

Ovulation induction and pregnancies in 100 consecutive women with hypergonadotropic amenorrhea*

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The efficacy of a technique of gonadotropin suppression and human menopausal gonadotropins (hMG) to induce ovulation in women with hypergonadotropic amenorrhea was evaluated in 100 consecutive women. Ovulation was achieved in 19% of cycles (68/361), the pregnancy rate per cycle was 5.2% (19/361), and the viable pregnancy rate was 2.2% (8/361). In the majority of the successful cases, estrogen was used to decrease the elevated luteinizing hormone and follicle-stimulating hormone levels, especially where the ethinyl estradiol therapy alone induced a rise in endogenous 17 β -estradiol levels with hMG used to boost the follicle to maturation. Although the success rate is low, this technique can result in some successes in otherwise almost hopeless cases. *Fertil Steril* 53:811, 1990

Successful ovulation induction and achievement of pregnancies have been reported in women with apparent menopause.¹⁻⁴ Sporadic conceptions have, in fact, been recorded while patients were taking estrogen replacement,¹⁻³ oral contraceptives,^{1,4} and even spontaneously.¹ However, since the occurrence of premature menopause is estimated at 1% of all women during the reproductive years,⁵ the apparent rate of spontaneous ovulation and subsequent pregnancies must be quite low in

lieu of the paucity of conceptions reported. Treatment for infertility can be accomplished by first suppressing the pituitary gonadotropins with estrogen followed by ovarian stimulation with human menopausal gonadotropins (hMG).^{6,7} Induction of ovulation has also been reported in a patient with hypergonadotropic amenorrhea after therapy with leuprolide acetate (LA), with and without hMG therapy.⁸ Interestingly, very few pregnancies have been reported with hMG alone.⁹ The results of these techniques in achieving ovulation and pregnancy in 100 consecutive infertile women having amenorrhea, estrogen deficiency, and elevated serum gonadotropins are presented.

MATERIALS AND METHODS

The object was to evaluate infertility treatment of 100 women with elevated gonadotropins and estrogen deficiency. Patients with elevated gonadotropins were those with serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) > 35 mIU/mL. Estrogen was considered deficient if the

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serum estradiol (E_2) was <25 pg/mL. Further requirements for inclusion in the study were a minimum of 12 months of amenorrhea and failure to have withdrawal menses despite treatment with medroxyprogesterone acetate (10 mg \times 10 days). Also, only those patients who allowed at least four treatment cycles were included. The ages ranged from 19 to 47 years with a mean age of 34 years.

The initial hypothesis was that lowering the gonadotropins by means of estrogen followed by hMG stimulation might allow ovulation to occur. Only if the estrogen therapy was not tolerated was the patient switched to LA.⁸ Initially, the first four patients were treated with conjugated estrogens; subsequently, the estrogen was changed to ethinyl estradiol (EE_2) beginning at 50 μ g/d because this estrogen has very little cross-reactivity with the serum 17β - E_2 radioimmunoassay.¹⁰

Patients 1 to 26 were initially treated for a minimum of 2 weeks with estrogen therapy until the gonadotropins were within the normal range. The hMG was then started at 150 IU/d and was increased or kept at the same dosage based on the serum E_2 level obtained after 5 days of therapy. Failure to significantly increase the serum E_2 prompted an increase in hMG dosage and a repeat serum E_2 was obtained 3 to 4 days later. The E_2 level at that point dictated continuance of the same dosage or an increase in amount of hMG. Failure to increase the serum E_2 above 50 pg/mL despite 4 days of hMG therapy at 375 IU/d indicated cessation of therapy for that cycle. Medroxyprogesterone acetate 10 mg \times 10 days was then given to induce menses and the same therapeutic schedule and process was to be repeated within the next cycle.

Pelvic sonography and serum E_2 levels were employed to monitor follicular maturation. If the patient attained a follicle with a minimum average diameter of 17 mm and a serum E_2 of at least 200 pg/mL, the hMG was discontinued and $10,000$ IU human chorionic gonadotropin (hCG) was given intramuscularly. A repeat sonogram 3 days after hCG was then performed to determine ovum release. After demonstration of follicular collapse, progesterone (P) vaginal suppositories at a dosage of 25 mg twice daily were started. A timed endometrial biopsy was obtained 2 weeks from the time of hCG for purposes of dating the biopsy; ovulation was assumed to have occurred 36 hours after hCG. In determining whether the endometrial biopsy was in-phase (or out-of-phase), a biopsy out-of-phase by >2 days prompted an increase in the P

REGIME A (PTS 1-26) INDUCTION OF OVULATION IN OVARIAN FAILURE

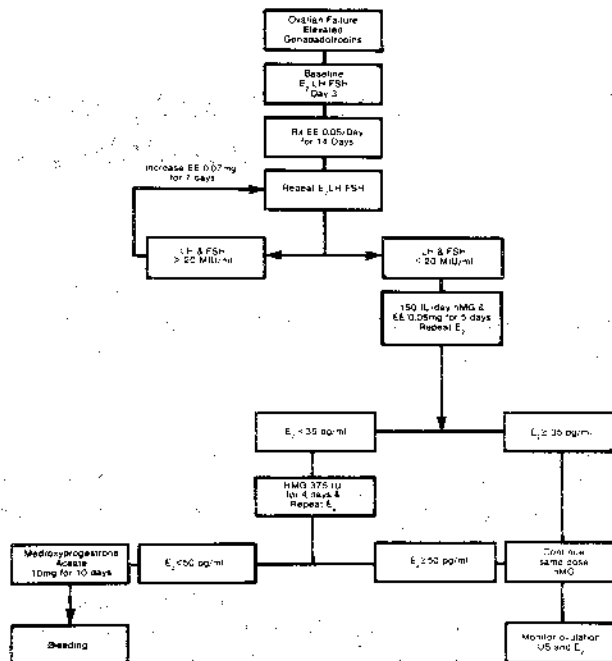


Figure 1 Regime A: flow chart of therapy used for patients 1 through 26 where gonadotropins were first suppressed to normal and then hMG was employed to stimulate follicular genesis.

dosage for the next cycle and the biopsy was then repeated. A midluteal phase serum P level was obtained, with a level <12 ng/mL, prompting an increase in the P dosage. It should be noted that the estrogen therapy was continually maintained throughout hMG therapy, but was discontinued the day hCG was administered. A summary of this technique is described in Figure 1 (Regime A).

For the remaining patients 27 through 100, there was a slight change in technique. Serum E_2 , LH, and FSH were all measured after only 1 week of EE_2 therapy. If the serum E_2 was <35 pg/mL, the estrogen therapy was continued for another week, at which time the serum E_2 and gonadotropin levels were repeated. A rise in serum E_2 above 35 pg/mL prompted initiating hMG therapy even if the gonadotropins were still not within the normal range. In fact, frequently the hMG was not employed until the serum E_2 reached at least 85 pg/mL. Failure to suppress the LH and FSH within normal levels despite 2 weeks of 50 μ g of EE_2 daily prompted either increasing the dosage to 70 μ g/d (if the 50 - μ g dosage was well tolerated) or maintaining at the same level and repeating the blood levels once again in 1 week. A summary of this modified technique is seen in Figure 2 (Regime B).

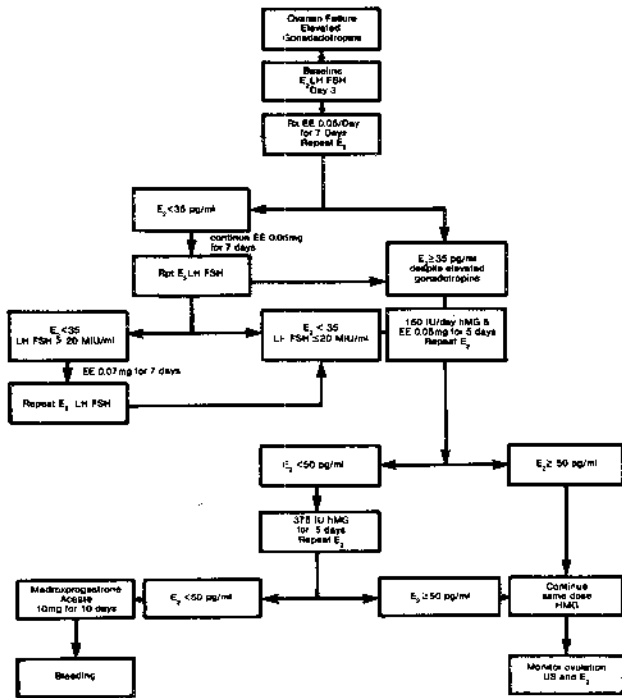


Figure 2 Regime B: patients 27 through 100, technique used when estrogen was used to see if a spontaneous E₂ rise would occur before full suppression of elevated gonadotropins to normal. In this case the hMG was merely used to augment the full maturation process.

Leuprolide acetate 1 mg subcutaneously was to be employed in lieu of estrogen if there were side effects to the estrogen therapy, such as headache, nausea, vomiting, or a previous history of a condition that contraindicated the use of estrogen, such as thrombophlebitis. The LA was employed in a similar fashion much like the estrogen therapy in that each week the serum E₂ and gonadotropins were measured and the decision to begin hMG was made according to the previous guidelines. As with the estrogen therapy, the LA was continued throughout hMG therapy because stopping either treatment would result in a rapid elevation of the serum LH and FSH. (Both therapeutic regimens were based on the possibility that elevated gonadotropins may have caused down-regulation of receptors to LH and FSH thus preventing the few follicles from responding to endogenous or exogenous gonadotropins).

Severe male factor problems or bilateral tubal disease precluded the use of the gonadotropin suppression-hMG stimulation technique and these patients were excluded from the study. Thus, 111 patients initially sought treatment and 11 were elimi-

nated. The males with mild oligospermia or asthenospermia were first treated with either split ejaculate insemination, varicocelelectomy, or clomiphene citrate (25 mg/d). Before initiating therapy, each patient was required to have either hysterosalpingography or laparoscopy. Those who had only the hysterosalpingography were offered laparoscopy if at least one successful ovulation cycle occurred after therapy.

Treatment was generally terminated if no follicular maturation was achieved despite four cycles of therapy. However, on patient insistence, a maximum of six unsuccessful cycles were occasionally offered. But successful ovulation cycles during the first four attempts allowed indefinite continuance of the therapy, only discontinuing with a pregnancy or secondary to the patient's wishes after failure to conceive.

If no spontaneous menses occurred 15 days from presumed ovulation (i.e., 36 hours from the hCG injection), an hCG β-subunit was obtained. So there would be no possibility of falsely diagnosing pregnancy by measuring residual hCG from the injection to release the ova, only women with serum levels > 100 mIU/mL at least 16 days after hCG injection and also demonstrating a rise in the level when serum was redrawn 2 to 3 days later, were considered pregnant. The pregnant patients were carefully monitored during the first trimester and fetal viability was evaluated by pelvic sonography at a minimum 5 and 10 weeks from conception.

RESULTS

The success of gonadotropin suppression-hMG therapy in accomplishing ovulation and pregnancy in 100 patients with hypergonadotropic hypogonadism is presented in Table 1. Eight viable pregnancies have been delivered. One woman had a

Table 1 The Success of Estrogen-hMG Therapy Versus LA-hMG Therapy in Women with Amenorrhea and Hypergonadotropic Hypogonadism

	Estrogen-hMG	LA-hMG
No patients stimulated	91	9
No. cycles attempted	311	43
No. ovulations	61	7
No. patients ovulating	34	3
No. patients pregnant	19	0
No. patients aborting	10	0
No. stillbirths	1	0
No. premature births	5	0
No. viable births	8	0

Table 2 Life Table Analysis Regarding Pregnancy Achieved in Women Treated with Hypergonadotropic Hypogonadism

No. of cycles	No. of patients	Pregnancies achieved	Lost to follow-up	Length of treatment	Pregnancy rate	Cumulative probability of pregnancy
				<i>mo</i>	<i>/mo</i>	
1	100	2	0	99.00	0.02	0.02
2	98	1	0	97.50	0.01	0.03
3	97	1	0	96.50	0.01	0.04
4	96	1	0	95.50	0.01	0.05
5	95	1	30	79.50	0.01	0.06
6	64	0	34	47.00	0.00	0.06
7	30	1	21	19.00	0.05	0.11
8	8	1	6	4.50	0.22	0.31
9	1	1	0	0.50	2.00	1.69

stillbirth at 34 weeks. Six of the 38 women ovulating at least once in 4 cycles ovulated in all of their first 4 cycles (19%). There were a total of 68 ovulations in 361 attempts (16%). The pregnancy rate per therapeutic cycle was 5.2% (19/361) and the pregnancy rate per successful ovulation was 28% (19/68), but approximately 50% aborted. Unfortunately there were no successful chromosome studies obtained on any of the abortuses. Two of the 10 aborted pregnancies had first demonstrated viability at 5 weeks from conception, whereas 4 had normal sacs but no fetal pole, and 4 spontaneous abortions were diagnosed by dropping hCG levels alone. For those conceiving, there was an average of 4.4 ovulatory cycles before conception. Three patients required 9, 8, and 7 ovulatory cycles, respectively, before conception occurred. A life table analysis is provided in Table 2.

Twenty-four patients had a late luteal phase biopsy on a nonconception ovulatory cycle. The biopsy was out-of-phase by >2 days in 22 patients. Both of the 2 patients with in-phase biopsies conceived with 1 aborting and the other successfully delivering.

All 19 pregnancies occurred with estrogen-hMG therapy. Leuprolide acetate was used in only 9 patients; 3 ovulated at least one time, but no pregnancies ensued. One woman who was counted in the estrogen-hMG statistics and who conceived (but aborted) on her seventh cycle, was actually treated with LA and ovulated all seven times. So, in fact, 4 of 10 (40%) females ovulated with LA-hMG, but no pregnancies were achieved.

Five of the 19 pregnancies (26%) occurred in the first 26 patients treated with a minimum of 2 weeks of estrogen therapy before hMG. Fourteen pregnancies occurred in the 72 patients (19%) given the opportunity to use hMG if the serum E_2 was rising even if the serum gonadotropins were still elevated.

Eleven of these 14 pregnancies (79%) occurred with the latter, whereas in 3 the gonadotropins fell to submenopausal levels when the serum E_2 spontaneously elevated.

Forty of the 68 ovulations (58.8%) occurred with hMG used after the EE_2 alone recruited a follicle. The average amount of hMG employed was 1,050 U. Twenty-one ovulations (32.2%) occurred with hMG employed only after reduction of serum LH and FSH into the normal range; the average amount of hMG required was 2,850 U hMG.

Twenty-seven of the 38 women who ovulated after gonadotropin suppression had previously failed to ovulate using hMG therapy alone in 46 cycles. Most of them had received high doses of hMG. Nineteen of these patients had failed to raise the serum E_2 over 35 pg/mL despite an average of 3,400 U of hMG.

The average time from diagnosis of ovarian failure to initiation of therapy in 17 of the 21 women who became pregnant (when this knowledge was available) was 2.2 years in contrast to an average of 4.8 years in 65 patients who did not conceive. The mean age for the pregnancy group was 33.4 and for the nonpregnancy group 34.8 (not significant); the mean serum FSH for the responders was 70.3 mIU/mL and was 66.5 mIU/mL in the nonresponders (not statistically significant). In all cases the baseline serum E_2 was <20 pg/mL. All baseline blood values were repeated twice at least 1 month apart and averaged. The mean age and serum FSH levels were also similar in women who ovulated (32.6 and 69.1 mIU/mL, respectively) compared with the conceivers.

DISCUSSION

Although very few pregnancies have been reported with hMG alone,⁹ combining hMG therapy

in women pretreated with estrogen enabled 2 women to ovulate and conceive despite failing to stimulate any degree of folliculogenesis with hMG alone.⁶ Yet 89 of the 100 ovarian failure patients reported herein had been treated with estrogen replacement therapy, as were all 19 women conceiving, but no pregnancies or even apparent ovulations had been reported previously in this group.

Our data suggests that combining estrogen therapy with hMG can stimulate ovulation in about 20% of cycles with 17% of these ovulating cycles resulting in viable pregnancies. Some experimental data in rats has suggested that E₂ might enhance FSH binding to receptors.^{11,12} If the mechanism of ovulation induction in our series of 100 involved priming of FSH receptors with estrogen, then our data would suggest that the synthetic EE₂ is also effective. However, the estrogen could be acting to increase the biological effectiveness of endogenous gonadotropins. This latter hypothesis would not explain the previous failure of many of these patients to respond to hMG. It should be noted that without a randomized control study comparing the efficacy of estrogen therapy alone versus hMG alone, versus estrogen-hMG therapy, versus placebo controls, no definite conclusion can be made that estrogen is even needed for the technique to work.

The dosage of estrogen used in our reported series was high and more than enough to lower the elevated gonadotropins. The theory was that the elevated gonadotropins may have caused down-regulation of gonadotropin receptors and that lowering the serum LH and FSH could restore the sensitivity of the remaining follicles. However, because a low dose of estrogen was not compared with the higher dose, no conclusions can be drawn as to the most effective dosage of estrogen. Theoretically, the estrogen might enhance a gonadotropin response by direct effect on the receptors or by lowering the elevated LH and FSH levels, thus restoring down-regulated receptors. Although the majority of patients stimulated with Regime B did not need the gonadotropins suppressed to the normal level (which might favor direct enhancement of receptors without need for gonadotropin suppression), nevertheless the possibility exists that enough reduction of LH and FSH occurred to restore down-regulated receptors.

One woman with diagnosed hypergonadotropic hypogonadism who failed to stimulate a rise in serum E₂ with hMG alone was able to ovulate to both a combination of LA and hMG, and to LA alone.⁸

This lends some support to the possibility that the important operating mechanism in achieving ovulation even in the estrogen treated women was restoring down-regulated gonadotropin receptors by reducing elevated levels of serum LH and FSH. However, an alternate explanation is that the LA was operating based on its initial agonistic action and there was no need to lower gonadotropin levels. The use of a pure antagonist when available might help to elucidate the mechanism.

More patients were treated with estrogen rather than LA because (1) initially, LA was not commercially available, (2) LA has the disadvantages of being expensive and an injectable, and (3) it is not officially approved for this type of therapy in women. A randomized study comparing the efficacy of estrogen versus LA in aiding ovulation induction in these patients would be of interest. We have noted that suppressed gonadotropins will begin to rise by 3 days after stopping estrogen and it was for this reason that the EE₂ was continued throughout the hMG therapy. Nevertheless, a randomized study comparing continuous estrogen therapy versus stopping estrogen when hMG is started needs to be performed before any definite conclusions are made.

The high spontaneous abortion rate might possibly be related to chromosomal abnormalities similar to those occurring in chronologically older patients (e.g., aneuploidy). Unfortunately, our attempt to karyotype the abortuses to support or refute this hypothesis failed. Also, the estrogen used to suppress gonadotropins may have formed an abnormal endometrium or caused a luteal phase defect refractory to P therapy. This high dose EE₂ therapy, however, has also been used to treat cervical factor complications and the pregnant patients in this study did not demonstrate a higher abortion rate.¹⁰ Although each pregnant patient was offered chorionic villus sampling (CVS) or amniocentesis, only 6 of the 21 pregnant women decided to do so and 4 aborted before testing. Two women demonstrating fetal viability on pelvic sonography had previously agreed to CVS but changed their minds after a live fetus was demonstrated. Nevertheless, since the majority of patients tested had out-of-phase endometrial biopsies despite supplementary P therapy, the luteal phase defect could have also contributed to the high spontaneous abortion rate. Obviously, it is not practical to use mechanical contraception in this group of women until the biopsy is corrected.

Recently Surrey and Cedars¹³ failed to corroborate

rate previous case reports of ovulation-induction and pregnancy in ovarian failure patients with the technique of gonadotropin suppression followed by hMG stimulation. Employing three different techniques, they achieved only one ovulation out of 14 patients in 22 treatment cycles and only 12 cycles actually employed the technique of EE_2 and hMG. The majority of the patients may have started with a high dose of hMG similar to in vitro fertilization (IVF). We have found better responses to lower dose hMG and have hypothesized that the slow clearance of FSH might still cause down-regulation of gonadotropin receptors, thus negating the theoretical benefits of the estrogen therapy. Furthermore, even using the lower dose hMG technique, we were unable to induce ovulation nearly so frequently using Regime A as in the first few reported cases, and we found Regime B to be more effective.

Regime B also had the advantage of being far less expensive, requiring only one-third the dosage of hMG to achieve ovulation. Furthermore, since higher percentage occurs of ovulations after follicular recruitment by the estrogen with just a boost of hMG to complete follicular maturation, patients without sufficient funds for hMG need only invest in the cycles that offer a higher percentage success of ovulation induction (when the endogenous serum E_2 begins to rise before hMG). In fact, it is not really known if the follicles might have completed follicular maturation with the estrogen alone without hMG. Although the success rate per cycle is certainly higher with IVF of a donor egg and subsequent transfer, it is our experience that most patients desiring pregnancy despite ovarian failure prefer to try with their own ova rather than with those of the donor's, even though there is less chance of success.

There were no obvious differences in the mean age, baseline serum E_2 or LH and FSH levels, or the ability to suppress gonadotropins in those patients

made to ovulate versus the nonovulators. The only difference was in the shorter mean length of time from menopause diagnosis to time of treatment in conceivers versus nonconceivers.

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