

Ovulation Induction in Anovulatory Patients with Polycystic Ovary Syndrome

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Abstract: Ovarian dysfunction is probably the pivotal feature of polycystic ovary syndrome (PCOS) making this syndrome the major cause of anovulatory infertility in developed countries. Several approaches have been proposed to induce ovulation in PCOS patients. Notwithstanding lifestyle modifications, clomiphene citrate, surgery and, finally, gonadotropins are the classical and still effective therapeutic options, new drugs, such as metformin and aromatase inhibitors, are today available in the treatment of anovulation related to PCOS. The aim of the present review is to describe all therapeutic approaches to the anovulatory PCOS patients.

Key Words: Anovulation, infertility, ovulation induction, PCOS, treatments.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common female disorder of fertile age.

The pathogenesis remains still today not completely clear. However the syndrome is characterized by an increased frequency of LH pulse over FSH favouring the androgen production by ovarian theca cells and the increase of 17 β -estradiol conversion in granulosa cells. Insulin plays also a key role in the pathogenesis of PCOS acting synergically with LH on theca cells, and reducing the sex hormone binding globulin (SHBG) and thus increasing the biologically active androgen levels. In addition, several paracrine and autocrine factors mediate the effect of LH and insulin.

Several criteria were proposed to define PCOS [1,2]. The Rotterdam consensus workshop concluded that PCOS is a syndrome of ovarian dysfunction and its diagnosis is confirmed by the presence of two of the following three disorders: oligomenorrhea or amenorrhea, hyperandrogenism (e.g., hirsutism, acne, alopecia) or hyperandrogenemia (e.g., elevated levels of total or free testosterone), and polycystic ovaries on ultrasonography (Fig. 1) [2].

According to the ESHRE/ASRM criteria different phenotypes of PCOS patients can be distinguished including both anovulatory and ovulatory women [3], furthermore anovulation remains a key problem of the syndrome. Because ~75% of anovulatory infertility cases are associated with PCOS, it represents a heavy social burden. Here we describe the procedures used to induce ovulation in PCOS patients, medical treatments and the surgical approach.

DIET, PHYSICAL ACTIVITY AND WEIGHT LOSS

Obesity and overweight are common features in the PCOS patients and they carry many health consequences, including some reproductive disorders. Several evidences demonstrated a relationship between obesity and infertility [4]. In fact, obesity is often related to insulin resistance and

associated hyperinsulinemia plays a pivotal role in ovarian steroidogenesis and androgen blood transport and/or activity in the target tissues [5]. Obese PCOS women are more likely to suffer from hirsutism and infertility than normal-weight PCOS subjects [6,7]. A wide study on PCOS women has shown that the sterility rate is about 40% higher in women with a body mass index (BMI) >30 compared to those with a BMI <30 [7]. Only 12-22% of these obese women had regular menstrual cycles vs. 28-32% of normal-weight women [7].

Weight loss improves ovary function in obese PCOS women, probably by affecting obesity related hyperinsulinemia [8,9]. A loss of at least 5% of the body mass often leads to restoration of a normal menstrual cycle in PCOS obese women with amenorrhea [8,10]. Weight loss also improves the pregnancy rate in untreated PCOS patients [11] and in women who have undergone fertility treatment [12,13]. Finally, in PCOS patients, a low protein diet seems to be superior to a high protein diet in terms of endocrine change [14].

Therefore, weight loss should represent the first-line approach in the treatment of obese and overweight PCOS women, since it significantly improves hormonal and metabolic abnormalities and may favour spontaneous ovulation and improve fertility rate in the majority of patients. Weight loss associated with a moderate physical activity is desirable because physical exercise reduces insulin resistance [15].

CLOMIPHENE CITRATE (CC)

Since 1962 CC has been used for ovulation induction in anovulatory infertility [16]. Studies on CC treatment in PCOS women have demonstrated an ovulation rate of 60-85%, a pregnancy rate of 30-40%, and a miscarriage rate of 13-25% [16]. CC acts at central level with an agonist effect on estrogen receptor (ER) decreasing the negative feedback of estrogens and increasing the gonadotropins pulse frequency, which in turn induces ovulation [17], whereas at peripheral level it antagonizes ER affecting negatively the endometrial and/or cervical factor [18-21]. Although endometrial thickness is not necessarily predictive of pregnancy in CC-stimulated cycles [22], the simultaneous

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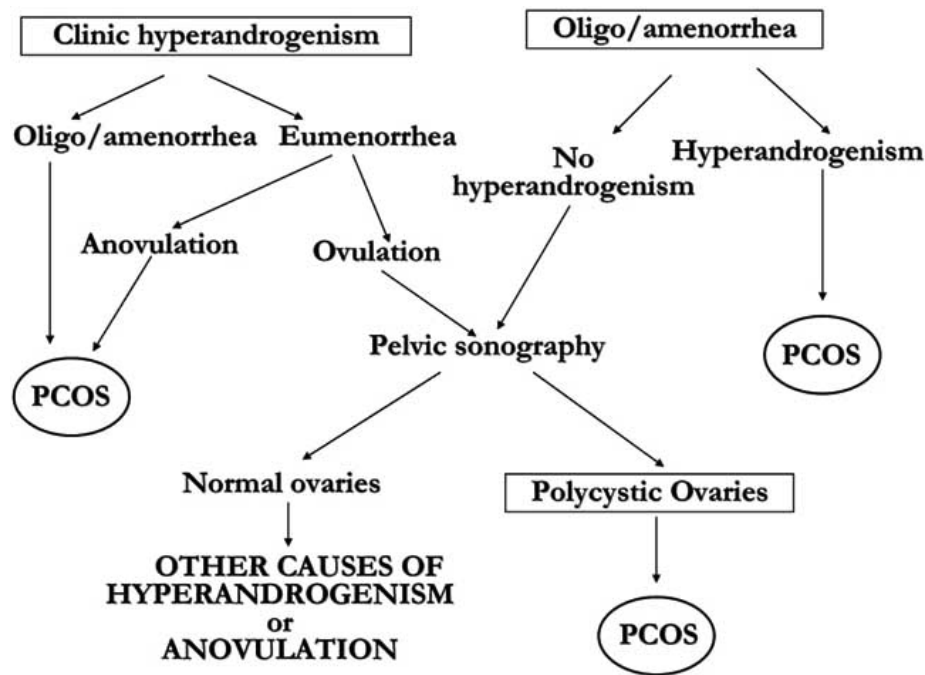


Fig. (1). A diagnostic workout according to the ESHRE/ASRM criteria (2).

administration of estrogens after ovulatory follicle selection has been recommended [23-25]. *In vitro*, CC interferes with the ovarian production of LH receptors and could thus reduce progesterone production [26]. There is some controversy about the quality of oocytes after CC administration [27,28] and the decrease in uterine blood flow at uterine level during the implantation phase [29]. CC is cheap and easy to administer, has rarely side effects, and induces follicular growth very similar to spontaneous growth. A meta-analysis demonstrated that CC is really effective to induce ovulation in PCOS patients [30]. However, high CC doses have been associated with ovarian hyperstimulation and multiple pregnancies albeit infrequently [16]. 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. When ovulation did not occur after 3-4 cycles of CC treatment at the maximum dosage a patient is classically defined "CC-resistant". To date, a PCOS woman is defined "CC-resistant" when ovulation is not achieved after 3 cycles of CC at 150 mg/day. In fact "managed care" studies [31] have shown that the most effective dosage is 100-150 mg/day and over 75% of ovulations occur already within a dosage of 100 mg/day [31].

GONADOTROPINS

When a patient is "CC-resistant" or when pregnancy is not achieved after 6 ovulation cycles with CC, the traditional option is to administer gonadotropins [32], which, however, are associated with an enhanced risk of multiple pregnancies and ovarian hyperstimulation, particularly higher in PCOS patients [33,34].

There is little evidence to support the administration of urinary FSH (uFSH) instead of human menopausal gonadotropin (HMG) to induce ovulation in PCOS patients [35]. However, the two preparations induce ovulation without any

difference in pregnancy rate and uFSH is associated with fewer cases of moderate and severe ovarian hyperstimulation syndrome (OHSS), and spontaneous abortions [35]. Thus, given their similar cost, uFSH should be more widely used.

Bayram *et al.* reviewed studies comparing the use of uFSH, recombinant FSH (rFSH) and different FSH regimens in terms of safety, ovulation rate, pregnancy, abortion, multiple pregnancy and OHSS in CC-resistant PCOS patients [36]. No differences emerged between the two FSH preparations in any of the evaluated outcomes. Similarly, there were no differences between the usual "step-down" and "low-dose stepup" regimens [36]. On the other hand, in a study of 50 PCOS CC-resistant women a "low-dose" rFSH regimen was more efficient and safer than uFSH [37].

The "low-dose" and "very-low-dose" step-up protocols consist of im or sc administrations of FSH at a dose of 75 UI/day or 37.5 UI/day for 10-14 days. If follicle diameter is at least 10 mm and serum estradiol is 60 pg/ml, the FSH dose is maintained until the follicle measures 18-20 mm, at which point ovulation is induced with 10000 UI of hCG. Otherwise, the dose is increased by 37.5 UI/day for at least one week [38]. Pre-treatment with gonadotropin-releasing hormone (GnRH) analogs does not significantly increase the rate of clinical pregnancy, or reduce spontaneous miscarriages. On the contrary, it could increase the risk of OHSS [39].

SURGICAL APPROACH

Ovarian wedge resection has been the first surgical approach to PCOS [40] and, with the advent of laparoscopy, the surgery for PCOS is today gaining ground [41]. In particular, the laparoscopic ovarian drilling (LOD), first performed in 1984 [42], consists of performing three to six punctures with an insulated needle as perpendicularly as possible to the ovarian surface using a unipolar current.

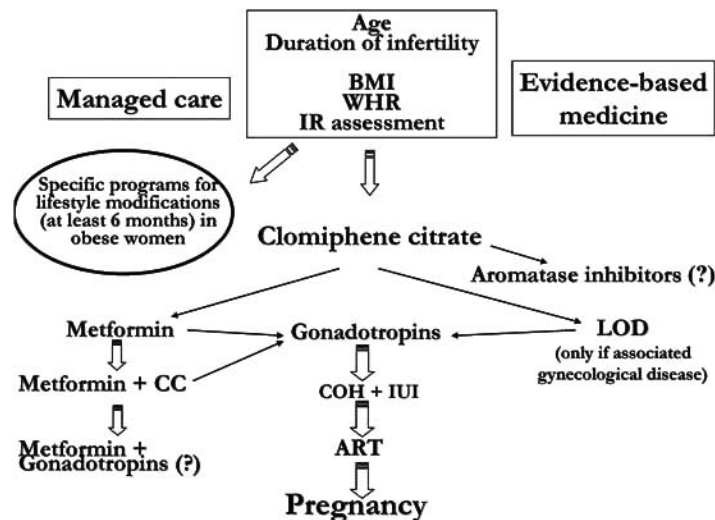


Fig. (2). Different treatment choices to induce ovulation in PCOS patients.

The short-term effectiveness of LOD has been widely demonstrated, whereas there are fewer data about the long-term effectiveness not only in terms of ovulation and pregnancy rate [43] but also regarding the restoration of the endocrine profile. In fact, Amer *et al.* [44] reported that the beneficial endocrine and morphological effects of LOD appear to be sustained for up to 9 years in most PCOS patients.

It is not known why and how these surgical procedures act. It is possible that surgery alters the ovarian structures involved in androgenic production so causing a temporary decrease in testosterone, androstenedione and LH levels [45-47]. Despite these LOD-induced hormonal changes, insulin resistance did not improve in normo-insulinemic women with PCOS [45,46], although it improved in a few hyperinsulinemic PCOS women subjected to LOD [47]. Stegmann *et al.* [48] concluded that insulin resistance and adhesions at surgery were negatively associated with pregnancy in infertile PCOS women treated with LOD.

We do not know whether LOD or gonadotropins are the most effective means of inducing ovulation in CC-resistant patients with PCOS [49,50]. A meta-analysis did not reveal clear differences in cumulative ongoing pregnancy rates between LOD and 6 cycles of gonadotropin-induced ovulation as primary treatment for anovulatory PCOS patients, although multiple pregnancy rates were considerably lower in women who conceived after LOD [50]. Bayram *et al.* in a randomized controlled trial (RCT) have recently compared the effectiveness of an electrocautery strategy vs. ovulation induction using recombinant follicle stimulating hormone in CC-resistant patients with PCOS concluding that both strategies were similarly effective in terms of ongoing pregnancy rate but the former strategy was related to a lower risk of multiple pregnancy [51]. The same Authors have performed an economic comparison between these procedures showing that the electrocautery strategy is less expensive in term of ovulation induction than rFSH [52].

LOD seems to increase ovarian response to gonadotropin for simple ovulation and IVF [53,54], and to reduce the risk

of OHSS [55]. Finally, a recent RCT has shown that LOD is less effective and more expensive than metformin in CC-resistant PCOS women [56].

METFORMIN

Metformin cloridrate is an oral biguanide used in type-2 diabetes mellitus and recently introduced for the treatment of PCOS. It has been well-documented that the glucose metabolism is altered in PCOS and that the prevalence of hyperinsulinemia due to insulin resistance is higher in this syndrome than in healthy controls. Based on these considerations, insulin-sensitizing drugs, i.e. metformin could result useful in the management of PCOS patients. Several data show that metformin, administered initially at a low dose and subsequently building up to 1500-2500 mg daily, improves clinical and biochemical features of PCOS, restores regular menses, and induces ovulatory cycles in anovulatory CC-resistant or non-resistant patients [57]. In addition, metformin increased the ovulation and pregnancy rates in combination with CC in unselected and CC-resistant PCOS patients [57].

Metformin treatment is also related to very poor side-effects consisting of nausea, gastrointestinal symptoms, and very rarely to chetoacidosis [57]. To the present, metformin therapy could be considered a cheap, safe, and easy alternative to CC [58]. Recent data on anovulatory non-obese PCOS women, in fact, showed that metformin and CC were similarly efficacy to induce ovulation, whereas the pregnancy and the abortion rates resulted significantly higher and lower, respectively, in women treated with metformin, while a trend was observed for the live-birth rate [59].

In addition, it has been demonstrated that metformin is more cost-effective than LOD as second-step procedure to treat overweight CC-resistant PCOS women [56]. The predictors of success of metformin therapy have not been demonstrated. In some studies [60,61] metformin seems to be less effective in lean PCOS patients probably because insulin resistance is less pronounced and less frequent in lean PCOS patients, and hence the effect is less evident [62]. In

more recent reports [63,64] metformin was effective in non-obese/lean PCOS patients as well as in obese or/and overweight PCOS patients. In a controlled double blind study metformin was not more effective than weight loss alone in obese PCOS patients [65], whereas in another controlled double-blind study, metformin and a hypocaloric diet had a synergistic effect [66]. Finally, in extremely obese PCOS patients with a body mass index (BMI) higher than 35 kg/m², metformin did not improve the reproductive or endocrine outcomes compared with weight loss alone [67]. However, the latter study was uncontrolled and included ovulating PCOS women [67].

The effect of metformin in CC-resistant PCOS women treated with FSH is controversial [68-70]. In one study, pretreatment with metformin for one month resulted in a more orderly follicular growth and a reduction in multifollicular development decreasing the ovarian hyperstimulation rate [68], whereas in another study metformin plus rFSH was not better than rFSH alone [69]. Palomba *et al.* [70], have recently evaluated the effect of metformin pretreatment and co-administration in controlled ovarian stimulation (COS) followed by timed intercourse (TI) or intrauterine insemination (IUI). In this last study [70], metformin increased the mono-ovulatory cycles and reduced the days of stimulation for non-cancelled cycles and the number of vials of gonadotropins used. Stadtmauer *et al.* [71,72], in two retrospective studies, demonstrated that metformin decreases the risk of OHSS in CC-resistant PCOS women treated with gonadotropin and improves reproductive outcomes in IVF programs, also after the "coasting" procedure. Metformin also decreased the spontaneous abortion rate during the first trimester of pregnancy, which is above 50% in PCOS patients [73], and improved cervical scores [74].

AROMATASE INHIBITORS

Aromatase is a cytochrome P450 that catalyzes the limitative reaction leading to estrone and estradiol production by conversion of androstenedione and testosterone [75,76]. Aromatase inhibitors act by decreasing estrogen serum levels, thus inducing a positive feedback at a pituitary level and gonadotropins release [76], which induces follicular growth. Follicular development is compatible with severe estrogen deficiency and low or absent intrafollicular estrogen levels are compatible with regular follicular growth and development of fertilizable oocytes [77]. It is likely that follicular growth and oocyte maturation during treatment with aromatase inhibitors are secondary to the increased androgen intra-follicular levels, which amplify the effects of FSH [78,79], and to the induction of high IGF-I intra-follicular concentrations, which synergize with FSH [80]. In PCOS patients, aromatase inhibitors induce ovulation without anti-estrogenic effects on the endometrium [81]. They were related with higher pregnancy rates and lower multiple pregnancy rates than CC and similar pregnancy rates to gonadotropins [81-84]. When compared with other ovarian stimulation treatments, pregnancies after letrozole were associated with similar miscarriage and ectopic pregnancy rates [82]. The dose used was 2.5 [82,83,85] or 5 [82] mg/day of letrozole, administered from day 3 to 7 of the

menstrual cycle or a single dose of 20 mg of letrozole on day 3 of the cycle [86]. With both treatment regimens, estradiol suppression peaked between days 5-7 of the cycle, estrogen levels rapidly decreased after day 7 and periovulatory LH peaked on days 13-14 of the cycle. Fisher *et al.* [87] compared the administration (for 5 days from day 5 to day 9 of the cycle) of 2.5 mg/day letrozole with 50 mg/day CC in PCOS patients who underwent intrauterine injection. There was no significant difference in the number of follicles between CC-stimulated cycle and letrozole-stimulated cycle [87]. On the other hand, Fatemi *et al.* [88] reported more follicles and a higher ovulation rate in PCOS patients who received 2.5 mg/day letrozole compared to 100 mg/day CC. Endometrial thickness at mid-cycle was similar in two treatment regimens in both studies [87,88].

Data on aromatase inhibitors in IVF programs are still little [89-93]. It is known that letrozole increases serum androstenedione and stimulates FSH receptor gene expression [90]. Aromatase inhibitors have been shown to decrease the number of FSH vials required to induce ovulation and the risk of OHSS, without anti-estrogenic effects, in normal-responders [91] and in low-responders [92,93] treated with FSH.

CONCLUSIONS

The first-line approach in the treatment of obese PCOS women remains weight loss and regular physical activity. CC has been considered for many years the first-line therapy to induce mono-ovulation in PCOS women. Furthermore, to the present, both CC and metformin can be considered the treatments of choice for mono-ovulation induction. Furthermore, more data need to be acquired before metformin can be considered the gold standard therapy from an endocrine viewpoint.

Gonadotropins may be considered as second-line treatment for ovulation induction in anovulatory patients after CC and metformin treatments alone or in combination, or in women who, having ovulate, did not conceive after 6 ovulatory cycles. Gonadotropins administration gives a high success rate but is related with extensive monitoring, high costs, and several complications. Of the other, still experimental medical therapies, only aromatase inhibitors seem to hold promise for the treatment of anovulation in PCOS patients. In CC-resistant women with suspected organic gynecological disease, such as endometriosis or leiomyoma, LOD could be considered a valid option, otherwise, it should be avoided because there are not evidences about its superior efficacy in comparison with the other therapeutic available options.

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