

Ovulation-induction in women with ovarian failure with high-dose estrogen and gonadotropin therapy

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ABSTRACT

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. (Nakano et al, 1978) and (Jewelewicz and Schwartz, 1986). 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 resistance. (Catt et al, 1979). 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). (Check and Chase, 1984). 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 were 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 was under 20 pg/ml.

Inclusion in the study required the patient to first fail to increase her serum estradiol (E2) level over 40 pg/ml despite a total of 4500 IU of hMG. Each patient was then treated with 50 micrograms of ethinyl-estradiol (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 micrograms 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 micrograms if there was inadequate gonadotropin suppression and re-evaluation occurred 5 days later. The maximum EE dosage used was 100 micrograms 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 estradiol (E2) was under 40 pg/ml. The patient would then be re-evaluated by the serum E2 level within at least another 5 days and the dosage raised to 300 IU in 2 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 E2 over 40 ng/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-evaluate the serum E2 and depending on the rapidity of rise of the E2 the dosage maintained or increased. Serum progesterone (P) levels would be added to the monitoring once the E2 level increased above 40. 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 E2 levels were between 40 and 100 pg/ml and to every day when the E2 reached 100 pg/ml. A

follicle was deemed mature if an average diameter of at least 17 mm was attained (Hackeloer, 1978) and (Check, Goldberg et al, 1984) and if the serum E2 level was at least 200 pg/ml per mature sized follicle. (Check, Nowroozi, et al, 1987) and (Check, Chase, Nowroozi, et al, 1987). The patient would receive 10,000 IU human chorionic gonadotropin (hCG) if at least one mature follicle was attained. If 2 mature follicles seemed likely then hCG would be withheld until a serum E2 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 1 ng/ml despite 2 follicles seen sonographically.

A repeat pelvic sonogram was performed 48-72 hours following the hCG to check for the release of the ovum. (Coulam et al, 1982), (Kerin et al, 1983) and (Check, Chase, Adelson et al, 1986). 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 described (Check, Chase, Nowroozi et al, 1987) to lower the incidence of the theoretical increased risk of spontaneous abortion related to luteal phase insufficiency that these patients may have. (Check, Wu, Adelson, 1985) and (Check, Chase, Wu et al, 1987) Therapy was discontinued if the patient failed to produce a mature follicle within 4 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 a fasting 8 A.M. 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 3 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.

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 x1	# Ovulating More Than x1	# Preg.	# Spont. Abortions
24 (56%)	17 (40%)	13 (30%)	6 (14%)
# Delivering Live Infants	# Stillbirths	# Premature Births	
6 (14%)	1 (2%)	2 (5%)	

There were no fetal anomalies in any of the 6 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 age 37 (who had the stillbirth) and one woman age 41.

Three of the women were found to have tubal occlusion bilaterally. Only 1 woman agreed to a tuboplasty and 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 2 patients had Turner's syndrome (45 X). No patient was found to have adrenal insufficiency, type 1 diabetes, or hypocalcemia, but 4 had hypothyroidism seemingly related to Hashimoto's disease.

The age distribution of the 43 patients was as follows: 4 over 40; 6 between 35 and 39; 19 between 30 and 34; 14 under 30. The 6 women delivering babies distributed as follows: over 40-1; 35-39-0; 30-34-3; under 30-2. The woman with the stillbirth was age 36. The abortions were as follows: over 40-1; 35-39-1; 30-34-2; under 30-2.

DISCUSSION

The fact that each patient in the study failed to ovulate when challenged with hMG alone but now over-achieving an ovulation with hMG when high doses of estrogen were simultaneously given helps support the concept 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 (Szlachter et al, 1979) and (Wright and Jacobs, 1979) 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-progestogen therapy. (Polansky and De Papp, 1976), (Shangold et al, 1977) and (Starup et al, 1978). 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 1 report of conception 3 months after 1 cycle of gonadotropin therapy). (Johnson and Peterson, 1979).

Aiman and Smentek summarized data on 14 pregnancies recorded in patients with ovarian failure including 2 of their own cases. (Aiman and Smentek, 1985). They estimated that 129,000 women have premature ovarian failure and thus the fact that only 14 pregnancies had been reported between 1964-1984, the probability of pregnancy must be less than one per 9200. Our data using the EE-hMG therapy was associated with 13

pregnancies in 43 cases (30%) and for this reason we believe 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 by its ability to suppress gonadotropins is provided by a recent study demonstrating ovulation induction 4 times 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 alone. (Check, Wu and Check, 1988). In fact 3 times successful ovulation occurred with just 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 does exist, 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 factor. (Check, Wu, Dieterich et al, 1986). We speculate a chromosomal etiology, e.g. trisomies, hypothesizing that the elevated gonadotropins or decreased inhibin levels may increase the occurrence of non-disjunction of the chromosomes. Unfortunately, we do not have evidence to support this hypothesis since we failed to obtain CVS 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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