Diagnosis and treatment of cervical mucus abnormalities

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Summary

Purpose: To present causes of cervical mucus problems leading to poor postcoital tests and options for treatment.

Methods: Presentation of mostly original research dealing with diagnosis and treatment of cervical mucus abnormalities.

Results: The simplest but least effective therapy was guaifenesin. Short-term use of ethinyl estradiol can be effective. Sometimes the ethinyl estradiol must be used for a longer time period which suppresses follicular maturation, so exogenous gonadotropin must be used to counteract suppression.

Conclusions: In contrast to the conclusions of a meta-analysis by Griffith and Grimes the author believes that performing a postcoital test is a very valuable tool in investigating infertility as long as it is performed at the appropriate time as determined by serum estradiol, progesterone, luteinizing hormone and ultrasound. Clomiphene citrate therapy is the most common etiology for abnormal postcoital tests in the modern era.

Key words: Postcoital test; Clomiphene citrate; Estrogen; Guaifenesin.

Introduction

Diagnosis of cervical factor

Estrogen stimulates cervical mucus production. As the serum estradiol (E2) level rises in the follicular phase, the mucus becomes more abundant, thin and watery and allows sperm to easily penetrate and travel through channels. Progesterone (P) inhibits cervical mucus production and renders it opaque and viscous and it is not easily penetrated by sperm. Thus mucus is at its peak quality for penetration by sperm 36 hours prior to ovulation when the serum E2 reaches the peak mid-cycle level and serum P is still suppressed. The high E2 level stimulates a positive luteinizing hormone (LH) surge which results in a drop in the serum E2 and a rise in the serum P. This causes the mucus to decrease in quality and thus the cervical mucus is far superior 36 hours prior to ovulation than at the time of ovulation. Thus, one cause of poor postcoital tests may be related to performing the test too soon before the peak serum E2 or after the LH surge [1].

Other causes may be related to an ovulatory defect where the oocyte releases from the follicle before the serum E2 reaches a level of 200 pg/ml [1]. Obviously, semen abnormalities, e.g., low volume, oligoasthenozoospermia, or antisperm antibodies can be the cause of a poor postcoital test. In fact, sometimes the postcoital test may be the referee on deciding if a male with semen parameters below WHO standards has subfertile sperm. Also a poor postcoital test may be related to mechanical factors, e.g., hypospadius, obesity, or vaginismus.

When conditions are met for proper timing and proper follicular maturation while the postcoital is being performed, and there are normal male semen parameters, and no apparent mechanical factors, the failure to find any sperm with forward motion in the mucus 6-12 hours after intercourse would be considered related to poor quality or quantity of cervical mucus.

Etiology

I have been practicing reproductive endocrinology and infertility since 1974, and for at least the first half of the 31 years of practice abnormal cervical mucus was quite commonly related to intrauterine exposure to the estrogen diethylstibesterol (DES). This effect of DES may have been the reason why one study from 1982 found the cervical factor as etiologic in 30% of infertility cases [2]. With the discontinuation of this drug in all pregnant women, this cause of cervical factor is no longer found.

Today the most common cause of abnormal quality or quantity of cervical mucus is the use of anti-estrogen drugs aimed at inducing or improving ovulatory defects, especially clomiphene citrate [4, 5]. My group found in the first

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cycle of clomiphene citrate therapy in our office, that 69% (40/58) of the women failed to show any sperm in the cervical mucus with intercourse at least eight hours before in an appropriately timed postcoital test (based on ultrasound and serum E2 and P criteria) [5]. This percentage could be somewhat higher than would occur in the general population since some of these patients may have had prior treatment in other offices with clomiphene and possibly the poor postcoital test may be why they did not conceive. In cycle 2, all 16 of the group of 18 who had had a normal postcoital test in cycle 1 and did not conceive still had sperm with progressive motion in the cervical mucus, though half had ethinyl estradiol added as follicular maturation approached because of an obvious decrease in amount and quality of the mucus [5].

For the 40 patients with poor postcoital tests 34 were given ethinyl/estradiol after the clomiphene was stopped in a dosage of either .02 or .05 mg until ovulation [5]. Only one of the six (16.7%) who did not have added supplemental estrogen showed sperm with linear progressive motion in the mucus vs 43.7% (7/16) taking .02 mg ethinyl estradiol and 55.5% (10/18) using .05 mg ethinyl estradiol [5]. There were no pregnancies achieved in cycle 1 in the 40 women who had poor postcoital tests (IUI was not performed) vs 11.1% (2/18) who demonstrated sperm with linear progressive motion.

Clomiphene citrate acts predominantly like an anti-estrogen drug by binding to and eventually depleting nuclear estrogen receptor. The blocking of estrogen effect results in a lack of estrogen suppression of follicle stimulating hormone (FSH) leading to a rise in serum FSH which in turn causes ovulation. However, it also blocks the estrogen effect on cervical mucus. Sometimes this negative effect on mucus can be negated by adding estrogen after clomiphene is stopped for the following five to nine days until ovulation is achieved. The reason for using ethinyl estradiol over other estrogen preparations is that it does not measure in the assay for E2 and thus the effect of clomiphene citrate on follicular maturation can be better determined.

There are other anti-estrogen drugs, e.g., tamoxifen, which are similar in structure to clomiphene citrate. However tamoxifen is weaker in binding to the estrogen receptor and thus has fewer adverse effects on cervical mucus. However, this class of drugs is less effective in ovulation induction and follicular maturation. More recently ovulation induction has been achieved with aromatase inhibitors, e.g., letrazole which also has fewer adverse effects on cervical mucus.

Importance of the postcoital test

It is not clear without the adverse effects of drugs on cervical mucus and the absence of in utero exposure to DES in the present population, how common's hostile cervical mucus. Shockingly a meta-analysis by Griffith and Grimes concluded that the postcoital test has poor validity as a diagnostic test for infertility and encouraged physicians to abandon the test [6]. If the definition of a poor postcoital test is considered as the absence of sperm with progressive forward motion in the cervical mucus, we found only 10% of patients conceived over six months vs 74% who did demonstrate sperm with progressive forward motion in the mucus [7]. Similarly in natural cycles there was only a 3.4% pregnancy rate per cycle when there was no motile sperm in the mucus vs 21.2% with properly timed intrauterine insemination (IUI) [7]. Thus, I strongly believe that this simple inexpensive test should still be performed even though today the frequency of abnormalities is low [8]. I certainly do not agree with Griffith and Grimes who state that $50,000 a year is wasted on this test per year [6]. Even if the cervical factor per se is not so frequent, the postcoital test is frequently helpful in determining if a somewhat subnormal semen analysis is clinically important or can be useful in detecting anti-sperm antibodies bound to sperm despite an apparent normal postcoital test [9]. Anti-sperm antibodies in the cervical mucus as a cause of the poor postcoital test is very rare [10].

For patients not taking anti-estrogen medications the most common etiology that I found is previous cervical surgery, e.g., conization. However, a poor postcoital test may detect mechanical problems, e.g., hypospadius or impotence in the male partner, or vaginismus in the female partner.

Treatment of the cervical factor

One of the simplest and cheapest treatment methods of the cervical factor is to use guaifenesin (600 mg twice daily) from day 3 to ovulation [11]. Once the follicle is mature sometimes cervical mucus can be enhanced by adding a short course of estrogen [12]. Other methods include raising the mid-cycle serum estradiol by stimulation of multiple follicles using exogenous gonadotropins [13]. Ethinyl estradiol (20-40 μg per day) can be used in the early follicular phase to the time of ovulation and low-dose gonadotropin injection can be added to compensate for suppression of endogenous gonadotropins [14].

When all other therapies fail, the cervical factor can be effectively treated with IUI which is usually performed approximately 40 hours after the LH surge [15]. Many physicians will use IUI if something as simple as guaifenesin is ineffective rather than using gonadotropin therapy. However, some couples for religious or personal reasons prefer not to do IUI. We found that as long as IUI is performed for hostile cervical mucus, that clomiphene citrate was just as effective as gonadotropins in anovulatory women for the first three treatment cycles [16].

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