
Ovulation induction and pregnancies in women with ovarian failure (reversing menopause)

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INTRODUCTION

Ovarian failure is associated with a decreased number of follicles in the ovaries. At least 50% of patients diagnosed with this condition demonstrate ovarian follicles on ovarian biopsy^{1,2}. These follicles are frequently arrested in the antral phase of follicular development and resist gonadotropin stimulation. Down-regulation of the gonadotropin receptors because of the elevated gonadotropins has been hypothesized as a possible mechanism for the gonadotropin resistance³. Increased sensitivity of these follicles to gonadotropin stimulation with subsequent ovulation and pregnancies has been previously reported in a few cases following suppression of endogenous gonadotropins by high-dose estrogen followed by ovarian stimulation with human menopausal gonadotropins (hMG)⁴. The results of ovulation induction, pregnancies achieved and occurrence of abortions in an enlarged series of women with failure treated with this high-dose estrogen (HDE)-hMG technique is presented.

MATERIALS AND METHODS

A total of 46 patients with a diagnosis of ovarian failure seeking help to achieve a pregnancy was enlisted in the study. The diagnosis was established in these patients (all of whom had amenorrhea and failure to have withdrawal menses following 10 days of medroxyprogesterone acetate) by demonstrating elevated serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) of at least 40 mIU/ml while the serum estradiol (E₂) was under 20 pg/ml.

Inclusion in the study required the patient to first fail to increase her serum E₂ level over 40 pg/ml despite a total of 4500 IU of hMG. Each patient was then treated with 50 µg of ethinylestradiol (EE) for 10 days when repeat gonadotropin levels were obtained. If both the serum FSH and LH were

under 25 mIU/ml, then 150 IU of hMG was started while the patient also continued on the EE. Failure to suppress the level below 25 mIU/ml would prompt continuing therapy with 50 μ g EE for another 5 days and if repeat gonadotropins were adequately suppressed the hMG would also be started. The EE dosage would be raised to 70 μ g if there was inadequate gonadotropin suppression and re-evaluation occurred 5 days later. The maximum EE dosage used was 100 μ g if 70 was found to be inadequate. If the patient had significant side-effects from the EE they were eliminated from the study. The gonadotropin therapy was initiated at 150 IU daily and this would be increased to 225 IU after 5 days if the serum E_2 was under 50 pg/ml. The patient would then be re-evaluated by the serum E_2 level within at least another 5 days and the dosage raised to 300 IU in two divided doses for at least another 5 days. The same process would be repeated raising the dosage by 75 IU.

Failure to increase the serum E_2 over 40 pg/ml despite 5 days of 450 IU/day of hMG would terminate the therapy for that cycle. The patient would then be placed on medroxyprogesterone acetate 10 mg for 10 days, the EE would be maintained, and both drugs would be stopped for 4 days to allow menses to occur. The EE would then be resumed on the 5th day and the process repeated.

Reaching a level over 40 pg/ml of EE with any dosage of EE would prompt continuing the same dosage for 2 more days, re-evaluating the serum E_2 and, depending on the rapidity of rise of the E_2 , the dosage would be maintained or increased. Serum progesterone (P) levels would be added to the monitoring once the E_2 level increased above 40 pg/ml. Attaining a level of 100 pg/ml would initiate monitoring ovarian follicular size by pelvic sonography to the evaluation process.

The frequency of monitoring would increase to every other day when serum E_2 levels were between 40 and 100 pg/ml and to every day when the E_2 reached 100 pg/ml. A follicle was deemed mature if an average diameter of at least 17 mm was attained^{5,6} and if the serum E_2 level was at least 200 pg/ml per mature sized follicle^{7,8}. The patient would receive 10000 IU human chorionic gonadotropin (hCG) if at least one mature follicle was attained. If two mature follicles seemed likely then hCG would be withheld until a serum E_2 level of 400 pg/ml occurred. However, since sometimes 'follicles' appear on ultrasound that are 'empty' the hCG would be given if the serum P level approached 2 ng/ml despite two follicles seen sonographically.

A repeat pelvic sonogram was performed 48–72 h following the hCG to check for the release of the ovum^{9–11}. Following the demonstration of ovum release, the women were placed on natural progesterone vaginal suppositories beginning at 25 mg twice daily and the dosage adjusted as previously described⁷ to lower the incidence of the theoretical increased risk of spontaneous abortion related to luteal phase insufficiency that these patients may have^{12,13}. Therapy was discontinued if the patient failed to produce a mature follicle within four cycles. If the patient did not have a previous laparoscopy prior to starting therapy they were offered this procedure if they produced a mature follicle at least one time following the EE–hMG technique.

The possibility of autoimmune endocrine disease was assessed by measuring

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a fasting 08:00 serum cortisol, glucose, calcium, thyroxine, tri-iodothyronine uptake, thyroid-stimulating hormone, anti-nuclear antibody levels, and anti-thyroglobulin antibodies. Ovarian antibodies were not performed nor were ovarian biopsies. A karyotype was obtained on 36 patients.

RESULTS

A total of three patients were not able to tolerate the EE and thus this left 43 patients with ovarian failure to be treated with the EE-hMG technique. The results of this therapy are seen in Table 1.

There were no fetal anomalies in any of the six live births. The cause of death in the stillbirth at 34 weeks was attributed to a nuchal cord. None of the abortuses were able to be examined for anomalies or to evaluate chromosome analysis. None of the pregnant patients wanted to have chorionic villus sampling or amniocentesis including one woman aged 37 years (who had the stillbirth) and one woman aged 41 years.

Three of the women were found to have tubal occlusion bilaterally. Only one woman agreed to a tuboplasty. She became pregnant with the EE-hMG therapy and she did not abort. There were no ectopic pregnancies.

Five of the 43 patients were Turner variants (45 X mosaics) whereas two patients had Turner's syndrome (45 X). No patient was found to have adrenal insufficiency, type 1 diabetes, or hypocalcemia, but four had hypothyroidism seemingly related to Hashimoto's disease.

The age distribution of the 43 patients was as follows: four over 40; six between 35 and 39; 19 between 30 and 34; 14 under 30. The six women delivering babies were distributed as follows: one over 40 years, none in the 35-39-year-olds, three in the 30-34-year-olds, two under 30 years. The woman with the stillbirth was aged 37 years.

DISCUSSION

The fact that each patient in the study failed to ovulate when challenged with hMG alone but over half achieved ovulation with hMG when high doses of estrogen were simultaneously given, helps to support the concept

Table 1 Patients with ovarian failure treated with high-dose estrogen suppression of endogenous gonadotropins followed by gonadotropin stimulation therapy with hMG ($n = 43$)

Ovulating	
at least once	24 (56%)
more than once	17 (40%)
Pregnant	13 (30%)
Spontaneous abortions	6 (14%)
Delivering live infants	6 (14%)
Stillbirths	1 (2%)
Premature births	2 (5%)

of the need to suppress gonadotropins to allow restoration of receptors to LH and FSH that had been previously down-regulated. However, since spontaneous ovulations have been reported in some patients with a diagnosis of ovarian failure^{14,15}, the possibility exists that the ovulations were coincidental to, rather than directly caused by, the EE-hMG therapy. The possibility also exists that the EE alone would have been sufficient to initiate ovulation since some pregnancies have been recorded during estrogen-progesterone therapy¹⁶⁻¹⁸. However, the likelihood that gonadotropin therapy alone would have been effective is unlikely in view of previous failures with this therapy and the fact that no pregnancies are recorded directly related to conceiving on a gonadotropin stimulated cycle (just one report of conception 3 months after one cycle of gonadotropin therapy)¹⁹.

Aiman and Smentek summarized data on 14 pregnancies recorded in patients with ovarian failure including two of their own cases²⁰. They estimated that 129 000 women have premature ovarian failure and thus the fact that only 14 pregnancies had been reported between 1964 and 1984, leads to the probability of pregnancy being less than one per 9200. Our data using the EE-hMG therapy were associated with 13 pregnancies in 43 cases (30%) and for this reason we believe that the data supports an active role of this therapy in ovulation induction and subsequent pregnancies. Further support of the concept that the estrogen itself is not intrinsic to the success of therapy directly, but merely is able to suppress gonadotropins, is provided by a recent study demonstrating ovulation induction four times in a row following the lowering of serum LH and FSH with a gonadotropin releasing hormone (GnRH) agonist, leuprolide acetate, followed by hMG stimulation in a woman with ovarian failure who previously failed to ovulate with hMG therapy alone²¹. In fact, successful ovulation occurred three times with leuprolide acetate therapy alone in this 41-year-old woman.

The etiology for the high incidence of spontaneous abortions in this series is not known. Though the possibility exists that the high-dose estrogen induces an abnormal endometrium or interferes with progesterone receptors, this explanation seems less likely in view of the fact that no such increased abortion occurrence was reported in women achieving pregnancies with a very similar EE-hMG treatment for cervical factor²². We speculate a chromosomal etiology, e.g. trisomies, hypothesizing that the elevated gonadotropins or decreased inhibin levels may increase the occurrence of non-dysjunction of the chromosomes. Unfortunately, we do not have evidence to support this hypothesis since we failed to obtain chorionic villus samples or amniocentesis data in those patients going on to abort nor were we able to determine the karyotypes of those aborted fetuses.

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