

**HIGH-DOSE ESTROGEN TO PREVENT PREMATURE  
SPONTANEOUS OVULATION DURING HMG THERAPY:  
TWO CASE REPORTS**

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Abstract

There is a significant dichotomy between the rates of successful ovulation induction by human menopausal gonadotropins and subsequent pregnancies. One of the factors responsible for this discrepancy may be spontaneous ovum release before complete follicular maturation has been achieved. Two cases are described where premature release of the ova was detected by pelvic sonography. These women had failed to conceive despite multiple HMG treatment cycles. By employing high-dose estrogen concomitantly with HMG complete follicular maturation was accomplished and ovum release occurred after human chorionic gonadotropin injection. These women became pregnant quickly when this new technique was employed. Pelvic ultrasound allows the determination as to when to stop HMG and give HCG since serum estradiols would be unreliable since exogenous estrogen is given.

Introduction

Human menopausal gonadotropin (HMG) therapy for anovulation is a very potent and effective therapy for ovulation defects. Various reports indicate a wide range of successful ovulatory and subsequent fertility rates. Thompson's cumulative report of

HMG data from almost 100 investigators, indicate that 75% of individuals ovulated with approximately 25% becoming pregnant.<sup>1</sup> Other contributory factors, e.g. tubal or male factor, may explain the differences from the apparent ovulation rate and fertility rate in some instances. However, in most cases, while no apparent problem other than anovulation can be detected, successful pregnancies are not achieved despite multiple treatment cycles.

We report two cases where pelvic ultrasound detected premature release of the ovum prior to human chorionic gonadotropin (HCG) injection despite multiple HMG-treated cycles with seemingly good ovulations. Successful pregnancies were achieved by employing high-dose estrogen therapy along with the HMG in order to keep pituitary gonadotropins suppressed.

#### Case Reports

##### Case #1

A 33 year old infertile woman returned for medical therapy in order to achieve her second pregnancy. Prior to her first pregnancy, she was treated for an ovulation defect with clomiphene 100 mg on her fifth and sixth day of menstrual cycle and 150 mg on days seven to nine. She was also treated with five mg conjugated estrogens days ten to seventeen of her cycle. She conceived on her second cycle.

When the baby was six months old, the patient returned for fertility therapy. She was still not ovulating as evidenced by amenorrhea and monophasic basal body temperature (BBT) charts. Her estrogen level was assessed as good by her vaginal cytology and her moderate menstrual flow following progesterone withdrawal. She had a typical gonadotropin pattern of polycystic ovarian syndrome with a

serum LH of 28 MIU/ml (normals 2-20 MIU/ml) and a serum FSH of 3.4 MIU/ml (normals 2-8 MIU/ml). This time, however, she failed to ovulate on clomiphene citrate therapy despite 150 mg clomiphene for five days with five mg prednisone each evening. She was then changed to HMG.

For the next three cycles, the patient's HMG therapy was monitored by the clinical appearance of her cervical mucus, vaginal cytology and rapid serum estradiol levels. In all three cycles, spontaneous ovulation occurred without HCG as manifested by a rise in the BBT and regression of cervical mucus with estradiol levels in each respective cycle the day before of 213, 290, and 510 pg/ml. In our experience our assay resulted in pregnancies more frequently when levels between 800-1200 pg/ml are achieved. The patient had a twelve day temperature elevation despite the use of progesterone supplementation (50 mg/day beginning the third day of the consecutive temperature rise).

The monitoring of the HMG therapy was then switched to ultrasound evaluation of follicle size.<sup>2</sup> Our objectives were to reach a minimum dominant follicle size of 20 mm, at which point HMG would be stopped and 10,000 units of HCG would be given. However, in nine of ten subsequent treatment cycles, spontaneous ovulation occurred when the maximum follicle size was only 17 mm, with the majority of cysts measuring 15 mm. In one cycle, a 20 mm dominant cyst was achieved and 10,000 units HCG was given but no pregnancy was achieved. The patient was placed on five mg of conjugated estrogens beginning on her fifth day of her cycle in conjunction with HMG. In the first cycle on this regimen she was able to form a dominant follicle in the left ovary of 35 x 26 mm and one in the right of 11 x 17 mm.

HCG (10,000 units) was given and she became pregnant but had an early first trimester abortion (24 days from conception). On her second HMG-estrogen treatment cycle the patient developed a 22 mm diameter follicle in the right ovary and an 18 mm follicle in the left ovary. HCG was given and a pregnancy was again achieved. The patient has successfully completed her first trimester.

Case #2

A 31 year old woman presented with an eight year primary infertility history. The couple's problem involved multiple factors:

- 1) male factor with baseline semen ranging from  $8 \times 10^6$ /cc to  $20 \times 10^6$ /cc
- 2) a luteal phase defect with the serum progesterone at mid-luteal phase averaging 1038 ng/100 ml from two cycles. However, an endometrial biopsy taken in the late luteal phase dated five days early. Her serum LH was 18 MIU/ml (normals 2-20 MIU/ml) and serum FSH was 5.4 (normals 2-8 MIU/ml).
- 3) A cervical factor
- 4) Congenital absence of the left fallopian tube.

The male factor was treated with Bromocryptine (2.5 mg daily) and split ejaculate insemination. The spermogram improved to a normal level averaging  $38 \times 10^6$ /cc, 70% motility and grade 3 of 4 quality in the first portion of the ejaculate. The luteal phase was treated with progesterone suppositories 25 mg twice per day from the third day of the temperature rise on the basal body temperature chart (BBT) to the menses. The cervical factor was treated from day five to the rise in the BBT with diethylstilbestrol 0.1 mg and tetracycline 250 mg four times/day. The combined treatment of both male and cervical factor resulted in an average of three sperm per high powered field with good linear progressive motion in the mucus two hours after the insemination of the better portion of the split ejaculate.

The patient failed to conceive despite therapy for one year with the above treatment regimes. The patient was empirically started on clomiphene citrate 50 mg days five to nine of menstrual cycle. However, this adversely effected the cervical mucus which remained poor despite supplemental conjugated estrogens. She was then empirically treated with Bromocryptine (2.5 mg daily) though her prolactin was normal at 12.3 ng/100 ml.<sup>3</sup> All other therapy for male factor and cervical factor and luteal phase defect were maintained. The patient still failed to conceive after therapy for another year during which time pelvic ultrasound for follicle size was performed at mid-cycle and in three cycles she never reached a dominant follicle size greater than 15 mm in diameter.

The patient was then started on HMG therapy. In five of the next six cycles, she failed to achieve an 18 mm follicle on ultrasound evaluation before spontaneous disappearance of the follicle suggesting premature ovum release. In one cycle, when a 20 x 18 mm dominant follicle was attained, the patient had good cervical mucus at the 15 x 13 mm cyst size but poor quality mucus at the later stage. This suggested the possibility of luteinization of the follicle without rupture of the ovum.

The patient was placed on 5 mg conjugated estrogens by mouth beginning on day five of her cycle along with HMG intramuscularly. During the first cycle, she had follicular cysts on the right ovary of 11 x 16 mm and 15 x 16 mm and on the left of 25 x 24 mm. Unfortunately, the left fallopian tube was absent. On her second HMG-estrogen cycle, the HMG-estrogen regime allowed the development of a 21 x 23 mm follicle in the right ovary. HCG (10,000 units) was given and the patient successfully conceived.

### Discussion

Pelvic ultrasonography used during HMG-treated cycles in these two cases suggests that one of the reasons for the dichotomy between apparent successful ovulation induction and subsequent pregnancy may be the release of the ovum before complete follicular maturation. The purpose of the high dose estrogen in these cases is to suppress the LH surge and thus inhibiting ovum release. Pelvic ultrasound indicated when the follicles had reached a mature stage and subsequent ovum release is then accomplished by injecting HCG.

Thus, in cases where there has been a failure to achieve a pregnancy with an adequate number of treatment cycles with HMG and no apparent explanation for the lack of success, one should look for possible release of an ovum from an immature follicle. This would especially apply to those cases where spontaneous ovulation had occurred prior to HCG injection. The use of five mg conjugated estrogens given concomitantly with the HMG can adequately suppress ( the pituitary gonadotropins thus allowing development of mature follicles, as determined by ultrasound, before their release with HCG.

In our experience we rarely ever see spontaneous ovulation without HCG in the hypogonadotropic hypogonadism cases treated with HMG. However, we find spontaneous ovulation in HMG treated patients without HCG not uncommon when endogenous baseline estrogen levels are good. We hypothesized that this may somehow be related to baseline high LH levels. For this reason high doses of estrogen were employed concomitantly with the HMG in order to cause suppression of pituitary gonadotropins via its negative feedback effects.

Without concomitant use of estrogen there were 13 out of 15 HMG-treated cycles documented where spontaneous ovum release occurred

prior to appropriate follicular maturation. In contrast when high-dose estrogen was employed, in 4 out of 4 cycles the follicle did reach a minimum 18 mm size and pregnancies were achieved in 3 of 4 cycles.

Case I had 13 treatment failures with HMG and case II had 6 prior to concomitant treatment with high dose estrogen. One possible explanation for these failures is that spontaneous ovulation occurred prior to administration of HCG. By ultrasound monitoring it appeared that spontaneous release of the ovum occurred prior to complete follicular maturation.

Most often HMG is used in patients with hypogonadotropic hypogonadism and estrogen deficiency. However it is also employed in patients who have failed to conceive with clomiphene therapy. In both cases there was a good level of estrogen production as evidenced by vaginal cytology and progesterone withdrawal bleeding. In both cases LH was higher than normal. However case I failed to ovulate despite 150 mg clomiphene x 5 days and in case II higher doses of clomiphene could not be tried because of the complication of poor quality cervical mucus.

These 2 cases suggest the possibility that one cause of HMG therapy failure is spontaneous ovum release prior to adequate follicular maturation. At least in these cases this problem seemed to be corrected by adding high-dose estrogen to the treatment regime. The exact mechanism of its action is not known for sure but may be related to suppression of endogenous LH.

#### References

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