

The effect of a rise or fall of serum estradiol the day before oocyte retrieval in women aged 40-42 with diminished egg reserve

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Summary

Purpose: To determine the effect of a drop in serum estradiol the day after injection of human chorionic gonadotropin (hCG) in in vitro fertilization-embryo transfer (IVF-ET) cycles in women aged 40-42 with diminished oocyte reserve. **Materials and Methods:** Retrospective study with further requirement that the female partner had a day 3 serum follicle stimulating hormone (FSH) of ≥ 12 mIU/mL and \leq five antral follicles. **Results:** A drop in serum estradiol the day after hCG injection is not associated with a lower chance of pregnancy compared to those women whose serum estradiol increases. However, their chances of releasing the oocyte before retrieval is significantly higher. **Conclusions:** A drop in serum estradiol in women of advanced reproductive age with diminished oocyte reserve should not signal the need to cancel the retrieval.

Key words: Estradiol; hCG injection; Advanced reproductive age; Diminished egg reserve.

Introduction

In in vitro fertilization-embryo transfer (IVF-ET) cycles in women with normal egg reserve who receive conventional controlled ovarian hyperstimulation (COH) generally the serum estradiol (E2) will increase the day after the injection of human chorionic gonadotropin (hCG) related to the multiple follicles. In natural ovulatory cycles serum E2 levels generally drop after the luteinizing hormone (LH) surge.

Women with diminished egg reserve have been relatively successful with IVF-ET especially with minimal stimulation protocols [1]. A significant proportion of women with diminished egg reserve with minimal stimulation protocols may only develop one dominant follicle. Thus it would seem likely that serum E2 would be more likely to decrease in these women than women with normal egg reserve given conventional COH.

Some women included under “minimal stimulation” have fairly close to natural cycles with just a small boost of 75 IU FSH for one to three days or none at all [1, 2]. Possibly women diagnosed with diminished egg reserve whose serum E2 increases after the injection of human chorionic gonadotropin (hCG) have more follicles than those women whose serum E2 drops the day after hCG injection. The possibility exists however that the follicles with the poorest quality are more likely to demonstrate a decrease in serum E2 post-hCG injection. The possibility also exists that those women with a drop in serum E2 may be the ones

more likely to release an egg before retrieval because the drop in serum E2 may be more likely to occur closer to ovulation and could suggest advancement of meiosis has already been initiated by a spontaneous LH surge initiating release of proteolytic enzymes and prostaglandins that will lead to detachment of the oocyte and thinning of the follicular wall.

A previous study of women aged ≤ 39 found no difference in live delivered pregnancy rates in women with diminished egg reserve when serum E2 dropped the day after hCG injection (19.0%) vs. those where the serum E2 increased (23.6%) or implantation rates (23.9% vs. 23.4%) [3]. However 34% in the group with the drop in E2 released the oocyte before retrieval vs. only 4.6% of those whose E2 increased [3]. The present study evaluated these parameters according to drop in serum E2 or not in women aged 40-42.

Materials and Methods

An observational study over a five-year time period was performed in women with diminished egg reserve receiving minimal FSH stimulation. IVF cycles included were those completely natural without any exogenous gonadotropin stimulation or those women not using more than 150 IU of FSH daily (except possibly increasing to 225 IU if in the late follicular phase a GnRH antagonist was initiated) [1, 2].

Only those women aged 40-42 with serum FSH on day 2 or 3 of ≥ 12 mIU/mL and an antral follicle count of \leq five were included. In some women with markedly diminished egg reserve, ethinyl E2 was used to lower the elevated serum FSH level to the-

Table 1 – Comparison of outcome in women aged 40-42 with diminished oocyte reserve undergoing IVF-ET according to whether the serum E2 increased or decreased the day after the hCG injection.

	Group 1 (E2 decreased)	Group 2 (E2 increased)
Number of initiated cycles	85	221*
Premature egg release	30 (35.2%)	11 (5.0%)*
Number of oocyte retrievals	55	210
Number of retrievals with no oocytes	4 (7.2%)	20 (9.5%)**
No. retrievals with fresh embryo transfer	36 (65.4%)	122 (58.0%)**
No. clinical pregnancies (viable at eight weeks)	5 (13.9%)	18 (14.8%)**
No. live deliveries	3 (8.3%)	11 (9.0%)**

* $p < 0.001$; ** $p = \text{NS}$.

oretically restore sensitivity of the follicle to FSH by restoring downregulated FSH receptors [4, 5].

When a follicle reached an average diameter of $\geq 17\text{mm}$ and the serum E2 approached or exceeded 200 pg/mL $10,000\text{ U}$ of hCG were given and egg retrieval was planned 34 hours later. Serum progesterone (P) and LH were also carefully monitored. If a rise in LH or P or a drop in sera E2 was noted before the hCG injection, the interval from hCG injection to retrieval was shorter taking the best guess when the LH surge began. Sera E2 levels were measured the day after the hCG injection. This retrospective observational study was approved by the IRB of Cooper Hospital/University Medical Center.

Results

There were 306 cycles evaluated as seen in Table 1. A drop in serum E2 occurred in 85 cycles (27.7%) (group 1) and increased in 221 (72.3%) (group 2). Premature oocyte release occurred in 30 of 85 (35.2%) group 1 IVF cycles vs. 11 of 221 (5.0%) of group 2 cycles ($p < 0.001$, chi-square). No oocytes were obtained in four of 55 (7.2%) group 1 oocyte retrievals vs. 20/210 (9.5%) of group 2 retrievals ($p = \text{NS}$). Embryo transfers occurred in 36 of 55 (65.4%) of group 1 retrievals vs. 122/210 (58.0%) for group 2 ($p = \text{NS}$). The live delivery rate was 8.3% (3/36) for group 1 vs. 9.0% (11/122) for group 2 ($p = \text{NS}$).

Discussion

A study performed in the early days of IVF found that a drop in the serum E2 the day after the hCG injection in women undergoing normal controlled ovarian hyperstimulation was associated with such poor pregnancy results that they suggested canceling the cycle [6]. However a subsequent study failed to corroborate these conclusions [7].

The present study is the first to evaluate the effect of a drop in serum E2 the day after the hCG injection during IVF-ET in women age 40-42 with diminished egg reserve. This study reached the same conclusions as the Meyer *et al.*

study of women with normal ovarian reserve, i.e., the egg quality is comparable to those women who show a rise in serum E2 as evidenced by similar pregnancy rates.

Though a decrease in serum E2 the day after hCG injection was associated with a higher percentage of women releasing their eggs before oocyte retrieval, this did not seem to be related to a lower production of eggs since the number of embryos available for transfer in those where eggs were retrieved was the same. Since pregnancy and fertilization rates were also similar comparing both groups, it would appear that one of the main reasons for egg release before retrieval is associated with an earlier spontaneous rise in endogenous LH. Thus the egg quality in those women with a drop in E2 is similar to those with a rise in serum E2 but the chance of spontaneous ovulation before retrieval is more likely.

From a practical standpoint, if a drop in serum E2 was associated with a lower pregnancy rate, there would be enough time to cancel the retrieval which would be scheduled for the next day. Our policy is to perform an ultrasound on the day of oocyte retrieval shortly before starting anesthesia. Thus with comparable pregnancy rates to group 2, it would seem prudent to advise group 1 women to still keep their appointment for oocyte retrieval. Patients living at a distance requiring air travel could still have enough time to cancel depending on the distance if they think the odds of egg release are too high to warrant coming in for egg retrieval.

There were 17.1% (38/222) of the IVF-ET cycles reported by Meyers *et al.* in women with adequate egg reserve who showed a decrease in serum E2 the day after hCG injection compared to 22.1% (100/451) ET cycles in women with diminished egg reserve [7].

Thus a decrease in the serum estradiol level, the day after the injection of hCG in women aged 40-42 with diminished egg reserve using a minimal FSH stimulation protocol is not associated with a greater risk of failed fertilization or lower pregnancy rate following oocyte retrieval and embryo transfer, compared to similar women whose serum E2 rises the day after hCG. However, there is a greater chance of the egg releasing before the oocyte retrieval. Therefore the conclusion reached in this study is similar to the one reached in the sister study of women \leq age 39 [3]. The pregnancy rates were lower but this would be expected because of their ages [8, 9].

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