Original Articles

Reproductive Biology Section

Three successful pregnancies following natural conception over an 8-year time span despite serum follicle stimulating hormone level greater than 15 mIU/ml

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Summary

Purpose: To demonstrate that the concept that a level of serum follicle stimulating hormone (FSH) of > 15 mIU/ml on day 3 of a younger woman's menstrual cycle suggests that the remaining eggs are of very poor quality consistent with a woman of very advanced reproductive age is a fallacy. *Methods:* A woman with a serum FSH > 15 mIU/ml on day 3 was studied over an 8-year time period. *Results:* Despite the absence of therapy with follicle maturing drugs, and at the latter part of the study the development of oligomenorrhea, the woman had three successful conceptions over eight years without ART techniques. Though two of her pregnancies were treated with progesterone starting in the luteal phase, her last pregnancy was without any treatment. *Conclusions:* The policy of certain physicians to advise couples that their eggs are extremely unlikely to develop into a normal pregnancy because of increased day 3 serum FSH and that they should immediately proceed to using donor oocytes (even if that is not their desire) is wrong. These women should be given an attempt to achieve a pregnancy with their own eggs. However, the treating physician should avoid the use of high-dosage follicle maturing drugs.

Key words: Elevated serum FSH; Natural conception; Egg quality vs quantity.

Introduction

Some studies suggest that when a woman has an elevated serum follicle stimulating hormone (FSH) on day 3 not only does she have a diminished egg reserve, but these eggs are of poor quality [1-7]. Evaluation of in vitro fertilization (IVF) statistics published by The Center for Disease Control shows extremely poor success rates despite transfer of normal appearing embryos universally among various IVF centers in women ≥ age 45. As age advances with less egg reserve, and therefore less antral follicles selected, there is less inhibin B produced by these follicles and thus less of an inhibitor of pituitary release of FSH. The explanation for poor pregnancy rates in these reproductively older women is that over the years there has been a natural selection for the best eggs and when a woman reaches age 45 there are very few good eggs left.

Those IVF centers finding poor outcome in younger women with elevated day 3 serum FSH hypothesize that these younger women for some reason have had a more rapid rate of atresia leaving them with lower quantity and quality of eggs. Thus some have stated that even younger women with elevated day 3 serum FSH levels should proceed immediately to donor egg programs without even giving their own eggs a try [6, 7].

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However, other studies make it clear that the dismal prognosis given by these studies is not related to poor egg quality but possibly related to an adverse effect of the high-dose gonadotropins used to try to stimulate these women with diminished egg reserve [8-15].

Instead of the theory that diminished egg reserve in younger women is related to a more rapid atresia process leaving lower number and quality of eggs (i.e., equivalent in quality to women of advanced reproductive age), the data showing good pregnancy rates as long as high-dose gonadotropins are not used suggest that areas of the ovary become damaged leading to less ovarian egg reserve but those remaining have the same quality as their age peers with normal egg reserve [12-15].

With the theory of ovarian damage rather than rapid atresia, the process could be ongoing or may have happened in the past. Thus, the woman may take several years before entering into menopause. One woman who achieved three successful deliveries in four IVF-ET cycles over eight years supports the concept of past damage leading to fewer eggs but the ones remaining having quality equal to their age peers [16]. To date this was the longest known interval between successful pregnancies in a woman with elevated day 3 serum FSH [16]. The present case describes another woman with three successful pregnancies over an eight-year time span that did not require IVF-ET.

Case Report

A 30-year-old woman presented with six months of primary infertility. On evaluation her day 3 serum FSH was 17 mIU/ml in November, 1999. She was found to have regular menses and normal fallopian tubes by hysterosalpingogram and her husband had a normal semen analysis. At mid-cycle she attained a mature follicle of 19.5 mm with a serum estradiol (E2) of 274 pg/ml. A post-coital test was normal. Three days later the follicle collapsed by 8 mm evidence of egg release. She was treated with progesterone vaginal suppositories, 100 mg twice daily in the luteal phase. She conceived and the progesterone dosage was increased to 200 mg twice daily. She delivered a healthy full-term baby boy.

Her first conception was in December 1999. She then spontaneously conceived in August, 2002 but had only a chemical pregnancy. Her serum FSH was 21 mIU/ml. She then conceived again three months later and had a miscarriage at seven weeks. She had not taken progesterone supplementation for either of these pregnancies.

For pregnancy number 4 she conceived again spontaneously in February 2003 but was placed on supplemental progesterone once she had had a positive pregnancy test. However she still had another miscarriage at six weeks. Her day 3 serum FSH was 22 mIU/ml.

With her next pregnancy (no. 5) progesterone was started in the early luteal phase. She conceived after three treatment cycles in July, 2003 and delivered a full-term healthy girl.

In November, 2006 she conceived again but was not on any progesterone and miscarried at seven weeks.

Her menses had become irregular by that time and she thought that she would no longer be able to conceive because a repeat serum FSH was 24 mIU/ml and on ultrasound (US) the ovaries were small and no follicles over 1 mm were seen. However, because of pregnancy symptoms she attained a serum beta-hCG test in November 2007 which was 2412 mIU/ml and her serum progesterone was 55.5 ng/ml. Since the progesterone level was sufficient she was not supplemented with any additional progesterone. Her seventh pregnancy resulted in the delivery of a full-term healthy baby.

It should be noted that in her last two successful pregnancies she ovulated on day 7.

Discussion

As mentioned there has been a previous case report of three successful pregnancies despite elevated serum FSH over an 8-year time span following IVF-ET [16]. The case described here is the first case report of three successful pregnancies over the same 8-year time span despite elevated serum FSH involving natural conception.

Based on a recent study from a highly reputable IVF center that claimed no live pregnancies despite the transfer of normal appearing embryos in women of any age when the day 3 serum FSH was > 15 mIU/ml, there are many reproductive endocrinologists who will not even try to help a woman to conceive with her own eggs if this level of serum FSH is found but automatically suggest donor eggs [6]. Though successful pregnancies have been recorded in women still menstruating and even in women in apparent menopause with serum FSH levels > 100 mIU/ml, some infertility specialists may consider these cases as miracles that could not ever happen again [17-21].

The present case describing so many pregnancies including three successes over such a long time span suggests that many women with diminished egg reserve, have egg quality more consistent with their age peers rather than women of advanced reproductive age so that successful pregnancies are common if treated properly, i.e., without high-dose gonadotropins.

All of this woman's pregnancies were without the use of follicle maturing drugs and this supports the concept that the use of high-dose FSH stimulation by raising the serum FSH further, down-regulates the FSH receptor in granulosa theca cells for an FSH-dependent key protein needed for implantation, which in turn, may lower pregnancy potential [8-10, 12, 15]. It is our belief that most women who ovulate despite elevated serum FSH have luteal phase defects and benefit from taking extra progesterone in the luteal phase [11, 12]. It is interesting that our patient's last pregnancy was totally without progesterone supplementation. Also of interest is that the woman had two successful pregnancies ovulating on day 7. There seems to be a lower pregnancy rate when there is a short follicular phase possibly by not allowing sufficient estrogen exposure to induce adequate progesterone receptors in the endometrium [22, 23].

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