Original Articles

Reproductive Biology Section

Three successful pregnancies with in vitro fertilization embryo transfer over an eight year time span despite elevated basal serum follicle stimulating hormone levels. Case report

J.H. Check, *M.D., Ph.D.*; **B. Katsoff,** *B.A.*

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, N.J. (USA)

Summary

Purpose: To demonstrate that elevated basal follicle stimulating hormone (FSH) does not necessarily signify poor quality eggs.

Methods: In vitro fertilization-embryo transfer (IVF-ET) performed because of unexplained infertility and male factor related to low hypo-osmotic swelling test.

Results: Three live pregnancies following lowering of elevated serum FSH with ethinyl estradiol followed by gonadotropin therapy. The patient had seven attempted oocyte retrievals and five led to ET. Despite markedly elevated basal serum FSH levels she achieved a delivered pregnancy rate of 42.8% per retrieval, 60% per transfer and an implantation rate of 27.2%/embryo transfer.

Conclusions: This study clearly shows that high serum FSH in a woman of younger reproductive age does not mean egg quality is poor. The case also shows that since ovulation induction was still possible eight years later that the paucity of eggs in younger women is more likely related to a previous catastrophic event that markedly diminished egg reserve but that egg atresia proceeds at the normal rate thereafter.

Key words: FSH; Hypergonadotropism; In vitro fertilization; Diminished egg reserve.

Introduction

Almost 15 years ago an article was published that stated that basal follicle stimulating hormone (FSH) level is a better predictor of in vitro fertilization (IVF) performance than age [1]. This was supported by other studies at that same time showing very poor pregnancy outcome following IVF-embryo transfer (ET) when the day 3 serum FSH was elevated [2-6]. One study even concluded that if the day 3 serum FSH is elevated in one cycle, then subsequent pregnancy rates are poor even if the FSH is subsequently normal in the cycle of controlled ovarian hyperstimulation (COH) [7].

However, we have published studies that suggest that advanced reproductive age prognosticates a poor pregnancy outcome much more than elevated serum FSH. In 1990 we evaluated a series of 100 consecutive cases of apparent menopause and the effect of treatment aimed at inducing ovulation. The pregnancy rate was much higher in the younger than older women [8]. Another study of 45 women with increased basal serum FSH but still demonstrating estrogen production showed a much higher pregnancy rate in women not using assisted reproduction technology who were ≤ 39 vs ≥ 40 [9].

The aforementioned studies from our infertility center involved non-IVF cycles. Thus, possibly the high serum FSH for some reason only adversely effects embryos obtained by IVF. However, a study of 71 IVF cycles in women with basal serum FSH levels ≥ 12 mIU/ml, did find reasonable pregnancy rates in the younger group and much lower (but nevertheless there were pregnancies) pregnancy rates in the older group [10].

Our conclusions that age is a better predictor of pregnancy potential than basal FSH levels in women undergoing IVF-ET have been supported by other studies, e.g., the one by Chuang *et al.* in 2003 [11]. Subsequently we demonstrated that even in a population of women with elevated basal FSH levels who had such poor egg reserves that they basically only had single embryo transfers that quite reasonable pregnancy rates and implantation rates could be obtained in women ≤ 35 (delivered pregnancy rate/transfer of 27.3%) and in women 36-39 (30.8% delivered pregnancy rate/transfer). For the older group, there was still a respectable delivered pregnancy rate of 21.7% in 23 ETs in women aged 40-42 but no live deliveries in the 25 transfers in the women ≥ 43 [12].

We thought that all of these data would dispel the notion started 15 years ago that elevated FSH at any age means poor quality eggs, i.e., equivalent to women age 46 and above. However, in 2005 an article was published in Fertility and Sterility concluding that there were no live pregnancies following IVF-ET in women with elevated day 3 serum FSH [13]. This manuscript completely

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ignored all the studies having opposite conclusions and suggested that rather than waste time and money, an elevated basal serum FSH level should warrant proceeding immediately to using donor eggs [13].

The writing of this case report involving pregnancies in a woman with high serum FSH levels is for two purposes. First, it is an opportunity to try to do some damage control to prevent a group of patients who really want a child with their own gametes to proceed to donor oocytes or adoption by exposure to some other data that had reached opposite conclusions. Actually, just as important as convincing the patients, is convincing the treating physicians to give these patients the opportunity of trying IVF-ET with their own eggs.

The second purpose is that we believe the information provided by this case report is very convincing and that the argument proposed by several other fertility centers, that once the FSH is elevated that the egg quality is poor (even if it only elevated once and subsequently is normal), is fallacious [1-7, 13].

Case Report

A 30-year-old woman presented with primary infertility of six years duration. She had been under the care of a reproductive endocrinologist for one and a half years. She had been treated by follicle maturing drugs with luteal phase progesterone support. Despite a normal sperm concentration the male partner had a slightly reduced percentage of motile sperm so intrauterine inseminations (IUI) were performed.

Early in the investigation with her previous reproductive endocrinologist a laparoscopy had been performed which found Stage I endometriosis which was removed by laser vaporization. However despite the treatment her symptoms did not abate.

When she presented to our infertility center we measured her day 3 serum FSH and estradiol (E2). Her serum FSH was elevated at 14 mIU/ml and the serum E2 was 41 pg/ml.

We repeated the semen analysis and performed an important test that had never been performed before – the hypoosmotic swelling test. A previous study found no pregnancies with intercourse or intracervical insemination if < 50% of the sperm demonstrated tail swelling when exposed to the hypoosmotic medium [14]. This defect allowed the sperm to fertilize the egg but the embryos did not implant [15, 16]. The male partner scored only 31%. They were explained that although pregnancies had been achieved by treating sperm prior to IUI with the protein digestive enzyme, chymotrypsin, the pregnancy outcome was not nearly as good as the success when performing IVF with intracytoplasmic sperm injection (ICSI) [17-19]. They chose to do IVF with ICSI.

For the first in vitro fertilization cycle - controlled ovarian hyperstimulation (COH) was the luteal phase leuprolide acetate/gonadotropin regimen. Eight mature eggs were retrieved, two immature and one atretic egg. Three embryos (4, 5, and 8 blastomeres) of good morphology were transferred and two were cryopreserved. She conceived that cycle and delivered a full-term healthy girl.

In vitro fertilization cycle 2 was performed 15 months later. The COH regimen used was the microdose flare protocol. Only two eggs (both mature) were retrieved despite 450 IU gonadotropins used daily. Her peak serum E2 was 442 pg/ml. Only one embryo cleaved to day 3 and a single 7-cell embryo was transferred on day 3. She failed to conceive.

In vitro fertilization cycle 3 was performed three months later. A microdose flare protocol was used again. Her day 2 FSH was 12 mIU/ml. She responded better than cycle 2 and had five mature eggs retrieved. Her peak E2 was 1143 pg/ml. She transferred four embryos (8, 6, 6, and 4 blastomeres), conceived, and delivered a full-term healthy girl.

In vitro fertilization cycle 4 was performed seven years after her first one. She was now age 37. Her serum E2 was 38 pg/ml and the serum FSH was 17 mIU/ml. The COH regimen was with the gonadotropin releasing hormone (GnRH) antagonist ganirelix started with a 14 mm average diameter follicle after first being treated by 20 μg of ethinyl estradiol per day to lower the serum FSH and recruit follicles. She was only stimulated with gonadotropins with 150 IU for two days and 300 IU for two days. She retrieved four mature eggs and three fertilized. Three embryos (4, 4, and 8 blastomeres) were transferred. She failed to conceive.

In vitro fertilization cycle 5 was performed six months after cycle 4. Her baseline serum FSH was 15 mIU/ml. She was treated with ethinyl estradiol to lower the serum FSH. Despite 450 IU increasing to 525 IU/day of gonadotropins she stimulated one dominant follicle. She attained a peak serum E2 of only 326 pg/ml. One mature egg was retrieved and the egg did not fertilize.

For IVF cycle 6, her day 2 serum E2 was 50 pg/ml and her serum FSH was 7 mIU/ml. Another natural cycle was tried. She attained a peak E2 of 143 but because her follicle stopped growing and the serum E2 only increased by 13 pg/ml after one day, an egg retrieval was attempted but there was no egg retrieved.

For IVF cycle 7, the plan was to merely observe follicular development and at the appropriate time give minimal boosting with low dose gonadotropins. Cycle 7 was performed two months after cycle 6. The plan was to begin 75 IU gonadotropin once the E2 attained 80 pg/ml. After two days there were four antral follicles visualized with average diameters of 14 mm, 10 mm, 10 mm, and 6 mm. The gonadotropin dosage was increased to 150 IU/day and the three largest follicles grew. The serum E2 reached 156 pg/ml and cetrotide 250 μg was added. The luteinizing hormone (LH) was 6 mIU/ml and the serum FSH was 9 mIU/ml. After starting cetrorelix the next day the serum E2 dropped to 103 pg/ml. The dosage of gonadotropins was increased to 225 IU for two days and the serum E2 rose to 207 pg/ml and the follicles reached 15, 10, and 10 mm. After another 225 IU the E2 rose to 323 pg/ml with a follicle of 17.7 mm, 11.7 and 10.3 mm. With one more day of stimulation the serum E2 increased to 438 pg/ml with the follicles of 19, 15, and 11.6 mm with an 11 mm thickness of the endometrium with a triple line pattern. Oocyte retrieval occurred 34 hours later. Two metaphase-2 (mature) eggs were retrieved and one immature (metaphase 1). Two fertilized and one cleaved to day 3. A 7-cell embryo was transferred and she conceived. She delivered a healthy full-term healthy boy.

Once the cycle of conception started her serum baseline FSH was 15 mIU/ml and the serum E2 was 19 pg/ml. However these FSH levels were kept suppressed by chronic therapy with ethinyl estradiol. Her first and third pregnancies occurred eight years apart. During this eight-year span her serum FSH reached 36 mIU/ml three years from the first retrieval and yet she was able to have a successful IVF cycle five years later. She was 37.7 years old when she conceived.

Discussion

This case is unique in several ways. It is the first reported case of three IVF pregnancies in the same person, all with elevated serum FSH levels. Certainly, the case is the longest documented time period of first knowledge of increased FSH to achievement of a successful pregnancy by IVF-ET.

The publication of this case is important to re-emphasize concerns about the conclusions reached by a world renowned IVF center and published in a world renowned fertility journal that if one has elevated serum FSH three times, the live pregnancy rate will be zero [13]. Similar conclusions recently published in Human Reproduction were reached by another IVF center [20]. For some reason, in their IVF center they were not successful, but other IVF centers should not be discouraged to try themselves even under the circumstances of decreased egg reserve. It does not seem appropriate to refuse to give a couple a chance for a baby with their own gametes if this is strongly desired and to push them into a donor oocyte cycle.

This present case demonstrates that despite the high serum FSH, a live delivery rate of 42.8% per retrieval and 60% per transfer was achieved. The implantation rate per embryo transferred was 27.2%.

As mentioned, there are published manuscripts that state that if the FSH is even elevated one time, and subsequently comes down to normal, even if oocyte retrieval and embryo transfer occurs, the potential viability of the embryo is poor [7]. In other words these studies suggest that the quality of the oocytes are the equivalent to the well known extremely poor live pregnancy rate with advanced age despite embryo transfer (at Cooper Center for IVF the live delivery rate at age 45 is 2.2% per transfer and zero percent from age 46-49). We believe that since we clearly show a large difference in pregnancy rates in younger vs older patients with similar decreased egg reserve based on baseline serum FSH, that there is a difference in etiology for decreased egg reserve in the majority of younger women compared to older women going through natural menopause [9-11].

Based on our data, our hypothesis is that from menarche there is a mechanism that some factor allows the selection of better quality primordial follicles to proceed to the pre-antral stage. It is possible that once selected, these follicles produce an inhibitor preventing the recruitment of other primordial follicles, or that alternatively, there may be intrinsic programing allowing the best quality follicles to be selected first and the worst quality later. For younger women with premature, incipient, or imminent ovarian failure the predominant mechanism does not involve a programed increased rapid atresia rate, but instead is most often associated with some catastrophic event that destroyed a good portion of the egg supply. However, the remaining follicles, though in numbers similar to what is left in the women with advanced reproductive age, are the same quality as their peers with normal egg reserve. Furthermore, our hypothesis is that atresia of these remaining few follicles occurs at a normal rate.

This case supports this theory. Just 15 months after being able to stimulate eight mature eggs she was only able to produce two. However 15 months from her first retrieval she retrieved five eggs. Finally six and a half years after her second IVF cycle she was able to retrieve the same number of mature eggs, i.e., two. Furthermore, as evidenced by the successful pregnancy, the quality remained good.

The COH protocol was changed to natural or minimal stimulation for her last four IVF cycles for a couple reasons. For one, there reaches a certain degree of paucity of follicles where giving gonadotropins has a paradoxical effect of suppressing follicle development [21]. We believe that the rising serum FSH from the slow clearance of the injected FSH causes down-regulation of the FSH receptors in the granulosa cells. Anecdotally, we have observed this many times. We use this principal in trying to induce ovulation in women with apparent menopause by lowering the high endogenous serum FSH levels with exogenous estrogen (usually using ethinyl estradiol so that 17 beta estradiol contribution can be accurately measured since ethinyl estradiol does not increase the serum E2 level [8, 22].

Even if the woman is at a state where we could get the same number of follicles or even one or two more with exogenous high dose gonadotropins, we would rather use natural or minimal gonadotropin stimulation because the strong possibility exists that the embryo quality or endometrial environment may be superior with less drugs. First there are data that support that the COH regimen may effect the endometrial environment based on the demonstration that recipients sharing eggs with infertile donors who supply the eggs have superior pregnancy and implantation rates following fresh but not frozen ET [23-25]. This could possibly be related to a uterine environment that predisposes to premature trophoblast invasion [26]. Based on the extremely poor pregnancy rate despite transfer of multiple appearing normal embryos in women with high FSH [13, 20], yet the extremely good outcome in women with such poor reserve that, basically, only a single embryo was transferred following minimal or no gonadotropin stimulation [12], our theory is that raising the FSH further in these women adversely effects the embryos per se. The data on the adverse effects of COH in women with normal FSH is predicted to involve only about 20% of the women and thus could not account for such a large discrepancy in pregnancy rates seen in women with marked decreased egg reserve using high vs low dose gonadotropin stimulation [26]. In fact, the implantation rate in women up to age 42 with a marked decreased egg reserve was 50% higher than our normal population with normal gonadotropins having an average of three embryos transferred [12].

Sometimes a case report can support a certain tenet as well if not better than a retrospective study or even some prospective controlled studies. For example a case report of an anovulatory woman with a normal basal FSH who failed to respond to six years of ovulation induction, with

clomiphene and gonadotropins and luteal phase support with progesterone also failed to conceive despite ten IVF cycles in which 92 embryos had been transferred (her last 6 ETs she had 12 embryos transferred each time). Yet the first time she had ET with frozen/thawed embryos in the absence of COH she conceived and delivered [27]. She successfully conceived again two years later naturally at age 40 on her first cycle of luteal phase support without follicle stimulating drugs [28].

There have been case reports in women with high baseline FSH that have provided significant insight into the management of this condition for purposes of procreation. They have also provided more support for the hypothesis that marked decreased egg reserve in younger women from a reproductive standpoint is not synonymous to the condition in women over 45 where not only is the egg reserved markedly diminished but also the egg quality is poor. Two case reports in women aged 33 and 39 showed that one could induce ovulation and achieve successful delivery despite having such a paucity of follicles that the ovaries appeared as streaked gonads [29, 30]. These two case reports support our contention that diminished egg reserve in younger women does not usually represent an acceleration of egg atresia but represents catastrophic events damaging the ovaries but the follicles remaining have the same quality as age-matched peers with normal egg reserve [29, 30]. In fact, in one case her last menstrual cycle was over one year before and she failed to get menses with medroxyprogesterone acetate. Her serum FSH was 124 and 112 mIU/ml on two separate occasions. Gonadotropin therapy failed to induce even a slight rise in her serum E2 which was < 20 pg/ml [29]. However once her FSH was decreased with ethinyl estradiol she ovulated five consecutive months with gonadotropin boosts and conceived on cycle 5 [29]. Thus, this case supports the contention that lowering the elevated serum FSH restores sensitivity of the follicles [29].

One might think that the aforementioned case sets the limit for how high the serum FSH can be and still achieve ovulation and pregnancy but it does not [29]. A 25-year-old woman was described who appeared to be in overt menopause with an FSH of 164 mIU/ml but she was made to ovulate seven of ten cycles, conceived and miscarried on cycle 4, and successfully delivered on cycle 10 [31].

All these cases mentioned to date were without IVF-ET technology; thus the possibility that for unknown reasons these conclusions do not apply to IVF could still exist. However a case of a woman with imminent ovarian failure with damaged fallopian tubes was described who achieved a twin clinical pregnancy following suppression of FSH with estrogen followed by gonadotropin therapy [32]. One died so she delivered a single healthy baby [32]. A similar case supporting this conclusion was also described, only this time in a 42-year-old woman who ovulated solely by suppressing elevated serum FSH with ethinyl estradiol [33].

Sometimes case reports help to establish precedents. We concur that pregnancy in women age ≥ 45 with elevated basal FSH have an extremely poor prognosis. So should all such women be pushed into donor oocyte programs? Sometimes a woman would be willing to try as long as she knew that some precedent exists so that she would know that it was not totally impossible. Indeed a case was reported of a 45-year-old women with a day 3 serum FSH of 43 mIU/ml in apparent menopause who ovulated two times in a row on just ethinyl estradiol and had a successful pregnancy from cycle 2 [34]. A case was described of a successful delivery in a euestrogenic woman aged 46 with elevated basal FSH though it took 14 non-IVF cycles [35].

There are couples who for personal or religious reasons cannot consider a donor egg program. Many of these couples are willing to go through the trials and tribulations of IVF-ET and its expense even for lower odds of success. Some, even with insurance coverage, are being denied treatment by various IVF centers. It is the belief at the Cooper Center of IVF that these couples should be presented data relevant to their situation both pro and con and be familiarized with the various anecdotal reports. Then they can make the decision of trying to correct ovulatory defects without IVF, do a retrieval despite less oocytes, consider donor egg or embryo programs, consider adoption, or just decide to live without children.

The case described here clearly shows that high FSH does not indicate poor egg quality with three live pregnancies over an eight-year time span with high implantation rates. The case also provides hope for some women with high FSH who are single and not ready to achieve a pregnancy that they do not necessarily need to proceed with donor sperm insemination or fertilize and freeze embryos for the future, or consider egg freezing. The case also shows that since ovulation induction was still possible eight years later that the paucity of eggs in younger women is more likely related to a previous catastrophic event that markedly diminished egg reserve but that egg atresia proceeds at the normal rate thereafter.

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Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)