

Ovulation induction in hypergonadotropic amenorrhea with estrogen and human menopausal gonadotropin therapy

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The combination of amenorrhea, estrogen deficiency, and elevated gonadotropins in a woman under age 35 is usually indicative of premature ovarian failure and, less commonly, the gonadotropin-resistant gonad. In either case, the prognosis for future fertility is poor. There have been some reports of pregnancies in patients with hypergonadotropic amenorrhea following the use of exogenous estrogen¹ and also following the use of human menopausal gonadotropin (hMG) therapy.^{2,3}

We report the successful induction of ovulation in three of five women with premature ovarian failure with elevated follicle-stimulating hormone (FSH) levels and estrogen deficiency by employing estrogen to suppress endogenous gonadotropins and then hMG to stimulate ovulation. A pregnancy was achieved in one case after two treatment cycles and in a second case after five treatment cycles. The third patient, despite two seemingly perfect cycles of normal ovulation and normal postcoital tests, has failed to conceive.

CASE REPORTS

CASE 1

A 27-year-old woman with 3 years of primary infertility presented with a history of oligomenor-

rhea and finally 6 months of amenorrhea. Her vaginal cytologic studies showed 80% small intermediate cells and 20% parabasal cells. She failed to have withdrawal menses following 10 mg medroxyprogesterone acetate (MPA) for 10 days. Her serum estradiol (E₂) was 20 pg/ml. The serum FSH was elevated at 39.2 mIU/ml (normal premenopausal values were < 16 mIU/ml). A repeat FSH measurement 2 weeks later was still elevated at 52 mIU/ml. The prolactin level was normal at 7.6 ng/ml.

The patient was started on hMG, 150 IU intramuscularly (two ampules) daily, which was increased to 300 IU daily, but failed to form any follicles close to the minimum acceptable size of 17 mm, despite a total of 3000 IU of hMG. She was then placed on 2.5 mg conjugated estrogens for 25 days and 10 mg MPA for 10 days for two cycles. Withdrawal menses occurred both times after stopping the estrogen-progestin combination. Three weeks after the 2.5-mg dosage of conjugated estrogens was started, a repeat serum FSH was normal at 10 mIU/ml. hMG was then restarted on the fifth day of the menstrual cycle.

After 1350 IU of hMG (150 IU for 9 days), the patient formed follicles with a diameter of 23.7 mm, 22.7 mm, and 16.3 mm on the right ovary and 21.7 mm, 15.3 mm, and 14 mm on the left ovary. A mature follicle was considered between the sizes of 18 and 24 mm. Human chorionic gonadotropin (hCG) was given in a dosage of 10,000 IU 36 hours from the last hMG injection, and a repeat ultrasound 2 days later demonstrated release of the ova (as evidenced by a shrinkage of

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the follicle by at least 5 mm) from two follicles on the right and one on the left. The patient's serum progesterone (P) level 7 days premenstrually was 17 ng/ml (normal midluteal phase level, > 12 ng/ml).

The next cycle, the patient formed mature follicles after 1500 IU of hMG. hCG was given on cycle day 15, and she conceived in this cycle. The patient has successfully completed her first trimester with a single viable fetus.

CASE 2

The patient presented at age 32 with primary infertility and secondary amenorrhea. Sexual development began at age 14, and her menarche at age 16. She only had a total of three more spontaneous menses thereafter. P-withdrawal menses had been induced six times up to the age of 20. At this point she had been placed on oral contraceptives, which were stopped at age 26 in an attempt to conceive. There were no spontaneous menses, nor were they able to be induced with P. Vaginal cytology showed marked estrogen deficiency, as did the serum E_2 (18 pg/ml); and both serum FSH and luteinizing hormone (LH) were increased (average of three samples: FSH, 96 mIU/ml; LH, 57.5 mIU/ml). The patient was then treated with hMG but was unable to increase her E_2 levels after 4500 IU, and so this therapy was terminated.

When she first presented to us at age 32, the patient was still markedly estrogen-deficient and hypergonadotropic (FSH, 65.4 mIU/ml; LH, 34 mIU/ml). She was treated first with 1.25 mg conjugated estrogens for 30 days and 10 mg MPA on days 21 to 30, and on day 30 a serum FSH measurement was drawn. hMG was then employed at 150 IU, beginning on day 5 of the next cycle. After 1500 IU of hMG, there were no follicles > 8 mm as seen by ultrasound examination, and the serum E_2 was only 40 pg/ml. The serum FSH value was now available; and because it was still elevated at 36 mIU/ml, the hMG therapy for this cycle was terminated and the patient was placed on 5 mg conjugated estrogens. A repeat serum FSH measurement after 30 days of 5 mg conjugated estrogens was now 12 mIU/ml, and hMG was restarted and the estrogen was stopped. The patient ovulated in the next two consecutive cycles, as evidenced by ultrasound criteria (one follicle each cycle) and a serum P level 1 week after forming a mature follicle > 15 ng/ml. In each cycle, 2400 IU hMG was employed. Successful

ovulation occurred in the next three consecutive cycles, and a pregnancy was achieved in the fifth treatment cycle after 3000 IU (40 ampules) hMG. Pelvic sonography demonstrated a single viable fetus 7 weeks from conception.

CASE 3

The patient, aged 26, had secondary hypergonadotropic (FSH averaged 120 mIU/ml in two samples) amenorrhea and estrogen deficiency. She failed to have withdrawal menses to 10 mg MPA for 10 days. Her menarche was induced by MPA at age 17. At age 19, MPA failed to induce withdrawal menses.

She was first treated with 2.5 mg conjugated estrogens for 2 months. The repeat serum FSH level after 3 weeks of therapy was now normal at 12 mIU/ml. She then ovulated with 4800 IU (64 ampules) hMG on the first cycle and 3750 IU hMG on the second cycle. The estrogen was stopped prior to using hMG. In this cycle there were two mature follicles 18.5 and 22 mm in diameter with a serum E_2 level of 640 pg/ml and one follicle 19 mm in diameter in the second cycle with a serum E_2 level of 450 pg/ml. hCG was employed after the E_2 results were noted. In our laboratory an E_2 level associated with a high percentage of ovulation is ~ 200 pg/ml per mature follicle. hCG is withheld if the E_2 exceeds 500 pg/ml per mature follicle. The postcoital test was excellent in both cycles but so far no pregnancy has been achieved. In the first cycle the midluteal phase serum P level was 13.2 ng/ml, and in the second cycle it was 15.6 ng/ml. The patient had declined both a hysterosalpingogram and laparoscopy, but she has agreed to have a laparoscopy if she fails to conceive after five ovulatory cycles.

CASE 4

The patient presented at age 26 with a history of menarche at age 14 and secondary amenorrhea since age 17. At age 22, she was treated with hMG (up to 52 ampules) but failed to ovulate. At age 26 she sought our opinion concerning her infertility. She had been on 1.25 mg cyclic conjugated estrogens for 25 days and 10 mg MPA for 10 days. Her serum LH was 52 mIU/ml, and her serum FSH was 58 mIU/ml. Her conjugated estrogens were elevated to 5 mg, and after 1 month the repeat values for LH and FSH were normal at 8 and 14 mIU/ml, respectively (normal, up to 30 mIU/ml for both). However, despite 40 ampules of

Table 1. Summary of the History and Treatment of Five Cases of Premature Ovarian Failure

Patient	Age of secondary amenorrhoea	No. of ampules of hMG to achieve ovulation in first two cycles with estrogen suppression of FSH	No. of ampules of hMG used when failure to achieve ovulation without FSH suppressed	Age when therapy with estrogen and hMG started in this study	Dose of conjugated estrogens used for suppression of FSH
					mg
1	27	18,20	40	27	2.5
2	17	10,32	60	32	5
3	21	64,50	No prior therapy	26	5
4	17	40,48 ^a	52	26	5
5	19	52 ^a	No prior therapy	22	5

^ahMG was stopped at this point because the follicles were not increasing in size and the serum E₂ was not rising.

hMG, she failed to stimulate any follicles > 10 mm, as determined sonographically. She was switched to 0.05 mg ethinyl E₂ which does not cross-react in our serum E₂ assay, and tried again with hMG, but still failed (despite 48 ampules of hMG) to stimulate any follicles > 10 mm; and the serum E₂ failed to rise > 30 pg/ml.

CASE 5

The patient presented at age 22 for evaluation of a 1-year history of infertility. At age 16, she had one spontaneous menstrual flow and again at age 19. She had over ten failing attempts during the 5 years of secondary amenorrhoea to have withdrawal periods with MPA. Vaginal cytology on examination showed 70% parabasal cells indicative of marked estrogen deficiency. The serum E₂ level was only 12 pg/ml, LH was 105 mIU/ml, and FSH was 112 mIU/ml. She was treated with 5 mg conjugated estrogens for 1 month. The repeat FSH level was now 21 mIU/ml (normal premenopausal level, 5 to 30 mIU/ml). The estrogen was stopped, and two ampules hMG per day was started on the fifth day of the withdrawal period. The patient was raised to 3 ampules per day but failed to stimulate any follicles > 10 mm despite 52 ampules of hMG (Table 1).

DISCUSSION

Three of five patients with a diagnosis of ovarian failure appeared to achieve successful ovulation with hMG. No laparoscopies or ovarian biopsies were performed because it was reasoned that if follicles were found present, that would still be no guarantee of a response to hMG; the absence of follicles might be related to the size and the location of the sample obtained and therefore not ensure failure to respond to hMG. A therapeutic

trial of hMG seemed to us and the patients (all were given the option of laparoscopy) to be the more benign and more effective approach. Karyotyping was performed on patient 3 because she was only 60 inches tall and was 46,XX. The other patients were 64 inches or greater, and karyotyping was not performed.

All three patients who responded were treated with estrogen and hMG. Cases 1 and 2 seemingly did not respond to hMG when the estrogen level was low but became sensitive to therapy after adding exogenous estrogens. This association cannot be made certain, because in an ovary with only a few follicles it is possible that at any given time there may not be any follicles that are in the stage of development that can be recruited by the hMG. Thus, it may have been fortuitous that the estrogen was deficient just when there were no follicles able to be recruited.

However, another possibility is that the elevated FSH levels down-regulate FSH receptors on the granulosa cells. Suppressing the FSH with estrogen allows the restoration of FSH receptors and thus enables some follicles to respond to exogenous FSH given in the form of hMG. Alternatively, the first three cases may have produced a defective FSH which still competed with exogenous FSH for the receptors, thus making the gonad resistant to hMG therapy.

We suspect that with a larger series of cases we will not achieve ovulation in 60% of the cases, as in this study. Nevertheless, the data at least suggest that a patient with hypergonadotropic amenorrhoea and estrogen deficiency deserves at least a trial of estrogen and hMG. Some patients may prefer to have an ovarian biopsy and/or laparoscopy before trying the estrogen-hMG therapy because of the expense of hMG. However, with these findings, even if they supposedly failed previously to respond to hMG, they deserve at least one more

trial after suppressing their serum FSH to normal with estrogen. Interestingly, successful ovulation induction after gonadotropin suppression has been recently reported in a woman with alleged "ovarian failure" after therapy with a gonadotropin-releasing hormone analog.⁴

The use of conjugated estrogens with hMG in the treatment of cases 1 and 2 precluded determining what proportion of the serum E₂ was contributed by the follicles versus the pills. Thus, serum E₂ was not employed for monitoring the hMG therapy. We have recently determined that ethinyl E₂ does not cross-react with 17β-E₂ in our E₂ assay. Therefore, to improve the accuracy of the hMG monitoring so that serum E₂ and pelvic sonograms would be employed, all future patients will be treated with ethinyl E₂ rather than with conjugated estrogens.

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