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TREATMENT OF CERVICAL FACTOR WITH COMBINED HIGH-DOSE ESTROGEN AND HUMAN MENOPAUSAL GONADOTROPINS

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The treatment of the cervical factor may include low-dose estrogen therapy, clomiphene citrate followed by high-dose estrogen, antibiotics directed against *Ureaplasma* (T-mycoplasma),¹ cryosurgery of the cervix, donor cervical mucus,² and condom therapy,³ and this subject has been reviewed by Blasco.⁴ Despite the multitude of different treatment modalities, pregnancy rates may be under 30%.⁴

We have seen instances where either thick, tenacious mucus or very scant mucus would improve to the degree of allowing a good postcoital test following treatment with high-dose estrogen while failing to improve with low-dose estrogen therapy. Unfortunately, high-dose estrogens usually suppress ovulation. In the two cases presented, pregnancy occurred with high-dose conjugated estrogen therapy and concomitant treatment with human menopausal gonadotropins (hMG).

CASE REPORTS

Case 1. The patient presented at age 36 with 1½ years of infertility. The couple's problem was assessed to encompass an ovulation defect, cervical factor, male factor, and patency of only one tube (as demonstrated by hysterosalpingography). The idiopathic oligospermia was treated with clomiphene citrate and the count increased to over 40 million/ml. The diagnosis of anovulation was established by monophasic basal body tempera-

ture charts and a low serum progesterone level (0.9 ng/ml) 1 week before menstruation.

The patient ovulated with 100 mg of clomiphene citrate daily on days 5 to 9. At midcycle (day 16) her mucus was abundant but extremely thick and viscous (could not be aspirated with a tuberculin syringe) and was yellow-green in color. Attempts to improve the mucus with conjugated estrogens (up to 5 mg daily from days 10 to 16) failed even with adjunctive tetracycline therapy.

Clomiphene citrate was stopped and the patient was treated with diethylstilbestrol, 0.2 mg from days 5 to 16, but despite ovulation the mucus was still so thick that it could not be aspirated; examination of a sample removed with forceps revealed no motile sperm. This therapy was tried for 2 more months with insemination of the first portion of the husband's split ejaculate. However, the mucus continued to be very thick, and in the second cycle there was evidence of an inadequate corpus luteum.

The patient was then treated with 5 mg of conjugated estrogens only for 2 weeks and demonstrated excellent mucus with good spinnbarkeit, and good ferning; it was practically acellular. This time the postcoital test (mucus removed from the external os by a tuberculin syringe 2 hours after insemination) was excellent. However, ovulation did not occur.

The patient was treated for three cycles with human menopausal gonadotropins (hMG). The mucus remained thick despite bringing the rapid serum estradiol assay to 3800 pg/ml (no human chorionic gonadotropin [hCG] was given because of the poor mucus).

The patient was then treated with 5 mg of conjugated estrogens by mouth with one ampule of human menopausal gonadotropins intramuscularly

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daily beginning on day 5 of the cycle until a good postcoital test (10 sperm/high-power field with good linear progressive motion) was achieved. A total of eight ampules of hMG were used, and 10,000 units of hCG were given; however, she only had a 7-day luteal phase. In the second treatment cycle with this combined therapy, 10 ampules of hMG were administered before hCG was given. The serum progesterone level on the 7th day of the temperature rise was 29 ng/ml. She achieved pregnancy during this cycle. Ultrasound showed a single viable fetus.

Case 2. The patient presented at age 30 with 3 years of secondary infertility. Two years following delivery she had undergone cervical conization for chronic cervicitis. Her infertility problem was found to be secondary to absent cervical mucus. She had been treated by three other infertility specialists with various low-dose estrogen regimens and inseminations without success.

We first treated the patient for two cycles with donor sperm and donor mucus. She was then treated with 5 mg of conjugated estrogens, and a small amount of good-quality mucus was produced. A postcoital test revealed six sperm per high-power field with good linear progressive motion. The patient was then treated with 5 mg of conjugated estrogens plus 10 ampules of hMG and 10,000 units of hCG. She ovulated. During the next cycle, with 12 ampules of hMG and 10,000 units of hCG, she achieved pregnancy. Ultrasound showed a single viable fetus.

DISCUSSION

If low-dose estrogen therapy can improve cervical mucus in many patients with a cervical factor problem, it is only logical that high-dose estrogen treatment may improve the mucus in some women who fail to respond to a lower dose. Unfortunately, high-dose estrogen usually inhibits ovulation by suppressing hypothalamic pituitary gonadotropin function.

By concomitantly treating with hMG, which acts directly on the ovaries, ovulation can be achieved despite pituitary suppression. The problem is that the normal parameters for judging how much hMG to use (e.g., vaginal hormonal cytology,

cervical mucus, serum estradiol assay) are not applicable in these cases. The approach used, therefore, was to continue hMG until a good postcoital test was achieved. If ovulation did not occur, as judged by progesterone measurements, then a slight increase in the hMG dose was made for the next cycle.

In view of the increased risks of multiple births and hyperstimulation syndrome, this therapeutic approach should be reserved for those patients failing with all other therapy, and the patient should be fully cognizant of the increased risks. That is, since the rapid estradiol assay and cervical mucus and vaginal cytology parameters cannot be utilized appropriately because of the influence of the conjugated estrogens, a priori, it would seem that the risks of multiple births and ovarian hyperstimulation syndrome would be greater than the risk involved with hMG therapy without conjugated estrogens. We do have available a good rapid estradiol assay, but this was not utilized in these two patients because the values could not be interpreted in view of the contribution of the conjugated estrogens. In the future, it may be feasible to perform an estradiol assay while the patient is taking conjugated estrogens alone and then when she is taking hMG and conjugated estrogens together; perhaps some modification can thus be established to indicate an appropriate range of estradiol levels so that hCG can be given even when conjugated estrogens are used with hMG.

hMG plus high-dose conjugated estrogen therapy is apparently useful for infertile women with thick, hostile mucus or absent or very scant mucus, as illustrated by these two cases. Thus far these have been the only patients treated with this regimen.

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