

Viable Pregnancy in a Woman with Premature Ovarian Failure Treated with Gonadotropin Suppression and Human Menopausal Gonadotropin Stimulation

A Case Report

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Ovulation and pregnancy were achieved in a woman with premature ovarian failure by mildly suppressing the elevated gonadotropins and following with a small dose of human menopausal gonadotropins for completion of follicular maturation.

Introduction

Ovulation and subsequent pregnancy, according to a previous study, can be achieved by first suppressing elevated gonadotropins with a high dose of estrogen and promptly following with high doses of gonadotropin stimulation.¹ All of the patients described had amenorrhea, estrogen deficiency and a previously demonstrated failure to stimulate a rise in the serum estradiol (E₂) despite human menopausal gonadotropin (hMG) stimulation.

In the case described below, the recruitment of a follicle was first accomplished with a mild reduction in the still-elevated gonadotropins followed by completion of the follicular maturation process with small amounts of hMG. The technique differed slightly from the previously described technique in that serum E₂ was measured before adequate gonadotropin suppression had occurred, and a rise in the serum E₂ prompted the earlier use of hMG even with elevated gonadotropins.

Case Report

A 37-year-old woman, gravida 1, para 0, presented with a history of secondary amenorrhea at age 34. Vasomotor symptoms had begun at age 35, and she failed to have progesterone-withdrawal menses at age 35. She sought help in achieving pregnancy. Her first pregnancy had ended in a first-trimester spontaneous abortion 13 years earlier. The patient reported a history of luteinizing hormone (LH) and follicle stimulating hormone (FSH) elevations; both times those levels had been obtained upon the request of her previous specialist. After the diagnosis, which was established at age 35, the patient had eight cycles of clomiphene citrate (up to 200 mg for five days) with no rise in the E₂ level > 20 pg/mL. She also failed to experience a rise in her serum E₂ despite two stimulation attempts with hMG using 4,200 IU the first time and 4,500 IU the second.

The physical examination revealed the patient to be 64 in tall and to weigh 118 lb. Her blood pressure was 116/82 mm Hg. The thyroid was of normal size, without bruits or tenderness. The heart rate was 60/min, without any murmurs. The lungs, abdomen and skin were also normal. The breast examination was

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negative, and no galactorrhea was expressed. Also, there was no evidence of hirsutism or alopecia. The pelvic examination revealed a normal-sized, anteverted uterus without adnexal enlargement or tenderness.

Laboratory studies were performed on the patient's initial presentation to our office. The serum FSH was elevated, 36 mIU/mL (normal, 3.5–16.9), and the LH was 51 mIU/mL (normal, 3.7–31.2), while the serum E_2 was low, 12 pg/mL. The serum thyroxine, thyroxine binding globulin, triiodothyronine on radioimmunoassay, cortisol, antinuclear antibody, testosterone, dehydroepiandrosterone sulfate, complete blood cell count, fasting serum glucose and calcium levels were all normal. Results of a chromosome analysis revealed 46,XX.

The patient was first treated with conjugated estrogens, 1.25 mg/d, for 25 days each month followed by medroxyprogesterone acetate, 10 mg/d for 10 days, and experienced withdrawal menses. Her initial serum gonadotropin elevation occurred despite the estrogen therapy.

The patient was treated initially with ethinyl estradiol (EE), 20 μ g daily, and after one week her serum estradiol was <20 pg/mL, FSH was 37 mIU/mL and LH was 25 mIU/mL. After two weeks the FSH measured 55 mIU/mL and LH, 28 mIU/mL. The EE was increased to 50 μ g; three days later the serum E_2 was <20 pg/mL, LH was 19 mIU/mL and FSH was 29 mIU/mL, but the patient had to interrupt the cycle for personal reasons.

After a withdrawal menstrual cycle with medroxyprogesterone acetate, the patient was started on 50 μ g of EE; after one week her serum FSH was 33 mIU/mL and LH, 45 mIU/mL. Four days later, with the EE continued, the serum E_2 rose to 75 pg/mL, FSH to 19 mIU/mL and LH to 92 mIU/mL. A 14-mm-diameter follicle was released prematurely two days later, with a decrease in the serum E_2 to 53 pg/mL and an increase in the serum progesterone to 2.2 ng/mL.

One week of estrogen therapy in cycle 3 allowed the patient's serum E_2 to rise to 106 pg/mL, while the serum FSH was 11 mIU/mL and the LH, 23 mIU/mL. The EE, 50 μ g daily, was continued, while hMG was added at 150 IU daily. After two days the serum E_2 increased to 159 mIU/mL, while the LH was 22 mIU/mL. Pelvic sonography demonstrated a right ovarian follicle with an average diameter of 16.6 mm. The patient received another 150 IU of hMG. The next day, however, the serum E_2 decreased to 135 pg/mL, with the LH surging to 76 mIU/mL and the follicular diameter increasing to 18.3 mm.

The patient received human chorionic gonadotropin (hCG), 10,000 units, and follow-up sonography two days later demonstrated follicular collapse consistent with ovum release. Progesterone vaginal suppositories were started at 50 mg twice daily, and the patient had a positive β -hCG subunit level of 570 18 days from her hCG injection.

The progesterone dosage was increased to 100 mg twice daily. Fetal viability was confirmed sonographically when the patient was 8.5 weeks pregnant, and appropriate growth and viability were confirmed at 14 weeks.

Discussion

One of the theories of ovulation induction and its achievement in a woman with apparent ovarian failure is that the elevated serum LH and FSH levels may cause down regulation of gonadotropin receptors in the remaining ovarian follicles, thus inhibiting their ability to respond to the elevated endogenous gonadotropins. Originally the technique of ovulation induction required the gonadotropins first to be suppressed to the normal range, and then hMG was added while the estrogen was continued.¹ Subsequently it was found that another method of suppressing gonadotropins, using gonadotropin releasing hormone (GnRH) agonist (leuprolide acetate), could induce ovulation in some cycles before a reduction in the LH and FSH to normal levels and without the need for hMG.² Because the agonist has a stimulating effect on the pituitary before it suppresses, it is not clear whether a mild reduction in gonadotropins occurs, generating some restoration of gonadotropin receptors (thus allowing the follicles to respond to a combination of endogenous LH and FSH plus leuprolide), or whether the mechanism is related to some direct ovarian effect of the GnRH agonist.

The patient described above demonstrated, in both of her treatment cycles, the ability to increase her serum E_2 levels with only estrogen suppression of the gonadotropins rather than with potent follicle-stimulating drugs, such as clomiphene citrate and hMG. In fact, previously those drugs had failed to increase her serum E_2 . Another patient with hypergonadotropic amenorrhea conceived after a reduction in her LH and FSH levels with oral contraceptives despite previously failing to respond to clomiphene citrate or hMG.³

The patient described above was not able to complete maturation of the follicle with estrogen therapy alone. The third treatment cycle enabled the hMG to boost the follicle to maturity only after initial recruit-

ment and early stimulation were achieved with the estrogen. Thus, the hMG was administered while the gonadotropins were still elevated. The possibility does exist, of course, that the estrogen alone, without the hMG, could have been sufficient to allow follicular maturation. Furthermore, it is also possible that the proposed mechanism of restoring previously down regulated gonadotropin receptors was not causative in our patient or in the patient who responded to oral contraceptives, as mentioned above.³ For example, the problem may have been related to gonadotropin receptor antibodies. For some reason the two women might have gone into spontaneous remission, restoring their sensitivity to LH and FSH.

Autoimmune oophoritis (AO) has been described as another possible cause of ovarian failure.^{4,5} That condition may be associated with the expression of trigger antigens for the autoimmune response to be present only in maturing follicles. Thus, primordial follicles would be spared. Reducing gonadotropin stimulation with oral contraceptives for three weeks may have allowed a mitigation of the autoimmune response by decreasing the antigenic burden, thus allowing follicular maturation to occur. Since the patient responding to oral contraceptives³ and the initial responders to that technique¹ underwent no morphologic or histopathologic studies of their unresponsive ovaries, either the AO hypothesis or the depletion of down-regulated receptors could explain the induction of ovulation and pregnancy achieved by those patients.

The case of ovulation and pregnancy described in another report on a woman with hypergonadotropic amenorrhea and hypoplastic ovaries lends greater support to the concept of restoration of gonadotropin receptors with pituitary suppression with exogenous, high-dose estrogen.⁶ The case described above also suggests that hypothesis because the rise in serum E₂ occurred quickly, before an adequate ovarian "respite" could be given.

Waiting until the gonadotropins are reduced to a normal level and then adding hMG usually requires a

high dose of very expensive gonadotropin therapy. However, by starting the hMG only after an initial rise in the serum E₂, indicating recruitment and stimulation of a follicle with estrogen alone, only 450 IU of hMG was needed to complete follicular maturation. Thus, we recommend a modification of the technique originally described in that the physician should measure the serum E₂ after only one week of EE therapy, and if an initial rise in the serum E₂ is demonstrated, hMG therapy should be initiated even if the serum gonadotropins are still elevated (with the EE maintained with the hMG). The delay of two weeks might allow enough suppression of LH and FSH to cause atresia of the recruited follicle. Our estrogen preference is EE because we have found only 1:250 cross-reactivity to the 17β-E₂ assay, indicating that the serum E₂ measured reflects endogenous E₂ production by the follicle rather than exogenous sources. Whether this modified technique would also prove effective in women with more severely elevated gonadotropins remains to be determined.

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