CHAPTER 17

FSH priming in IVM cycles

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BACKGROUND

The experience in handling immature oocytes has been obtained from two main groups. The first group is women suffering from polycystic ovarian syndrome (PCOS), as these women are extremely sensitive to stimulation with follicle stimulating hormone (FSH) in assisted reproduction, and they have a significant risk of developing ovarian hyperstimulation syndrome (OHSS). The second group is regularly cycling women with normal ovaries referred for in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). In both groups aspiration of immature oocytes has been performed in unstimulated cycles and after priming with FSH, and/or after priming with human chorionic gonadotropin (hCG) before aspiration. In this chapter the experience obtained after handling immature oocytes after FSH priming is summarized.

Immature oocytes can be obtained from women who are undergoing routine superovulated IVF (rescue in-vitro maturation, IVM). During controlled ovarian hyperstimulation the oocyte population may be heterogeneous and this leads to retrieval of oocytes at different stages of maturation. About 15% of oocytes will remain in prophase I of meiosis. These oocytes can be matured in vitro and develop into viable embryos. In 1983, Veeck and co-workers[1] reported two pregnancies from transfer of embryos developed from immature oocytes obtained from stimulated cycles in their IVF program. Several groups have since made similar reports[2,3]. These oocytes failed to mature although the follicles were exposed to supraphysiologic concentrations of FSH and may represent an inferior population of oocytes. Therefore these clinical cases are not included in this review.

IMMATURE OOCYTES OBTAINED FROM WOMEN WITH PCOS

No priming

Trounson et al.[4] described the first pregnancy with immature oocyte retrieval and subsequent in-vitro maturation (IVM) in a woman with PCOS. The following year another pregnancy was reported in a patient with PCOS treated with IVM, combined with ICSI and assisted hatching[5,6]. Barnes et al.[6] compared rates of maturation, fertilization, and cleavage between untreated regularly ovulating and irregularly ovulating or anovulatory polycystic women. In almost all the parameters analyzed, oocytes from regularly cycling patients performed better. However, the reasons for this were not determined.

Later Cha et al.[7] reported a pregnancy rate of 27.1%. However this high pregnancy rate was obtained after transfer of an average 6.3 embryos per patient, and the implantation rate was still low (6.9%). To compensate for this, endogenous priming with FSH[8,9] or hCG[10,11] has been suggested before immature oocyte retrieval and subsequent IVM.

Priming with FSH

It has been postulated that FSH stimulation before oocyte retrieval might increase either the number of immature oocytes retrieved or the maturational potential and developmental competence of these oocytes. Suikkari et al.[8] proposed using low-dose (37.5 IU) recombinant FSH (rFSH) from the previous luteal phase until the leading follicle reached 10 mm. This resulted in maturation and fertilization rates in women with PCOS comparable with those in regularly cycling women, however no pregnancies were achieved in 12 patients.

A beneficial effect of higher dose FSH priming was, however, found in a later prospective randomized study[9]. Oocytes obtained after priming with rFSH (150 IU per day) for 3 days were compared with oocytes obtained in unstimulated cycles. FSH priming resulted in an improved pregnancy rate (29% vs. 0%) and implantation rate (21.6% vs. 0%) compared with the non-primed group. This was partly explained by the increased size of the folllicles in the primed group compared to the non-primed group. Previous studies have demonstrated that human oocytes appear to have a size dependent ability to resume meiosis and complete maturation[12].

Furthermore, it has been hypothesized that oocyte differentiation may be incomplete during follicular growth, and that oocytes from plateau phase follicles have increased competence[13]. Therefore, not only FSH priming but also the following FSH deprivation caused by withholding exogenous FSH should enhance the competence of the oocytes.

Priming with hCG

In 1999 Chian et al.[14] reported that giving 10 000 IU of hCG 36 hours before oocyte retrieval improved the maturation rate of immature oocytes from PCOS women. In a prospective randomized study they later demonstrated that hCG priming not only improved the maturation rate, but also hastened the maturation process[10]. Pregnancy rates of 30–35% and implantation rates of 10–15% have been reported using hCG priming[15,16]. Additional FSH priming (75 IU per day for 6 days initiated on day 3), however, did not further improve the pregnancy rate or the implantation rate[16].

IMMATURE OOCYTES FROM REGULARLY CYCLING WOMEN WITH NORMAL OVARIES

No priming

Control of the menstrual cycle is a complex process involving both the hypothalamic–pituitary axis as well as local (paracrine and endocrine) factors. The follicles destined to ovulate will be selected from a cohort of follicles, which enter the follicular phase of the menstrual cycles with a diameter of 2–6 mm. The selected follicle will grow to a diameter of 20–25 mm at the time of ovulation. Circulating levels of FSH and LH regulate the follicular growth and development. The rise in serum FSH levels during the early follicular phase causes a cohort of follicles responsive to FSH stimulation to grow and the dominant follicle can be distinguished from other cohort follicles by size (>10 mm diameter). Synthesis of estradiol is closely linked to development of the preovulatory follicle and the concentrations of estradiol in the follicle and serum correlate significantly with the size of the follicle. The increase in the concentration of estradiol is the principal factor for establishment of dominance. It has a negative feedback on the hypothalamus axis with a subsequent decrease in the level of FSH. The dominant follicle withstands this decline, while subordinate follicles are susceptible to a decline in gonadotropins and these follicles undergo atresia. The subordinate follicles, however, can be rescued and thereby avoid atresia by stimulatory treatments with FSH or by retrieval of these immature oocytes and their subsequent IVM.

The timing of oocyte aspiration in unstimulated cycles may be critical, allowing as many follicles as possible to reach sufficient size for cytoplasmic competence of the oocytes[17], while avoiding a prolonged negative effect of the developing dominant follicle. The first births from IVM of immature oocytes from unstimulated cycles used oocytes that had been retrieved at different times in the menstrual cycle[6,18–20].

Up to the point of dominant follicle selection all oocytes in the cohort undergo processes such as RNA transcription, protein synthesis, and organelle modifications and redistributions that prepare them for the potential of resumption of meiosis and eventual fertilization. Mikkelsen et al.[21–23] aimed to coincide oocyte collection with selection of the dominant follicle. Oocytes were aspirated after a leading follicle of 10 mm and an endometrial thickness of at least 5 mm were observed at ultrasound. A pregnancy rate of 18–24% per transfer was obtained in cycles with a detected increase in the level of estradiol on the day of aspiration. Oocytes originating from the ipsilateral ovary did not show an impaired competence to mature and cleave compared to oocytes originating from the contralateral ovary[23].

FSH priming

A few studies have examined the effect of priming with FSH before aspiration of immature oocytes in regularly menstruating women[8,16,23–25]. The series are small and a variety of stimulation regimens have been used, therefore only limited information can be drawn.

Wynn et al.[24] administered 600 IU rFSH to women over 5 days (300 IU on day 2, 150 IU on day 4, and 150 IU on day 6). A mean of 7.5 oocytes were retrieved from rFSH compared with 5.2 from unprimed women. Wynn et al.[24] did not perform fertilization of the oocytes and no conclusions concerning the developmental capacity of the oocytes can be drawn from that experiment.

Later studies of the treatment of women for 1 or 3 days with rFSH early in the follicular phase showed no difference in recovery rate of oocytes, or rates of maturation, fertilization, or cleavage in culture[17]. This was confirmed in a prospective randomized study[25]. In one group oocytes were aspirated after priming with rFSH (150 IU per day) for 3 days followed by deprivation for 2–3 days. In the other group oocytes were obtained in unstimulated cycles and the day of aspiration was fixed in the same way (after a follicle of 10 mm could be demonstrated). FSH priming did not increase the number of oocytes recovered and no benefit of FSH priming compared to the natural cycle on the maturation rate, fertilization rate, cleavage rate, or pregnancy rate could be demonstrated.

Studies in cattle indicate an advantage of using moderate follicle stimulation followed by a period of FSH deprivation to obtain optimal embryo production from bovine oocytes[13]. Similar studies in humans are lacking. Mikkelsen et al.[26] compared 2 vs. 3 days of priming and were unable to demonstrate any difference in the implantation rate between the two groups.

CONCLUSIONS

Recent data taken together suggest that in future immature oocyte retrieval combined with IVM could possibly replace standard stimulated IVF in selected patients. Priming with FSH for 3 days followed by deprivation for 2–3 days before harvesting of immature oocytes from patients with PCOS may improve the maturational potential of the oocytes and the implantation rate of the cleaved embryos. No beneficial effect of FSH priming has been observed in regularly cycling women[25]. In unstimulated cycles the recovery of oocytes has to coincide with selection of the dominant follicle. In stimulated cycles a time interval between FSH administration and aspiration has been found to improve the developmental capacity of oocytes.

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