Pregnancy despite imminent ovarian failure and extremely high endogenous gonadotropins and therapeutic strategies: Case report and review

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Summary

Purpose: To attempt ovulation induction in a woman with premature ovarian failure who had very high serum follicle stimulating hormone (FSH) levels (e.g., 164 mIU/ml) by merely using ethinyl estradiol without gonadotropins.

Methods: Ethinyl estradiol (20-40 μg) was used to lower serum FSH. Monitoring of follicular maturation was performed using sonography to determine follicle size and serum estradiol. Progesterone vaginal suppositories (200 mg twice daily) were used following demonstration of oocyte release from the follicle.

Results: Follicle maturation and ovulation was achieved in six of ten treatment cycles. A clinical pregnancy occurred in the ninth treatment cycle and a live delivery of a helathy baby accurred.

Conclusions: Despite small ovaries, amenorrhea, and failure to have withdrawal menses following progesterone, absence of antral follicles on initial ultrasound, and consistently extremely high serum FSH, ovulation and pregnancy is possible by merely lowering the serum FSH.

Key words: Ethinyl estradiol; Premature ovarian failure; Hypergonadotropism.

Introduction

There are some publications suggesting that elevated serum follicle stimulating hormone (FSH) level or high early follicular phase serum estradiol level forebode a poor pregnancy rate even in women with regular menses [1, 2]. One study suggested that if serum FSH is elevated in one cycle, the oocytes remaining in the ovaries are of poor quality and pregnancy rates (PRs) in subsequent cycles will be extremely poor even if the serum FSH is normal in subsequent cycles [2]. There are many infertility clinics even today that no matter what the age of the woman recommend donor oocytes and refuse to treat the woman otherwise. Sometimes they may try treating the woman with controlled ovarian hyperstimulation (COH) and conclude that donor oocytes are needed because of poor response not realizing that the induced rise in serum FSH may down regulate FSH receptors and provide a paradoxical poor response [3].

Elevated day 2 or 3 serum FSH levels are associated with two circumstances, estrogen deficiency and normal estrogen. The latter is frequently observed even with fairly regular menses. However, even in the former instance pregnancies were recorded [4-6]. Though an occasional report of success with just gonadotropin stimulation has been recorded, in general this therapy under these circumstances is ineffective [7, 8].

Studies have been published, however, showing that response to gonadotropins could be improved considerably under the conditions of hypergonadotropia and estrogen deficiency by first lowering FSH with estrogen before starting gonadotropins [8-12]. Initially, the therapy involved using 20-50 μg ethinyl estradiol per day to lower serum FSH and this was continued when gonadotropins were added [8]. Ethinyl estradiol was used in lieu of other estrogens because it does not cross-react with serum beta estradiol and this allows the clinician to best determine when a follicle seen by sonography is mature. Sometimes this treatment regimen resulted in the recruitment of a hormone producing follicle and sometimes it did not. Thus some patients spent money for expensive gonadotropins without seeing a response. The cost efficiency of this technique was improved by waiting for a rise in serum estradiol before using gonadotropins or waiting to see if just the use of ethinyl estradiol alone might allow a follicle to reach maturity [14].

One question that arises is how does one know that the ovulation found in these circumstances are really treatment related. Indeed some ovulations and pregnancies have occurred with no treatment at all [15-17]. Alman and Smentek summarized data on 14 pregnancies in women with premature ovarian failure and estimated that the probability of pregnancy without treatment was one in 9,200 based on only 14 pregnancies recorded from 1964-1984 despite an estimate of 129,000 women with this condition [18]. The fact that this therapy resulted in ovulation in 19% of attempted cycles in women with hypergonadotropism and estrogen deficiency, that 34% of these patients ovulated at least once in several treatments, and that 19 of 91 women (20.8%) achieved a pregnancy suggests that this therapy is far more likely to induce ovulation and pregnancy compared to expectant therapy [14].

Revised manuscript accepted for publication June 1, 2004

The need to suppress serum FSH to restore down-regulated FSH receptors is supported by reports of ovulation induction with and without added gonadotropins by lowering serum FSH levels in other ways without using estrogen [19, 20]. The study of 100 consecutive women with hypergonadotropism and estrogen deficiency (91 having FSH lowered by ethinyl estradiol and 9 with leuprolide acetate) concluded that the prognosis improved with lower age and shorter time interval from diagnosis to treatment [14]. However, exceptions do occur and one woman with this condition had successful ovulation induction and pregnancy despite her age of 45 [21].

Since pregnancies can occur in women with increased serum FSH and estrogen deficiency, it should be easier to achieve in those women with elevated gonadotropins but with a normal estrogen state. One study did, in fact, demonstrate a 46% pregnancy rate and 34.6% live delivery rate in such women given six months of therapy [22]. The therapeutic strategies sometimes allowed the women to mature their own follicles naturally, and other times helped the maturation of the follicle with a boost of a small dose of gonadotropins as the follicle approached maturity, and in some instances after lowering serum FSH with ethinyl estradiol or leuprolide acetate [8-14, 19, 23].

Some women if given a poor prognosis prefer to immediately go to a donor oocyte program. Some women however will want to try with their own oocytes exclusively for at least a few cycles even with a poor prognosis. Thus some patients are interested in whether there are ceilings or limits beyond which conception is not possible. Consequently some patients will proceed with trying with their own oocytes as long as a previous precedent has been established. To date, the oldest woman to have a successful delivery despite high baseline serum FSH was 46 [24]. The highest serum FSH where a pregnancy was recorded was 143 mIU/ml [21]. The case described here shows that pregnancy is even possible with a serum FSH greater than 143 mIU/ml. Furthermore, in contrast to the woman with the 143 mIU/ml serum FSH who had fairly regular menses, this patient was estrogen deficient with failure to establish menses with progesterone withdrawal.

Case Report

A woman who had regular menses up to the age of 23 started oral contraceptives for contraception when she got married. However when she stopped the oral contraceptives for purposes of conception, she had withdrawal menses but none thereafter spontaneously.

She presented at age 25 hoping that some treatment could make her ovulate despite the diagnosis of premature ovarian failure. This diagnosis was established by failing to induce menses by progesterone withdrawal alone, development of menses with estrogen and progesterone therapy, and three elevated serum FSH levels (144.9, 145.6, and 164.2 mIU/ml). Serum luteinizing hormone (LH) was similarly elevated (109.6, 111.8 and 111.5 mIU/ml).

She had no familial history of premature ovarian failure, surgery to her ovaries, pelvis or abdomen, or previous chemotherapy or radiation therapy.

On initial presentation she was taking .625 mg conjugated estrogen and 2.5 mg medroxyprogesterone acetate daily. Her ovary size was 18 x 11 x 13 mm for the right ovary and 15 x 12 x 17 mm for the left ovary. There were no antral follicles noted. The endometrial thickness was 3 mm.

In the cycle where the ethinyl estradiol was started, her serum FSH was 92 mIU/ml. A hysterosalpingogram showed a normal uterus and bilateral tubal patency. Her husband had an above normal semen analysis and postcoital tests were normal. She formed a mature follicle in five of her first nine treatment cycles and in cycle 9 attained an 18.3 mm follicle with a serum estradiol of 398 pg/ml. The dosage of ethinyl estradiol varied between 50 to 40 μg each cycle. She had a chemical pregnancy. The next cycle (no. 10) she ovulated again and conceived one more time. She has successfully delivered a full-term baby.

In all six ovulatory treatments follicular maturation occurred just with ethinyl estradiol without gonadotropins. Progesterone vaginal suppositories (200 mg twice daily) were used in the luteal phase.

Discussion

This case sets a new precedent for the highest serum FSH to date in a woman who established an ongoing pregnancy. Furthermore, this case shows that no level of serum FSH should discourage an attempt to try to induce ovulation even under conditions of imminent ovarian failure.

One of the therapeutic options that was considered was whether oocyte retrieval and in vitro fertilization-embryo transfer (IVF-ET) should be offered if a follicle was obtained. The couple was advised that live PRs over 25% per transfer were found in women with elevated baseline serum FSH despite transferring only a single embryo [25]. In fact, we advised them of two cases of successful delivery following IVF-ET despite imminent ovarian failure with follicle recruitment mainly by lowering serum FSH by ethinyl estradiol [26, 27]. However most of these cases had IVF-ET because of tubal or male factor and these parameters were perfectly normal in this woman, so they decided against IVF-ET.

Our patient had two of the best prognostic factors – youth and a short interval from diagnosis to treatment [14, 22, 28]. This illustrates the point that with imminent ovarian failure one may not always detect antral follicles at one given moment, and that failure to ovulate despite treatment, does not preclude successful ovulation in a subsequent cycle. The case also illustrates the fact that ovulation induction can occur by merely lowering high serum FSH, hypothetically, allowing restoration of down-regulated FSH receptors and thus allowing response to endogenous FSH without using exogenous FSH [14, 27].

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