DERLEME / *REVIEW*

Polycystic Ovary Syndrome and Ovulation Induction

POLİKİSTİK OVER SENDROMU VE OVULASYON İNDÜKSİYONU

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Abstract

In polycystic ovary syndrome (PCOS), the first treatment choice is clomiphene citrate. A significant proportion (~20%) of women remain anovulatory following this drug. Induction of ovulation exogenous gonadotrophins is generally indicated in this patients. Low-dose protocols of FSH are the second line of treatment, effective in inducing monofollicular development. This treatment modality has been proven to be effective, but treatment requires skill and experience to avoid multiple pregnancies and ovarian hyperstimulation syndrome. Laparoscopic ovarian drilling (LOD) can be an alternative but not as a first choice treatment in clomiphene-resistant patients. In obese women with PCOS, weight loss and exercise should be recommended as the first line of therapy. Newer agents including aromatase inhibitors and insulin sensitizers, although promising, need further evaluation.

Key Words: Ovulation induction; anovulation; infertility, female; polycystic ovary syndrome

Özet

Polikistik over sendromunda (PKOS) ovulasyon indüksiyonu uygulamalarında ilk seçenek klomifen sitratdır. Ancak olguların %20'si klomifene rezistans göstermektedir. Klomifene rezistant olgularda ikinci seçenek gonadotropinler ile indüksiyonudur. En çok kabul gören yöntem kronik low-dose protokoldür. Laparoskopik ovaryan drilling (LOD), klomifen resistant seçilmiş olgularda uygulanabilir. Obez olgularda kilo verilmesi, egzersiz uygulamalarının dışında insulin duyarlaştırıcı ajanlarda sıklıkla kullanılmaktadır. Aromataz inhibitörleri ile ilgili daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Ovulasyon indüksiyonu, gonadotropin, infertilite, polikistik over sendromu

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by two of the following criteria; oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystis ovaries.[1] PCOS are commonly detected by ultrasound or other forms of pelvic imaging, with estimates of the prevalance in the general population being in the order of 20-33%. However, not all women with polcystic ovaries demonstrate the clinical and biochemical features which define the syndrome of PCO. Normogonadotrophic anovulatory infertility can be identified in 18-25% of the couples presenting with infertility.[1] Pathophysiology of the syndrome appears to be multifactorial and polygenic.[2] Although several definitions and various criteria have been used to define PCOS, the pivotal feature of this syndrome may stil be considered oligo-anovulation.[1,2]

Infertility has been attributed to various factors, which anovulation is the cause of about 40% of female infertilities. PCOS is the major cause of anovulation, the incidence of which has been reported to reach 6% in infertile female.[3] Traditional and well validated treatments used for ovulation induction in women PCOS are administration of clomiphene citrate (CC) and gonadotrophins, and the surgical ovulation induction with the use of laparoscopic ovarian diatermy (LOD). New treatments, which have been gaining a lot of popularity in clinical practice, are the use of insulin sensitiz-

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ing drugs such as metformin and specific lifestyle programs for obese women with PCOS.[4] The first line therapy is usually clomiphene citrate. However, ~20% of PCOS women are CC-resistant and therefore need to benefit from gonadotrophins to achieve ovulation. For those who fail to ovulate with CC, the principal options include ovulation induction with gonadotrophins or laparoscopic electrocautery of the ovaries. Traditionaly, exogenous gonadotrophins (especially FSH) are considered second-line therapy in case of failure to ovulate or conceive following CC. This treatment modality requries frequent monitoring due to inherent risks of multiple follicle development resulting in increased chances for ovarian hyperstimulation syndrome (OHSS) and multiple gastation, especially in PCOS patients.[3-5]

Last years, increased attention has focused towards alternative treatment options such as the insulin-sensitizing agents,[6] aromatase inhibitors, laparoscopic surgery of ovaries or assisted reproduction such as intrauterin insemination (IUI) or IVF. The association of insulin resistance contributing to anovulation has led to the novel and promising therapy of administering insulin-sensitizing drugs to women with PCOS to restore ovulation and enhance pregnancy.

There is currently no concensus on the best algorithm to induce ovulation in infertile patients with PCOS. In particular, the best initial care for obese infertile women with PCOS should be the lifestyle modifications to improve their reproductive functions.

Ovulation Induction Agents Weight Loss

It has been shown that loss of weight in obese patients wiyh PCOS improves substantialy hyperandrogenemia and insulin sensitivity, decrease LH concentrations and restores normal fertility.[7] Even a 5-10% reductions in body weight has been shown to be quite successful.[8] Obese women are less fertile in both natural and ovulation induction cycles and have higher rates of miscarriage than their counterpart of normal weight; they also require higher doses of ovulation induction agents.[9] In one study, in which 13 obese clomiphene-resistant women with PCOS lost 6 kg, ovulation was evident within a few in 12 month.[10] Apart from diet, exercise is also important in improving insulin sensitivity.[7-9]

Some 80% of obese women with PCOS have insulin resistance and consequent hyperinsulinaemia. They almost inevitably have the stigma of hypernadrogenism and irregular or absent ovulation. Insulin stimulates LH and ovarian androgen secretion and decreases sex hormone-binding globulin (SHBG) concentrations. Central obesity and body mass index (BMI) are major determinants of insulin resistance, hyperinsulinaemia and hyperandrogenaemia.[9-11]

As obesity therefore expresses and exaggerates the signs and symptoms of insulin resistance, then loss of weight can reverse this process by improving ovarian function and the associated hormonal abnormalities. Curiously, in obese women with PCOS, a loss of just 5-10% of body weight is enough to restore reproductive function in 55-100% within 6 months of weight reduction (Figure 1).[10]

Antiestrogens

The two main antiestrogens used for ovulation induction are clomiphene citrate and tamoxifen. Although tamoxifen is as effective as clomiphene in inducing ovulation, its use is very limited.[6] It

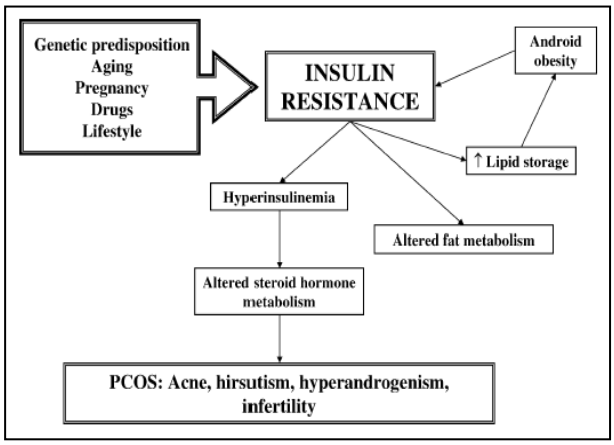

Figure 1. Pathways to insulin resistance and polycystic ovary syndrome primary aetiology? Cristello F. Therapeutic strategies for ovulation induction in infertile women with polycystic ovary syndrome. 2005.

was first syntesized in 1956 and has been commercially avaible since 1961. Clomiphene, by blocking the negative feedback effect of E2, stimulates the secretion of gonadotrophins from the pituitary gland. This lead to follicle secretion and estrogens production with the final occurence of a midcycle LH surge. It is also used in the functional assessment of the gonadal axis, may be combined with gonadotrophins in the therapy of selected cases of controlled ovarian hyperstimulation, and can be used with or without gonadotrophins in assisted reproductive techniques.[6,12]

Clomiphene is given for 5 days following the onset of spontaneous or a progestagen-induced period, starting any time from days 2,3,4 or 5, as there is no difference in the outcome between these time-points.[13] The recommended starting dose is 50 mg/day, as almost half of the pregnancies are achieved with this dose. A simplified monitoring, when treatment starts on day 2, involves measurement of serum progesterone values on days 21 and 28 of the cycle. Unless normal ovulation occurs (progesterone > 30 nmol/I), the dose is increased in each of the next cycles by 50 mg/day up to a maximum dose of 150 mg/day.[13,14]

Clomiphene will restore ovulations in approximately 80% of patients, but willl results in pregnancy in only about 35-40%.[11] The clomiphene dose may be increased progressively up to a maximum of 200 mg/day for 5 a days. Fewer than 50% of hyporeacting patients will ovulate at that dose. Approximately 50% of normal women ovulate with a dose of 50 mg, and an additional 20% will ovulate with 100 mg/day, the overall ovulation rate ranging from 70 to 85%. Additionally, around 20-25% anovulatory women with normal FSH concentrations will not respond at all to clomiphene and are considered to be 'clomiphene-resistant'.[15] Patients who do not respond to clomiphene are likely to be more obese, insulin-resistant and hyperandrogenic than those who do respond.[15] High basal LH levels are also likely to respond to clomiphene treatment.[16] Only 40-50% of ovulatory patients become pregnant. The discrepancy observed between the ovulation index and the fecundity index could be due to many factors. These include the coexistence of a male factor, the existence of other causes of infertility or anti-estrogenic effect of clomiphene on some effectors of the reproductive tract. This effect is known to arise in cervical mucus and its interaction with spermatozoa, in tubal transport of ova, and in the function and synchronization of the endometrium.[12] The large discrepancy between ovulation and pregnancy rates in patients treated with clomiphene may in part be explained by elevated LH levels, but the most probable factor involved is the anti-estrogenic effects of clomiphene at the level of the endometrium and cervical mucus.[11,12,15,16]

Predictors of the ovulatory response to clomiphene are body mass index, the free androgen index, ovarian volume and low concentrations of IGF-BP-I. On the other hand, pregnancy predictors with clomiphene are age and the severity of the cycle disorders, i.e. better responses occur in women of a younger age and with maintained oligomenorrhoea or amenorrhoea, suggesting that FSH threshold and oocyte quality are specifially regulated.[17] Hyperinsulinemia must be corrected. Anovulatory women who present with polycystic ovary syndrome and hyperinsulinemia are most resistant to clomiphene therapy. The best treatment for such patients, who are usually obese, is weight reduction, since both hyperinsulinemia and hyperandrogenism diminish when there is weight losss. Weight reduction should represent at least 5% of the initial weight. This metabolic improvoments is linked to an increase of the ovulation and pregnancy rates. It has been shown that when the body mass index drops under 27, both insulin and free testosterone concentrations fall, so improving fecundity.[17]

Depending on the aetiology of the condition, several drugs can be administrated with clomiphene, including the following. The first is human chorionic gonadotrophin (HCG), which is used when anovulation in spite of good follicular development and adequate estrogen production. It is administrated at doses 5000-10.000 IU, when the dominating follicle reaches a diameter of >18 mm and the concentration of estrogens exceeds 200 pg/ml, HCG can also be added in cases of luteal failure.

Corticosteroids are especially indicated in hyperandrogenic chronic anovulation, using 0.5 mg-1.0 mg dexamethasone q.h.s, which leads to a 70-90% increase in the ovulation rate. The idea behind giving doses of dexamethasone, 0.5 mg at bedtime, as an adjunct to clomiphene therapy is that the supression of adrenal androgen secretion may induce responsivess to clomiphene in previous non-responders with elevated concentrations of dehidroepiandrosterone sulphate (DHEAS). Similar doses of dexamethasone, taken only during the follicular phase of a clomiphene cycle, are beneficial for clomiphene-resistant patients regardless of DHEAS levels.[11] Beneficial effects have been reported during co-administration of clomiphene with dexamethasone or when clomiphene was preceded by the oral contaceptive pill. Dopaminergic agonists are indicated in chronic anovulation associated with hyperprolactinaemia.[11]

For functional evaluation of clomiphene administration, one possible practical scheme is the so-called 7-7-7 sheme, which consists of the following steps: 7 days after the last clomiphene tablet, follicular development is evaluated with a servical mucus test and vaginal ultrasound, including estrogens concentrations in selected cease. Mid-luteal progesterone concentrations are determined 7 days later. Finally, 7 days afterwards, the occurrence or absence of menses is recorded, in attempt to detect a short luteal phase or an early pregnancy. Consequently, clomiphene is the recommended drug for the treatment of infertility associated with PCOS, where the main objective is to obtain development of a single follicle and a reduction in multiple pregnancies.

Aromatase Inhibitors

Aromatase inhibitors are agents that suppress the biosynthesis of estrogen and, therefore, reduce the negative feedback effect on the hypothalamic-pitutary- system. This results in increased secretion of FSH that can lead to follicle selection and maturation. The third generation aromatase inhibitors has been recently used for ovulation induction in anovulatory PCOS women resistant to clomiphene or with inadequate endometrial thickness during clomiphene treatment.[6] Letrozole, the best known aromatase inhibitör, does not have the adverse anti-estrogenic effects of clomiphene but, by surprising estrogen production, it mimics the central reduction of negative feedback through which clomiphene works. At daily dose of 2.5 mg from days 3 to 7 of mentsrual cycle, ovulation was seeen in nine of 12 cycles (75%) treated with letrozole and only in eight of 18 cycles (44.4%) treated with clomiphene, while endometrium on the day of HCG administration was ticker in the letrozole group.[18] Pregnancy occurred in three patients treated with letrozole (25%). Although these are early days in terms of accumulation of evidence from larger trials, some encouragement may be taken from the solidity of the working hypothesis and the success of the initial experience. Before the onset of letrozole administration, early pregnancy should be ruled out, since information regarding possible teratogenic effects of this drug limited. Large prospective randomized studies are required to investigate the efectiveness of aromatase inhibitors in ovulation induction.[6,18]

Insulin Sensitizers

Insulin-sentizing agents that have already been tested in PCOS include metformin, an oral biquanide, thiazolidinediones troglitazone, rosiglutazone and piaglutazone, and D-chiro-inositol, a mediator of insulin action.[19] Individual studies have shown that metformin alone can restore regular menstrual cycles and reinstate ovulation in 25-95% of cases. A large number of studies have been published on the effect of metformin in a dose of 1500-2000 mg per day in women with PCOS. The vast majority of these studies have demonstrated a significant improvement in insulin concentrations, insulin sensitivity, and serum androgen concentrations accompanied by decreased LH and increased SHBG concentrations. The restorations of regular mentsrual cycles by metformin has been reported in the large majority of published series and the reinstatement of ovulation occurred in 78-96% of patients.[20] The variability in the results among the different studies is probably related to differences in the design, the dosages used, the duration of treatment and the primary end-points.[19,20]

A meta-analysis of 13 randomized controlled trials has shown that metformin treatment increased the ovulation rate 3.88 times (95% confidence interval (CI): 2.25-6.69) compared to placebo or no treatment (seven trials) and 4.41 times (95% CI: 2.37-8.22) when it was administered in combination with clomiphene-resistant women (two trials), a significantly higher ovulation rate for metformin plus clomiphene treatment as compared to clomiphene plus placebo has beeen shown [odds ratio (OR): 9.34, 95% CI: 3.97-21.97]. In tree trials, a significant increase in clinical pregnancy rate for metformin plus clomiphene as compared to clomiphene alone was also found (OR:4.4, 95% CI:1.96-9.85).[21]

A meta-analysis of eight randomized controlled trials has shown that metformin plus clomiphene may be superior to clomiphene alone or with placebo regarding ovulation (relative risk: 3.04, 95%: 1.77-5.24) and pregnancy rates (relative risk: 3.65, 95%: 1.11-11.99). A benefit of metformin versus placebo in pregnancy rate was not demonstrated, although all trials were underpowered to assess pregnancy as an outcome.[22]

Except for metformin, other insulin sensitizers have been also used, but experience is limited. A recent systematic review and meta-analyses of eight randomize controlled trial demonstrated that metformin co-treatment dose not significantly improve ovulation, pregnancy, or live birth rates in women with PCOS undergoing gonadotrophin OI.[23] A small, observational, non-blinded study approaching the issue of PCOS women not optimally responsive to metformin has suggested that pioglitazone added to metformin could improve menstrual regularity as well as hormonal and metabolic milieu. One of the thiazolidinediones, troglitazone, although effective in women with PCOS in increasing spontaneous ovulation as well as ovulation induced by clomiphene, is no longer avaible due to severe hepatic side-effects.[20-23]

Many reports have shown that metformin is effective treatment to restore ovulatory menstruel cycles and improve fertility in PCOS women not only after CC failure (administrated alone and/or in addition to CC) but also as a first-line treatment. Metformin, similarly to LOD, exert beneficial effects at hormonal and metabolic levels and has no necessity for intensive monitoring. LOD anf metformin were similarly effective for ovulation induction, but metformin was more efective on the other reproductive outcomes, i.e. abortion, pregnancy and live-birth rates, and it is at least twenty-fold less expensive.[24]

Safety issues advocate metformin utilization since it appears to be safe during pregnancy. In addition, metformin reduces first trimester spontaneous miscarriage rate and the incidence of gestational diabetes. However, rosiglitazone and pioglitazone should not be continued after conception.[22,24]

Laparoscopic Ovarian Drilling

A further treatment option for women with anovulatory infertility associated with PCOS is LOD by diatermy or laser. Surgical treatment of anovulation in PCOS patients by wedge resection of the ovaries has been abandoned due to serious adverse effects, such as adhesions and substantial tissue loss. This ‘update’ of ovarian wedge resection employs a unipolar coagulating current or puncture of the ovarian surface with a laser in four to ten places to a depth of 4-10 mm on each ovary. LOD introduced by Gjönnaess (1984) restored ovulation in 92% of patients with a pregnancy rate of 69%. Besides the usual laparoscopic access, the procedure has been also carried out by transvaginal hydrolaparoscopy. Several investigators have shown that there is no statistically significant difference in ovulation rates following LOD with or laser (83% vs 77.5%; odds ratio (OR): 1.4, 95% CI 0.9-2.1), although there is a significantly higher cumulative pregnancy rate at 12 months after surgery (65% vs. 54.5%; OR:1.5, 95% CI 1.1-2.1).[25,26]

The mechanism of action is still not clear; however, LOD is associated with a decrease in androgen levels and changes in gonadotrophin secretion and estrogen levels after the procedure. There are many theories to explain why the destruction of androgen-producing ovarian stroma may prove beneficial in PCOS patients. First, the hypotalamic-pituitary-

ovarian axis may be released from negatif feedback owing to a decrease in substrate available for peripheral aromatization to estrogens, with increase FSH secretion and, consequently, follicular maturation and ovulation. This phenomen may be enhanced by a decrease in levels. Second, a decrease in intra-oavrian androgens also positively affects follicular maturation and ovulation.[27]

A meta-analyses of six trials mostly comparing LOD with gonadotrophin therapy, showed similar cumulative ongoing pregnancy rates after 6-12 months follow-up and three to six cycles of gonadotropin therapy.[28] This cochrane analyses highlighted the main advantage of ovarian drilling a significant reduction in multiple pregnancy rates compared with gonadotropin therapy. Further possible advantages of LOD are a reported reduction in miscarriage rates.[28]

A recent randomized controlled trial including 168 clomiphene-resistant PCOS patients showed a 12 month cumulative ongoing pregnancy rate of 67% whether the women were treated with LOD combined with subsequent treatments of clomiphene anf rFSH (in the case of peristent anovulation) or treated with rFSH alone. However, the major difference between the LOD strategy study arm (LOD alone, or LOD plus clomiphene, or LOD plus clomiphene plus rFSH) and the rFSH arm was the significantly higher multiple pregnancy rate found with FSH alone (one of 83 versus nine of 85 patients).[29] A randomized controlled trial has shown that metformin treatment for 6 months in overweight anovulatory infertile clomiphene-resistant PCOS patients induced an ovulation rate comparable to LOD (54.8 versus 55.1%), but significantly higher pregnancy (18.6 versus 13.4%) and live birth (82.1 versus 64.5%) rates and a lower miscarriage rate (15.4 versus 29.0%).[29,30]

Reported adhesion formation artes following LOD range from zero to 100%. Therefore, surgical induction of ovulation may be useful only selected cases: women with PCOS resistant to clomiphene for whom gonadotropin therapy is unsuccesful.

Ovulation Induction with Gonadotrophins

Induction of ovulation using exogenous gonadotropins is generally indicated in patients with normogonadotrophic anovulatory infertility who failed to ovulate or conceive during previous clomiphene treatment. Since the early 1960s, many anovulatory patients have been treated with hMG and hCG to induce ovulation. This treatment modality has been proven to be efective, but the risks of OHSS and multiple pregnancies are considerabyl increased. Therefore, administration of low doses of FSH in a stepwise fashion (step-up, step-down protocol or combination of step-up and step-down) has been suggested and proved to be efective to significantly reduce those risks. Determining the most appropriate starting dose has been shown to be critical to reduce the rate of hyperstimulation.[30-34]

Recent studies have focused on the prediction of ovulation induction outcome based upon initial screening characteristics of WHO 2 anovulatory infertile women. It could be demonstrated that some clinical, sonographic and endocrine characteristics are predictive of ovulation and conception during clomiphene citrate treatment. Outcome parameters of gonadotropins treatment in these women correlated with women's age, ovarian response to preceding clomiphene citrate medication, BMI, the mean follicle number, serum levels of FSH, testosterone, androstenodione, and initial insulin-like growth factor-I (IGF-I).[35,36]

The aim of gonadotrophin ovulation induction in anovulatory infertility is healty live-birth, preferably from a singleton pregnancy. This is often hard to achieve despite the recent introduction of low-dose incremental or decremental regimens. An individualized treatment regimen, based on valid outcome predictors, might optimize ovulation induction strategies by improving the balance between success and complications.[37]

Treatment Protocols

Conventional and Low-Dose Step-Up Protocol

Conventional 'step-up' treatment with gonadotrophins for women with PCOS who failed to conceive with, or are 'resistant' to, clomiphene citrate yields an acceptable cumulative conception rate.[38] When starting dose of 150 IU/day HMG was given to patients belonging to WHO group 2, the success rate was significantly lower and the OHSS

significantly higher than in patients belonging to WHO group 1.[39,40] For these reasons, protocols involving 'chronic low doses' of HMG were introduced in the early 1980s.[41] An established method for patients with PCOS is the 'low-dose step up' protokol, which involves a starting FSH dose of 75 IU/day given for 7-14 days.[42] The major issue of the step protocols is the duration of initial dose and the FSH dose adjustment. Regarding the step-up protocols, many studies have clearly shown that a chronic administration of low FSH doses for 14 days according to the so called 'Chronic Low Dose' is safer than regimen with FSH dose adjustment after 7 days. Therefore, a strict adherence to a 14-day starting period using a persistent dose seems to be critical to prevent the risk of hyperstimulation. Treatment starts any time, provided low ovarian activity is present and is monitored by ultrasound scans. Unless a follicle >12 mm is seen in the ovaries, the dose is increased by 37.5 IU/day at weekly interval up to a maximum dose of 225 IU/day. HCG is injected when the leading follicle is >18 mm in diameter with no other follicles >14 mm, although in these patients the positive feedback mechanism is intackt.[43] This basic thinking behind this regimens is the 'threshold theory', which demands the attainment and maintenance of follicular development with exogenous FSH without exceeding the threshould requirement of the ovary (Brown, 1978), who showed that the increase in dose should not exceed around one-third of the preceding dose, went completely unheeded (Figure 2).[38-40,42-44]

A low dose, step-up gonadotropin therapy should be preferred to the now outdated conventional therapy for patients with PCOS, and the strong justification seems to be the almost complete elimination of OHSS and multiple pregnancy rate of 6%.[27,42,43] Indeed, in women treated with a chronic low-dose, significantly less follicles >10 mm and a lower level E2 on the day of HCG administration were found compared with women treated with the conventional regimen. A comparative prospective study of the conventional regimen with chronic low-dose administration of FSH for anovulation associated with PCOS (Homburg et al., 1995) involved 50 participants. All were treated with FSH, half of them using a conventional stepwise protocol and half with a regimen of chronic low dose. Compared with the conventional dose protocol, the chronic low dose regimen yielded slightly improved pregnancy rates (40 versus 24%).[27,42,43,45]

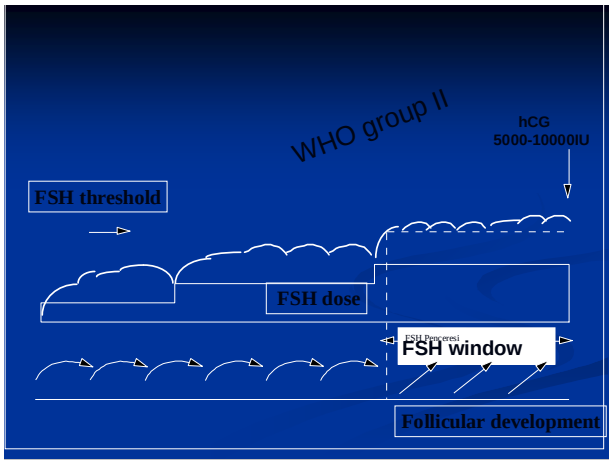

Figure 2. Chronic low-dose step up. Hedon et al., 1998. A large French multicentre study results.

A large French multicentre study with an identical objective and protocol design compared conventional and chronic low dose regimens in 103 anovulatory WHO group 2 women (Table 1). The comparison of low with conventional dose revealed pregnancy rates 33.3 versus 20%, and with a multiple (twins) pregnancy rate of 14 and 22%, respectively.[46] The results of experience on low-dose step-up protocol using recombinant FSH (rFSH) in 122 patients (252 cycles) are given in Table 2.

Step-Down Protocol

Another approaches to the treatment of PCOS patients with gonadotropins is the step-down protocol. In order to mimic more closely the events of the normal ovulatory cycle, Fauser's group use a step down dose regimen with a starting dose of 150 IU and decrease the dose by 0.5 ampoules when a follicle of 10 mm ensues and by the same amount every 3 days if follicular growth continues (Figure 3). Concerning the step-down protocols, the timing of the FSH dose reduction is also a major determi-

Table 1. 103 anovulatory WHO II Group women.

	Chronic low-dose	Conventional
Ovulation	71.4%	63
Pregnancy rate	33.3%	20
Multiple pregnancy	14%	22
No.of cycle monoovulation	74%	27
Number of > 10 mm follicul	3.0±2.6	6.3±6.5
Estradiol	504±477	988±740

Hedon et al.,1998. A large French multicentre study results.

Table 2. Results of the low-dose step-up protocol. Values are means ± SD.

Cycle cancellation (%)	23 (9)
Hyper-response (%)	7 (3)
No response (%)	16 (6)
Threshold FSH dose (IU/day)	112.8 ± 45.4 (38-300)
Duration of stimulation (day)	14.1 ± 6.1 (5-36)
Estradiol od day of HCG (pg/ml)	510 ± 447 (101-1500)
No.of ovulatory cycles (%)	214 (85)
No.of monofollicular cycles[a] (%)	128 (56)
No.of pregnancies	53
Per cycle attempted (%)	21
Per ovulatory cycle (%)	25
Cumulative pregnancy rate (%)	
1st cycle	17.1
2nd cycle	36.3
3rd cycle	46
No.of multiple pregnancies (%)	4 (8)
No.of miscarriages (%)	14 (26)

[a] Only single follicle >14 mm in diameter on the day of HCG

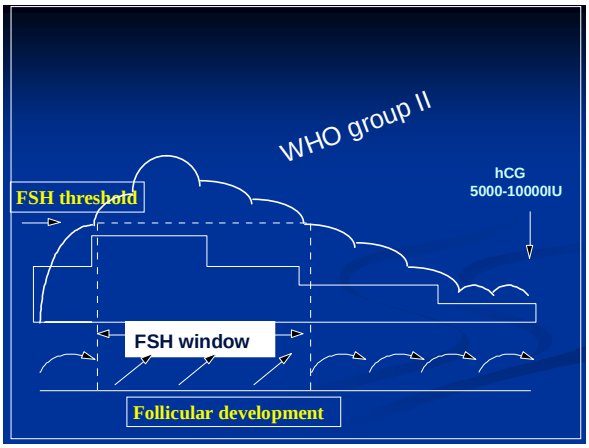

Figure 3. Low-dose step down. Hedon et al., 1998. A large French multicentre study.

nant of the number developing follicles. Indeed, by decreasing the circulating FSH level, the number of medium size follicles is significantly reduced. A comparison of this regimens with the classic step-up regimen demonstrated a monofollicular growth rate of 88% of cycles in the step-down regimen compared with 56% with the step-up protocol. In the step-down group, the median duration of treatment was significantly reduced by half to 9 days, and a mean of six ampoules less were needed than when using the classic step-up dose regimens. The major inconvenience of step-up protocols is a longer duration of FSH administration.[47]

In the step-down regimen, monofolicular development has been found in 56% of the cycles with a pregnancy rate of 16% per treated cycle and a cumulative pregnancy rate of 47%. So far, the results from only small prospective comparative studies are conflicting. In one of them, a shorter duration of treatment was found in the step down protocol, but monofollicular development was significantly lower (32 versus 68.2%) and multifollicular development (36 versus 4.7%), serum estradiol concentrations and the hyperstimulation rate (11 versus 2.25%) were significantly higher than in the step-up protocol (Table 3).[48] In a smaller study, the step-down was found to be superior to the step-up protocol regarding monofollicular development, in agreement with previous prospective randomized study.[49] However, in the study by Balasch et al. (2001), a modified step-down protocol was used, with a loading dose of 300 IU FSH followed by 3 days free of tretament and then by 75 IU FSH daily that was thereafter individually adjusted using a step-up protocol.[48,49]

Sequential Step-up and Step-Down Protocol

Another variations on the theme is the sequential step-up and step-down regimens in which the

Table 3. The clinical pregnancy rate during the study did not differ two group.

	Low dose step-up	Step down
Monofollicular development	68.2%	32.%
OHSS	2.25%	11.%
Pregnancy/cycle	18.7%	15.8%

Recombinant FSH study group, Christin-Maitre and Hugues, 2003.[48]

FSH threshold dose reduced by half when the leading follicle reaches a diameter of 14 mm. When compared step-up protocol (increments of 37.5 IU every 6 days) a significantly smaller number of intermediate size follicles was produced and mid-luteal phase estradiol concentrations were also significantly lower (350 ± 77 and 657 ± 104 pg/ml respectively).[48] At the time of HCG administration, cycles treated with sequential protocol exhibited significantly lower estradiol concentrations and the number of medium-sized (14-15 mm) follicles was significantly reduced compared with cycles treated with the low-dose step-up protocol. The authors concluded that decreasing the FSH dose step-up follicular selection might be an alternative method to avoid multifollicular development.[48]

Parameters that can predict the outcome of treatment with clomiphene or human gonadotropins are free androgen index, BMI, amenorrhoea, ovarian volum and age. Low responders have characteristics of more severe PCOS, such as obesity, hyperandrogenism and polycystic ovaries as compared with good responders. Finally, an approach to ovulation induction might be the development of protocols with use of various FSH isoforms.[49-51] Therefore, whatever the protocol used, clinicians must take into account the choice of gonadotrophin to determine the starting FSH dose and to adjust the dose adequatly. The starting FSH dose should be chosen according to predictive factors.[51-58]

Pulsatile GnRH

For patients who have anovulation due to hypogonadotrophic hypogonadism but have an intact pituitary gland, then treatment with pulsatile GnRH is tailor-made. Compared with gonadotrophin treatment, pulsatile GnRH therapy needs little or no monitoring and yields a much higher rate of monofollicular ovulation. Pulsatile GnRH has been tried in women with PCOS, but with much less success and has largely been abandoned for this indication.[51,59]

GnRH Agonist

The idea behind the use og GnRH agonist in patients with PCOS was to supress basal LH values when elevated and, therefore, to alleviate any adverse effects that high tonic LH might have on the outcome of treatment. The place of GnRH agonist co-treatment in FSH-treated cycles is routine and not really disputed. Although earlier data regarding ovulation and pregnancy rates using the GnRH agonist in FSH-treated cycles were encouraging, subsequent studies demonstrated an increased risk of OHSS.This was evident even when a starting dose of FSH as low as 37.5 IU/day was used.[49,59]

GnrRH agonist are not recommended as a treatment of choice for ovulation induction in PCOS. This increased incidence of OHSS is attributed to the low percentage of monofollicular development with the use of GnRH agonists, which in one study was found to be as low as 22% as compared to 80% with low-dose FSH alone.[51,52]

GnRH Antagonist

The use of GnRH antagonist in combination with gonadotrophins for ovulation induction in PCOS has until now been very limited. There is only one report of two cases as well as one study, in which 18 patients were divided into two group basec on the degree of insulin resistance. In that study, after pretreatment with the oral contraceptive pill, treatment started with the antagonist alone, whileFSH added when the LH concentrations had been supressed. Patients with insulin resistance were obese and required a longer period of stimulation and a higher number of FSH vials. Large prospective studies are required to examine whether the GnRH antagonist in combination with FSH can have advantage over the use of FSH alone.[53,54]

Conclusion

The new concern about PCOS women and the ongoing research about the genetic and prenatal implications of this condition suggest use of a multidisiplinary approach in these patients. The main goal is to increase the patient' chances of conceiving spontaneously once they enter the fertile age.

The first approach in a PCOS woman, with assessed bilateral tubal patency who seeks pregnancy, is to pay attention to weight loss and lifestyle modifications. In particular, the best initial care for obese infertile women with PCOS should be the lifestyle modification to improve their reproductive function, since both hyperinsulinemia and hyperandrogenism diminish when there is weight losss. These changes alone are sometimes able to restore cyclic menstruation and ovulation. Hyperinsulinemia must be corrected by weight loss or insulin-sensitizing agents. In a young overweight woman (BMI <30 kg/m^2), one can adopt expectant management for at least 6 months before starting treatment.[27]

On the contrary, non-obese PCOS patients shoul be initially treated with CC for no more than 3 cycles. When CC therapy fails, the second step should be metformin treatment alone or in coadministration with CC. The next step is controlled ovarian hyperstimulation with FSH. After 4-6 cycles of controlled ovarian hyperstimulation it is advisable to resort to IVF techniques. Because of the requirement for general anesthesia and the not so negligible surgical risk, LOD is suggested only in cases in which there is a concomitant reproductive disease, such as endometriosis, ovarian cysts or suspected tubal injury. Current evidence, although documenting the therapeutic efficacy of LOD, does not justify its use as a first line treatment for clomiphene-resistant PCOS patients (Figure 4).[4,27,29,57]

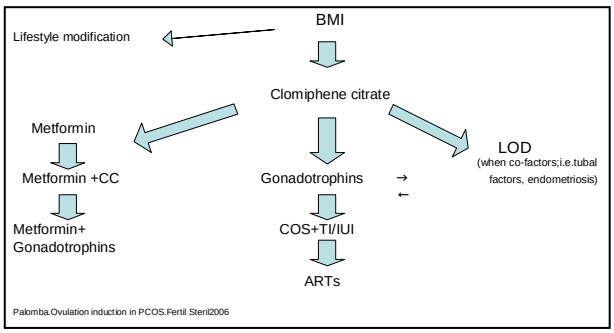

Figure 4. Flow chart for the management of the infertility anovulatory women with PCOS, COS, contolled ovarian stimulation; TI, timed intercourse.[30]

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