Austin Journal of Invitro Fertilization

Open Access

Austin Publishing Group

Special Article - Ovarian Hyperstimulation Syndrome

In Vitro Maturation: A Tool for Avoiding Severe Ovarian Hyperstimulation Syndrome and Expanding Patient Options

Rose BI*
Department of Obstetrics and Gynecology, Baptist Health, USA

***Corresponding author:** Bruce I. Rose, Brown Fertility, 8149 Point Meadows Way, Jacksonville, FL 32256, USA

Received: June 12, 2017; **Accepted:** July 10, 2017; **Published:** July 17, 2017

Abstract

In vitro maturation (IVM) is the only advanced reproductive technology with which all forms of ovarian hyperstimulation syndrome can be avoided. This is because of how it impacts Vascular Endothelial Growth Factor (VEGF) production and interferes with the activation of VEGF mediated processes while still enabling pregnancy. Many other treatments developed to prevent or to attenuate severe OHSS also play off the VEGF system, but they do so less effectively than IVM. IVM is also unique in preventing mild OHSS, which reduces the burden on patients requiring advanced reproductive technologies.

An understanding of why IVM is effective also allows the IVF practitioner to utilize IVM techniques to avoid severe OHSS in settings where other approaches are unlikely to work. This provides the practitioner with an alternative to cycle cancellation.

Keywords: IVM: *In vitro* maturation; Rescue IVM; IVF with EAR; Severe OHSS; Hyperstimulation; GnRH agonist trigger; VEGF; Ovarian physiology; Treatment of OHSS

Introduction

Many consider Ovarian Hyperstimulation Syndrome (OHSS) to be the most significant side effect of Controlled Ovarian Hyperstimulation (COH) and of IVF procedures. Severe OHSS occurs frequently enough that anyone considered a practitioner of IVF has managed difficult patients with this condition. Because deaths due to severe OHSS have been reported, management of patients with severe forms of OHSS is a stressful undertaking. Patients may require management in a hospital's intensive care unit since they may experience the same physiological problems as those of the critically ill. However, because of a very different underlying etiology, the necessary management is different from the more routine patients in the intensive care setting. The IVF practitioner may have to undertake responsibilities of a critical care physician. Since the stakes of experiencing severe OHSS are so costly, the best management of severe OHSS is to avoid having it occur [1,2].

Our primary objective in this review is to discuss an uncommon approach to avoiding severe OHSS, namely, the use of *In Vitro* Maturation (IVM) techniques. Awareness of the utility of IVM can change a physician's options in providing IVF care because it offers a much gentler approach to achieving pregnancy for patients at high risk for OHSS. However, it can also expand the tools that the IVF practitioner can provide to his/her patients threatened with the potential development of severe OHSS even in programs that do not routinely offer IVM.

Ovarian Hyper Stimulation Syndrome (OHSS)

OHSS presents with a continuum of symptoms. Severe OHSS can become life threatening. Moderate OHSS needs close follow-up since OHSS is a changing condition and it may become severe OHSS. Mild OHSS is simply uncomfortable for the patient. Over the years, various practitioners have published criteria defining OHSS [3-5]. The most recent widely referenced definition of OHSS is due to Golan [5] and the key determinant of moderate OHSS in his classification is the presence of ascitic fluid on transvaginal ultrasound examination. Golan states that mild OHSS is a common consequence of COH and therefore clinically unimportant. This is consistent with current medical practice. It is sufficiently common for a patient to report that her "ovaries hurt when she moves", that both physicians and patients accept this as a normal side effect of COH rather than a complication of COH. However, earlier classifications viewed these symptoms as constituents of mild or moderate OHSS [3,4]. The lack of importance of these symptoms of discomfort to physicians may be more related to their being unavoidable during COH than to their not imposing a burden on patients to bear as a side effect of IVF therapy.

Some researchers note that the incidence of OHSS is likely to be under-reported in retrospective reports and in IVF registries [6]. Perhaps this reporting deficit is likely to increase as experience with IVF and OHSS becomes more common. Even severe OHSS can now often be safely managed in an outpatient setting [7]. Managing moderate and severe OHSS has evolved into a part of the IVF management process rather than a significant complication of IVF. OHSS is likely to be viewed as a complication of IVF only when the physician feels that the patient requires hospitalization because of it. The United States CDC IVF registry provides no guidance on when to define OHSS as a complication [8].

There are two different common variants of OHSS seen after COH for IVF. The most frequent is an early-onset form, which

Citation: Rose BI. *In Vitro* Maturation: A Tool for Avoiding Severe Ovarian Hyperstimulation Syndrome and Expanding Patient Options. Austin J In Vitro Fertili. 2017; 4(1): 1033.

generally occurs about three to five days after administration of hCG. The other is a late-onset form of OHSS that presents about 12-15 days after administration of hCG [9,10]. The symptoms of these forms of OHSS are the same, but the late-onset form usually requires that a gestation has occurred. A less frequently seen form of severe OHSS is often referred to as "familial OHSS". Its occurrence has to do with abnormal activation of the FSH receptor due to mutations coding for the FSH receptor [11]. Perhaps the difficulty in predicting which patients will develop severe OHSS is also related to natural variants on FSH receptors. Some researchers believe that this receptor variation provides the best explanation of why medical therapies are not uniformly effective for all patients [12-14].

The occurrence of OHSS requires production of Vascular Endothelial Growth Factor (VEGF). VEGF is an angiogenic factor that induces the vascular permeability that is responsible for much of the symptomatology of OHSS [15-18]. VEGF is produced by granulosa cells and is found in a high concentration in the follicular fluid of periovulatory follicles. VEGF production markedly increases with a midcycle LH surge or hCG administration [18-20]. As an angiogenic factor, VEGF is required for the extensive vascular network that forms around the preovulatory follicle and the neovascularization that occurs with the formation of the corpus luteum. VEGF greatly enhances vascular permeability, a cause of many of the problems of OHSS. The enhanced vasculature of the preovulatory follicle is thought to be responsible for the increased responsiveness of the dominant follicle to FSH. Thus FSH secretion can decrease below what is required for the growth of non-dominant follicles while allowing the dominant follicle to continue to grow [21]. The amount of VEGF produced during *in vitro* culture of granulosa cells also varies with individual granulosa cells (presumably related to idiopathic differences of patients) [16]. After a week in culture, granulosa cells exhibit a sudden increased responsiveness to hCG with the production of high levels of VEGF. This temporally corresponds to the timing of hCG production by the embryo and may also explain why there is a late-onset form of OHSS [16].

Since granulosa cells produce VEGF, their presence is a necessary condition for the development of OHSS. The number of granulosa cells contained in a follicle is directly related to its diameter. Small antral follicles, 4 mm in diameter, contain approximately 1 million granulosa cells. Large antral follicles, 12 mm in diameter, contain approximately 10 million granulosa cells. Preovulatory follicles, 20 mm in diameter, contain about 50 million granulosa cells [22]. At-risk patients have a large number of pre-ovulatory follicles; thus, the at-risk patient is likely to have more than a billion active granulosa cells.

The ability of granulosa cells to respond to LH or hCG requires activity of LH receptors. Significant expression of LH receptors on granulosa cells does not take place until preovulatory follicle maturation, which occurs when the follicle diameter is approximately 16 mm. Until adequate LH receptors have been synthesized by the granulosa cells, the follicle is not able to respond to the midcycle gonadotropin surge [21].

In summary, VEGF production is a requirement for OHSS to occur. VEGF is produced by granulosa cells, which are present in large numbers only in larger follicles. VEGF production is required at times of high demand for neovascularization; namely, prior to ovulation, at the formation of a corpus luteum, and to rescue the corpus luteum when a pregnancy occurs. In all of these situations, LH (or hCG) appears to be the primary trigger for VEGF production. Significant LH receptors are present in the follicle only in the late stages of its development.

In Vitro Maturation (IVM)

IVM is an advanced reproductive technology that involves harvesting oocytes from antral follicles. Practitioners differ about the size of the largest antral follicle at which the decision to retrieve oocytes is made, with some practitioners making the decision when all antral follicles have diameters under 10 mm [23], 12 mm [24] or 14 mm [25]. The choice depends on the importance the practitioner places on avoiding either the selection or the impact of a dominant follicle on the IVM procedure. Estrogen may also be used to suppress the development of a follicle likely to become dominant [26]. Even at 14 mm, follicles only have developed a small portion of their future granulosa cell population and thus have at most a small component of their future secretory capacity of estradiol [22]. Follicles with diameters less than 14 mm have not developed the full capacity to respond to an LH surge. In particular, the follicles present during an IVM retrieval have a limited capacity to respond to LH or hCG compared to larger follicles.

Practitioners also differ in their use of adjunctive gonadotropins (referred to as "priming") with some using nothing [27], some using small amounts of FSH [23], some using hCG [24], and some using both FSH and hCG [28]. The most common use of FSH is 150 IU for 3 days in the beginning of the cycle [25,29]. There are also other ways that FSH can be used [30], but the total dose is almost always less than 500 IU during the cycle. FSH use in IVM is an attempt to improve oocyte competence rather than over-stimulate the ovary to maximize mature oocyte production as in conventional IVF. With IVM, the use of hCG is not to trigger the mechanisms of ovulation as it does in IVF, but to primarily enhance the competence of the oocytes to become mature in culture [31]. HCG is usually given 36 to 38 hours prior to oocyte retrieval, and as noted above, at a time when all follicles have diameter less than 14 mm. The combined use of low dose FSH together with hCG is also used to try to optimize early oocyte competence [29].

The best approach to IVM has not been established since advocates of these differing approaches have all been successful with their programs. All approaches to IVM involve aspiration of follicles with much simpler architectures and very different secretory capacities than during conventional IVF. Even when FSH and/or HCG is used during an IVM cycle, the timing of oocyte aspiration occurs in a different environment than during conventional IVF. On a theoretical basis, given the role that VEGF plays in the development of OHSS, early-onset OHSS (mild, moderate, or severe) should not occur during an IVM cycle. Late-onset OHSS should also not occur since there is no corpus luteum to stimulate with hCG produced by the pregnancy. For patients with familial OHSS, IVM (without FSH priming) is the only safe management approach. The medical literature supports the theory that use of IVM prevents OHSS. As Guzman, et al stated "…IVM is currently the only ART with no reported cases of OHSS" [32].

Table 1: Studies Comparing OHSS1 in IVM and Conventional IVF.

Author	Type of study	Patient diagnoses	Number of cases	CPR/ Transfer (%)	Cases cancelled for OHSS risk	No transfer (cryo) for OHSS risk	Coasting for OHSS risk	Hospitalized for OHSS risk	Moderate or severe OHSS[2] (% of cases)	Total OHSS burden[3] (% of cases)
Gremeau, et al. [38]	Retrospective case control	PCO and PCOS matched for age, diagnosis, ovulatory status	IVF- 97	49/90 (54.4)	Not stated	4	9	8	8 (8.2)	14 (14.4)
			IVM- 97	19/93 (20.4)	0	0	0	0	0	0
Child, et al. [39]	Retrospective case control	PCO pattern matched for age, diagnosis, month of procedure	IVF- 107	36/105 (34.3)	1	0	Not stated	1	12 (11.2)	13 (12.1)
			IVM- 107	23/105 (21.9)	0	0	0	0	0	0

[1]Golan, et al [5]
[2]As stated in reference
[3]Based on content of reference

Table 2: Treatments to avoid or mitigate OHSS and their probable impact via VEGF.

Treatment	Impact	Comments
Freeze all approach	Avoids impact of hCG from pregnancy, thus avoiding late increased VEGF production by rescued corpus luteum.	Avoids late onset OHSS. Likely speeds resolution of early onset OHSS.
Coasting	Down regulates VEGF gene expression and decreases potential of granulosa cells to produce VEGF by causing apoptosis [9].	No impact on late onset OHSS.
Albumen infusion	Unclear.	Mitigates impact of increased vascular permeability.
GnRH agonist	Attenuated LH surge caused by GnRH agonist leads to impaired development of corpus luteum with early and complete lysis of corpus luteum [41].	Effective for both early and late onset OHSS. Mild and moderate OHSS commonly occurs. Cases of severe OHSS tied to suboptimal GnRH agonist induced LH surges and to low dose hCG [41,42].
Dopamine agonist	Inhibits phosphorylation of VEGF receptor-2 and induces VEGF receptor internalization and lower activation [17,43].	Long treatment course needed to impact both early and late onset OHSS.
Pericentesis	May decrease VEGF availability by removal of fluid containing VEGF.	Highest production of VEGF occurs 48 hours after hCG [43].
IVM	Oocytes are removed before adequate granulosa cells are available to produce very high levels of VEGF. HCG is given before the follicular unit is fully capable of responding. No corpus luteum is formed.	Effective for both early and late onset OHSS.

The use of IVM instead of IVF currently is controversial in some quarters. The literature over the last twenty-five years describes many variations of approach with widely different implantation and clinical pregnancy rates. This is the basis, in part, for the American Fertility Society practice committee viewing IVM as an experimental procedure [33]. Although some reassuring safety data for IVM has been published [34,35], it is dwarfed numerically by the safety data available for conventional IVF. Another recent concern is that culturing immature oocytes in media containing very high doses of FSH likely promotes aneuploidy. For example, Roberts et al., showed a dose response increase in aneuploidy of mouse oocytes cultured in 2 to 2000 ng/ml of FSH [36]. Xu et al, using discarded immature human oocytes after conventional IVF and culturing in media supplemented with 5.5 to 2000 ng/ml of FSH, showed a similar result [37]. It is important to recognize that these studies were intended to provide insight into the use of high dose gonadotropins in the setting of conventional IVF and not IVM. Media used for human IVM typically has an FSH concentration of 5-8 mg/ml (0.075 to 0.1 IU/ml). This concentration of FSH is lower than that in follicular fluid during a typical IVF cycle [37].

The use of IVM on patient populations at high risk for OHSS has been a driving force in the development of IVM [24,27]. Two studies have compared patients treated by conventional IVF to patients treated by IVM in contemporaneous cycles in the same program [38,39]. Information about the occurrence of OHSS in these studies is summarized in (Table 1). Moderate or severe OHSS was not seen in patients treated by IVM. The incidence of severe OHSS in the 204 IVF patients was 9.8%, but the burden of dealing with the risk of severe OHSS was clearly higher. Although the occurrence of mild and moderate OHSS was not reported in these studies, there is clearly a decreased incidence, since the incidence of mild OHSS for IVM is likely 0%. All the IVM cases listed in (Table 1) used 10,000 U hCG as priming medications prior to oocyte harvesting. Since OHSS did not occur, it is likely that the granulosa cell mass and LH expression was inadequate to respond sufficiently to hCG to produce symptoms in these patients.

Based on the available data, IVM eliminates severe OHSS in patients who are candidates for IVM. If one views the primary benefit of IVM as its ability to reduce the incidence of OHSS, then it is worthwhile to try to understand what burden OHSS presents for IVF. At present, IVM is primarily used for patients with ovulatory PCO and an ovulatory PCO (PCOS) [24-27,32,38,39]. In 2006, Heijnen, et al, published a meta-analysis of case-control studies of IVF cycles in patients with and without PCOS [6]. They found nine studies meeting their criteria, but these often did not provide information on cycle cancellations specifically for hyper-response or on the incidence of OHSS. Overall cycle cancellation (for any reason) was four times as frequent for PCOS patients than for non-PCO patients. Three studies provided information on OHSS. In one study, two patients (11%) were hospitalized for moderate to severe OHSS. The second study reported a 16.9% incidence of mild to moderate OHSS and a 3.9% incidence of severe OHSS. The third study reported two cases

Table 3: Advantages and disadvantages of treatments to avoid or mitigate OHSS.

Treatment	Advantages	Disadvantages	Comments
Cancel cycle	Avoids risks and limits discomfort of OHSS. Enables physicians to achieve a better outcome next cycle.	Loss of resources used for current cycle. Disruption of patient's plans.	Patient may not be able to undertake another cycle for economic or psychological reasons.
Freeze all approach	Avoids worsening a high-risk situation by production of hCG if pregnancy were to occur.	Delays time to pregnancy for patient. Incurs additional costs associated with cryopreservation and delayed embryo replacement.	Insurance may not pay for additional associated costs.
Coasting	Decision to coast can be made late in the ovulation induction.	Lengthens cycle and adds monitoring costs. Cycle may need to be cancelled if estradiol drops too quickly or not quickly enough.	Significant OHSS may still occur [44].
Albumen infusion	Treats some symptoms of OHSS.	Not sufficiently adequate alone.	Meta-analysis suggests that this saves one case of severe OHSS for every 18 high-risk women [45].
GnRH agonist	Easy to use as long as all high-risk patients utilize antagonist ovulation inductions.	Requires careful management of luteal phase and early pregnancy. Ascertaining adequacy of induced LH surge may be useful. Mild and moderate OHSS can still occur.	Lower ongoing pregnancy rate than with hCG in meta-analysis [46]. Dual trigger may make less effective in preventing OHSS [42].
Dopamine agonist	Easy to use.	Requires management of luteal phase. Some concerns about ergot derived dopamine agonists leading to cardiac damage. Concerns about drug tolerability of non-ergot derived dopamine agonists [17]. All forms of OHSS can still occur [47].	Need long duration of medications to reduce both early and late OHSS.
Pericentesis	Enables management of severe OHSS as outpatient [7]. Improves hospital management of OHSS.	Can be unpleasant for the patient without anesthesia.	Patients experiencing a cycle where this was required is unlikely to want to repeat it.
IVM	Prevents early and late-onset OHSS. Symptoms related to high estradiol levels avoided. Simpler, gentler, cheaper, shorter duration cycles than conventional IVF.	Lower pregnancy rates per cycle than conventional IVF in most published studies.	Requires management of early pregnancy until placental function adequate.

of OHSS in PCOS patients and one case in a non-PCO patient. At best, we conclude that OHSS is not rare in IVF patients with PCOS. Again, our understanding of the factors influencing the development of OHSS and the differences between IVM and IVF suggests that severe OHSS should not occur with IVM in patients with PCOS. IVM also prevents the discomfort that patients feel due to mild OHSS. The number of such patients with mild OHSS is even harder to quantify, but avoiding pain and discomfort in patients is a routine part of good medical care.

Diverse management approaches or treatments for patients, either known to be high risk for OHSS before the start of an IVF cycle or who becomes high risk for OHSS in the course of an IVF cycle, have been advocated. Some of the patients who become high risk for severe OHSS during a cycle are managed by cycle cancellation prior to oocyte aspiration and they incur considerable wasted expense in terms of medications, monitoring costs and time missed from work. In 2014, more than 4294 women in the United States under age 38 had cycles cancelled prior to oocyte aspiration [8]. At least some of these cancellations were due to OHSS risk. In an ESHRE questionnaire survey, up to 20% of IVF physicians would manage patients having very high estradiol levels by cycle cancellation [1]. In a Web-based internet study, 18% of physicians from 262 centers and 68 nations would also manage a patient with a very high risk of severe OHSS by cycle cancellation [40].

There are several treatments to mitigate or prevent the development of severe OHSS that are widely used. They are not as effective as IVM because they are less effective in modifying the impact of VEGF on the patient (Table 2). Most of these interventions impose extra burdens on patients that they would not experience with IVM (Table 3).

The most effective of these treatments (after IVM) is using a GnRH agonist to trigger oocyte maturation. GnRH agonists produce an LH surge that it shorter in duration than a physiological surge. This LH spike is adequate to promote oocyte maturation, but not adequate to establish a corpus luteum. Early luteolysis eliminates the period of highest production of VEGF and also prevents late-onset OHSS since there is no corpus luteum to be rescued. Some of this benefit may be lost with the concomitant use of low doses of HCG, which may be used with a GnRH agonist trigger to improve the pregnancy rate. This is because the half-life of hCG is much longer than that of LH, and hCG activates the VEGF system more effectively than does LH [41-48]. Table 4 is a sample listing of reports in the literature of OHSS occurring in cycles utilizing a GnRH agonist to trigger oocyte maturity. One may hypothesize that these episodes of OHSS are due to severe OHSS occurring prior to the use of the GnRH agonist, that the patient had an atypical response to the GnRH agonist, that there was a confounding effect of low dose hCG use, or that the patient had a genetic mutation of her FSH, LH, or VEGF receptor [12-14]. Similar to IVM for which a corpus luteum is not present, when a GnRH agonist is used, the luteal phase and early pregnancy need to be managed with supplemental estrogen and progesterone.

Rescue IVM and IVF with EAR

Experience with IVM or IVM techniques can also be useful to prevent severe OHSS in patients who become high-risk patients in the course of their COH. Physicians may elect a COH approach for some patients using a GnRH agonist who respond by developing early severe OHSS. For example, on day six of gonadotropins a patient might have an estradiol level of 5000 pg/ml with ovaries containing multiple follicles all less than 12 mm in diameter. The standard approach to this situation could be to cancel the cycle and try again in the future with a different approach to COH. Based on

Table 4: OHSS after use of GnRH agonists to trigger oocyte maturation.

Author	Cases	Oocyte maturation	Comments
Van der Meer, et al. [49]	Three cases of moderate OHSS in 27 high-risk patient cycles.	2.4 mg buserelin acetate.	
Gerris J, et al. [50]	One case of moderate OHSS out of 9 cases.	0.5 mg GnRH	
Lee, HS, et al. [51]	Clinically significant OHSS in 6 out of 50 cases. Three cases were hospitalized.	0.2 mg triptorelin with 500 U HCG given on day of oocyte retrieval.	
Griesinger G, et al [52]	One case of severe early onset OHSS out of 51 patients	0.2 mg triptorelin.	
Griffin D, et al. [53]	One case of mild OHSS out of 34 with dual trigger. None with GnRHa only (n = 68)	1 mg luprolide acetate. Dual trigger also used 1000 U hCG.	Clinical pregnancy rate 58.8% with dual trigger and 30.9% without.
Shapiro BS, et al. [42]	One case of clinically significant late-onset OHSS out of 182 using dual trigger. No significant OHSS in patients with GnRH agonist only (n = 115)	4 mg luprolide acetate. Dual trigger used 33 U hCG/kg at same time.	Highest pregnancy rate with dual trigger. Decrease in pregnancy loss rate with dual trigger or enhanced luteal support.
Radesic B, Tremellen K [54]	One case of severe OHSS requiring hospitalization out of 71 cases.	2 mg luprolide acetate with 1500 U hCG at retrieval.	
Hamaidan P, et al. [55]	Two cases of moderate late-onset OHSS in high-risk dual trigger group. Two cases of severe late onset OHSS occurred in low risk group with extra hCG dose.	0.5 mg buserelin with 1500 U hCG at same time and second low risk for OHSS group getting second dose of 1500 U hCG on day of retrieval	
Seyhan A, et al. [56]	Six out of 23 women developed severe early OHSS after dual trigger protocol. Five of these women required hospitalization. In three cases, embryo transfer was withheld.	1 mg buserelin acetate or 0.2 mg triptorelin with 1500 hCG given at the same time.	
Iliodromiti S, et al. [57]	Two cases of severe OHSS in 275 cycles.	Various GnRHa triggers with 1500 U hCG given at aspiration.	
Fatemi HM, et al. [12]	Two cases of severe OHSS. Both cases required hospitalization.	0.3 mg triptorelin or 0.2 mg decapeptyl.	Agonist trigger and "freeze-all" approach and cabergoline or agonist trigger and "freeze-all" approach.
Gurbuz AS, et al. [13]	Three cases of severe OHSS. All three cases required hospitalization.	1 mg luprolide acetate.	Combined agonist trigger and "freeze-all" approach.

accumulated experience from IVM, a better approach would be to treat the patient with 10,000 U of hCG either on this day or the next and harvest oocytes 36 hours after administering hCG. We would expect that 20 to 30% of the oocytes recovered would be mature and capable of being fertilized. This should provide the patient with one or two good quality embryos to transfer and a chance at pregnancy instead of cycle cancellation. This approach has been referred to as IVF with Early Aspiration Rescue (IVF with EAR) [58]. If the IVF program routinely provides IVM, then the patient may be provided an even better chance at achieving pregnancy by culturing the large number of initially immature oocytes and achieving maturity in approximately 60% of them. This has been termed rescue IVM.

As noted above, the number of granulosa cells present in follicles less than 14 mm is small compared to the number present in a normal IVF cycle [19]. Also follicular structures fewer than 14 mm are not able to fully respond to hCG and a corpus luteum is not formed. Thus, severe OHSS is unlikely to occur [58,59]. Rose reported a clinical pregnancy rate for IVF with EAR of 60% with five cases [58]. Lim, et al reported a clinical pregnancy rate of 46.1% with 17 cases (with use of hCG) [59]. Bergeron, et al. reported on five cases all of who achieved clinical pregnancies after rescue IVM using hCG [60]. Brigante, et al. reported a 37.5% clinical pregnancy rate in eight cases in which IVM without hCG was used [61]. Severe OHSS did not occur in any of these 36 cases.

The key to IVF with EAR or rescue IVM being successful has to do with the number of follicles that a patient has follicles in the 8 to 14 mm range. The closer the follicles are to 14 mm in size, the higher the probability that a follicle will contain a mature oocyte. Scott, et al found MI or MII oocytes in 9% of follicles fewer than 11 mm in diameter and in 30% of follicles between 12 and 14 mm collected during conventional IVF [62]. The IVM literature suggests that when oocytes have been exposed to exogenous gonadotropins and hCG (priming with both), then 20% of the oocytes will be mature [29,63]. The constraint of this approach is that the decision to convert the IVF cycle to IVF with EAR or IVM rescue must be made early enough to avoid the development of severe OHSS (having a maximal follicle less than 14 mm).

Another positive feature of this approach is that routine IVF tools can be used. A special aspiration needle is not required. A different aspiration pressure is not required. All IVF practitioners are used to aspirating oocytes from follicles in the 10 to 14 mm range (and occasionally slightly smaller). Physicians may continue to use their routine approaches and equipment. Routine laboratory techniques for oocyte identification can also be used. Given the high response to gonadotropins, mature oocytes will have moderate to full expressions of their cumulous. An experienced embryologist should be able to identify oocytes without additional equipment or training.

Conclusion

IVM is the only ART preventive approach for which OHSS has not been reported to occur. Given our current understanding of the central role of the VEGF system in the development of OHSS, OHSS cannot occur in response to an IVM cycle. This is not true of other current popular approaches to preventing or mitigating severe OHSS. Unlike these other approaches, IVM also likely avoids the patient having to experience mild OHSS.

Rescue IVM and IVF with EAR are ART techniques which utilize ideas from IVM. These are additional approaches to prevent severe OHSS that are justified through experience with IVM. They should be available to a wide range of IVF practitioners.

References

1. Delvigne A, Rozenberg A. Preventive attitude of physicians to avoid OHSS in IVF patients. Hum Repro. 2001; 16: 2491-2495.
2. The Practice Committee of the American Society for Reproductive Medicine. Ovarian hyperstimulation Syndrome. Fertil Steril. 2006; 90: 178-183.
3. Rabau E, David A, Serr DM, Mashiach S, Lunenfeld B. Human menopausal gonadotropins for anovulation and sterility. Results of 7 years of treatment. Am J Obset Gynecol. 1967; 98: 92-98.
4. Schenker JG, Weinstein D. Ovarian hyperstimulation syndrome: a current survey. Fertil Steril. 1978; 30: 255-268.
5. Golan A, Weissman A. A modern classification of OHSS. Reprod BioMed Online. 2009; 19: 28-32.
6. Heijnen EM, Eilkemans MJC, Hughes EG, Laven JS, Macklon NS, Fauser BC. A meta-analysis of outcomes of conventional IVF in women with polycystic ovary syndrome. Hum Reprod Update. 2006; 12: 13-21.
7. Smith LP, Hacker MR, Aper MM. Patients with severe ovarian hyperstimulation syndrome can be managed safely with aggressive outpatient transvaginal paracentesis. Fertil Steril. 2009; 92: 1953-1959.
8. Center for Disease Control. IVF Success Rates: 2014 National Summary.
9. Garcia-Velasco JA, ZunigaA, Gomez R, Simon C, Remohi J, Pellicer A. Coasting acts through down regulation of VEGF gene expression and protein secretion. Hum Reprod. 2004; 19: 1530-1538.
10. Dahl Lyons CA, Wheeler CA, Frishman GN, Hackett, Seifer DB, Haning RV. Early and late presentation of the ovarian hyperstimulation syndrome: two distinct entities with different risk factors. Hum Reprod. 1994; 9: 792-799.
11. Rizk B. Symposium: update on prediction and management of OHSS. Genetics of ovarian hyperstimulation syndrome. Reprod Biomed Online. 2009; 19: 14-27.
12. Fatemi HM, Popovic-Todorovic B, Hamaidan P, Kool S, Banker M, Devroey P, et al. Severe ovarian hyperstimulation syndrome after gonadotropin-releasing hormone (GnRH) agonist trigger and "freeze-all" approach in GnRH antagonist protocol. Fertil Steril. 2014; 101: 1008-1011.
13. Gurbuz AS, Gode F, Ozcimen N, Isik AZ. Gondaotropin-releasing hormone agonist triggers and freeze-all strategy does not prevent severe ovarian hyperstimulation syndrome: a report of three cases. Reprod Biomed Online. 2014; 29: 541-544.
14. Fatemi HM, Garcia-Velasco J. Avoiding ovarian hyperstimulation syndrome with the use of gonadotropin-releasing hormone agonist trigger. Fertil Steril. 2015; 103: 870-873.
15. Levin ER, Rosen GF, Cassidenti DL, Yee B, Meldrum D, Wiscot A, et al. Role of vascular endothelial cell growth factor in ovarian hyperstimulation syndrome. J Clin Invest. 1998; 102: 1978-1985.
16. Lee A, Christenson LK, Patton PE, Burry KA, Stouffer RL. Vascular endothelial growth factor production by human luteinized granulosa cells *in vitro*. Hum Reprod 1997; 12: 2756-2761.
17. McClure N, Healy Dl, Rogers PA, Sullivan J, Robertson DM, Haning RV, et al. Vascular endothelial growth factor as a capillary permeability agent in ovarian hyperstimulation syndrome. Lancet. 1994; 344: 235-236.
18. Soares SR. Etiology of OHSS and use of dopamine agonists. Fertil Steril. 2012; 97: 517-522.
19. Anasti JN, Kalantaridou SN, Kimzey LM, George M, Nelson LM. Human follicular fluid vascular endothelial growth factor concentrations are correlated with luteinization in spontaneously developing follicles. Hum Reprod. 1998; 13: 1144-1147.
20. Gordon JD, Mesiano S, Zaloudak CJ, Jaffee RB. Vascular endothelial growth factor localization in human ovary and fallopian tubes: possible role in reproductive function and ovarian cyst formation. J Clin Endocrinol Metab. 1996; 81: 353-359.
21. Gougeon A. Regulation of ovarian follicular development in primates. Endocrine Rev. 1996; 17: 121-155.
22. McNatty KP, Smith DM, Makris A, Sathanondh R, Ryan KJ. The microenvironment of the human antral follicle: Interrelationships among the steroid levels in antral fluid, the population of granulosa cells, and the status of the oocyte in vivo and *in vitro*. Clin Endocrinol Metab. 1979; 49: 851-860.
23. Mikkelson AL, Lindenberg S. Morphology of *in vitro* matured oocytes: impact on fertility potential and embryo quality. Hum Reprod. 2001; 16: 1714-1718.
24. Child TJ, Abdul-Jalil AK, Gulekli B, Tan SL. *In vitro* maturation and fertilization of oocytes from unstimulated normal ovaries, polycystic ovaries, and women with polycystic ovary syndrome. Fertil Steril. 2001; 76: 936-942.
25. Junk SM, Yeap D. Improved implantation and ongoing pregnancy rates after single-embryo transfer with an optimal protocol for *in vitro* oocyte maturation in women with polycystic ovaries and polycystic ovarian syndrome. Fertil Steril. 2012; 98: 888-892.
26. Vitek WS, Witmyer J, Carson SA, Robins JC. Estrogen-suppressed *in vitro* maturation: a novel approach to *in vitro* maturation. Fertil Steril. 2013; 99: 1886-1890.
27. Soderstrumm-Antillia V, Makinen S, Tuuri T, Suikkara AM. Favorable pregnancy results with insemination of *in vitro* matured oocytes from unstimulated patients. Hum Reprod. 2005; 20: 1534-1540.
28. Fadini R, Del Canto MB, Renzini MM, Brambilasca F, Corni R, Fumagalli D, et al. Effect of different gonadotropin priming on IVM of oocytes from women with normal ovaries: a prospective randomized study. Reprod BioMed Online. 2009; 19: 343-351.
29. DeVos M, Ortega-Hrepich C, Albuz FK, Guzman L, Polyzos NP, Smitz J, et al. Clinical outcome of non-hCG-primed oocyte *in vitro* maturation treatment in patients with polycystic ovaries and polycystic ovary syndrome. Fertil Steril. 2011; 96: 860-864.
30. Elizur SE, Son WY, Yap R, Gidoni Y, Levin D, Demirtas E, et al. Comparison of low-dose human menopausal gonadotropin and micronized 17β-estradiol supplementation *in vitro* maturation cycles with thin endometrial lining. Fertil Steril. 2009; 92: 907-912.
31. Chain RC, Buckett WM, Tulandi T, Tan SL. Prospective randomized study of human chorionic gonadotropin priming before immature oocyte retrieval from unstimulated women with polycystic ovarian syndrome. Hum Reprod. 2000; 15: 165-170.
32. Guzman L, Ortega-Hrepich C, Polyzur NP, Anckaert E, Verheyen G, Coucka W, et al. A prediction model to select PCOS patients suitable for IVM treatment based on anti-Mullerian hormone and antral follicle count. Hum Reprod. 2013; 28: 1261-1266.
33. The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology and Society for Assisted Reproductive Technology. *In vitro* maturation: a committee opinion. Fertil Steril. 2013; 99: 663-666.
34. Basatemur E, Sutcliffe A. Health of IVM children. J Assist Reprod Genet. 2011; 28: 489-493.
35. Fadini R, Mignini Renzini M, Guanieri T, dal Cato M, de Ponti E, Sutcliffe A, et al. Comparison of obstetric and perinatal outcomes of children conceived from *in vitro* or in vivo matured oocytes *in vitro* maturation treatments with births from conventional ICSI cycles. Hum Reprod. 2012; 27: 3601-3608.
36. Roberts R, Iatropoulou A, Ciantar D, Stark J, Becker DL, Franks S, et al. Follicle-stimulating hormone affects metaphase I chromosomal alignment and increases aneuploidy in mouse oocytes matured *in vitro*. Biol Reprod. 2005; 72: 107-118.
37. Xu YW, Peng YT, Wang B, Zeng YH, Zhuang GL, Zhou CQ. High follicle-stimulating hormone increases aneuploidy in human oocytes matured *in vitro*. Fertil Steril. 2011; 95: 99-104.
38. Gremeau AS, Andreadis N, Fatum M, Craig J, Turner K, McVeigh E, Child T. *In vitro* maturation or *in vitro* fertilization for women with polycystic ovaries? A case-control study of 194 treatment cycles. Fertil Steril. 2012; 98: 355-360.
39. Child TJ, Phillips SJ, Abdul-Jalil AK, Gukekle B, Tan SL. A comparison of *in vitro* maturation and *in vitro* fertilization for women with polycystic ovaries. Obstet Gynecol. 2002; 100: 665-670.

40. Brezina PR, Mensah V, Balen A, Leong M, Weissman A, Zhao Y, et al. Fertility management in the PCOS population: results of a web-based survey at IVF-worldwide.com. J Assist Reprod Genet. 2013; 30: 1169-1174.

41. Kol S. Luteolysis induced by gonadotropin-releasing hormone agonist is the key to prevention of ovarian hyperstimulation syndrome. Fertil Steril. 2004; 81: 1-5.

42. Shapiro BD, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Comparison of "triggers" using leuprolide acetate alone or in combination with low-dose human gonadotropin. Fertil Steril. 2011; 95: 2715-2717.

43. Soares SR, Gomez R, Simorn C, Garcia-Velasco JA, Pellicer A. Targeting the vascular endothelial growth factor system to prevent ovarian hyperstimulation syndrome. Hum Reprod. 2008; 14: 321-333.

44. D'Angelo A, Brown J, Anso NN. Coasting (withholding gonadotropins) for preventing ovarian hyperstimulation syndrome (Review). Cochrane Database Syst Rev. 2011; 15.

45. Aboulgar M, Evers JH, Al-Inany H. Intravenous albumen for preventing severe ovarian hyperstimulation syndrome: a Cochrane review. Hum Reprod. 2002; 17: 3027-3032.

46. Griesinger G, Diedrich K, Devroey P, Kolibianakis EM. GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis. Human Reproduction Update. 2006; 12: 159-168.

47. Youssef, van Wely M, Hassan MA, Al-Inany HG, Mochtar M, Khattab S, et al. Can dopamine agonists reduce the incidence and severity of OHSS in IVF/ICSI treatment cycles? A systemic review and meta-analysis. Hum Reprod Update. 2010; 16: 459-466.

48. Cerrillo, Pacheco A, Rodriquez S, Gomez R, Delgrado F, Pellicer A, et al. Effect of GnRH agonist and hCG treatment on VEGF, angiopoietin-2, and VE-cadherin: trying to explain the link to ovarian hyperstimulation syndrome. Fertil Steril. 2011; 95: 2517-2519.

49. Van der Meer S, Gerris J, Joostens M, Tas B. Endocrinology: Triggering of Ovulation using a gonadotropin-releasing hormone agonist does not prevent ovarian hyperstimulation syndrome. Hum Reprod. 1993; 8: 1628-1631.

50. Gerris J, DeVits A, Joostens M, Van Royen E. Triggering of ovulation in human menopausal gonadotropin-stimulated cycles: comparison between intravenously administered gonadotropin-releasing hormone (100 and 500 ug), GnRH agonist (buserelin, 500 ug) and human chorionic gonadotropin (10 000 IU). Hum Reprod. 1995; 10: 56-62.

51. Lee HS, Jeong HJ, Kim MH, Chung MK. GnRH agonist trigger with low dose human chorionic gonadotropin successfully rescues luteal phase, prevents ovarian hyperstimulation and improves IVF outcomes. Fertil Steril. 2012; 98: 52.

52. Griesinger G, Schultz L, Bauer T, Broessner A, Frambach T, Kissler S. Ovarian hyperstimulation syndrome prevention by gonadotropin-releasing hormone agonist triggering of final oocyte maturation in a gonadotropin-releasing hormone antagonist protocol in combination with a "freeze-all" strategy: a prospective multicentric study. Fertil Steril. 2011; 95: 2029-2033.

53. Griffin D, Benadiva C, Kummer N, Budinetz T, Nulsen J, Engmann L. Dual trigger for oocyte maturation with gonadotropin-releasing hormone agonist and low-dose chorionic gonadotropin to optimize live birth rates in high responders. Fertil Steril. 2012; 97: 1316-1320.

54. Radesic B, Tremelien K. Oocyte maturation employing a GnRH agonist in combination with low-dose hCG luteal rescue minimizes the severity of ovarian hyperstimulation syndrome while maintaining excellent pregnancy rates. Hum Reprod. 2011; 26: 3437-3442.

55. Humaidan P, Polyzos NP, Alsbjerg B, Erb K, Mikkelson AL, Elbaek HO, et al. GnRHa trigger and individualized luteal phase HCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients. Hum Reprod. 2013; 28: 2511-2521.

56. Seyhan A. Ata B, Polat M, Son W-Y, Yarali H, Dahan MH. Severe early ovarian hyperstimulation syndrome following GnRH agonist trigger with the addition of 1500 IU hCG. Hum Reprod. 2013; 28: 2522-2528.

57. Iliodromiti S, Blockeel C, Tremellen KP, Fleeming R, Tournaye H, Humaiden P, et al. Consistent high clinical pregnancy rate and low ovarian hyperstimulation syndrome rates in high-risk patients after GnRH agonist triggering and modified luteal support: a retrospective multicentre study. Hum Reprod. 2013; 28: 2529-2536.

58. Rose BI. A new treatment to avoid severe ovarian hyperstimulation utilizing insights from *in vitro* maturation. J Assist Reprod Genetics. 2014; 31: 195-198.

59. Lim K-S, Son W-Y, Yoon S-H, Lim J-H. IVM/F-ET in stimulated cycles for prevention of OHSS. Fertil Steril. 2002; 78: 10.

60. M Fatum, C Ross, Bergeron M-E, Turner K, McVeigh E, Child T. Rescue *in vitro* maturation in polycystic ovarian syndrome patients overresponding/underresponding to ovarian stimulation *in vitro* fertilization treatment: Is it a viable option? 2013; 100: 271.

61. Brigante CMM, Renzini MM, Del Canto M, Coticchio G, Caliari I, Fadini R. IVM rescue in high responder patients at risk of OHSS. Fertil Steril. 2013; 100: 419.

62. Scott RT, Hofmann GE, Muasher JJ, Acosta AA, Kreiner DK, Rosenwaks Z. Correlation of follicular diameter with oocyte recovery and maturity at the time of transvaginal follicular aspiration. J *In Vitro* Fert Embryo Transf. 1989; 6: 73-75.

63. Rose BI, Laky D. A comparison of the Cook single lumen immature ovum IVM needle to the Steiner-Tan pseudo double lumen flushing needle for oocyte retrieval for IVM. J Assist Reprod Genet. 3013; 30: 855-860.

Austin J In Vitro Fertili - Volume 4 Issue 1 - 2017
ISSN : 2471-0628 | www.austinpublishinggroup.com

Citation: Rose BI. *In Vitro* Maturation: A Tool for Avoiding Severe Ovarian Hyperstimulation Syndrome and Expanding Patient Options. Austin J In Vitro Fertili. 2017; 4(1): 1033.