A new treatment to avoid severe ovarian hyperstimulation utilizing insights from in vitro maturation therapy

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Introduction

Ovarian hyperstimulation syndrome (OHSS) can be a serious complication of gonadotropin ovulation induction for IVF. There are a number of therapies (Table 1) designed to mitigate or avoid severe OHSS, but all of these generally either require pre-planning or alter the normal flow of an IVF-ET cycle. In vitro maturation with IVF (IVM) is an established approach for avoiding any degree of OHSS in patients requiring advanced reproductive technology treatment since oocytes are harvested from medium to large antral follicles before in vivo follicle selection begins [1, 2]. With IVM, immature oocytes complete meiosis II over the next 48 h and are then fertilized once they become mature. Some IVM practitioners have advocated “rescue IVM” as a way of preventing severe OHSS in the setting of conventional IVF [3]. “Rescue IVM” means that the physician has concluded that a conventional IVF cycle can not safely proceed and the physician changes the treatment direction by immediately applying that

program’s IVM protocol to the cycle. If aspiration occurred before follicle selection takes place, then the risk of OHSS was eliminated.

We utilized “rescue IVM” for five patient cycles and found that the procedure provided a reasonable chance for patients to achieve pregnancy and appeared to prevent OHSS, but importantly did not directly require any component of our expertise with IVM. Our plan to undertake rescue IVM enabled us to justify intervention in cycles that were moving toward a high probability of severe OHSS and aspirate oocytes before dominant follicle selection had taken place. The number of medium and large antral follicles was adequate for enough mature oocytes (MII) to be obtained so that sufficient embryos were available for transfer on day three. This approach to preventing severe OHSS was simpler for both the patient and the IVF program than most other approaches, because it shortened the treatment process and did not add any new features to patient management.

Case report

Demographic information on the five patients is presented in Table 2. Three of these patients did not meet the diagnostic conditions for PCOS [9]. All patients were pretreated with oral contraceptives for cycle timing. Patients were all started on gonadotropins on day three of bleeding or 6 days after stopping oral contraceptives. Patients were then evaluated by ultrasound and hormone testing after 6 and after 8 days of gonadotropins. Table 3 summarizes clinical information at the time the decision was made to proceed with

Capsule Early aspiration of small follicles in patients at risk for severe OHSS appears to prevent OHSS and provide a good chance for pregnancy.

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Table 1 Treatments to manage high risk of severe OHSS

Treatment	Comments
Cycle cancellation with embryo cryopreservation	Mitigates OHSS severity by avoiding pregnancy. Lengthens time and increases costs required to complete cycle [4].
Coasting	Increases time required to complete cycle and does not always lead to embryo transfer [5].
GnRH agonist trigger	Can only be used with antagonist ovulation induction cycle [6].
IVM	Requires specific expertise [1].
Post-retrieval interventions	The impact of dopamine agonist on the miscarriage rate not well established [7]. Paracentesis is a significantly unpleasant additional intervention for the patient [8].

rescue IVM. With the decision to proceed with rescue IVM, all patients received 10,000 units of hCG 36 to 38 h prior to retrieval. In all cases, ICSI was used for fertilization and patients had day three or four transfers. Table 4 presents relevant data about the retrieval, transfer, and pregnancy outcome for each case. High quality day three embryos had seven to nine cells and less than 10 % fragmentation. High quality day two embryos (employing IVM) had four cells and less than 10 % fragmentation.

Case 4 differed from the other cases as the diagnosis of hypothalamic hypogonadism precluded a diagnosis of PCOS. This patient had a slow response to gonadotropins and appeared likely to produce one or two mature size follicles and a very large quantity of medium size antral follicles. The decision to move to rescue IVM occurred later than in the other cases.

Case 3 was also atypical in that the patient had six prior IVF cycles most of which produced low numbers of oocytes consistent with this patient's low anti-Mullerian Hormone (AMH) level and moderately low total antral follicle count (AFC). The plan for this cycle was to treat the patient with low doses of gonadotropins as some physicians choose to do for patients with decreased ovarian reserve [10].

Of the 76 oocytes retrieved, 33 (43.4 %) were MII on the day of aspiration. Although additional embryos were created for all patients utilizing an IVM approach, the resulting embryos did not appear to be as worthy of transfer as did embryos fertilized on the day of retrieval. Collectively, these cases produced nine high quality day three embryos from oocytes mature on the day of aspiration (27.3 %). All patients would have had good or adequate embryos to transfer on day three without using any in vitro maturation techniques. No patient chose to utilize cryopreservation. No patient experienced moderate or severe ovarian hyperstimulation.

Discussion

The five cases presented above involved a mixture of patients prospectively at high risk for severe OHSS and patients unexpectedly found to be at high risk for severe OHSS. In all cases, after several days of conventional IVF ovulation induction, patients were found to have a large number of large antral follicles and a moderate estradiol level, but would have required several more days before follicles would meet standard criteria for oocyte retrieval. We chose to manage these patients with “rescue IVM”. However, in each of these cases, in vitro maturation did not appear to significantly enhance the patients' potential for pregnancy. Different

Table 2 Demographic information

Patient/case	Age	BMI ^a	AMH ^b	Total AFC ^c	Years infertile	Prior IVF cycles	Diagnoses
1	23	28.0	7.6	15	4	0	Severe male factor (not PCOS)
2	36	26.6	na ^d	25	5	2 (prior moderate OHSS)	PCOS, endometriosis, uterine adenomyosis
3	36	30.6	0.4	9	5	6 (with 2–11 oocytes)	Ovarian dysfunction (not PCOS)
4	35	24.1	na ^d	8	3	0	Hypothalamic hypogonadism
5	33	27.3	2.4	64	5	2	PCOS, severe male factor

^a Basal Metabolic Index

^b Anti-Mullerian Hormone (ng/mL)

^c Antral Follicle Count

^d Not available

Table 3 Clinical cycle information

Patient/ case	Cycle type	Gonadotropin daily dose (U)	Gonadotropin total dose (U)	Days of gonadotropins	Largest 3 follicles (mm)	Peak estradiol level (pg/ml)	Total antral follicles
1	Long	200	1150	7	13.5, 13.5, 13	2594	>25
2	Long	150	1050	7	14, 13.5, 12	1942	31
3	GO ^a	150	1050	7	14, 12.5, 12.5	492	18
4	GO ^a	150	2550	11	14, 12.5, 12.5	2972	24
5	Long	300	1700	7	16.5, 14.5, 12.5	1964	> 26

^a GnRH antagonist was planned, but gonadotropins were used without pituitary suppression

media, oocyte identification techniques, multiple maturation assessments and serial fertilization procedures did not enhance patients' chances of pregnancy beyond routine follicle aspiration, ICSI of mature oocytes and routine transfer of the best embryos.

Since nomenclature for IVM type procedures appears to be slow in evolving [11], we propose that this treatment be referred to as early aspiration rescue (EAR). The patient will have received treatment with conventional IVF with EAR [12], which does not involve any form of IVM.

Finding a large number of mature oocytes should have been expected based on Fadini, et al's observation in a randomized study of non-PCO patients looking at priming approaches for IVM [13]. One arm of that study was treated with 150 U of gonadotropins for 3 days and was given hCG prior to aspiration. These patients were found to have 20 % of their oocytes (obtained from follicles with diameters less than 14 mm) to be MII at the time of aspiration. Our IVM program, using a similar protocol for patients with a PCO pattern by ultrasound, found the same result [14].

Early oocyte retrieval has been advocated to avoid OHSS in earlier literature, but "early" refers to the interval from hCG to retrieval (10–12 h) rather than early in terms of follicle development [15]. In the IVF

literature, Chian, et al. has shown that increasing the interval from the administration of HCG to retrieval increases the oocyte maturation rate [16]. "Truncated IVF" has been described as a procedure applicable to patients with PCOS in which moderate doses of gonadotropins are used with a plan to perform conventional IVF when a lead follicle reached 14 mm in diameter [17]. Uzelac, et al. described their successful use of this technique in an abstract that concluded that pregnancy rates with truncated IVF were similar to those of conventional IVF and that no cases of OHSS occurred in their study group [17]. Unlike IVF with EAR, truncated IVF is not a rescue technique and therefore required pre-cycle planning. Both procedures likely benefited from the fact that an adequate number of MIIs can be obtained from small follicles after the administration of gonadotropins and hCG in patients with a large number of antral follicles.

Oocyte identification during retrieval is generally more difficult with IVM than with conventional IVF because there is usually less of a cumulus mass to observe. However, the longer time period of treatment with gonadotropins used in our patients treated with rescue IVM and the use of hCG, likely increased the size of the cumulus masses and made the oocyte identification process similar to conventional IVF [18].

Table 4 Cycle laboratory information

Patient/case	Oocytes retrieved	III oocytes	MI oocytes	III oocytes fertilized	High quality day 3 embryos	Late/IVM fertilized oocytes (high quality)	Embryos transferred	Pregnancy outcome
1	10	5	3	5	2	0 (0)	2	Biochemical hCG 16
2	16	9	1	5	1	1 (0)	3	Chorionic sac on ultrasound; hCG 574
3	14	4	2	3	2	4 (0)	3	Delivered at term
4	12	2	2	1	1	3 (0)	3	Cardiac activity (triploid)
5	24	13	2	10	3	2 (0)	2	Biochemical hCG 141

Conclusion

Administration of hCG as soon as a determination has been made that the patient is at risk for severe OHSS will allow a program to proceed with a conventional IVF retrieval and likely provide the opportunity for a good prognosis transfer. If the decision is made early enough in the ovulation induction (before full sensitivity to FSH has occurred), the risk of ovarian hyperstimulation will likely be avoided. This process is clearly easier and less expensive for patients than some of the more widely used approaches to treating patients at risk for severe OHSS. Further confirmation of the effectiveness of this approach in achieving pregnancy and avoiding severe OHSS will require a study with randomized comparative treatment cycles.

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