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Multiple Follicles in an Unstimulated Cycle despite Elevated Gonadotropins in a Perimenopausal Female

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Key Words

Hypergonadotropic hypogonadism
Unstimulated cycle
Multiple follicles
High estradiol

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Abstract

The presence of estrogen deficiency associated with elevated gonadotropins usually signifies menopause. However, there have been a few case reports of ovulation and pregnancy despite hypergonadotropic hypogonadism. Described herein is a case of a perimenopausal woman who not only failed to ovulate in response to clomiphene citrate therapy but also failed to generate a level of serum estradiol (E_2) over 30 pg/ml. Following pharmacologic suppression of her elevated gonadotropins with ethinyl estradiol, she spontaneously formed 3 mature follicles, and her serum E_2 climbed to 868 pg/ml. This case suggests that some perimenopausal women may respond to their own endogenous elevated gonadotropins as if they are taking ovulation-inducing drugs and may, as a consequence, form multiple follicles.
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Introduction

The occurrence of ovulation and achievement of pregnancy despite the presence of hypergonadotropic amenorrhea and estrogen deficiency are well known [1]. One mechanism which may explain why estrogen therapy occasionally helps to induce ovulation is the restoration of down-regulated gonadotropin receptors in the few remaining follicles after both the elevated serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels have been decreased. A case was recently reported of 'spontaneous' ovulation and pregnancy occurring between cycles in a woman enrolled in a donor oocyte program [2]. At the least, the case raises speculation as to whether the estrogen therapy was necessary or coincidental when ovulation occurred.

The present report is of a 42-year-old female with a presumed diagnosis of ovarian failure. The stimulation of multiple follicles in this case supports the concept that the estrogen deficiency in some hypergonadotropic amenorrhea cases may not be secondary to total follicular exhaustion but may, instead, be related to a reversible problem.

Case Report

A 42-year-old female presented with a history of secondary infertility and a presumed diagnosis of ovarian failure. She reported the delivery of a full-term infant by cesarean section at age 40, followed by 1 year of infertility at which time she sought the opinion of a reproductive endocrinologist. The patient was placed on clomiphene citrate 50 mg for 5 days based upon the following: short menstrual cycles of 23 days and a short luteal phase on the basal body temperature chart.

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Two months prior to the initial visit in our office, her serum levels for FSH and LH were twice obtained – 1 week apart. The initial FSH (on day 3 of the cycle) was slightly elevated at 26 mIU/ml (normal: 16 mIU/ml), the LH was normal at 9.4 mIU/ml (normal: 3–30 mIU/ml), and the serum estradiol (E_2) level was found to be extremely low at < 20 pg/ml. One week later, all levels had increased: the FSH level was 76.9 mIU/ml (on day 10 of the cycle), the LH rose to 43.9 mIU/ml, and the serum E_2 was also higher, at 97 pg/ml. Menses ensued 11 days later. The patient was then treated with clomiphene citrate for 2 cycles, 50 mg \times 5 days then 100 mg \times 5 days, and, for the first time, spontaneous menses failed to occur in either cycle. In fact, she failed to have withdrawal menses after 10 mg of medroxyprogesterone acetate for 10 days, but did so when given the progestin for another 10 days plus conjugated estrogens 1.25 mg \times 10 days. In the second cycle, she again failed to menstruate despite 100 mg clomiphene citrate on days 3–7. Serum for E_2 , LH and FSH were obtained on days 6, 10, and 15 in both cycles; the minimum serum FSH in either cycle on these 3 days was 74.2 mIU/ml and for LH, it was 52.6 mIU/ml. The serum E_2 never went above 30 pg/ml. Medroxyprogesterone acetate alone was insufficient to induce withdrawal menses.

The patient, having been told that she was in ovarian failure and that her only hope for conception was the use of donor oocytes, arrived at our office 2 months later for a second opinion. Her initial visit was on day 8 of the induced menstrual cycle. FSH measured 36 mIU/ml (nl = 3.5–16.9 mIU/ml) and LH was 69 mIU/ml (nl = 3.7–31.2 mIU/ml).

In an effort to try to induce ovulation, the patient was placed on ethinyl estradiol 50 μ g daily in accordance with the protocol for regime B as previously described [1]. After drug therapy, her serum E_2 peaked at 110 pg/ml, LH measured its lowest decrease to 9.9 mIU/ml and FSH was 13.4 mIU/ml. In the next cycle, and without therapy, she formed 3 follicles with average diameters of 21.1, 21.6, and 21.3 mm and her serum E_2 reached 868 pg/ml. The patient was given 10,000 U human chorionic gonadotropin, resulting in the collapse of 2 out of 3 follicles. Her mid-luteal phase serum P reached 17.5 ng/ml, but she failed to conceive.

The patient's case was further complicated by hypothyroidism documented by an increased serum thyroid-stimulating hormone (TSH; Irma) of 22.8 μ U/ml (normal: 0.5–5.0 μ U/ml) and a positive microsomal antibody titer (11,409; normal: < 1,100 μ U/ml); morning serum cortisol was normal at 14.5 μ g/dl (normal: μ g/dl). Following therapy with *L*-thyroxine 0.1 mg, her repeat TSH was 0.5 μ U/ml, and the thyroxine level was 7.8 μ g/dl (normal: 4.8–13.0 μ g/dl).

Conclusion

This case is interesting in that after probable further elevation of gonadotropins following clomiphene, a perimenopausal woman with regular menses was converted into a hypergonadotropic woman with amenorrhea and estrogen deficiency. The degree of gonadotropin elevation may have been sufficient to down-regulate receptors to a critically low level, causing resistance to gonadotropins.

The opposite effect might also have occurred following suppression of gonadotropins to the normal range after

estrogen therapy. The receptors may have been restored, and with the fortuitous recruitment of several follicles in the cohort, the patient responded to the rapid rise in LH and FSH when inhibition from ethinyl estradiol was no longer present. Thus, the rapid elevation of gonadotropins may have created a situation analogous to the treatment with human menopausal gonadotropin (hMG), allowing a serum E_2 over 800 pg/ml and the 3 dominant follicles seen with sonography.

We previously published a similar case report of a 43-year-old perimenopausal woman with hypergonadotropic hypogonadism who had also been treated with high-dose estrogen and became resistant to the treatment (i.e. she could not generate a serum E_2 level over 30 pg/ml). She was, however, able to attain a serum E_2 of 285 pg/ml on day 10 of the cycle despite never reaching a spontaneous level over 30 pg/ml [3]. This response was attributed to the agonistic effect of leuprolide acetate, but, in actuality, considering the case described herein, perhaps a similar mechanism was responsible and the gonadotropin-releasing hormone agonist was never really needed. Even more analogous to the present case was the case description of a woman with 'ovarian failure' who was resistant to hMG therapy but who ovulated and conceived approximately 2 weeks after stopping oral contraceptives [4].

A study of 100 women with hypergonadotropic hypogonadism treated with a combination of supraphysiologic dosages of ethinyl estradiol and hMG reported 38 women ovulating at least once (68 ovulations in 361 attempts) [1]. Although the serum E_2 levels were above 200 pg/ml in all ovulating cases, not 1 case exceeded 400 pg/ml and not 1 had more than one follicle. We did find 1 perimenopausal 41-year-old woman who was unable to generate a serum E_2 above 200 pg/ml despite hMG therapy, but who did generate 3 follicles with an E_2 of 641 pg/ml during the cycle after hMG was discontinued – and who conceived [5]. However, she was taking leuprolide during that cycle, and the case once again questions whether the response was spontaneous or related to the agonistic action of leuprolide acetate.

The case presented herein clearly demonstrates that a perimenopausal woman who fails to generate E_2 levels over 30 pg/ml in two cycles, even if associated with elevated LH and FSH levels, may in a subsequent cycle produce multiple follicles and a supraphysiologic E_2 level without any stimulation. As long as there are enough follicles in the cohort for that cycle, the patient may respond to her own elevated gonadotropins as if she were taking ovulation-inducing drugs. Whether some type of preceding estrogen therapy or lowering of gonadotropins is nec-

essary can only be speculated. There is also the possibility that clomiphene, by raising the gonadotropins too high, may have caused down-regulation of gonadotropin receptors leading to a gonadotropin-resistant gonad which allowed rebound increased sensitivity.

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