

Improvement of Cervical Factor by High-Dose Estrogen and Human Menopausal Gonadotropin Therapy With Ultrasound Monitoring

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Conventional treatment of the cervical factor has proved unsuccessful, with fertility rates under 30% usually quoted. Low-dose estrogen has been one of the main therapies but carries the complication of ovulation interference. It is hypothesized that higher doses of estrogen would improve mucus but would have an even greater adverse effect on ovulation. However, the latter could be obviated by concomitant use of human menopausal gonadotropin (hMG). The hMG would then be monitored by pelvic ultrasound because the ingested estrogen would interfere with estrogen assays. Eighty-two percent of 34 infertile women with no motile sperm on baseline postcoital tests improved their levels after therapy with this high-dose estrogen hMG technique. To date, 56% of these women for whom therapy had previously failed have conceived. Nevertheless, simpler and less expensive techniques should be used initially. (*Obstet Gynecol* 63:179, 1984)

The treatment of the cervical factor has been unsuccessful in the past, with pregnancy rates under 30% usually quoted.¹ Therapy has included low-dose estrogen, baking soda douche, and cryosurgery. Other methods include antibiotics,² donor cervical mucus,³ condom therapy,⁴ high-dose glucocorticoids,⁵ and guaifenesin.⁶ Emphasis has also been placed on improving the sperm concomitantly with the mucus.⁷

If low-dose estrogen might stimulate improved cervical mucus, it would seem likely that higher-dose estrogen could be even more effective. However, one main complication of low-dose estrogen is interference with ovulation, and high-dose estrogen would suppress pituitary gonadotropins in the majority of cases. A technique was devised whereby the high-dose estrogen would stimulate the mucus glands while the

ovarian follicles could be directly stimulated with exogenous gonadotropins (human menopausal gonadotropin).

The authors reported the first two successful cases using high-dose estrogen and human menopausal gonadotropin (hMG) in 1980.⁸ The problem, though, was that the estrogen used in the therapy interfered with monitoring the dosage of hMG by serum estradiol levels. Therefore, an educated guess was taken as to when to cease the hMG and begin treatment with human chorionic gonadotropin (hCG). Thus the patient would be at a higher risk for failure to induce ovulation, multiple births, or hyperstimulation syndrome.

Recently, techniques of determining follicular maturation using ultrasound have been described.⁹ These techniques have also been used for monitoring hMG therapy.^{10,11} Recently reported were two cases with improvement of the high-dose estrogen/hMG therapy by ultrasound monitoring.¹² The present report describes the results of this technique in a more extensive study of 34 patients with a cervical factor problem not correctable by any of the other conventional techniques.

Materials and Methods

Thirty-four patients were selected whose only fertility problem was determined to be the cervical factor (semen analysis indicating at least 40×10^6 spermatozoa per cubic centimeter, 2 cm³ volume, 70% motility, and grade 3 of 4 quality, and 80% normal morphology; tubal patency established by hysterosalpingogram or laparoscopy; good ovulation as evidenced by a serum progesterone over 10 ng per milliliter 1 week before menses). Furthermore, another qualification was that

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the mucus have poor quality (as judged by spinnbarkeit, cellularity, and amount). Other requirements for selection were that the patient fail, in two consecutive cycles, to have any sperm survival two hours after intercourse before the rise in the basal temperature even after treatment with guaifenesin (the expectorant in many cough syrups), low-dose estrogen, baking soda douche, and/or antibiotics. Appropriate timing of the test was confirmed by ultrasound.

A minimum of 2.5 mg conjugated estrogens per day was started on day 5 of the cycle in conjunction with 75 IU of hMG for three days, after which the dosage was increased to 150 IU of hMG. Serial ultrasound was started on day 10 of the cycle and repeated at least every other day. Postcoital tests were performed at the same time. The estrogen was doubled to 5 mg if a 15-mm follicle was achieved without at least some sperm on postcoital testing with linear progressive motion. The 2.5-mg dosage would be continued if there were motile sperm seen by day 10 or when a 15-mm follicle was achieved. The postcoital test was performed two to four hours after intercourse.

The hMG and estrogen would be continued until at least one follicle was a minimum of 18 mm in diameter. Attempts to avoid a follicle greater than 25 mm were made. If good follicle and good sperm survival occurred, 10,000 U of hCG were given. If the judgement of the postcoital test was only fair and the follicle under 20 mm, then another day of estrogen without hMG was given before the hCG injection.

A maximum of six treatment cycles and a minimum of two were also required for this study. The postcoital test was judged as good (if there were at least three sperm per high-powered field with grade 3/4 or better quality motion), fair (some sperm present with linear progressive motion but less than three per field or quality 3- or less), and poor (no sperm moving or motile in place only).

Results

Twenty-eight of 34 women (82%) showed good postcoital tests after treatment. The remaining six patients showed fair postcoital tests. Thus all patients showed at least some improvement because initially there were no motile sperm.

Thus far, 19 women have conceived (56%) in an average of 3.2 months. In the 15 patients who have not conceived as yet, there has been an average of 4.5 treatment cycles. All pregnancies occurred in the group showing good improvement in postcoital testing.

In all 34 patients, there was at least one cycle where ovulation was accomplished as judged by achieving at

least one follicle of an 18-mm size and release of the ovum by ultrasound evaluation. In some cycles (9%), luteinization of the follicle occurred before an 18-mm size was achieved and in some cycles (6%) there appeared to have been an unruptured follicle.

None of the patients developed hyperstimulation syndrome. Two patients delivered triplets by cesarean section, and three patients had twins.

Discussion

A more extensive evaluation of a new technique for treating cervical factor using high-dose estrogen and human menopausal gonadotropins was undertaken. The authors published this technique only as four case reports.^{8,12} The present study showed this technique effective in improving the mucus from poor to good in 82% of the cases and a fertility rate of 56%. This is despite the fact that cervical factor has always been a difficult fertility problem to treat. Furthermore, the 34 cases were already preselected as the failures of other therapies.

One could question whether or not the hMG without the additional estrogen could have improved the mucus. Theoretically, by stimulating several follicles, one could increase endogenous estrogen, which could then improve the mucus. Human menopausal gonadotropin exclusively had been used in 11 of the patients in the present study. Not one patient improved the mucus sufficiently with hMG alone to allow any sperm motility. No patients conceived during these 11 cycles. Nine of these eleven patients after therapy with high-dose estrogen and hMG had excellent postcoital tests and six of 11 (55%) conceived. Human menopausal gonadotropin is very expensive and, considering its failure to improve the mucus greatly in these 11 patients when estrogen was subsequently added, the authors could not justify comparing hMG plus estrogen therapy to hMG alone in their private patients. Nevertheless, a randomized study comparing both forms of treatment would make a more valid scientific study. It is hoped the present study may encourage others who may be able to supply hMG for free to not only corroborate these data but to perform this more scientific study with a randomized control group receiving hMG only.

Despite the good success of the described therapy, it must be stressed that other, simpler techniques should be attempted first. One needs to consider the cost of hMG and ultrasound monitoring; the average cost of each treatment cycle was \$650.00. Though there were no episodes of hyperstimulation syndrome, the risk for this potentially serious complication always exists. Finally, there is a definite increased risk of multiple

gestation. In the present series, the rate was 26% with three sets of twins and two sets of triplets.

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