

The effect of diminished oocyte reserve in younger women (age ≤ 37) on pregnancy rates in natural cycles

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Summary

Purpose: To determine the relative confounding effect of diminished oocyte reserve on the chance of successful pregnancy in non-in vitro fertilization-embryo transfer (IVF-ET) cycles. **Materials and Methods:** Matched controlled study comparing pregnancy outcome in women aged ≤ 37 years with severely decreased oocyte reserve as manifested by a day 3 serum follicle stimulating hormone (FSH) ≥ 15 mIU/ml compared to women with normal oocyte reserve (serum FSH ≤ 8 mIU/ml). Couples were excluded if they did not have tubal patency or a semen analysis that required IVF-ET. Only couples that tried at least three natural cycles (unless pregnancy occurred first) were included. **Results:** The live delivered pregnancy rates within a maximum of five cycles of luteal phase support with progesterone (P) or at most mild FSH stimulation, or intrauterine insemination for mild male factor or cervical factor was 33.3% (8/24) with increased day 3 FSH and 62.5% (16/24) for the normal group ($p = 0.08$, Fisher's exact test). **Conclusion:** Women with marked oocyte depletion are half as likely to conceive with assisted reproductive techniques compared to women with normal oocyte reserve.

Key words: Natural cycles; Diminished oocyte reserve; Live delivered pregnancy rates.

Introduction

One study from a world renowned in vitro fertilization (IVF) center concluded that live deliveries simply did not occur following the transfer of embryos that appeared to have normal morphology if the serum day 3 follicle stimulating hormone (FSH) ever exceeded 15 mIU/ml [1]. Based on this aforementioned study and others, the philosophy used by many specialists in reproductive endocrinology and infertility is to advise women whose day 3 serum FSH is > 15 mIU/ml that pregnancy with their own oocytes is highly unlikely and that they should proceed to using donor oocytes [1].

In contrast, it has been demonstrated that a reasonably good live-delivered pregnancy rate can be achieved following in vitro fertilization-embryo transfer (IVF-ET) in women who not only had serum FSH levels > 15 mIU/ml but whose response following gonadotropin stimulation was so poor that they only had a single embryo to transfer [2]. The explanation for these opposite conclusions is that women with diminished oocyte reserve are extremely sensitive to the adverse effects of high-dose FSH controlled ovarian hyperstimulation and that mild stimulation or even natural cycles are needed to attain good pregnancy rates combined with luteal phase progesterone (P) support [3]. In fact, live deliveries have been recorded by reversing apparent menopause by FSH receptor modulation without IVF-ET in women whose serum FSH exceeded 100 mIU/ml [4-7].

The possibility exists that the use of even mild gonadotropin stimulation during IVF-ET in this group of women with diminished oocyte reserve may have nega-

tive consequences in some women in this group, though not nearly as high a percentage following high dosage FSH stimulation. The objective of this present study was to compare pregnancy rates in women with normal oocyte reserve vs women with marked diminished oocyte reserve with serum FSH levels exceeding 15 mIU/ml without IVF-ET where purposeful FSH stimulation was not used to create multiple follicles but where FSH would be only used, if at all, in extremely low dosages to boost one follicle to maturity.

Materials and Methods

A matched controlled study was performed to compare pregnancy rates in women whose FSH was increased above 15 mIU/ml to those with normal oocyte reserve. Because of tubal patency and relatively normal semen parameters, IVF-ET was not considered needed. All women aged ≤ 37 years with a day 3 serum FSH > 15 mIU/ml who had bilateral patent fallopian tubes and a male partner with a normal semen analysis, resulting in a normal post-coital test, were enlisted in the study. They were matched to the very next woman meeting these same criteria whose age was within two years of the woman to whom they were being matched (as long as the age was ≤ 37) with normal oocyte reserve as manifested by a day 3 serum estradiol (E2) < 50 pg/ml and a serum FSH ≤ 8 mIU/ml.

All women received vaginal P in the luteal phase. They were exclusively treated with P if they achieved a follicle in a natural cycle of 18-24 mm with a serum E2 > 200 pg/ml [8, 9]. If they did not achieve a mature follicle they were given a small boost of low dosage (75 IU usually, occasionally 150 IU) of gonadotropins [8, 9].

The principle used for those with increased FSH was not to start any exogenous FSH until the rise of endogenous E2 decreased the serum FSH level below 11 mIU/ml [10]. Occasionally ethinyl E2 at usually 20 micrograms per day (rarely increased to 40 micrograms/day) was used early in the follicu-

lar phase to lower serum FSH without adding to the serum E2 level to restore down-regulated FSH receptors in women not showing follicular development with increased FSH [11]. The principal was never use any exogenous FSH if the serum FSH was > 11 mIU/ml [10]. Ethinyl E2 was also used to lengthen the short follicular phase or prevent premature luteinization [12].

The P dosage was titrated to achieve a mid-luteal homogeneous hyperechogenic endometrial echo pattern [13, 14]. Intrauterine insemination was not employed but only natural intercourse. The women selected had to have primary or secondary infertility of over one year duration. Pregnancy rates after a maximum of five natural cycles were determined and compared – a minimum of three treatment cycles for both partners was required.

Results

The clinical pregnancy rate for a maximum of five treatment cycles was for high FSH – 10/24 – 41.6% vs for normal FSH – 17/24 – 70.8% (chi-square analysis $p = 0.08$).

The live delivered pregnancy rate was for high FSH – 8/24 – 33.3% vs for normal FSH – 15/24 – 62.5% (Fisher's exact test $p = 0.08$).

The average number of cycles for conception in the high FSH group was 3.1 vs 3.2 for the normal group.

The mean FSH for the normal oocyte reserve group was 6.1 ± 2.8 mIU/ml vs 20.6 ± 5.5 mIU/ml for the diminished oocyte group.

Discussion

Live-delivered pregnancies are half as likely to occur following proper correction of ovulatory defects, e.g., correcting short follicular and luteal phases in infertile women with marked diminished oocyte reserve vs infertile women even with natural intercourse. Certainly the majority of women with serum FSH levels > 15 mIU/ml would prefer a 33.3% live pregnancy rate within five cycles of intercourse as opposed to going into a donor oocyte program.

We purposely chose a group with more severe depletion of oocyte reserve, i.e., those with serum FSH was > 15 mIU/ml. More women with diminished reserve may have day 3 serum FSH levels from 12 - 14 mIU/ml. This group from our anecdotal experience has even higher pregnancy rates than this study group. Yet even with this less severely oocyte depleted group, a frequent recommendation is to go immediately into the donor oocyte program.

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