

**THE USE OF PELVIC SONOGRAPHY AND SERUM
ESTRADIOL AND PROGESTERONE ASSAYS IN DIAGNOSIS
AND TREATMENT OF CERVICAL FACTOR**

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Abstract

Since estrogen stimulates production of cervical mucus we hypothesized that some cases with poor mucus and subsequent poor post-coital tests may be related to inadequate mid-cycle serum estradiol levels generated by some women. After evaluating a large number of women with normal endometrial biopsies we concluded that most women with normal ovulation produce mid-cycle serum estradiol levels over 200 pg/ml. We evaluated 62 consecutive women with poor post-coital tests (no sperm with linear progressive motion 6-12 hours after intercourse) and divided them into 4 groups: 1) inadequate serum estradiol (immature follicle), 2) premature luteinization, 3) pure cervical factor, and 4) controls. Significant improvement of cervical mucus was noted in all treatment groups when they were compared to the control group. The pregnancy rates in treatment groups (group 1: 73.7%, group 2: 25.0%, and group 3: 66.7%) were significantly ($p < 0.025$) higher than that of control group: 8.3%. Though we cannot be sure that therapy directed specifically for mucus in the group 1 patients could have also resulted in some pregnancies we feel the most logical approach employs an ovulation-inducing drug to cover the possibility that the immature follicle contains an ovum that is not sufficiently mature for conception.

Introduction

Estrogen stimulates cervical mucus to make it thin to allow sperm to penetrate. The peak serum estradiol (E2) occurs at mid-cycle which allows maximum sperm penetrability. Soon after

ovulation progesterone (P) increases and this makes the mucus thick.

A woman's mucus should be most appropriate immediately prior to ovulation. Most often the dominant follicle attains an average diameter of 18-24 mm, though, on occasion a follicle may be mature at 15-16 mm.¹⁻² We have determined a range in our lab of serum estradiol between 200-500 pg/ml at the time of a mature sized follicle in fertile women with normal endometrial biopsies. At that time the serum P level is under 1.5 ng/ml. We decided to evaluate 50 consecutive patients with an alleged cervical factor problem and determine as to what percentage was due to a poor functioning follicle (poor E2 level), or premature luteinization, (p increases above 1.5 ng/ml before follicle mature), or a true cervical problem.

Materials and Methods

Fifty consecutive patients with cervical factor were chosen with a minimum of 18 months of infertility. Inclusion in the study required that the patient accept the most efficacious therapy in our opinion for their problem. The suggestion for human menopausal gonadotropin (hMG) occurred in 12 cases and the patients refused therapy. Thus 62 women were needed to be evaluated to get 50 women for the study. The cervical mucus was first evaluated beginning 16 days before the expected menses. A requirement to be included in the study was that 1) no sperm with linear progressive motion was seen 6-12 hours after intercourse at mid-cycle when seeing a mature follicle of 18-24 mm in two consecutive cycles, 2) each patient had to have a serum P level over 10 ng/ml one week prior to her menses, 3) a minimum requirement

for the semen analysis was a count of 40×10^6 /cc with 70% motility, grade 3 of 4 quality, 2 cc volume. We did not require a hysterosalpingogram or laparoscopy, or hamster ova penetration test to be included in the study. In all cases the mucus had poor quality as evidenced by poor clarity, and poor spinnbarkeit. Antibody studies were not performed.

A patient was placed in group 1, subgroup A if at the time of a mature follicle of 18-24 mm the E2 level was under 200 pg/ml. E2 levels were checked daily and thereafter until P was above 1.5 ng/ml and the requirement was that at no time would E2 increase over 200 pg/ml. This group was then treated with clomiphene citrate, human menopausal gonadotropins, or bromocriptine. The decision on which ovulation-inducing drug to use was determined as follows: 1) if the prolactin level was elevated bromocriptine was employed, 2) clomiphene citrate was employed if the prolactin level was normal or if the prolactin level was elevated but either bromocriptine failed to improve the mid-cycle serum E2 or the patient had to stop bromocriptine because of side effects, 3) hMG was used if the patient failed to show improved mucus after clomiphene citrate even despite supplemental estrogen or in some cases without ever trying supplemental estrogen. Clomiphene citrate was initiated in general on day 5 of the cycle and was increased up to a maximum of 150 mg per day for 5 days in order to achieve a mature follicle. If a poor post-coital occurred with clomiphene, supplemental ethinyl estradiol was first tried beginning on day after stopping clomiphene at 20 micrograms per day and continued to follicular maturation. If the dosage was insufficient the dosage would be increased up to

100 micrograms per day. Failure to still improve the mucus would prompt a switch to hMG therapy which would be started usually on day 5 (occasionally day 3) with either 75 or 150 IU daily with increases to 300 IU daily if necessary. Monitoring of dosage was based on frequent pelvic sonography to determine follicular size and frequent measurement of rapid serum estradiol, progesterone and LH levels to help determine the need for more hMG or to use human chorionic gonadotropin (hCG), 10,000 units, to initiate release of the ova from the follicles.

A patient who attains a mature follicle with E2 over 200 pg/ml but P level exceeds 1.5 ng/ml was considered to be in group 2 with a diagnosis of premature luteinization. This group went through ovulating-inducing therapy similar to group 1.

Group 3 consisted of patients who had poor post-coital tests at the time of a mature sized follicle with an E2 over 200 pg/ml. This group was initially treated with estrogen and/or guaifenesin, and if not successful then treated with hMG-EE technique.

If despite follicle maturing drugs, further improvement for mucus was needed, then the patient was considered in subgroup B of groups 1 and 2. Thus a patient with low E2 placed on clomiphene who now required supplemental estrogen would be considered group 1, subgroup B whereas those not requiring additional estrogen were considered in group 1, subgroup A. The frequent side effect of poor cervical mucus caused by the anti-estrogen effect of clomiphene can be frequently corrected by the addition of supplemental estrogen beginning the day after stopping clomiphene.

The average age of the patients was 29.8 with a range of 21-36, and the average years of infertility was 3.6. The distribution of the 12 women who refused hMG therapy was as follows: 4 in group 1; 1 in group 2; 7 in group 3. These 12 women were treated with intrauterine insemination (IUI) with washed sperm^{3,4} and in addition clomiphene citrate was given to the 5 women in groups 1 and 2. These women were considered controls.

Results

Nineteen patients were found to be in group 1, 4 patients in group 2, and 27 patients were found to be in group 3. Eighty-eight % of the patients showed post-treatment normal post-coital tests as defined by 3-5 sperm with linear progressive motion 6-12 hours after intercourse.⁵ The number of patients conceiving within 8 months in the 3 different groups is seen in Table 1. The therapy used to achieve these pregnancies is summarized in Table 2. All three pregnancies with clomiphene were single pregnancies, whereas 3 of the 22 pregnancies with hMG were twins. Significant improvement of post-coital tests ($p < 0.005$) and pregnancy rate ($p < 0.025$) were noted in treatment groups when they were compared with the control group.

These therapies are listed out of general interest but this study was not designed to determine the relative efficacy of these different therapies, only the general category of the need for ovulation-inducing drugs versus therapy specifically aimed at treating mucus. In general guaifenesin was used as an ancillary measure with all therapies⁶ because it is inexpensive with very little side effects and does not interfere with ovulation, and in our experience is very helpful for cervical factor. The improved post-

Table I
Then Number of Conceptions According to Classification of
Etiologies for the Cervical Factor

Group	# of patients	# of patients with improved PK test	# patients conceiving
1A	11	11	9 73.7% (1)
1B	8	7	5
2A	1	1	0 25.0%
2B	3	2	1
3	27	23	18 66.7% (1)
Controls	12	0	1 8.3%

(1): Chi square analysis $p < 0.025$ when compared with control group

(2): A normal PK test considered 3-5 sperm/high powered microscope field with linear progressive motion

Legend for Table I

Group 1A- Patients with immature follicles as cause of cervical factor and treated with ovulation-inducing drugs

Group 1B- Patients with immature follicles as the cause of cervical factor and who also needed more estrogen to help the mucus

Group 2A- Patients with premature luteinization

Group 2B- Patients with premature luteinization who also needed additional estrogen to help the mucus

Group 3- Patients with mature follicles, thus pure cervical factor problems

Table II
The Therapy Used to Achieve Pregnancies in Patients with Cervical
Factor Problems

Group	Total Pregnant	hMG	cc	cc & HDE	hMG & HDE	Guaif &/or LDE	Don Muc
1A	9	7	2				
1B	5				5		
2	1			1			
3	18				10	7	1

Legend for Table II

hMG	Human menopausal gonadotropins
CC & HDE	Clomiphene citrate plus high-dose estrogen
hMG & HDE	Human menopausal gonadotropins plus high-dose estrogen ^{7,8}
Guaif &/or LDE	Guaifenesin only or guaifenesin and low dose estrogen
Don muc	Donor mucus ⁹

coital tests were always associated with improvement in mucus quality and quantity as manifested in decreased cellularity, decreased viscosity, improved spinnbarkeit, and sometimes improved volume. Only 1 of the 12 control patients treated with IUI achieved a pregnancy.

Discussion

The incidence of ovulation problems as a cause of cervical factor problems was assessed by requiring that a woman demonstrates a follicle of 18-24 mm with a serum E2 over 200 pg/ml

and a serum P under 1.5 ng/ml. We determined these values by evaluating hundreds of patient cycles in women who had normal endometrial biopsies. Nevertheless, we cannot state that ova collected from slightly smaller follicles with lower estradiols may not be able to be fertilized in an in-vitro fertilization program. Thus, in some cases it may be that the E2 levels generated by some women with mature ova are insufficient to stimulate adequate mucus quality and by stimulating more follicles a higher E2 level will be achieved and this will stimulate better mucus. To fully test the hypothesis that the ova in follicles that was associated with lower E2 levels are not fertilizable even if one could correct the mucus, it would be necessary to randomize such patients with poor post-coital test into one group where the mucus is improved and therefore the post-coital test is improved with ovulation-inducing drugs, and into another group where the mucus is improved through other means eg. low dose estrogen or guaifenesin; we are planning on performing this study.

The main point here however, is that even if the assumption that seeing an E2 level under 200 pg/ml is indicative of a poor follicle is incorrect, nevertheless the use of an ovulation-inducing drug resulted in a normal post-coital test and pregnancies in 14 of 19 cases (73.7%) and in 9 of 11 cases (81.8%) where no further therapy was needed to improve the mucus. Eight patients in Group 3 (the alleged pure cervical factor cases) of the total of 18 (44.4%) achieved a pregnancy with therapy directed toward the cervical factor only without an ovulation-inducing drug. Though using a drug eg. hMG could have possibly also improved the

cervical factor problem by raising endogenous E2 levels is certainly possible, nevertheless since this therapy is expensive and risky from the standpoint of multiple births, ovarian enlargement, etc. one would prefer therapy aimed specifically at improving mucus rather than ovulation. Nevertheless, 66.6% (22 out of 33 patients) achieving pregnancies used hMG: 12 of 14 pregnancies in the ovulation category (Group 1) (85.7%); and 10 of 18 (55.6%) of cervical factor (Group 3) problems exclusively.

Thus, by choosing a treatment regime for cervical factor based on mid-cycle E2 levels (under 200 pg/ml, then employ ovulation-inducing drugs) 66% of patients with an average infertility duration of 3.6 years achieved a pregnancy within 6 months. Furthermore, emphasis is placed on taking into consideration the possibility of P abnormalities (eg. premature luteinization) in contributing to cervical factor problems. We have seen quite frequently in our practice women with luteal phase defects (LPD) and normal post-coital tests with low mid-cycle E2 levels not conceive despite the correction of the LPD with progesterone until an ovulation-inducing drug is added. Probably at least some if not all of the women in this study with low mid-cycle E2 levels have an ovulation defect. Since treatment of these patients with an ovulation-inducing drug corrected both the mucus abnormality and raised the E2 level we feel that this is the most logical way to treat patients with cervical factor abnormalities and low mid-cycle E2 levels. Both potential abnormalities are thus corrected by this one technique and this was reflected in 73.7% of group 1 patients conceiving within 8 months.

Though anti-sperm antibody studies were not evaluated in this

study, nevertheless therapy aimed at lowering these levels especially in group 3 may have even further improved the efficacy of the treatment of the group with cervical factor problems exclusively.

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