Original Articles

Reproductive Biology Section

Ovulation induction and pregnancy in a woman with premature menopause following gonadotropin suppression with the gonadotropin releasing hormone antagonist, cetrorelix - a case report

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Summary

Objective: To determine if ovulation and pregnancy could be achieved in a case of amenorrhea, estrogen deficiency, and markedly elevated serum follicle stimulating hormone (FSH) through reduction of the serum FSH by a gonadotropin releasing hormone antagonist. *Methods:* A 37-year-old woman with hypergonadotropic secondary amenorrhea related to two courses of chemotherapy with alkylating agents and abdominal radiation therapy (Hodgkin's disease and breast cancer) was treated with cetrorelix in an attempt to induce ovulation by lowering elevated serum FSH and hopefully restore sensitivity of the few remaining follicles by restoring down-regulated FSH receptors. She was monitored with serum estradiol (E2), FSH, luteinizing hormone (LH), progesterone (P) levels and sonography. *Results:* As the serum FSH dropped the serum E2 rose and peaked at 200 pg/ml after ten days of cetrotide. She conceived in that cycle. A viable ongoing pregnancy with appropriate ultrasound findings was demonstrated 40 days from conception. *Conclusion:* This is the first case description of successful ovulation and pregnancy following induction of ovulation with the GnRH antagonist cetrorelix. The possibility exists that the ovulation was spontaneous but it seems unlikely. It has been estimated that the chance of spontaneous ovulation and pregnancy in cases of premature ovarian failure is 1:9,200.

Key words: Premature menopause; Gonadotropin releasing; Hormone antagonist; Pregnancy; Ovulation induction.

Introduction

Spontaneous ovulation and conception in women with premature menopause without any treatment is extremely rare [1]. In fact one case was described of a 33-year-old woman with hypergonadotropic amenorrhea and gonadotropin resistance who spontaneously ovulated and successfully delivered despite a serum follicle stimulating hormone (FSH) level of 124 mIU/ml and a previous laparoscopy demonstrating bilateral streaked gonads [2].

Despite the fact that spontaneous ovulation has occurred, most reported pregnancies that have not been intentional have been while the woman was taking replacement estrogen or even oral contraceptives [2-5].

Ovulation induction and pregnancies have been achieved in hypergonadotropic amenorrhea in a more controlled manner by the use of ethinyl estradiol (20-50 μg daily) with or without a small boost of gonadotropins [6]. This regimen was not random but was purposely used to lower the elevated serum FSH in an attempt to restore down-regulated FSH receptors in the few remaining follicles. The theory is that there are still viable follicles present, albeit a paucity of them, that are resistant to both endogenous and exogenous gonadotropins [7, 8]. Lowering the high serum FSH with a pharmacologic dosage of estrogen works more efficiently than mere replacement dosages of estrogen. Moreover by using ethinyl estradiol follicular recruitment can be determined by observing the serum estradiol (E2) levels because ethinyl estradiol is not measured by the ELISA assay or radioimmunoassay for serum E2 [7].

Aiman and Smentek estimated that the likelihood of spontaneous ovulation with or without estrogen replacement therapy was 1:9,200 [9]. In 91 women with ovarian failure there were 61 ovulations in 311 cycles using this technique (29% ovulation rate) with 19 of 91 (20%) achieving pregnancies [6]. This was far higher than the expected rate of 1:9,200.

Though the theoretical reason for using ethinyl estradiol was to lower the elevated FSH levels and hopefully restore receptors, the possibility exists that the estrogen works in some other way, e.g., a direct effect on the follicle. However a 43-year-old woman with amenorrhea and estrogen deficiency with a serum FSH of 45 mIU/ml tried to achieve a pregnancy with the ethinyl estradiol method [10]. She actually ovulated 12 of the 18 times that she used this technique; however she became refractory to the therapy and failed to ovulate in her last three trials. She was put on leuprolide acetate, a gonadotropin-releasing hormone agonist, and she ovulated on the tenth

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day of treatment without any gonadotropins [10]. She did not conceive this cycle or in the two other cycles (out of 5) where she ovulated with leuprolide alone, nor in three additional cycles with leuprolide acetate and human menopausal gonadotropins. However she was 45 years old when she started the leuprolide treatment.

In the summary of 100 consecutive cases of attempted ovulation induction in women in menopause, 91 used ethinyl estradiol but there were nine using leuprolide acetate for various reasons, mostly because of side-effects from the estrogen or trying something different in women failing to ovulate with ethinyl estradiol. There were seven ovulations in 43 cycles (16.3) in three of nine women so treated. However, there were no pregnancies [6].

Theoretically, if the theory of reducing the elevated serum FSH to restore receptors is valid, then lowering the FSH with a GnRH antagonist may also accomplish ovulation. The following case is not only the first case described of ovulation induction in a woman with premature menopause using a GnRH agonist but it is also the first ongoing pregnancy completing the first trimester.

Case Report

A 37-year-old woman presented with secondary infertility. She conceived at age 30 and successfully delivered a full term baby by cesarean section. At age 19 she was diagnosed with Hodgkin's disease. She was treated with radiation therapy using the mantle technique and inverted y without an oophoropexy. She was also treated with chemotherapy (MOPP).

At age 35 she had been diagnosed with breast cancer and had a right mastectomy. In addition she received chemotherapy including alkylating agents, e.g., cyclophosphamide.

Her menstrual periods had ceased following the diagnosis of breast cancer at age 35. She was told after subsequent testing of her serum follicle stimulating hormone (FSH) and estradiol (E2) that she was in premature ovarian failure related to her history of radiation therapy and chemotherapy.

In her treatment cycle her baseline serum E2 was < 7 pg/ml, luteinizing hormone (LH) 16.3 mIU/ml and FSH 50.0 mIU/ml. Four days later those same values were E2 < 7 pg/ml, LH 20.5 and FSH 55.8. Another three days later the serum E2 was < 7 pg/ml, LH 25.3 mIU/ml and FSH 67.2 mIU/ml.

The woman was aware of our studies of inducing ovulation with successful pregnancies in women with ovarian failure using ethinyl estradiol to decrease the elevated FSH and theoretically restore down-regulated FSH receptors. However, because of the history of breast cancer she was reluctant to take a pharmacologic dosage of estrogen, especially since she could be given this treatment for many months.

She was advised that we had also induced ovulation by lowering serum FSH with leuprolide acetate but had not had any successful pregnancies. She was told that we could possibly accomplish the same feat even quicker using a gonadotropin releasing hormone (GnRH) antagonist but this had never been tried before. Since there had been no pregnancies recorded with the GnRH agonists she elected to try the GnRH antagonist.

The woman began 250 μg of cetrorelix subcutaneously daily. Three days later the serum E2 was 8 pg/ml and the serum FSH was 31.1 mIU/ml. After eight days the serum E2 rose to 11 pg/ml and the serum FSH was reduced to 28.6 mIU/ml. After 11 days of therapy the serum E2 rose to 53 pg/ml and the serum FSH decreased to 21.9. On day 13 of therapy the E2 rose to 111 pg/ml and the serum FSH decreased to 13.5 mIU/ml. The next day the serum E2 climbed to 163 pg/ml, the serum progesterone (P) was 0.2 ng/ml, the LH 9.1 mIU/ml and the serum FSH 12.6 mIU/ml. An ultrasound showed a follicle with an average diameter of 13 mm on the left ovary on that day; the next day (treatment day 11) the serum E2 rose to 290 pg/ml, the serum P 0.2 ng/ml, LH 14.8 mIU/ml and the FSH 16.0 mIU/ml, the follicle was 15 mm in average diameter. On treatment day 17 the serum E2 dropped to 161, the serum P rose to 0.8 ng/ml, the LH surged to 52 mIU/ml and the serum FSH increased to 44.2 mIU/ml. The endometrial thickness at this time was 10 mm and the echo pattern was triple line using vaginal sonography.

Three days following the day of marked LH surge with decreasing serum E2, an ultrasound revealed collapse and luteinization of the follicle. The woman was started on progesterone vaginal suppositories 200 mg twice daily.

She conceived on that cycle and her first serum beta human chorionic gonadotropin (hCG) level was 58 mIU/ml. The serum P was 18.4 ng/ml and the serum E2 was 78 pg/ml. The serum beta hCG levels appropriately doubled every two days and the ultrasound 40 days from conception showed a viable single gestation with appropriate-for-date, crown rump length and sac size and normal heart rate. There was no subchorionic hematoma noted and the decidual reaction was appropriate. The yolk sac was not enlarged. Unfortunately she had an early second trimester miscarriage.

Discussion

Since the publication in 1990 of the 100 cases of attempted induction ovulation in women in ovarian failure with either ethinyl estradiol (n = 91) or leuprolide acetate (n = 9), there have been several anecdotal reports involving extreme cases and pregnancies in women with hypergonadotropic amenorrhea and estrogen deficiency using ethinyl estradiol but none with leuprolide acetate or other GnRH agonists. These included a 25-year-old woman with a serum FSH of 164 mIU/ml [11], a 45-year-old with a serum FSH of 43 mIU/ml [12], a 42-year-old woman with tubal factor who required in vitro fertilization-embryo transfer (IVF-ET) with a maximum serum FSH of 37.5 mIU/ml whose only follicular drug was ethinyl estradiol [13], and a 40-year-old woman who conceived and delivered a full-term baby following exclusive estrogen therapy who had a serum FSH of 123 mIU/ml (she claims that in another state it had been as high as 180 mIU/ml) but most amazingly she had failed to conceive in another IVF center despite four previous embryo transfers using donor oocytes (12 embryos transferred total) [14].

Thus this is the first case of proven ovulation induction and pregnancy achieved by lowering elevated serum FSH levels without the use of ethinyl estradiol. This case thus supports the concept that follicles remain in the ovaries of women in apparent ovarian failure. However they are resistant to both endogenous and exogenous gonadotropins. However, by lowering the elevated serum FSH down-regulated FSH receptors will be restored, thus improving sensitivity to FSH. Successful pregnancies indicate that at least some of these follicles contain normal eggs.

This case also demonstrates that it is not necessary to reduce the serum FSH to the normal range to improve

sensitivity of the follicle to FSH. Thus one should watch carefully for a rise in serum E2 generated by endogenous FSH rather than giving a longer course of GnRH antagonists, wait for the FSH to be suppressed, then add exogenous gonadotropins.

Since no pregnancies have been recorded following ovulation induction with GnRH agonists despite ovulation induction, GnRH antagonists should probably be the treatment of choice for women with premature ovarian failure who want to achieve a pregnancy with their own egg but where estrogen is contraindicated.

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