Pregnancy outcome following in vitro fertilization-embryo transfer (IVF-ET) in women of more advanced reproductive age with elevated serum follicle stimulating hormone (FSH) levels

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Summary

Purpose: To present data on the chances of pregnancy following in vitro fertilization embryo transfer, according to day 3 serum FSH and age groups in women ≥ age 36. *Materials and Methods*: Data were analyzed according to three age groups (36-39, 40-42, ≥ 43) and five serum FSH ranges (≤ 10, 11-12, 13-14, 15-16, ≥ 17). *Results:* No live pregnancies were found in women aged ≥ 40 with serum FSH ≥ 15 mIU/ml but they were seen in women aged 36-39. Live deliveries were seen in women even ≥ 43 with serum FSH 13-14 mIU/ml. *Conclusions:* The higher the serum FSH and the greater the age, the lower the chances of successful conception. However, reasonable pregnancy rates are found in women aged ≥ 36 with serum FSH ≥ 15 mIU/ml and a live delivered pregnancy rate of about 10% can occur even in women aged ≥ 43 with mild FSH elevations [11-14].

Key words: Advanced reproductive age; Diminished egg reserve; In vitro fertilization; Serum FSH.

Introduction

The prognosis for achieving a successful pregnancy following IVF-ET is related to certain variables. Lower chances of conception and higher rates of miscarriage are found with advanced age.

Elevated day 3 FSH is also a negative factor both in the quantity of eggs retrieved, and it is also considered to be associated with poor quality eggs. There are even some reports that state that live pregnancies following IVF-ET are not possible if the day 3 serum FSH is increased [1-3].

The present study evaluated the effect of day 3 FSH and age in women ≥ age 36 undergoing IVF-ET. More specifically, the study was aimed to determine the effect of the degree of age advancement and degree of increased serum FSH on pregnancy and implantation rates. The main objective was not to compare these groups to each other but more to determine if there is an age/FSH combination where live pregnancy is highly unlikely.

Materials & Methods

A retrospective review of all IVF-ET cycles in women ≥ age 36 over a 6-year time period was performed. For this study to allow adequate comparisons only women with ≥ 2 embryos transferred were included.

The data were analyzed according to FSH range (mIU/ml): < 10, 11-12, 13-14, 15-16, ≥ 17. The data were also analyzed according to age ranges: 36-39, 40-42, ≥ 43.

Clinical (ultrasound evidence of pregnancy at 8 weeks) and ongoing/delivered (live fetus > 12 weeks) pregnancy rates were determined according to serum FSH range and according to age range. Implantation rates were similarly analyzed.

Various controlled ovarian hyperstimulation protocols were used including: minimal gonadotropin stimulation (75-150 IU daily) with or without gonadotropin releasing hormone (GnRH) antagonists (either cetrorelix or ganirelix). Luteal phase leuprolide acetate was started in the mid luteal phase and continued with gonadotropin stimulation. Luteal phase leuprolide acetate (10 U daily) was stopped when gonadotropins were started. Microdose flare with controlled ovarian hyperstimulation (225-300 IU FSH) from day 2 with antagonists (250 μg per day) and a 14 mm follicle was another protocol.

Results

The clinical and delivery pregnancy rates in women aged 36-39 and implantation rates according to day 3 serum FSH levels are shown in Table 1. Clinical pregnancy rates were significantly higher for women aged 36-39 with day 3 serum FSH ≤ 10 mIU/ml vs all those > 10 mIU/ml (38.3% vs 23.2%, $p < .05$).

The live delivery rate per transfer was also significantly higher in women aged 36-39 with FSH < 10 vs ≥ 10 mIU/ml (31.6% vs 18.6%, $p < .05$) (Table 1). The implantation rates were also significantly higher for women aged 36-39 with serum FSH ≤ 10 vs > 10 mIU/ml (17.8% vs 10.1%, $p < .05$).

The clinical and live delivery rates in women aged 40-42 according to day 3 serum FSH are shown in Table 2. There were no significant differences in clinical pregnancy rates per transfer in women aged 40-42 with serum

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FSH ≤ 10 vs FSH 11-14 mIU/ml (31.6% vs 28.5%, p = NS). There were no significant differences in live delivery rates in women aged 40-42 with serum FSH ≤10 vs FSH 11-14 mIU/ml (24.1% vs 21.4%).

The clinical and live deliverey rates according to day 3 serum FSH in women aged > 43 are shown in Table 3. Clinical and live delivered pregnancies were less common in women aged ≥ 43 but the rates were similar in women with FSH < 10 vs 11-14 mIU/ml.

In contrast to women aged 36-39 there were no live pregnancies in 17 transfers in women > age 40 (including women ≥ 43) when the serum FSH was ≥ 15.

Table 1. — *Pregnancy and implantation rates in women aged 36-39 according to day 3 serum FSH range*.

FSH range mIU/ml	No. of transfers	% clin. pregnancies transferred	% ongoing delivered/transferred	% embryos implanted
≤ 10	373	38.3	31.6	17.8
11-12	23	26.5	17.6	9.2
13-14	7	25.6	28.6	10.5
15-16	5	20.0	20.0	10.0
≥ 17	8	12.5	12.5	6.7

Table 2. — *Pregnancy and implantation rates in women aged 40-42 according to day 3 serum FSH range*.

FSH range mIU/ml	No. of transfers	% clin. pregnancies transferred	% ongoing delivered/transferred	% embryos implanted
≤ 10	253	31.6	24.1	12.7
11-12	15	40	26.7	14.0
13-14	13	15.4	15.4	5.7
15-16	2	0	0	0
≥ 17	10	10	0	3.3

Table 3. — *Pregnancy and implantation rates in women aged ≥43 according to day 3 serum FSH range*.

FSH range mIU/ml	No. of transfers	% clin. pregnancies transferred	% ongoing delivered/transferred	% embryos implanted
≤ 10	139	15.1	10.8	4.7
11-12	14	14.3	7.1	5.0
13-14	10	10	10.0	3.4
15-16	1	0	0	0
≥ 17	4	0	0	0

Conclusion

Although there were no live pregnancies in this study following IVF-ET in women aged ≥ 40 with serum FSH ≥ 15 mIU/ml, there have been studies published of live deliveries with and without IVF in women with FSH ≥ 15.

A successful pregnancy in a 42-year-old woman with blocked fallopian tubes with imminent ovarian failure following ovulation induction with ethinyl estradiol without gonadotropins and with IVF-ET was reported [4]. The patient conceived on her second treatment cycle and serum FSH was 61 mIU/ml. Another woman in apparent ovarian failure aged 45 also conceived by lowering the high serum FSH (43 mIU/ml) with ethinyl estradiol on her second treatment cycle with intrauterine insemination for severe oligoasthenozoospermia [5]. Both of these women had healthy live babies.

There was also another 45-year-old who successfully delivered with a serum FSH of 16.1 mIU/ml [6]. Although she was ovulating, ethinyl estradiol was used to lengthen the follicular phase [7]. Another woman with a serum FSH of 23.6 actually conceived at age 46 and had a healthy baby [8]. In her case it took 14 cycles of IUI for mild male factor. All these cases were treated with progesterone supplementation in the luteal phase.

Two other cases of pregnancy at age ≥ 40 with a serum FSH > 15 mIU/ml are worth mentioning even though they were only 40 years old. One woman seemed to be in menopause (amenorrhea and estrogen deficient and unresponsive to gonadotropins) with a serum FSH of 124 mIU/ml [9]. She was made to ovulate in seven consecutive cycles by using ethinyl estradiol to lower serum FSH and restore down-regulated FSH receptors in the granulosa-theca cells and she conceived on her seventh cycle. She delivered a healthy baby by cesarean section, and her right ovary was described as a streaked gonad and the left ovary as markedly hypoplastic with an average diameter of 12-18 mm [9].

Another woman in apparent menopause with serum FSH of 123 mIU/ml was made to ovulate two consecutive times with ethinyl estradiol but she failed to conceive [10]. The same treatment regimen failed to make her ovulate in cycle 3. She decided to enter a donor oocyte program but since she lived 3000 miles away, she decided to have donor oocytes closer to her residence. Unfortunately she failed to conceive despite four transfers of fresh embryos derived from donor oocytes. She decided to try the donor oocyte program at our facility. Interestingly, in preparation for donor oocytes we placed her back on estrogen. She ovulated again and was treated with progesterone suppositories in the luteal phase. Miraculously, she conceived in this cycle with her own eggs and had a healthy baby [10]. She informed us that while undergoing the donor oocyte program her serum FSH once attained a level of 180 mIU/ml [10].

Though these rare pregnancies have been reported in women ≥ 45 with elevated day 3 serum FSH it is unusual to achieve a pregnancy in women aged ≥ 45. In our IVF program the live delivery rate per transfer in women aged ≥ 45 including women with normal serum FSH and even those who respond well is 0.5%. Yet extremely poor responders who only had one embryo to transfer aged ≤ 39 were reported to have a clinical and delivery rate per transfer of 3.8% and 3.8% with a 4-cell embryo transferred on day 3, 9.5% and 9.5% with 5-cells, 37.9% and 31.0% with 6-cells, 40.0% and 35.0% with 7-cells and 42.4% and 36.4% with 8-cells [11]. Six to 8-cell embryo transfers occurred 65% of the time [11].

These data on single embryo transfers show that when very little gonadotropin stimulation is used a respectable pregnancy rate can be achieved in younger (≤ 39) women with such marked diminished egg reserve that only a single embryo could be transferred. Their paucity of eggs makes them comparable to women age 49-50 from a

quantitative aspect. However, based on their pregnancy rates (clinical pregnancy rate of 27.8% and live deliveries of 22.4% per transfer) they behave more like their chronological peers from an egg quality standpoint.

Thus these data suggest a different etiology causing lower egg reserve in younger women with high FSH. We favor the hypothesis that some factor (possibly a product of mitochondrial DNA) is responsible for the recruitment of the monthly cohort of follicles and the best eggs are recruited. Therefore in advanced reproductive age the best follicles are already gone.

However, in the majority of younger women with decreased egg reserve, the mechanism of low egg reserve is not due to an acceleration of the normal process of atresia but is related to damage to portions of the ovary. Nonetheless the remaining undamaged section of ovary has the same proportion of good healthy eggs as its chronological peers with normal FSH, just less of them.

As mentioned, one theory is that a mitochondrial DNA factor is responsible for the monthly recruitment of the cohort of follicles. The hypothesis continues that this same factor is needed to prevent apoptosis of the cells of the embryos that occur after the blastocyst stage. Thus a woman of more advanced reproductive age is less likely to release an egg with this apoptosis releasing factor since the theory is that the follicles with more of this factor present will be selected chronologically before the others. Therefore the theory favors the marked reduction in oocytes present in some younger women and is not related to an accelerated rate of atresia, but instead, to a destructive process leaving the same proportion of "normal" eggs as their age peers with this apoptosis inhibiting factor still present.

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