twice daily with meals for one week and then, the dose is increased to 850 mg twice daily with meals and maintained at this level to three months (64).

When first starting this medication, patients often experience upset stomach or diarrhea, which usually resolves after the first week. This symptom appears to be dose-dependent, and it can be reduced by administering a small dose of metformin in the first week of treatment (65). Metformin does not cause clinical hypoglycemia through its unique antihyperglycemic action and for this reason it has been investigated in various non-diabetic patients with some features of insulin-resistance syndrome (66). Less frequent problems potentially encountered by PCOS patients using metformin treatment are megaloblastic anemia (possibly secondary to subnormal B12 levels) (64). Lactic acidosis is rare but severe adverse reaction of metformin that occurs mainly in patients with renal failure. However, metformin associated lactic acidosis can occur in patients without pre-existing renal insufficiency (67).

In a large trial involving fifty six patients with CC-resistant PCOS a significantly higher ovulation rate (78%) with metformin in combination with CC compared with placebo in combination with CC (14%) was noticed. In addition, significantly more patients conceived in the former treatment group (14% vs. 0%) (68).

In another randomized controlled study in CC-resistant PCOS women metformin treatment was given for 7 weeks followed by the addition of CC for up to six cycles if the patients were anovulatory on metformin alone. In this study the addition of metformin to CC resulted in a statistically significant improvement in both ovulation rate and pregnancy rate (75% and 55%, respectively) compared to placebo plus CC (27% and 7 %, respectively) (69). In crossover design, 19 cycles of conventional exogenous gonadotropin treatment were compared to 18 cycles of the same treatment with addition of 500 mg of metformin three times daily starting 30 to 35 days before the first FSH injection. Compared with the women who received FSH alone, the women who received both FSH and metformin had fewer dominant follicles (2.4 vs. 4.5, $P < 0.01$), a lower peak plasma E2 concentration (1,652 pmol/L vs. 2,643 pmol/L, $P < 0.001$), and a lower cycle cancellation rate because of excessive follicular development (0 vs. 32.0%, $P < 0.003$). The combination of FSH with metformin for ovulation induction resulted in a better controlled follicular growth and a reduction in multifollicular development, which probably decreased the risk of OHSS and multiple pregnancy (70).

Little is known about metformin use in IVF. Ovarian stimulation in metformin-treated and metformin-untreated groups was compared in the 59 cycles of patients undergoing IVF and embryo transfer. The decreased number of days of lower peak E2 levels seen in metformin-treated patients had a positive impact on both fertilization and pregnancy rates. Therefore the improvement in folliculogenesis with lower maximum E2 levels may result in improvement in the oocytes and embryos leading to improved pregnancy rate (17). In fact, in 72 cycles of IVF in patients with CC-resistant PCOS, the addition of 500 mg metformin three times daily for 6 weeks prior to gonadotropin stimulation had beneficial effect on the number of mature oocytes, fertilization rates, embryo cleaved and pregnancy rates (71).

Women with PCOS are at increased risk of miscarriage following either spontaneous or assisted conception. Rates of early pregnancy loss, defined as miscarriage during the first trimester are reported to be 30-50 % in women with PCOS (72). Hyperinsulinemia has been implicated as an independent risk factor for early pregnancy loss while insulin resistance has been shown to decrease circulating glycodelin and IGF-I binding protein concentrations (63). In recent pilot studies, dramatic reduction in miscarriage in PCOS patients treated throughout the pregnancy with metformin was noted and except for a single baby born with achondrodysplasia, metformin was not associated with any adverse fetal outcomes (63, 73). In our randomized clinical trial we compared metformin therapy versus laparoscopic ovarian drilling (LOD) for the treatment of CC-resistant PCOS. Cases who treated by LOD achieved

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a relatively higher total ovulation than metformin therapy (78.2% vs 52.1%). The relative risk (95% confidence interval) for ovulation at 6 month of observation for LOD compared with metformin was 1.50 (0.95-2.34). Patients who were treated by LOD achieved pregnancy relatively higher (56.5% vs 39.1%) than metformin therapy within the observation period. The relative risk (95% confidence interval) for pregnancy at 6 month of observation for LOD compared with metformin was 1.44 (0.77-2.69). Out of 9 pregnancies in metformin group 1 case (11.1%) had first trimester abortion while 2 cases out of 13 (15.3%) pregnancies in LOD group had first trimester abortion. The relative risk (95% confidence interval) for early abortion for LOD compared with metformin therapy was 1.38 (0.14-13.07). Comparison of the side effect and complications of therapy showed that out of 23 cases in metformin group 5 cases (21.7%) had mild side effects which were self-controlled and cured spontaneously within the first 2 month. However out of 23 cases in LOD group 3 cases (13.04%) had a serious complications including surgical emphysema, pelvic abscess and ectopic pregnancy.

2. Troglitazone

Troglitazone is one of the insulin sensitizing agents that improves oral glucose tolerance and insulin resistance in individuals with impaired glucose tolerance (74). It also decreased the circulating androgen levels in women with PCOS (60). The initial study on the effect of troglitazone on PCOS suggested a greater response with a daily dose of 400 mg than at daily dose of 200mg (75). Although the mechanism of action of troglitazone is not completely understood, it seem to enhance insulin action without directly stimulating insulin secretion (76). It acts as a selective ligand for the peroxisome proliferator-activated receptor (77). Peroxisome proliferator-activated receptor γ is a nuclear receptor found predominantly in adipose tissues where it plays a pivotal role in controlling of adipocyte gene expression and differentiation (74). The beneficial effect of troglitazone in PCOS may not be only due to improvement of peripheral insulin resistance, but also to a possible direct effect on ovarian steroidogenesis (78). Troglitazone has been associated with elevated liver enzymes (< 2% of patients) and in extremely rare cases, hepatic necrosis. Thus liver function should be monitored for any patients receiving troglitazone therapy (79). Another concern with this medication is possible teratogenic effects (57).

3. D-Chiro-inositol

D-Chiro-inositol is a novel insulin-sensitizing drug that is not yet commercially available (59). Evidence suggests that some actions of insulin are mediated by putative inositol phosphoglycan (IPG) mediators, also known as second messengers. Furthermore, a deficiency in a specific D-Chiro-inositol-containing IPG may contribute to insulin resistance in women with PCOS. In support of this idea, administration of D-Chiro-inositol has been demonstrated to improve glucose tolerance, decrease serum androgens and improve ovulation in PCOS patients (80). A preliminary study reported a three-fold increase in the frequency of ovulation in lean women with PCOS treated with D-Chiro-inositol, but this did not reach significance because of the limited statistical power of the study (81).

IV. Surgical management of PCOS

A surgical approach to PCOS patients was advocated initially by Stein and Leventhal (1935) who reported the results of wedge resection of the ovary. The wedge resection of the ovary can restore regular menstruation and lead to pregnancy. This mode of treatment has been accepted widely because it has a high success rate with resumption of regular menses in > 90% of patients and pregnancy rate of 50- 80%. Subsequent descriptions of associated tuboperitoneal disease, however, tempered the initial enthusiasm (82). A new surgical therapy, the laparoscopic ovarian drilling (LOD), can avoid or reduce the need for

gonadotropins for ovulation induction. This laparoscopic procedure can be done with fewer postoperative adhesions (83). Several potential mechanisms of action of LOD have also been suggested. The reduction of inhibin production following LOD is followed by an increase in FSH secretion and recruitment of a new cohort of follicles (84). Other theory is restoration of normal production of the putative gonadotropin surge after laparoscopic ovarian electrocautery (85). Moreover, drainage of androgens and inhibin from follicles surface may inhibit the excessive collagenization of overlying ovarian cortex and facilitate a softening of ovarian tunica (86). Neighboring follicles that are not undergoing atresia may then mature and gain access to the ovarian surface, facilitating ovulation. Initiation of normal inhibin B pulsatility by LOD appears to correlate with the postoperative onset of ovulatory cycles (87). It has been speculated that by physically opening the subcapsular cysts by drilling, the follicular fluid that contains androgens is drained, thereby decreasing intraovarian levels of androgens followed by a fall in E₂ and a decrease in the positive feed back on LH, resolving the block of ovulation (88).

In 1984, Gjonnaess was the first who proposed the use of laparoscopic multi-electrocauterization in the treatment of PCOS (89). He stabilized the ovary by grasping the utero-ovarian ligament and applying unipolar coagulating current (200-300 watt) against the ovarian capsule for 2 to 4 seconds until its penetration. A total of 4 to 10 points on each ovary were performed. The ovulation rate was 92% and the conception rate 69% (80% when patients receiving additional CC were included). More recently transvaginal ovarian drilling was performed under anesthesia using a 17-gauge, 35-cm long needle connected to a continued vacuum pressure. Each ovary was repeatedly punctured from different angles and all small follicles visible by ultrasound were aspirated and scraped (90). Transvaginal ovarian drilling is also effective in improving IVF outcomes in patients with PCOS, and it is less invasive and less expensive when compared with laparoscopic ovarian diathermy.

Laparoscopic laser drilling has also been introduced and used in treatment of PCOS within the last 15 years. Co₂, Argon, Nd:YAG and KTP lasers have all been used in surgical treatment of CC-resistant PCOS patients (91). Laser provides controllable power density, desirable depth of penetration and predictable thermo-damage of surrounding tissues. It also diminishes the risk of adhesions (92). Several reports have verified the results of laparoscopic treatment of PCOS which showed successful ovulation in up to 90% and pregnancy rates in up to 88 % (93).

The hormonal changes associated with ovarian drilling, however, are poorly understood (94). An increased responsiveness of serum LH to GnRH after electrocautery in PCOS patients was demonstrated (95). However, the serum levels of LH, FSH, androstenedione and testosterone were decreased after LOD and resulted in restoration of ovulatory cycle (96). In long-term follow-up studies, ovarian electrocautery in patients with PCOS, normalizes the serum levels of androgens and LH and the improved hormonal levels sustained for 18-20 years (89, 97).

Since the original description of ovarian electrocautery in patients with PCOS, several reports have verified the results of adhesion formation rate following laparoscopic ovarian drilling which ranged from 0-100% (90). The greater the damage to the surface of the ovary the greater the risk of periovarian adhesion formation (98). This leads to the development of the strategy of minimizing the number of diathermy points, in which the ovary is cauterized only at four points (99). Since unilateral ovarian diathermy resulted in ovulation from both ovaries, the reduction in damage produced by unilateral diathermy may reduce the postoperative adhesion formation (84). Furthermore, ovarian atrophy has been reported as a complication of excessive drilling of polycystic ovaries (97). It is therefore advised that no

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coagulation should be done within 8 to 10 mm of the ovarian hilum and the number of cauterization points should be individualized according to the ovarian size (98, 100).

CONCLUSION

Based upon the evidence, medical treatment remains the primary therapy for PCOS-associated infertility. CC is the primary treatment option for anovulatory patients with PCOS, but CC-resistance led to more aggressive therapies with gonadotropins or gonadotropins/GnRH agonists. Although these medical treatments are effective, they are associated with serious side effects, including OHSS and multiple pregnancies.

The other option for treatment is laparoscopic ovarian drilling, but this surgical treatment also has untoward side effects including the risk of surgical complications and postoperative adhesion formation with subsequent infertility. New discoveries of some of the underlying pathophysiological abnormalities have led to an array of new treatment option that is likely to increase quality of life in women with CC-resistant PCOS. The use of insulin-sensitizing agent in the management of PCOS patients may allow us to develop less aggressive therapy that is effective and safer for patients with CC-resistant PCOS.

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