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In Vitro Fertilization for Polycystic Ovarian Syndrome

JESSICA R. ZOLTON, DO,*
and SAIOA TORREALDAY, MD†

**Program in Reproductive Endocrinology and Gynecology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health; and † Walter Reed National Military Medical Center, Bethesda, Maryland*

Abstract: In vitro fertilization is indicated for infertile women with polycystic ovarian syndrome (PCOS) after unsuccessful treatment with ovulation induction agents or in women deemed high-risk of multiple gestations who are ideal candidates for single embryo transfers. PCOS patients are at increased risk of ovarian hyperstimulation syndrome; therefore, attention should be made in the choice of in vitro fertilization treatment protocol, dose of gonadotropin utilized, and regimen to achieve final oocyte maturation. Adopting these strategies in addition to close monitoring may significantly reduce the ovarian hyperstimulation syndrome risk. Future developments may improve pregnancy outcomes and decrease complications in PCOS women undergoing fertility treatment.
Key words: infertility, in vitro fertilization, polycystic ovarian syndrome, ovarian hyperstimulation syndrome, in vitro maturation

In vitro fertilization (IVF) for the treatment of anovulatory polycystic ovarian syndrome (PCOS) is considered third-line treatment for infertility. Guidelines indicate that IVF should be offered after failed ovulation induction with oral agents or gonadotropin treatment.[1] However, due to the risk of twins and higher order multiples, which is more commonly seen when gonadotropin medications are utilized, IVF may be considered after failed ovulation induction with clomiphene citrate or letrozole.[2] In addition, PCOS patients are ideal candidates for consideration of elective single embryo transfer to mitigate the risk of multiple pregnancies while undergoing IVF.

PCOS patients undergoing IVF, without additional infertility confounders, are generally good prognosis patients to achieve a live birth. During IVF stimulation, the large number of antral follicles seen within this population commonly results in a high number of oocytes retrieved, the development of supernumerary embryos, and consequently, excess embryos for cryopreservation. IVF cycles undertaken in the PCOS population are characterized by slightly longer stimulation (1.2 d longer),

Correspondence: Jessica R. Zolton, DO, Program in Reproductive Endocrinology and Gynecology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health; 10 Center Drive, Building 10, Room 8N248B, MSC 1840, Bethesda, MD. E-mail: jrzolton@gmail.com

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higher number of developing of follicles, higher estradiol levels, and retrieval of a higher number of cumulus-oocyte complexes (COC) [2.9 more COC; 95% confidence interval (CI) = 2.2, 3.6)] than in women without PCOS.[3] PCOS patients may require relatively high doses of gonadotropins at the start of stimulation due to their underlying hyperandrogenism, which contributes to altered steroidogenesis and impaired follicular development.[4] Increasing gonadotropin dosage should be cautioned and closely monitored as these patients are also prone to overrespond to stimulation, increasing the risk of developing ovarian hyperstimulation syndrome (OHSS). OHSS is an iatrogenic complication that results from the stimulation of multiple corpus lutei following exogenous human chorionic gonadotropin (hCG) administration. OHSS occurs in up to 3% to 6%[5] of all IVF cycles and results due to excess production of vascular endothelial growth factor (VEGF) and cytokines which cause arteriolar vasodilation and increased capillary permeability.[6] Women with an antral follicle count >24 and an anti-Mullerian hormone ≥ 3.5 ng/mL have been identified to be at increased risk of OHSS; both parameters are common in PCOS patients. During the IVF cycle, high estradiol values >3500 pg and ≥ 24 oocytes retrieved are also associated with an increased risk of OHSS.[7] Early-onset OHSS, which occurs within 10 days of oocyte retrieval, is due to exposure to hCG when used as a trigger for oocyte maturation. Late-onset OHSS (≥ 10 d from oocyte retrieval) is caused by the secretion of hCG by the developing embryo after embryo transfer. OHSS symptoms range from mild, with patients reporting abdominal distention, mild dyspnea, and nausea and vomiting, to moderate, with laboratory evidence of hemoconcentration and ultrasound evidence of ascites, to severe cases requiring hospitalization. In severe cases, patients may require fluid resuscitation and anticoagulation to treat oliguria/anuria, intractable nausea and vomiting, hypovolemia, and hypercoagulability. Electrolyte disturbances resulting in hyperkalemia, hyponatremia, and abnormal hepatic function are also commonly present.[7] Although severe cases of OHSS are rare, maternal deaths have been reported.[8] Therefore, it is important that infertility specialists identify women who are at risk of OHSS before the initiation of treatment and adopt strategies to prevent OHSS.

IVF Protocols

Treatment strategies employed during IVF aim to achieve "controlled" growth and development of a cohort of ovarian follicles that is available and responsive to exogenous gonadotropin stimulus, while concomitantly suppressing the hypothalamic-pituitary-ovarian axis. In the absence of a suppressive strategy, escalating estradiol levels that arise with the development of ovarian follicles can initiate an endogenous luteinizing hormone (LH) surge with subsequent ovulation. During the early days of IVF, suppression of the hypothalamic-pituitary-ovarian axis was extensively done utilizing gonadotropin-releasing hormone (GnRH) agonist in efforts to prevent the premature luteinization during controlled ovarian hyperstimulation. GnRH agonists bind to the pituitary GnRH receptors and stimulate the release of the endogenous gonadotropins, follicle-stimulating hormone (FSH) and LH. This sudden increase in FSH and LH secretion following receptor binding is often referred to as the "flare-effect." After continuous stimulation with a GnRH agonist, desensitization and downregulation of GnRH receptors occurs resulting in FSH and LH suppression.

There are 2 primary GnRH agonist protocols, the long luteal and the short GnRH agonist protocols, that are commonly used in IVF cycles. In the long luteal GnRH agonist protocol, the GnRH agonist is typically initiated in the luteal

phase of the preceding cycle and exogenous gonadotropins are not started until after downregulation has occurred. In contrast, in the short GnRH agonist protocol, GnRH agonist is administered at the beginning of the menstruation cycle concomitantly with the start of exogenous gonadotropins. The short GnRH agonist protocol is often reserved for poor responders due to the advantage of having the endogenous gonadotropin "flare-effect" and to prevent the excessive pituitary suppression often seen in long GnRH agonist cycles. Since GnRH agonist cycles exhaust the pituitary of its gonadotropin stores, the use of hCG as a surrogate LH surge is a necessity. hCG, which shares structural similarities to LH and therefore can bind to the LH receptor, induces luteinization of granulosa cells, achieves final oocyte maturation, and allows for resumption of meiosis.

In PCOS patients who are generally "good responders" to gonadotropins, the use of the short GnRH agonist protocol with subsequent "flare-effect" can result in an increased risk of OHSS. One study reported that GnRH agonist protocols with hCG trigger for oocyte maturation were associated with a 20% incidence of OHSS in PCOS patients compared with a 7% incidence in non-PCOS groups ($P = 0.53$).[9]

With the introduction of GnRH agonists for oocyte maturation in 1990[10] and GnRH antagonist protocols in 1995,[11] clinical management of IVF for PCOS patients have evolved. PCOS patients are ideal candidates for an antagonist protocol because there is no initial release of gonadotropins at the start of treatment, as evident with the short GnRH agonist protocol. In a GnRH antagonist protocol, the gonadotropin therapy is started following menstruation. The GnRH antagonist is initiated either around day 5 of gonadotropin stimulation (fixed protocol) or when a lead follicle of 12 to 13 mm is visible on ultrasound and estradiol levels range from 200 to 400 pg/mL (flexible protocol). GnRH antagonist protocols permit the use of either hCG or GnRH agonist trigger for final oocyte maturation, whereas, in a GnRH agonist cycle hCG trigger is the only option due to the depletion of pituitary LH stores. The disadvantage of exogenous hCG is that it has a longer half-life then LH (24 h vs. 60 min) and the duration of the hCG surge is also significantly longer than LH (24 to 36 h vs. 6 d).[12] As a result, hCG stimulates the corpus luteum for a prolonged period of time which promotes VEGF production and thus increases the risk of OHSS.[6]

For patients that receive an hCG trigger and are deemed high risk for OHSS, recommendation to delay transfer and subsequently cryopreserve all embryos is encouraged. Therefore, adopting a GnRH antagonist protocol with GnRH agonist trigger is more beneficial for PCOS patients. In a randomized controlled trial (RCT) of 220 patients with PCOS, GnRH antagonist protocols were associated with a decreased risk in OHSS in comparison to the GnRH agonist protocol (40% vs. 60%, difference −20%, 95% CI = −7.1 to −31.9%, $P < 0.01$).[13] hCG trigger was used in both groups which explains the high incidence of OHSS overall.[13] In a meta-analysis including 9 RCTs and 1294 women, GnRH antagonist protocols were associated with a decrease risk of OHSS in comparison to GnRH agonists protocols [odds ratio (OR) = 0.53; 95% CI = 0.3, 0.95].[14] Oocyte yield and ongoing pregnancy and live birth rates were not significantly different among the 2 protocols.[14] The use of a GnRH agonist for oocyte maturation almost entirely eliminates the risk of OHSS, with only a small number of published cases in the literature.[15]

For all patients who receive a GnRH agonist for oocyte maturation, there is concern for insufficient luteal phase support. A RCT found a significant reduction in clinical pregnancy rate [36% vs. 6% ($P = 0.002$)] and elevated risk of pregnancy

loss [4% vs. 79% ($P = 0.005$)] in patients receiving a GnRH agonist trigger versus hCG trigger.[16] The surge following GnRH agonist is shortened, as described previously, and serum levels of estradiol and progesterone are lower after GnRH agonist trigger when compared with a hCG trigger. Therefore, additional steps are necessary to ensure that appropriate luteal hormonal support is attained to adequately support a pregnancy. Although an optimal protocol has not been established, methods to compensate for the hormonal deficit include a microdose of hCG at oocyte retrieval and the addition of progesterone and estrogen supplementation.[17] For women at risk of OHSS, a microdose of hCG on day of oocyte retrieval may not be appropriate and should be cautioned. Supplementation with progesterone and estradiol in the absence of a hCG trigger has been associated with a higher risk of pregnancy loss.[16] An alternative approach is to adopt a freeze-all strategy in patients who undergo an antagonist cycle utilizing a GnRH agonist trigger.

As PCOS patients represent a high responder group, serum levels of estradiol and progesterone are usually markedly elevated in comparison to other patients undergoing controlled ovarian hyperstimulation. There is evidence that elevated progesterone levels on the day of hCG trigger are negatively associated with live birth rates in fresh cycles. However, employing a freeze-all strategy restores live-birth rates comparable to cycles without progesterone elevation, suggesting that the endometrial environment is negatively affected by the supraphysiological hormonal levels.[18] Further evidence supports the use of frozen embryo transfer (FET) cycles in all patients with PCOS regardless of clinical characteristics. Employing a freeze-all strategy in PCOS patients improved live-birth rate [49% vs. 42%; relative risk (RR) = 1.17; 95% CI = 1.05, 1.31; $P = 0.004$], and lowered the risk of pregnancy loss (22% vs. 32.7%; RR = 0.67; 95% CI = 0.54, 0.80; $P \leq 0.001$) and OHSS (1.3% vs. 7.1%; RR = 0.19; 95% CI = 0.1, 0.37; $P < 0.001$) compared with women with PCOS who had a fresh transfer.[19] Overall, IVF practice has shifted to an increase in FET cycles in all patient groups and it is anticipated that this trend will continue as studies consistently demonstrate an increase in live birth in freeze-all protocols.

Miscarriage Risk After IVF

Studies suggest that PCOS patients may be at an increased risk of miscarriage due to insulin resistance, hyperandrogenism, and increased body mass index (BMI).[20] These conditions usually coexist and independently are associated with negative pregnancy outcomes. Studies have suggested that pregnancy loss in PCOS patients is due to impaired endometrial receptivity[21] while others have suggested that embryonal aneuploidy is increased.[22] Alterations in endometrial receptivity have been suggested due to impaired insulin and glucose signaling and overexpression of androgen receptors in the endometrium[23] resulting in dysregulation of the cell signaling necessary for implantation.[20] Studies have also reported that embryonal aneuploidy is increased in PCOS patients compared with a non-PCOS patient population (61.3% in PCOS patients vs. 47.8% in the control group).[22] PCOS diagnosis was identified to be an independent risk factor for aneuploidy after adjustments for BMI, maternal age, embryo quality, and other infertility diagnoses. Although the mechanism for an increased aneuploidy rate in PCOS patients has not been elucidated, studies suggest that altered steroidogenesis and impaired oocyte metabolism in this patient population may lead to DNA instability.[24] More research in this area is needed to determine if PCOS patients have a higher inherent risk of creating aneuploid embryos.

Adjunctive Treatment

Metformin, an oral biguanide, is traditionally prescribed to PCOS patients due to the high incidence of insulin resistance in this population. Metformin decreases systemic insulin levels and acts at the level of the ovary to decrease androgen production through reduced CYP17 activity in PCOS women.[25] A double-blind RCT found that while metformin did not increase pregnancy rates among nonobese PCOS women undergoing IVF, it did result in an overall increase in clinical pregnancy and live birth rates as a result of an increase in spontaneous conceptions after randomization.[26] Metformin treatment may be most beneficial for women with increased BMI. A RCT, which included PCOS women with a mean BMI of 27 kg/m^2 who either received metformin or placebo, demonstrated that the patients who received metformin had a higher pregnancy and live birth rates compared with the those who were assigned to placebo.[27]

Metformin has also been proposed as an agent to decrease the incidence of OHSS in PCOS patients.[28] In vitro, lower insulin levels reduces the production of VEGF, a key player in the pathogenesis of OHSS.[29] Thus, metformin has also been used an adjunct to IVF cycles in efforts to decrease the risk of OHSS. A RCT including 120 patients found that metformin significantly reduced the incidence of OHSS and cycle cancellation in GnRH agonist cycles.[30] Peak estradiol levels were lower in women treated with metformin, likely a result of decreased insulin receptor signaling and, subsequently, lowering androgen precursors available for aromatization.[31] A Cochrane meta-analysis published in 2014 including 9 RCTS and 816 women found that PCOS patients who took metformin had a lower incidence of OHSS in GnRH agonist protocols (OR = 0.29; 95% CI = 0.16, 0.51, 758 women) but found no difference for GnRH antagonist protocols (OR = 0.3; 95% CI = 0.03, 3.15, 40 women).[32] Furthermore, there was no difference in live birth rate, miscarriage rate, number of oocytes collection, or cycle cancellation between the metformin and placebo groups. No set protocols for starting metformin exist; doses ranged from metformin 500 mg 2 to 3 times daily to 850 mg twice daily starting 16 weeks before IVF to the day of trigger.

Dopamine Agonists

Dopamine receptor (D2) agonists are routinely prescribed for patients with hyperprolactinemia undergoing infertility treatment but more recently has also been utilized to prevent OHSS. Cabergoline, a dopamine agonist, has been found to decrease vascular permeability in women at risk for OHSS. It has also been demonstrated in human granulosa cell culture that cabergoline decreases the production of VEGF.[33] Treatment is usually initiated on the day of hCG trigger in patients who are identified to be at increased risk for OHSS. A RCT including 182 women identified as being high risk for OHSS were randomized to receive either placebo or 1 of 3 assigned doses of the dopamine agonist starting on the day of hCG trigger. The study reported a reduced risk of moderate/severe OHSS (OR = 0.28; 95% CI = 0.09, 0.81; $P = 0.019$) with dopamine agonist treatment.[34] The incidence of moderate/severe OHSS in the study was significant higher in the placebo arm [23% (12/53)] than in the dopamine agonist arm [11% (14/129)].[34] Higher doses of the medication were most efficacious in reducing OHSS, however, the side effect profile consisting of nausea, vomiting, and dizziness was also more pronounced. A systematic review including 7 studies and 858 women also reported a decrease in OHSS in the dopamine agonist cohort compared with the no treatment group (RR = 0.38; 95% CI = 0.29, 0.51; $P < 0.00001$) without impacting clinical pregnancy rates.[35] Of note, the dose of

cabergoline and timing of treatment varied across the studies.[35] Although there is evidence in support of dopamine agonists for the prevention of OHSS, few studies have been performed exclusively in PCOS patients. One study suggested that women with PCOS treated with cabergoline may have a lower risk of cycle cancellation due to OHSS, although the overall low number of OHSS cancellations in the study limits the interpretation.[36] Overall, studies have demonstrated consistent evidence that dopamine agonists may be a modality to decrease the risk of OHSS.

Coasting

During ovarian hyperstimulation, ultrasound surveillance of ovarian response in conjunction with serum estradiol values assist in the identification of patients who are at risk of developing complications. Early practice was to simply cease gonadotropin stimulation and "coast" until estradiol levels plateaued, or the rate of follicular growth slowed. A 2017 Cochrane meta-analysis reported that coasting was associated with a reduction in OHSS (OR = 0.11; 95% CI = 0.05, 0.24) and a lower number of oocytes retrieved.[37] There were no differences in live birth or miscarriage between the 2 groups. The evidence was considered low quality due to incomplete data and small sample size. Other studies have similarly reported a reduction in oocyte yield and decrease implantation rate when coasting was applied.[38] As the evidence for coasting is weak, other interventions should be pursued to prevent the incidence of OHSS.

In Vitro Maturation (IVM)

IVM may be considered a future option for PCOS women who want to avoid the risk of OHSS entirely. Although IVM is currently considered experimental, it is expected that with increased experience and more research, IVM will be adopted as an additional treatment for infertility. The process involves retrieval of immature oocytes (arrested in prophase I) and IVM to the metaphase II stage. Since IVM protocols either involve mild ovarian stimulation or avoid stimulation of the ovary entirely, the process is less expensive and requires less monitoring.[39] hCG trigger during IVM retrieval is usually performed when the lead follicle is only 14 mm in size, which is earlier than conventional IVF protocols that administer the trigger when the lead follicle reaches at least 18 mm. There is no specific IVM protocol, but COCs are typically cultured in media with FSH, hCG, and growth hormone for 20 hours. Intracytoplasmic sperm injection is usually performed to facilitate fertilization. A retrospective review found that live birth rates in fresh cycles after IVM were suboptimal to IVF (18.8% vs. 31%, $P = 0.021$) although live birth rates in FET cycles were similar.[40] The total number of suitable blastocysts were lower in the IVM group compared with the IVF cohort (2.5 ± 2.1 vs. 3.9 ± 3.4, $P \leq 0.001$).[40] There was no difference in biochemical pregnancy, clinical pregnancy, or miscarriage rates between the 2 treatment groups in fresh or frozen cycles. Furthermore, cumulative pregnancy rate was lower and fewer blastocysts were available for cryopreservation. A retrospective case-cohort study reported a significant decrease in live birth rate (16.5 vs. 44.3, $P < 0.0001$) between IVM and IVF/intracytoplasmic sperm injection.[41] Although miscarriage rates were not different, IVM pregnancies had a lower implantation rate (12.9% vs. 25.6%, $P < 0.0001$) potentially due to impaired endometrial receptivity.[41] This may be due to embryo/endometrial asynchrony, as hCG trigger for oocyte maturation is done at a considerably earlier time in the menstrual cycle.[40] The lower implantation rate may also be a failure of oocyte cytoplasmic maturation, a process which modern technology still cannot assess.

The safety of IVM has also been questioned. Increased chromosomal abnormalities have been noted in oocytes that required prolonged culture time. However, IVM embryos created from oocytes that were matured for <48 hours showed chromosomal abnormalities that were comparable to IVF embryos.[42] Animal studies have also raised a concern for the potential of IVM to alter the genome permanently via epigenetic changes, thus increasing the incidence of imprinting disorders.[43] However, a study reporting on long-term outcomes (mean follow-up of 7.5 y) of 184 children born from IVM found no difference in birth weight, congenital anomalies, or growth development compared with 366 children conceived via IVF.[44] As more studies are published reporting the long-term health of infants born from IVM, IVM will likely be adopted as a routine assisted reproductive technique available to patients. Currently, however, while IVM may be an appealing strategy for younger women with PCOS because it eliminates the risk for developing OHSS, enthusiasm for this option is currently somewhat dampened by the lesser success rates.

Conclusions

The goal of IVF is to achieve a singleton pregnancy while minimizing the risks of OHSS and multiple pregnancies. Management of PCOS patients requires a detailed clinical assessment and risk stratification and the choice of therapy needs to be individualized for each patient. Serious attention should be made in the choice of IVF treatment protocol, dose of gonadotropin utilized, and regimen selected to achieve final oocyte maturation. Close monitoring of ovarian and hormonal response as well as preempting the risk for OHSS development is critical. As assisted reproduction technologies continue to improve, further development on ways to mitigate OHSS and improve outcomes in PCOS patients will likely continue to occur. The long-term health and safety of patients, with complete elimination of OHSS, is the goal of all health care providers and is well within reach.

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