

Successful pregnancy in a 42-year-old woman with imminent ovarian failure following ovulation induction with ethinyl estradiol without gonadotropins and in vitro fertilization

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Summary

Purpose: To describe the methodology used to induce ovulation in a 41-year-old woman with imminent ovarian failure and tubal factor so that in vitro fertilization-embryo transfer (IVF-ET) could be performed.

Methods: Ethinyl estradiol was used to suppress elevated serum follicle stimulating hormone (FSH) levels, thus theoretically allowing restoration of down-regulated FSH receptors and response to endogenous gonadotropins.

Results: One oocyte was retrieved and fertilized and one embryo was transferred. The patient conceived and is presently in her last trimester.

Conclusion: Successful pregnancy following IVF-ET is possible in women with imminent ovarian failure - even in women older than age 40.

Key words: Advanced age; Elevated FSH; In vitro fertilization.

Introduction

There are a variety of clinical presentations seen in women with elevated serum follicle stimulating hormone (FSH) levels. They may have regular menses and still be fertile, have regular menses and have luteal phase defects [1], have regular menses but be prone to premature luteinization [2], have shorter intervals between menses related to a short follicular phase [3] have oligomenorrhea but with irregular ovulation, have oligomenorrhea and be completely anovulatory, have amenorrhea but be eustrogenic as evidenced by withdrawal of menses following progesterone therapy, or may have amenorrhea and be estrogen deficient.

There have been various opinions as to the clinical significance of an increased serum FSH level. One opinion was that the serum FSH level in women with normal menses was a better predictor of in vitro fertilization (IVF) performance than age [4]. Some have gone so far as to state that if the serum FSH level is elevated in one cycle, then pregnancy rates (PRs) are poor in subsequent cycles even if the serum FSH is normal in those cycles [5]. Even a high estradiol in the early follicular phase suppressing the serum FSH in the normal range is suggested to be associated with an extremely poor prognosis [5]. The explanation given is that even if these patients ovulate, the oocytes released are likely to be defective [6-10].

Thus these clinicians frequently suggest to regularly menstruating women that if their FSH is high, even if

IVF is not deemed a clinical necessity (i.e., normal tubes and male factor), the couple should proceed to using donor oocytes. This is even more likely to occur in a couple where IVF is needed because poor quality eggs will be coupled with the likelihood of a paucity of eggs following retrieval [11, 12].

Not all clinicians share the extreme pessimism associated with increased FSH or that FSH is more important than age, especially in eustrogenic women [13]. One study found a six month PR of 46% in women ≤ 39 , but only 10.5% in women ≥ 40 despite similar mean baseline serum FSH levels [13]. In another study at the other end of the continuum with hypergonadotropic amenorrhea and estrogen deficiency, a greater chance of inducing ovulation and achieving pregnancy was found in younger women [14].

Though there have been many reported cases of ovulation and pregnancy in those women with hypergonadotropic amenorrhea closest to overt menopause [14-25], to date there has only been one case report of an IVF pregnancy following IVF-ET despite imminent ovarian failure [26]. This patient was age 32 when she conceived [26]. The case presented here is the first we are aware of which reports a successful pregnancy resulting from IVF in a woman over the age of 40 with imminent ovarian failure.

Case Report

The patient initially presented to the Cooper Center for IVF at age 41. She had primary infertility with a three-year history of infertility. At age 40 she had a baseline day 3 serum FSH of 5.2 mIU/mL, but her serum estradiol (E2) was 119 pg/mL and

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the serum FSH increased to 37.5 mIU/mL after clomiphene challenge. The highest baseline serum FSH recorded was five months prior to her IVF cycle and was 61 mIU/mL.

She was given one month of oral contraception followed by six ampules of 75 IU gonadotropin (Serono) for nine days which produced two follicles measuring 15 and 11.5 mm with an E2 of only 127 pg/mL after which the serum E2 dropped.

She had been evaluated for a possible autoimmune condition because of symptoms suggesting Sjogren's syndrome (dry eyes, mouth, and vagina) although her rheumatoid factor, antinuclear antibody, antisperm antibody, and sedimentation rates were negative.

The patient had a history of surgical removal of a 6 cm endometrioma at age 30. At age 41 she had laparoscopic surgery and the fimbria of the fallopian tubes were adherent to the right ovary and the right ovary adherent in the ovarian fossa. There were endometriotic lesions along both utero-sacral ligaments. The left fallopian tube could not be traced past its proximal half due to adhesions between the ovary and intestine. The ovary was adherent to the pelvic side wall. An endometrioma of the right ovary was removed; implants on both ovaries were vaporized with laser and adhesions were lysed.

She came to our center to attempt IVF because she was concerned that the adhesions and possible return of endometriosis would prevent in vivo conception. She had one cycle where the FSH was lowered into the normal range by ethinyl estradiol, 20 micrograms per day, followed by 100 mg clomiphene citrate. Human chorionic gonadotropin (hCG) (10,000 U) was given on day nine of the cycle with a 17.7 mm follicle (average diameter) and a serum E2 of 471 pg/mL. Following retrieval the follicle appeared mature but it failed to fertilize.

In the cycle of conception her day 3 serum FSH was 17.4 mIU/mL and the serum E2 was 85.2. She had already been on ethinyl estradiol 20 micrograms/day. Eight days later (day 11) the serum E2 dropped to 43.6 pg/mL and the FSH increased to 20.9 mIU/mL; the serum LH was 15.3 mIU/mL at this time. Six days later (day 17) the serum E2 was 227 pg/mL and the serum FSH dropped to 10 mIU/mL. The following day the serum E2 was 256 pg/mL, the serum progesterone 0.58 ng/mL but the LH increased to 41.4 mIU/mL. These results came back in the late afternoon but all blood tests were obtained at 8:00 a.m. The patient was instructed to take 10,000 U IM hCG at 6:00 p.m., oocyteretrieval occurred 24 hours from the LH surge. One 4-cell embryo with 25% fragmentation was transferred on day 3 and she conceived. Presently she is at 25 weeks' gestation and has had an amniocentesis which demonstrated a normal fetus. She was supported throughout the first trimester with 400 mg/day progesterone vaginal suppositories, IM progesterone in oil, 100 mg every other day with gradually increasing intervals, and 2 mg oral estradiol daily.

Discussion

There is no question that this patient's prognosis would have been far greater if she had chosen the donor oocyte program. However, this woman who was a Ph.D. in epidemiology, was very aware of this, yet strongly desired a baby with her own genetic contribution. She was willing to travel from a Southern state to our mid-Atlantic state with the support of the physician from her own state.

She was aware of the one published case of pregnancy with IVF despite imminent ovarian failure [26] and she was made aware of some unpublished similar cases.

However she was advised that we had data suggesting that elevated serum FSH levels have a worse prognosis in women ≥ 40 years of age [13, 14], and that to date we had not had a woman of this age with imminent ovarian failure conceiving by IVF. In fact, she was advised that women of advanced reproductive age with elevated serum FSH but still having fairly regular menstrual cycles had a much worse prognosis with IVF than younger women with similar serum FSH elevations [27].

One hypothesis to explain a better prognosis for younger women than older ones, despite similar serum FSH levels, may be that in the older patient there may have been a natural selection of the best oocytes, thus when serum FSH is increased, there is not only a fewer number of oocytes present but fewer quality ones. In contrast, younger women may have had a more frequent etiology for the paucity of oocytes, damage to certain portions of the ovaries; however the section spared may have the same proportion of good oocytes as age peers with normal serum FSH. The patient described here had two major surgical procedures for endometriosis of the ovaries and she could, despite her age, have had a better prognosis than many patients of comparable age with high FSH levels but where natural selection (because of a more rapid atresia process) had resulted in a lower number of remaining follicles.

As some women approach the end of the continuum towards complete ovarian failure, they not only lose the ability to make multiple follicles in response to follicle maturing and stimulating drugs, but these drugs may actually precipitate a reversible state of apparent complete ovarian failure [28]; these patients do better sometimes without follicle maturing drugs [28]. In fact merely stopping these drugs allows ovulation to resume sometimes with even multiple follicle production [28].

However some patients, e.g., the woman presented here, not only fail to respond or get worse when treated with clomiphene citrate or gonadotropins, but require suppression of the serum FSH which is usually in the form of a pharmacologic dose of estrogen, to allow follicle maturation to occur. As in this case, a convenient preparation is ethinyl estradiol because it does not cross-react in most assays for serum 17 beta estradiol and thus allows monitoring of estradiol production by the developing follicles. In contrast with the previously published case of successful pregnancy following IVF-ET, despite imminent ovarian failure in a woman in her early thirties, the case presented here is unique in that follicular maturation was achieved merely by the use of ethinyl without any gonadotropin stimulation.

The induction of apparent menopause and/or the failure to respond to gonadotropins, yet apparently responding merely to ethinyl estradiol, could have several explanations. One such hypothesis is that stimulation was tried during the majority of times when no follicles were recruited, but if one finally is recruited on an independent basis it could mature merely on its own. Careful monitoring can allow detection of the developing follicle thus

allowing proper timing of intercourse or insemination and allowing luteal phase support with progesterone. Indeed some spontaneous ovulations have been reported in women with apparent ovarian failure without any therapy [21, 25]. Thus treatment with ethinyl estradiol may not have been necessary in this scenario. However the authors favor a direct role of ethinyl estradiol in increasing the chance of follicular maturation because of data showing very frequent ovulation induction with this therapy in women with histories of long intervals of amenorrhea and apparent menopause [14]. The authors favor the hypothesis that ethinyl estradiol therapy works by lowering serum FSH levels and thus restores down-regulated FSH receptors in the follicle, allowing them to respond to endogenous or exogenous gonadotropins. This hypothesis is supported by case reports of ovulation induction in hypergonadotropic women with amenorrhea without estrogen therapy but with suppression of serum FSH with the gonadotropin-releasing hormone analogue, leuprolide acetate [14, 29].

Anecdotally, there have been other reports of women with high serum FSH levels with successful conception. The oldest woman documented to conceive with hypergonadotropism was 46 [30]. However she was still having fairly regular menses though was not forming a mature follicle [30]. Another woman, age 45, was almost at the end of the continuum in that she had serum FSH > 40 IU/mL, six months of amenorrhea, and was estrogen deficient, but she ovulated in both cycles of ethinyl estradiol therapy and successfully conceived and delivered a healthy child following ovulation in the second cycle [31]. The case described here is unique in that it is the first described case of a woman ≥ 40 failing to be stimulated with exogenous gonadotropins, but responding to exclusive stimulation of follicular maturation by ethinyl estradiol therapy, with successful conception following oocyte retrieval and subsequent embryo transfer.

Obviously IVF-ET is not recommended as a general measure for very poor responders with elevated serum FSH levels since most pregnancies reported have been in vivo. However, if severe male factor or tubal factor (as in this case) exist, then this case at least provides a precedent that successful conception is at least possible following IF-ET in women over 40 with imminent ovarian failure.

Certainly, in patients presenting with similar clinical situations, the use of donor oocytes would have a far greater chance of successful outcome. However for those patients who strongly want the opportunity to conceive with their own gametes, despite very low odds for success, this case may provide encouragement not only for patients but for other reproductive endocrinologists to at least attempt IVF in women ≥ 40 with elevated gonadotropins needing IVF-ET. This case report will also serve to re-introduce a technique of ovulation induction with ethinyl estradiol either alone [14], or with mild stimulation with gonadotropins after recruitment of a follicle with ethinyl estradiol [14, 23, 32].

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