

Serum Estradiols Versus Pelvic Sonography in Monitoring HMG Therapy

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ABSTRACT: Therapy with human menopausal gonadotropin (HMG) conventionally has been monitored by estrogen measurements. Pelvic sonography may offer a more accurate method of monitoring HMG therapy. In this study 67 anovulatory patients were treated with HMG until at least one follicle had a diameter of 17 mm. The serum estradiol level was noted at the time a mature follicle was achieved. There was a correlation between the ultrasound data and the serum estradiol range in 57% of the cases. However, in 24% it was necessary to push the estradiol level above the allowable maximum of 2000 pg/mL. Twenty percent of the patients attained a 17-mm follicle before reaching the minimum required estradiol level of 500 pg/mL. Sonographic monitoring should improve the efficacy of HMG therapy.

INTRODUCTION

THE CONVENTIONAL METHOD OF monitoring human menopausal gonadotropin (HMG) therapy has been through the measurement of plasma estradiols^{1,2} or urinary estrogen.³ Some recent studies have demonstrated the efficacy of using pelvic ultrasound to monitor HMG therapy.^{4,5}

In the study by O'Herlihy et al⁵ of 26 anovulatory patients, the decision for continuing or stopping HMG and adding human chorionic gonadotropins (HCG) was based on urinary estrogen measurements. They concluded that ultrasound was superior to estrogen monitoring in predicting hyperstimulation syndrome and in counting of preovulatory follicles. Furthermore, a reduced fertility rate may be present, since those patients with multiple follicles may not actually be ovulating when the HMG is monitored by estrogen measurement, each follicle in such a case contributing to the total estrogen and thus leading to the giving of the HCG prior to the maturation of any follicle. In the study, the conception rate was higher (11/28)

when a single ovulation was induced than when a multiple ovulation resulted (2/16). The study of Cabau and Bessis⁴ also concluded that pelvic sonography predicted ovulation better than did serum estradiol measurement.

We initiated a larger study of 67 patients to evaluate the efficacy of pelvic sonography in monitoring HMG (Pergonal®) therapy. However, in contrast to O'Herlihy's study, in which therapeutic decisions were based on the estrogen measurement with attention drawn to the ultrasound appearance at that time, our therapeutic decisions were based solely on the ultrasound appearance and the corresponding plasma estradiols were noted.

MATERIALS AND METHODS

Sixty-seven anovulatory patients were included in the study. They either had hypogonadotropic hypogonadism and were estrogen-deficient (22 patients), or were estrogenic but failed to ovulate with the aid of clomiphene citrate (45 patients). They also

had a minimum of 1 year of infertility. A laparoscopic examination with normal findings was required of each patient, as well as a semen specimen of the husband with a minimum of 30×10^6 spermatozoa/mL with 70% actively motile.

HMG was started on day 5 at 75 IU/day for 3 days, then increased to 150 IU/day. The average patient required 18 ampules of HMG and was treated for 10 days. Pelvic sonography was first performed on day 10. Each time an ultrasound was performed, a serum estradiol sample was drawn, and vaginal cytology and cervical mucus were assessed. The interval for the following evaluation was based on the results of the initial studies on day 10, but would be a maximum of 3 days later. If no further increase in follicular growth was noted, the HMG was increased to 225 IU/day.

Previous studies have shown that the ideal size for the follicle lies between 17 and 25 mm. Once at least one follicle had a diameter of 17 mm, HMG was stopped and 10,000 IU HCG was given. Whenever possible the interval from the last HMG injection to the injection of HCG was about 36 hours.

A follow-up ultrasound examination was performed 3 days after HCG administration. If there was evidence of release of the ovum (a shrinkage of at least 5 mm in follicle size and possibly fluid in the cul-de-sac), progesterone suppositories, 50 mg/day, were started. The progesterone supplementation was given in light of a study (unpublished) in which we have demonstrated a decreased incidence of spontaneous abortion in pregnancies achieved with HMG. All results were tabulated from the first HMG cycle in these 67 patients.

RESULTS

All 67 patients formed at least one follicle of 17 mm diameter. Four patients did not show evidence of the release of the ovum by ultrasound criteria. In our laboratory, the best results had been obtained previously by discontinuing HMG and giving HCG when the plasma estradiol level was between 500 and 1500 pg/mL. If the level of estradiol exceeded 2000 pg/mL, no HCG would be given.

Based on the above normal range for estradiol, we found that the plasma estrogen level correlated with pelvic ultrasound in 38 of 67 cases (56.7%). However, in 16 cases (23.9%) estradiol greater than 2000 pg/mL was needed to achieve one follicle of 17 mm diameter. A normal-sized follicle was attained in 14 cases (20.1%) with the estradiol level below 500 pg/mL.

Twenty-six patients (39%) conceived on this first cy-

cle of treatment. Two patients (both pregnant) had mild hyperstimulation syndrome (abdominal distention, multicystic 8–10-cm ovaries, but no anasarca). Five patients had multiple births (two sets of triplets, two sets of twins and one set of quadruplets).

DISCUSSION

The present study was designed differently from O'Herlihy's⁵ in that our patients were monitored predominantly by pelvic ultrasound and concomitant estradiol measurements were obtained to see if the correct decision would have been made by assessing the estrogen level alone. In contrast, their study based clinical decisions on urinary estrogen values, and the ovarian follicles as determined by ultrasound were merely noted at the time of the decision. Despite the difference in experimental design, both studies concluded that pelvic sonography was superior to estrogen monitoring of HMG therapy.

Pelvic ultrasound and estradiol values did correspond in 57% of cases; however, in 24% no pregnancies would have been achieved, since in order to obtain one follicle of 17-mm size, it was necessary to "push" the serum estradiol over 2000 pg/mL. This level, prior to ultrasound, had previously been considered the absolute cut-off point, the cycle then being cancelled and no HCG given. In all of the cases where the high estradiol was needed, there were several follicles developing in similar stages. Unfortunately, it was difficult not to get several follicles of fertilizable size in order to get one to a minimum 17 mm diameter. Four of the five women with multiple births and both women with mild hyperstimulation were in this group. Thus O'Herlihy et al suggested that one cause of failure to respond to HMG is that by giving HCG with a good estrogen level one may have multiple follicles all contributing to the total serum or urinary estrogen level, not one follicle, however, being in the fertilizable range. We showed that this group may achieve pregnancies by increasing HMG until at least one follicle is 17 mm while ignoring the estrogen measurements. However, this group is at greater risk for multiple births or hyperstimulation syndrome.

In contrast to the above case, 20% of the patients were found to have a mature follicle of 17 mm before the minimum accepted serum estradiol value of 500 pg/mL had been reached; thus, this group would be at greater risk for multiple births if HMG is continued to bring estradiol into the normal range.

O'Herlihy et al⁵ evaluated 55 cycles in 26 patients whereas we evaluated 67 cycles in 67 patients. All 67

patients in our study ovulated, whereas 11 of 55 cycles in their study were anovulatory. The anovulation was attributed to either insufficient HCG dosage or withholding HCG because of biochemical evidence of hyperstimulation. Our lack of any anovulatory cycles, in contrast, may be partially explained by our employing 10,000 units of HCG and that in none of our cycles was HCG *not* given. Ovulation was conventionally defined as a 14-day rise in the basal temperature and a midluteal phase serum progesterone level over 10 ng/mL. However, in four patients there was evidence of an unruptured follicle.

Thirteen patients achieved a pregnancy in the 55 treatment cycles in the study by O'Herlihy et al (a rate of 24%). A pregnancy was achieved in 26 of 67 patients (39%) on the first treatment cycle in our study; however, if we eliminate the O'Herlihy group's anovulatory cycles, then 13 of 44 patients achieved a pregnancy (29.5%). Previously, of a group of 30 patients in whom we monitored HMG therapy exclusively by serum estradiols, seven achieved a pregnancy on their first cycle (23%). When they compared the single ovulation group with the multiple ovulation group, the conception rates were 39% v 12.5%, respectively. In comparison with our data, we found the opposite, that is, a higher fertility rate in the multiple ovulation group v the single ovulation group. Eight of 24 (33%) single ovulators achieved a pregnancy on the first cycle, whereas 18 of 43 (42%) patients with multiple mature follicles became pregnant. This large discrepancy is not surprising, since O'Herlihy et al monitored the HMG by estrogen levels; and thus, because of the combined estrogen from a number of immature follicles, the appropriate estrogen level would be reached without any one being of normal size. We, in turn, monitored by ultrasound, and because of the greater number of mature follicles, the better were the chances of a pregnancy on a given cycle—but unfortunately the risks of multiple births and hyperstimulation syndrome were also greater.

Thus, monitoring with ultrasound will help improve the efficacy of HMG therapy by ensuring that a follicle is of appropriate size before HCG is given. In our study, five of 26 pregnant women (19%) had multiple births, including one set of quadruplets. This incidence is similar to the incidence seen in HMG pregnancies monitored by conventional means, but triplets and quadruplets were increased. However, these all occurred in women with multiple follicles who could have prevented this from occurring by refusing the HCG injection. Indeed, the risks of multiple gestations and hyperstimulation must be emphasized to the pa-

tient, who perhaps can be convinced to cancel the cycle with multiple follicles in the hope of modifying the HMG regimen for the following cycle to produce a lesser number of follicles.

We feel that ultrasound improves the efficacy and safety of HMG therapy, since the conception rate was almost twice as high when we used ultrasound monitoring as compared with when we used serum estradiol monitoring. Nevertheless, there are still many areas for potential pitfalls. We based the 17–25-mm follicular size on data presented by Brown et al,³ Cabau and Bessis,⁴ O'Herlihy et al^{6,7} and others, but perhaps for some patients smaller follicles or larger follicles may be appropriate. Another caveat is that seeing an appropriate-sized follicle does not necessarily ensure an appropriate ovum inside. Finally, in monitoring follicular growth, the possibility exists of missing the already released dominant follicle and stimulating other follicles even after progesterone production has been initiated by the corpus luteum.

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