

Assisted Reproduction Techniques in the Treatment of Polycystic Ovary Syndrome: Review

POLİKİSTİK OVER SENDROMU TEDAVİSİNDE YARDIMCI ÜREME TEKNİKLERİNİN YERİ

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Abstract

Polycystic ovary syndrome (PCOS) is the most common cause of female anovulatory infertility. The prevalence of PCOS is 4-7% in reproductive age women have PCOS and 25-33% of an otherwise normal population have isolated polycystic ovarian morphology (PCO) on ultrasound. Clomiphene citrate, are the first line therapy for ovulation induction in these patients and are capable of producing ovulation in 70-75% of cases. Exogenous gonadotrophins have been widely used to treat women with PCOS women as a second line intervention. Other traditional strategies, in addition, assisted reproductive technologies (ART) like intrauterine insemination (IUI), or in vitro fertilization (IVF) are increasingly applied in PCOS patients. Obesity and insulin resistance compromise the success of fertility treatment PCOS. Anovulatory infertility in PCOS often respond to clomiphene citrate treatment, ovulation induction with gonadotrophins, or ovarian surgery. In cases where these attempts fail or other fertility problems co-exist, IVF is the treatment of choice.

Key Words: Reproductive techniques, assisted, ovulation induction, polycystic ovary syndrome

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Özet

Polikistik over sendromu (PCOS) anovuluar infertilitenin en sık görülen sebebidir. %4-7 oranında reproduktif yaş, %25-33 oranında ise normal popülasyonda (USG'de polikistik over morfolojisi) rastlanmaktadır. PCOS'ta ovulasyon indüksiyonunda ilk tercih edilen tedavi klomifen sitrat olup olguların %70-75'inde ovulasyon sağlanabilir. PCOS'lu kadınlarda 2. basamak tedavide yaygın olarak ekzojen gonadotropinler kullanılmaktadır. Diğer geleneksel stratejiler, yardımcı üreme teknikleri (YÜT) intrauterin inseminasyon (IUI) gibi ya da in vitro fertilizasyon (IVF), tedavide artan oranda uygulanmaktadır. Obezite ve insülin direnci PCOS'da fertilité tedavisinin başarısını azaltmaktadır. PCOS'da anovuluar infertilite genellikle klomifen sitrat tedavisine cevap vermekte olup, gonadotropinlerle veya ovariyen cerahi ile ovulasyon indüksiyonu gerçekleştirilmektedir. Bu yollarla başarı elde edilmezse ya da eş zamanlı diğer fertilité problemleri varsa IVF tercih edilir.

Anahtar Kelimeler: Yardımcı üreme teknikleri, ovulasyon indüksiyon, polikistik over sendromu

Polycystic ovary syndrome (PCOS) is the most common cause of female anovulatory infertility. The prevalence of PCOS is 4-7% in reproductive age women have.¹ Women with PCOS present at least two of the following features: polycystic ovaries, hyperandrogenism and anovulation. Infertility has been attributed to various factors, amongst which anovulation is the cause of about 40% of all female infertilities.

PCOS is the major cause of anovulation, the incidence of which has been reported 18-25% in infertile females.²

Clomiphene citrate (CC), are the first line therapy for ovulation induction in these patients and are capable of producing ovulation in 70-75% of cases. Exogenous gonadotrophins have been widely used to treat women with PCOS women as a second line intervention.³ Although overall cumulative singleton live birth rates of 71% have been described after conventional ovulation induction, the multiple pregnancy rate is considerable (10%).⁴ Exogenous gonadotrophins (especially FSH) are considered second-line therapy in case of failure to ovulate or conceive following CC. This

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treatment modality requires frequent monitoring due to inherent risks of multiple follicle development resulting in increased chances for ovarian hyperstimulation syndrome (OHSS) and multiple gestation, especially in PCOS patients.⁵

Assisted reproductive technologies (ART), intrauterine insemination (IUI), or in vitro fertilization (IVF) are increasingly applied in PCOS patients.⁶ It is very important to define whether an infertile PCOS patient is or is not obese. Android obesity a common feature of PCOS is associated with low pregnancy rate after IVF and obesity is also associated with an increased risk of miscarriage.^{7,8} Anovulatory infertility in PCOS often respond to clomiphene citrate treatment, ovulation induction with gonadotrophins, or ovarian surgery. In cases where these attempts fail or other fertility problems co-exist, IVF is the treatment of choice.⁹

Weight Loss

The incidence of obesity in women with PCOS varies between countries and ethnic groups. In the USA about 50% of women with PCOS are overweight or obese, but this prevalence differs little from that in general community. In obese women with PCOS, progression from normal glucose function to impaired glucose tolerance or diabetes mellitus is more rapid than in women without PCOS.¹⁰ While female age is probably the most important single factor affecting fertility, maternal weight also seems to have a substantial effect. Obese women are less infertile in both natural and ovulation induction cycles and have higher rates of miscarriage than their counterparts of normal weight; they require higher doses of ovulation-inducing agent.^{7,8}

Pregnancy rates are decreased by approximately 30% in women with a BMI >35 compared with women of ideal body weight. Weight loss has recently been shown to improve the outcome of all forms of infertility treatments, including IVF.¹¹ Increased body weight in pregnancy is associated with certain complications that may be ameliorated with preconception weight loss. The risk of spontaneous abortion is increased in PCOS patients who conceived with IVF.¹² 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.^{11,12}

Insulin Resistance and Insulin Sensitizing Agents

Insulin resistance is independently related to PCOS, as normal-weight PCOS women show a degree of hyperinsulinemia and impaired glucose disposal after meals and during glucose tolerance tests. Hyperinsulinemia increases ovarian androgen production by stimulating an ovarian enzyme complex, cytochrome P450c17, either directly and/or by stimulating pituitary LH secretion. Studies have shown that women with PCOS have a high prevalence of hyperlipidemia, hypertension and progression to type 2 diabetes mellitus, similar to the features of the so-called 'metabolic syndrome' or 'syndrome X'.^{6,10,13}

Obesity may endanger IVF results in PCOS: high intrafollicular concentration of leptin are related to relative gonadotropin resistance during ovarian stimulation for IVF.⁷ Regardless of body weight, insulin-resistant in PCOS patients need higher gonadotrophin doses during controlled ovarian stimulation, and insulin resistance is also associated with a risk of multifollicular development and high cancellation rate. Hyperinsulinemic PCOS women are more likely to produce oocytes exhibiting low fertilization rates after IVF, and embryos that are unable to implant. Luteinized granulosa cells, derived from insulin resistant PCOS women undergoing IVF, release less progesterone in vitro than cells from non-insulin-resistant women.^{9,14}

Metformin, an oral biguanide, thiazolidinediones troglitazone, rosiglitazone and pioglitazone, and D-chiro-inositol, a mediator of insulin action.¹⁵ Studies have shown that metformin alone can restore regular menstrual cycles and reinstate ovulation in 25-95% of cases. A large number 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 menstrual cycles

by metformin has been reported in 78-96% of patients.¹⁶ 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.

Except for metformin, other insulin sensitizers have been used, but experience is limited. A recent systematic review and meta-analyses of eight randomized controlled trial demonstrated that metformin co-treatment dose not significantly improve ovulation, pregnancy, or live birth rates in women with PCOS undergoing gonadotrophin OI, with the length of ovarian stimulation, total dose of FSH used maximal E2 level all reduced with the use of metformin. Metformin reduces the total FSH dose used in IVF but no effect on the length of ovarian stimulation, serum E2 level on the day of HCG trigger or number of oocytes collected. The risk of OHSS in PCOS women undergoing IVF was reduced with metformin.¹⁷

Aromatase Inhibitors

Aromatase inhibitors are agents that suppress the biosynthesis of estrogen and, therefore, reduce the negative feedback effect on the hypothalamic-pituitary-system. This results in increased secretion of FSH that can lead to follicle selection and maturation. Letrozole, the best known aromatase inhibitor, does not have the adverse anti-estrogenic effects of clomiphene.¹⁸ At daily dose of 2.5 mg from days 3 to 7 of menstrual cycle, ovulation was seen 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 thicker in the letrozole group.¹² Pregnancy occurred in three patients treated with letrozole (25%). 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 effectiveness of aromatase inhibitors in ovulation induction.

Response of PCOS to Stimulation

During an assisted reproductive technology (ART) cycle, ovarian responsiveness to gonadotro-

pins is crucial for a successful clinical outcome. Recruitment and development of multiple follicles in response to gonadotrophin stimulation are the key factors leading to successful outcomes of in vitro fertilization/embryo transfer (IVF/ET) treatment. The mechanism by which a follicle acquires dominance remains controversial (Figure 1, 2). Studies that in humans and subhuman primates have demonstrated convincingly that regulation of the FSH window during the follicular phase is crucial not only for the initiation of preovulatory follicular development, but also for the selective maturation of a single follicle (Figure 2).

Ovarian stimulation is used in the majority of assisted reproduction units in order to increase the number good quality embryos available for transfer. In the polycystic ovary, follicular response tends to be initially slow, but explosive at later stages of

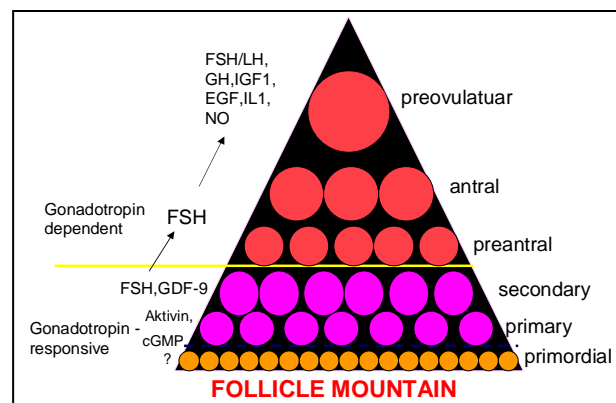


Figure 1. Follicular development.

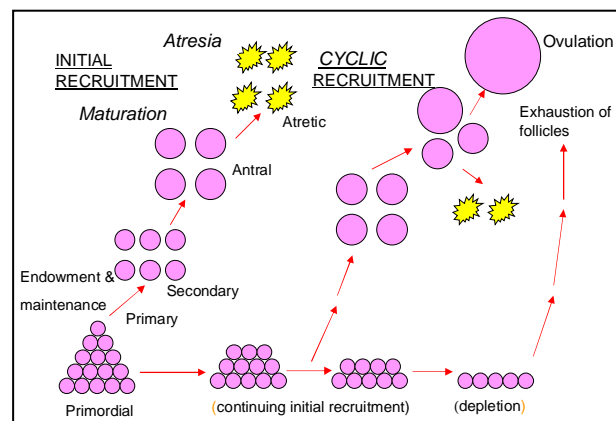


Figure 2. Life history of ovarian follicles.

stimulation. Dominant follicle selection is disturbed in PCOS, resulting in an increased number of follicles per ovary and presumably a variable number of healthy early antral follicles.¹⁵ Women with PCOS seem to be at risk for multifollicular development in response to gonadotrophin stimulation. The number of small dominant follicles (10-13 mm) stimulated during ovarian stimulation in anovulatory patients is increased. Previous observations reporting that normal inhibin B concentrations in PCOS patients, suggesting a normal number of healthy early antral follicles despite increased overall follicle numbers in these women.^{16,19}

Ovarian Stimulation Protocols for PCOS

Recent studies have focused on the prediction of ovulation induction outcome based upon initial screening characteristics of WHO 2 anovulatory infertile women. In PCOS, 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 antral follicle number ultrasound, serum levels of FSH, testosterone, androstenedione, and initial insulin-like growth factor-I (IGF-I).²⁰

Transvaginal ultrasound examination generally accurately predicts the response of the ovary to stimulation. Patient age, ovarian volume, and antral follicle count should be taken into account. Antral follicle count appears to be more predictive than others. When the sum of antral follicles in both ovaries was more than 15, these patients demonstrate an exaggerated response to gonadotropin stimulation.

Induction of ovulation with gonadotrophins is characterized by a small therapeutic range. In order to obtain monofollicular growth, the FSH threshold model has successfully been applied in low-dose, step-up treatment schedules for patients with polycystic ovary syndrome. In PCOS the FSH threshold is variable from patient to patient. According to the threshold model, an increase in the number of developing follicles can hypothetically be obtained

by increasing the length of time that the FSH level exceeds the threshold level, by increasing the number of small antral follicles with the same threshold sensitivity at the time of selection, or by a higher elevation of the FSH level above the threshold level. The FSH threshold may represent the severity of ovarian abnormalities in PCOS patients. Up to 30% of women with PCOS do not respond to increased endogenous FSH stimulation by clomiphene citrate administration, suggesting that they have a high FSH threshold. These patients are usually obese, hyperandrogenic, amenorrheic women with increased ovarian volume.^{21,22}

The higher sensitivity for gonadotropin stimulation in patients with PCOS cannot be explained by differences in FSH threshold and subsequent higher increments above the threshold. In studies on in vitro fertilization programs, this higher sensitivity is expressed in a higher oocyte recovery and a higher risk for the ovarian hyperstimulation syndrome.^{23,24}

In summary, the initial dose of gonadotrophin should be as low as possible. It is current practice to start the treatment at a dose of 150 IU/day considering the BMI. A lower dose protocol with a starting dose of 75 IU of rec-FSH have yielded impressive results in women with PCOS undergoing ovarian stimulation for IVF.²⁵

Both the absolute level of circulating LH as well as its relation to FSH levels are significantly elevated in women with PCOS compared with controls. This due to an increased amplitude and frequency of LH pulses. Elevated LH concentrations can be observed in approximately 60% of women PCOS.²⁶ The potential negative actions of LH on human reproduction are highly controversial. It has been postulated that high LH levels could have detrimental effects on oocyte maturity and fertilization, as well as results in lower pregnancy and higher miscarriage rates. Other studies have shown no actions of LH on oocyte and embryo quality or on fertilization, implantation, a pregnancy rates. Reduction of endogenous LH levels with GnRH agonist provided conflicting results. LH levels or the administration of exoge-

nous LH activity were not found to affect the changes of ovulation or achievement of pregnancy using clomiphene citrate or gonadotrophins.²⁶ A recent systematic review of randomized controlled trials evidence of a difference in efficacy and safety between rFSH and uFSH in PCOS patients. There was no evidence of a difference between uFSH and rFSH in clinical pregnancy, ongoing pregnancy, ovulation, miscarriage, OHSS, multiple pregnancy and cancellation rate. Total FSH dose used, duration of stimulation and estradiol level on the day of HCG administration did not differ significantly between rFSH and Ufsh.²⁷

In PCOS IVF cycles, obesity was correlated with an increased number of cancelled cycles (unexpectedly, mostly due to insufficient ovarian response) together with an increased amount of exogenous FSH administered.¹⁶ Obesity had a marked impact on IVF treatment in PCOS woman. Obesity is associated with higher gonadotrophin requirement during stimulation, and fewer collected oocytes. These effects were independent of insulin resistance index, suggesting that factors other than hyperinsulinaemia contribute to relative ovarian gonadotrophin resistance in obesity. One such factor could be the altered pharmacokinetics of gonadotrophins in obese women, resulting in lower effective concentrations of exogenous FSH.²⁸ Another possible factor inducing gonadotrophin resistance is adipocyte-derived hormone, leptin. Leptin inhibits the stimulatory effect of FSH on steroid synthesis by granulosa cells in vitro and high intrafollicular leptin concentrations are associated with relative gonadotrophin resistance in obese PCOS women.^{29,30}

GnRH Agonist

The incorporation of a GnRH agonist in the COS protocols to suppress elevated LH and androgen levels and prevent a premature LH surge appears to improve the pregnancy rate and reduce the miscarriage rate in PCOS patients undergoing IVF treatment. GnRH agonist in PCOS was to suppress basal LH values to prevent premature LH surges, which occur in ~ 20% of the cycles using gonadotrophins only.³¹ A meta-analysis of randomized controlled trials found that the adjunctive use of

GnRH analog in assisted reproduction cycles significantly reduced cancellation rates, increased the number of oocytes recovered, and improved pregnancy rate. The place of GnRH agonist co-treatment in IVF/ET cycle is routine. Homburg et al., who also showed decreased abortion rates and increased cumulative conception rates when GnRH analog were used in long protocol prior to HMG.³²

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. GnRH 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.^{27,31,33}

GnRH Antagonist

The antagonists have some advantages over the agonists and these may be utilized in the treatment of anovulatory PCOS. First, antagonists act by the mechanism of competitive bindings and this allows a modulation of the degree of hormonal suppression by adjustment of the dose. Antagonists suppress gonadotrophin release within a few hours, have no flare-up effect, and gonadal function resumes without a lag effect following their discontinuation. The use of an antagonist prevents premature luteinization and protects the oocytes from the deleterious effects of high LH concentrations. Compared with agonist cycles, the use of an antagonist gives the advantages of more conceptions and fewer miscarriages, reduces the amount of gonadotrophin required for ovarian stimulation, and decreases the prevalence of OHSS.³⁴

Craft et al. reported seven patients with polycystic ovary (seven IVF cycles) using cetrorelix acetate in combination with clomiphene citrate and FSH.³⁵ Three pregnancies were achieved from six completed cycles, with one ectopic pregnancy, one miscarriage and one live birth. There was one report, retrospectively comparing 13 cycles of IVF-ICSI in PCOS patients using the leuprolide long

protocol and 18 cycles using the ganirelix protocol. The pregnancy rate comparable, while the peak estradiol and total days of injections were significantly higher in the leuprolide long protocol.³⁶ Hwang et al. demonstrated that the incorporation of Diane-35 and cetrorelix acetate into the COS protocol for patients with PCOS undergoing IVF treatment could achieve a degree of pituitary suppression similar to that of the GnRH agonist long protocol at the start of HMG stimulation. The fertilization, pregnancy and implantation rate were similar to those of the GnRH agonist long protocol, with lower amounts of HMG used and lower serum estradiol levels on the day of HCG injection.³⁷ Doldi et al. found that the use of metformin with a GnRH antagonist improved the outcome of ovarian stimulation in IVF-ET cycles, reducing gonadotropin dose, serum estradiol on the day of HCG, the incidence of OHSS and the number of cancelled cycles.³⁸

Results of Assisted Reproduction in Women with PCOS

The outcome of assisted reproduction in women with polycystic ovary syndrome is similar to women with other form infertility. A recent meta-analysis demonstrated that an increased cancellation rate, but more oocytes retrieved per retrieval and a lower fertilization rate in PCOS undergoing IVF. Overall, PCOS and control patients achieved similar pregnancy and live birth rates per cycle.³⁹

According to current meta-analysis, despite the fact that more oocytes per cycle were obtained along with lower fertilization rates, PCOS and non-PCOS patients achieve similar pregnancy rates and live births per started IVF cycle. A total of 793 cycles in 458 PCOS patients were compared with 1116 cycles in 694 controls matched for age and duration of infertility who had normal ovarian morphology on baseline ultrasound. OHSS in the PCOS group compared with the control group. In contrast, another study found significantly more cycles cancelled in the PCOS group because of imminent severe OHSS (6% versus 1%).⁴⁰ No significant difference was observed in the number of ampoules used for ovarian stimulation between two

groups. The was weighted mean difference (WMD)-1.8 ampoules (95% CI=-4.2-0.5). The duration of ovarian stimulation was significantly extended in the PCOS group compared with non-PCOS group. The WMD was 1.2 days (95% CI=0.9-1.5).³⁹ No significant difference was observed for the clinical pregnancy rate per started cycle (37.4% versus 32.3%), OR= 1.0 (95% CI=0.8-1.3).

An increased number of oocytes were retrieved following ovarian stimulation in the PCOS group compared with controls, WMD 2.9 oocytes (95% CI=2.2-3.6). Significantly heterogeneity was detected between studies (P=0.0005). The random effects estimate of true variability of the number of oocytes per oocyte retrieval. The number of oocytes fertilized did not significantly differ between PCOS patients and controls, WMD 0.1 oocytes (95% CI= -1.4-1.6). PCOS patients demonstrated a significantly increased chance of cycle cancellation (12.8% versus 4.1%), OR=0.5 (95% CI=0.2-1.0).³⁹

Oocyte and Embryo Quality

An increased number of oocytes were retrieved following ovarian stimulation in the PCOS group compared with controls, but the fertilization rate was higher in the control group resulting in an equal total number of oocytes ferted in both groups. A number of published studies have addressed possible reasons for this observation. Laven and Fauser concluded that the number of healthy non-atretic follicles is probably not increased in PCOS women because a normal inhibin B level, produced by preantral and small antral follicles, was found in PCOS patients.⁴¹

Ludwig et al., compared the oocyte quality before intracytoplasmic sperm injection after the removal of the cumulus cells in PCOS and non-PCOS patients. No significant difference in rate of metaphase II oocytes, rate of germinal vesicles oocytes and fertilization arte was showed between the two groups.⁴² Sengoku et al., investigated the chromosomal normality of unfertilized oocytes from patients with PCOS and patients with tubal infertility. Cytogenetic analyses was performed on 74 oocytes from PCOS and 73 oocytes from control patients. Although no significant differences in

oocyte aneuploidy rates were found between the two groups, a reduced fertilization rate is not attributable to chromosomal aberrations or immaturity of oocytes recruited from patients with PCOS.⁴³

Elevated concentrations of LH in the follicular phase have been reputed to have a crucial role in reduced fertilization rates as well as pregnancy wastage in PCOS, since the reduction in LH induced by GnRH analog administration is associated with improved fertilization rates.^{34,40,44} Ashkenazi et al. demonstrated that the oocytes of patients with PCOS who were exposed to GnRH analog had a significantly higher implantation rate than those from patients treated with FSH and HMG alone in oocyte retrieval cycles.⁴⁵

Although the pathogenesis of PCOS is still unclear, elevated concentration of LH, insulin resistance and overproduction of androgens are associated with this syndrome. Elevated free insulin-like growth factor (IGF) and decreased IGF-binding protein-1 (IGFBP-1) concentrations in combination with LH may stimulate androgen production in PCOS patients through dysregulation of P450c17 α activity.⁴⁶ Based on the present results, this endocrine disruption, including possible effects on the growth hormone (GH)/IGF-1 system, may be mediated either via a modified accumulation of RNA or through the response of granulosa cells to FSH during oocytes.⁴⁷

High LH is thought to be detrimental to oocyte maturation and embryo quality, and furthermore may impair implantation and result in increased incidence of spontaneous abortions.³² But, more recently considerable disagreement has arisen with regard to the significance of elevated LH concentrations.⁴⁸ Likewise, the incidence of spontaneous miscarriage increases with increasing BMI both in women with and without.^{29,49}

Abnormal endocrine milieu resulting in elevated LH, elevated androgens, and hyperinsulinaemia may be responsible for altered oocyte quality in these women. Follicles from women with PCOS are more heterogeneous than those from normal ovaries and hypersecrete both estradiol and progesterone.³⁰ It is most likely that abnormal en-

docrine environment is relevant to abnormal oocyte maturation and decreased fecundity. Errors in embryogenesis resulting from abnormal oocyte maturation may explain the higher rate of pregnancy loss following gonadotrophin induced ovulation and IVF and embryo transfer. Another factor that may be considered is intrinsic abnormalities of the oocyte in patients with PCOS. Abnormal expression of growth differentiation factor-9 (GDF-9) was recently shown in oocytes from PCOS patients.⁵⁰

Implantation and Estrogen

The influence of high levels of E₂ during embryonic implantation is still controversial. High E₂ levels after controlled ovarian stimulation (COS) impair endometrial receptivity. The detrimental effects of very high estradiol concentrations on implantation may result from poor embryo quality, lower endometrial receptivity or a combination of both. Low implantation rates in high responders can be improved by using a step-down regimen in a subsequent cycle to decrease E₂ levels.⁵¹ Simon et al. showed that an increased receptivity when they compared step-down FSH regimens to conventional regimens in high responder patients.⁵²

Implantation depends on the synchronized development of both embryos and the endometrium. A significant reduction in nuclear receptors in both the glands and stroma for progesterone and estrogen receptors was found after ovarian stimulation in the presence of supraphysiological amounts of steroids and most of the endometrial biopsies were in phase. The influence of high steroid concentrations on the secretory products in the endometrial glands is largely unknown.

High E₂ concentrations associated with ovarian stimulation particularly in PCOS patients may be detrimental to embryonic implantation. Valbuena et al., demonstrated that high E₂ concentrations were deleterious to embryo adhesion mainly due to toxic effect at the cleavage stage.⁵¹ Contrary to this, however, Pena et al., sustained supraphysiological E₂ levels do not adversely affect the quality of developing oocytes and embryos. On the contrary, elevated E₂ levels are associated with a larger number of oocytes and embryos and high-

grade embryos for transfer/cryopreservation and, consequently, improved implantation rates.⁵³

In conclusion, supraphysiological E₂ levels of resulting from ovarian stimulation produce no adverse effects on the quality of developing human oocytes and embryos during IVF-embryo transfer cycles. On the contrary, elevated levels results in higher implantation rates and a greater number of oocytes and embryos for selection at the time of embryo transfer, as well as for cryopreservation. These findings imply that the possible decrease in embryo implantation rates seen with conventional IVF is largely due to an endometrial effect.

Ovarian Hyperstimulation Syndrome

In patients with PCOS are particularly prone to develop ovarian hyperstimulation syndrome (OHSS) because of the presumed enhanced ovarian response to gonadotrophins. The underlying mechanism of OHSS is still unclear. Recent studies suggest that a local ovarian renin angiotensin system and vascular endothelial growth factor (VEGF) may play a major role in the pathogenesis of OHSS through on angiogenesis and capillary permeability. In PCOS patients recruit excessive number of follicles and produce multiple corpora lutea following administration of HCG. These corpora lutea overexpress VEGF, which, if it release from the ovary may be responsible for the fluid shift from the vascular bed to the extravascular space. An increased expression of vascular endothelial growth factor (VEGF) mRNA within the hypertrophic stroma of polycystic ovaries has been associated with increased risk of OHSS.^{16,20}

Response of the PCO to ovarian stimulation is often unpredictable. Withholding gonadotrophin (coasting) in women undergoing reproduction therapy is effective in reducing the incidence of severe OHSS. Coasting, i.e. withholding gonadotropins whilst continuing GnRH agonist administration for pituitary down regulation, is being increasingly employed to prevent or minimize the incidence of severe OHSS. Gonadotrophin dose should be decreased once the stimulation threshold is reached. Coasting should be seriously considered when leading follicles reach or exceed 14 mm in size and se-

rum estradiol is >3000 pg/ml. Earlier coasting may be associated with cessation of follicle growth and precipitous drop in estradiol concentrations. In most studies a threshold value of 3000 pg/ml for serum estradiol was used. This strategy would allow coasting to be started at serum E₂ levels <3000 pg/ml rather than >3000 pg/ml as reported in most of the published data. But, prolonged coasting (over 3 days) or more than 20% drop in the estradiol concentration after HCG have been reported to be associated with poor clinical outcome.⁵⁴⁻⁵⁷

In Vitro Maturation of Oocytes

The major benefits of IVM treatment include avoidance of the risk of OHSS, reduced cost, and less complicated treatment. The first pregnancy in a woman with anovulatory infertility following IVM of immature oocytes and IVF was reported by Trounson et al.⁵⁸ Another pregnancy was achieved in a group of patients with PCOS treated with IVM combined with intracytoplasmic sperm injection (ICSI) and assisted hatching.⁵⁸

Immature oocytes recovered from unstimulated PCOS can be matured, fertilized and developed in vitro, the implantation rate of these cleaved embryos is disappointingly low.^{59,60} The number of immature oocytes retrieved for IVM is related to the number of antral follicles visualized at baseline ultrasonography. Pregnancy rate after IVM treatment is related to the number of immature oocytes retrieved, indicating that the best predictor factor for successful IVM treatment is the antral follicle number as measured by ultrasonograph of the patient's ovaries. Oocytes are retrieved from about 50% of all follicles >2 mm diameter ultrasonography. Pregnancy rate is found to be significantly higher in women when the number of retrieved oocytes is >10. However, recent data indicate that IVM treatment with FSH or human chorionic gonadotrophin (HCG) priming before immature oocyte retrieval can improve the clinical pregnancy and implantation rates in infertile women with PCOS.⁶¹

As an alternative approach, mild ovarian stimulation with FSH or HMG before immature oocyte retrieval has been applied, indicating that FSH or HMG pretreatment promotes efficient re-

covery of immature oocytes and maturation rate of the oocytes from women either with or without PCOS. The role of mild ovarian stimulation with normal ovaries is contradictory.^{62,63}

There have been more than 300 births of babies with IVM procedures, including in patients with PCOS, IVM has not become mainstream in IVF, with ovulation induction cycles with oocyte retrieval of mature (MII) oocytes still the highly favored protocol. In most clinic, the pregnancy and live birth rates with IVM do not match those reported for IVF cases using full hormonal protocols with triggered maturation in vivo.

Patients at risk for ovarian hyperstimulation syndrome might also benefit from IVM to avoid elevated levels of gonadotrophins and estrogen that might trigger or worsen OHSS. To avoid complications from the hormones used in controlled ovarian stimulation (COS) and considering the need for expediency, IVM might become the method of choice for patients diagnosed with cancer who want to undergo oocyte retrieval with the purpose of cryopreserving their oocytes.^{64,65}

Laparoscopic Ovarian Drilling

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. LOD introduced by Gjønnæss (1984) restored ovulation in 92% of patients with a pregnancy rate of 69%. Several investigators have shown that there is no statistically significant difference in ovulation rates following LOD with electrocoagulation or laser (83% vs 77.5%; odds ratio (OR):1.4, 95% confidence interval (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).⁶⁶

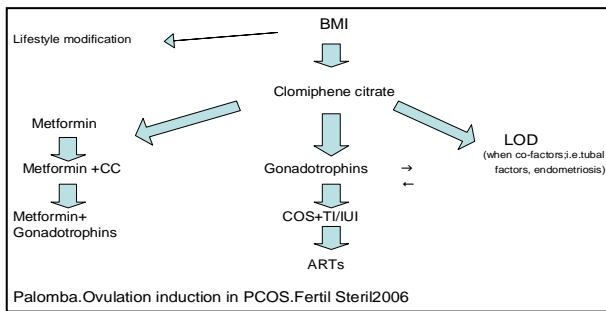
Amer et al. evaluated the impact of various clinical, biochemical and ultrasonographic features of PCOS on the clinical outcome of LOD in 200 PCOS women. Three main factors to have a significant impact on the efficacy of LOD, namely BMI, hyperandrogenism and duration of infertility. Women with marked obesity (BMI >35 kg/m²),

marked hyperandrogenism (testosterone >4.5 nmol/l, FAI >15) and/or with duration of infertility longer than 3 years seem to be resistant to LOD. With regards to LH levels, there was no impact on the pregnancy rates. Age, the presence or absence of acne, the menstrual pattern, LH/FSH ratio and ovarian volume did not seem to influence the outcome of LOD.⁶⁷

The mechanism by which diatermy alters ovarian function is unclear. Typically, decreased androgen and LH concentration following laparoscopic ovarian diatermy is reported to be the main mechanism by which reproductive outcome is improved, with elevated concentrations being associated with a reduction in oocyte quality, fertilization rates and embryo quality, and higher miscarriage rates.^{67,68} The authors suggested that pre-IVF ovarian electrocautery, especially in women who had previously had a cancelled cycle due to OHSS.¹⁵ There appears to be no improvement in pregnancy rates; but, there is a decrease in OHSS when laparoscopic ovarian drilling is used prior to ovarian stimulation for IVF.

Conclusion

In a woman with PCOS has a similar chance for pregnancy or live birth per started IVF cycle as a non-PCOS women. There seems to be a tendency for increased early pregnancy loss in PCOS patients resulting in a comparable overall live birth rate following IVF treatment. The risk of OHSS should be taken seriously. Coasting and other measures are usually necessary to prevent the occurrence of life threatening complications. Obesity is associated with an increased risk for cycle cancellations and requirements for increased amounts of exogenous FSH for IVF in women with PCOS following previous unsuccessful ovulation induction. More research is necessary to define the optimal place of IVF and ovulation induction therapies for anovulatory infertile PCOS patients and to investigate the specific role of strategies life style changes, insulin sensitizers, aromatase inhibitors and laparoscopic electrocautery of ovaries in the treatment strategy (Figure 3, 4).



COS, controlled ovarian stimulation; TI, timed intercourse.

Figure 3. Flow chart for management of the infertility anovulatory women with PCOS.

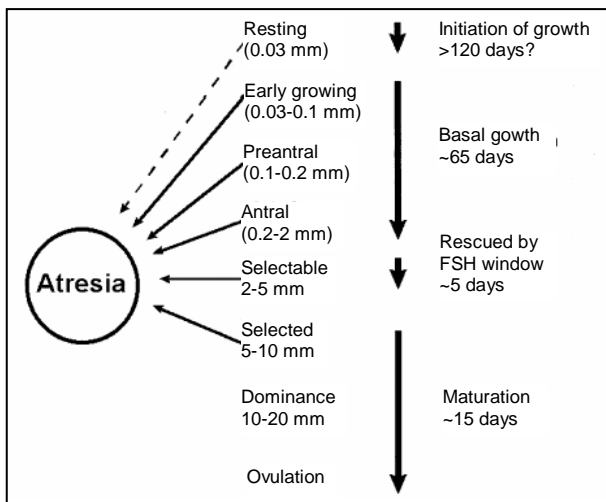


Figure 4. The various follicle stages in relation to the follicle diameter and the phase and time of growth in women with normal, menstrual cycles.

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