Editorial Articles

The multiple uses of ethinyl estradiol for treating infertility

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Summary

Purpose: To demonstrate the usefulness of ethinyl estradiol, a drug no longer commercially produced in most countries, in treating various fertility related issues. *Methods:* Twenty to 40 micrograms of ethinyl estradiol can be started on day 2 or 3 of the cycle and combined with exogenous gonadotropin can be useful in improving hostile cervical mucus or inducing ovulation in women with hypergonadotropic amenorrhea. It can be used from the day after stopping clomiphene citrate to help negate the adverse effect of this drug on cervical mucus. *Results:* Successful pregnancies have been achieved saving the couple the expense of intrauterine insemination (IUI) or using donor oocytes. *Conclusions:* This drug can be very helpful for those physicians who treat each infertile woman on an individual basis and carefully ascertain the couple's input as to their preferences rather than a "herd" type of medicine.

Key words: Ethinyl estradiol; Postcoital test; Clomiphene citrate; Premature ovarian failure; Premature luteinization.

Introduction

Ethinyl estradiol is one of the most consumed estrogen products in the world since it is the estrogen part of almost all oral contraceptives. Ethinyl estradiol without the progestin was distributed worldwide but eventually commercial production ceased by most pharmaceutical companies. Today it is only available as a commercial product in Germany from Schering. The reason why production stopped was because of lack of use. However, it can still be compounded by pharmacies if ordered.

I have been using ethinyl estradiol for 35 years and find it a very useful tool in treating infertility and use it frequently. This editorial will expound the various clinical uses for this drug when treating an infertile couple.

Cervical factor

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 [1]. 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 [2]. 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) [2]. Thus, I strongly believe that this simple inexpensive test should still be performed even though today the frequency of abnormalities in women not taking clomiphene citrate is low (approximately 3%) [3].

The most common cause of a poor postcoital test today is the use of clomiphene citrate. 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 serum assay for 17 beta-E2 and thus the effect of clomiphene citrate on follicular maturation can be better determined. Our group found in the first cycle of clomiphene citrate therapy 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 progesterone criteria) [4].

In cycle 2, all 16 of the group of 18 who 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 [4].

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Of 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 [4]. 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 [4]. 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.

Of course one might argue why worry about whether the cervical mucus kills the sperm or not and just do intrauterine insemination (IUI). In fact a common practice among infertility specialists is to perform an IUI each month without even checking a postcoital test. Some of these infertility specialists quote the aforementioned meta-analysis stating that the postcoital test has no validity [1], with the assumption that the test has no validity. Others, including our group, do not agree and believe that the postcoital test is a valuable fertility tool [3, 5].

Rather than "waste" such a high amount of money, as mentioned, many physicians treating infertility automatically do an IUI. If we assume that a postcoital test costs $100 and it usually needs to be performed only one to two times per patient, consider the immense costs of performing an IUI every month with prices ranging from $250 to $1,000 each month, not just per patient. Even if the IUI is paid for by insurance carriers, performing this procedure monthly (especially since the majority will not need it) increases the cost of the healthcare. As mentioned above, adding ethinyl estradiol after stopping clomiphene citrate until ovulation can improve cervical mucus in a significant percentage of women taking clomiphene citrate without interfering with the measurement of estradiol. This is important in determining if the use of clomiphene citrate has allowed the development of a mature follicle.

Clomiphene citrate is frequently prescribed by general gynecologists who do not have the facilities to perform an IUI. Adding ethinyl estradiol to the clomiphene citrate is even more important for these physicians since they could be creating iatrogenic infertility by inhibiting sperm getting to the uterine cavity. It is imperative that any doctor prescribing clomiphene citrate should perform an appropriately timed postcoital test. If poor, and IUI is an option, this procedure can be performed in this cycle. However, the woman should be given the option of continuing with clomiphene citrate and IUI or switching to gonadotropin injections which do not create poor quality mucus.

A woman may for various reasons have less sensitivity to estradiol so that poor quality mucus exists despite attaining an adequate mid-cycle serum estradiol. Of course the mucus glands are being exposed over a two-week course with a gradually rising serum estradiol. Ethinyl estradiol, as mentioned, is the component of the oral contraceptive that helps suppress ovulation by inhibiting the release from the pituitary of follicle stimulating hormone (FSH). If ethinyl estradiol is started from the early follicular phase in dosages of 20 to 40 μg the mucus glands will be exposed to a pharmacologic dosage of estrogen. This can sometimes improve the quality of the mucus. However, the follicular maturation would be thwarted by the ethinyl estradiol, but this could be counteracted by the concomitant use of gonadotropin stimulation [6]. Sometimes, the ethinyl estradiol can be added later in the follicular phase which may be too late to suppress follicular maturation but could still improve mucus so exogenous FSH is not needed [7]. Alternatively a short course of low-dose FSH could be added concomitant to the use of ethinyl estratiol which if the mucus abnormality is corrected allows a better chance of monofollicular recruitment [8, 9].

Inducing ovulation in women with ovarian failure

In 1984 our group demonstrated that the use of higher dosage estrogen of any kind can help to recruit follicular maturation in women in apparent premature menopause [10]. The mechanism is related to restoring down-regulated FSH receptors in the granulosa-theca cells by the chronic elevation of serum FSH. A reasonable pregnancy rate has been achieved [10-14]. Though all estrogens can restore sensitivity of gonadotropin-resistant follicles to either endogenous or exogenous gonadotropins, the advantage of using ethinyl estradiol is that it allows proper measurement of estradiol which aids tremendously in determining if a mature follicle has been attained.

Extending the length of the follicular phase

Sometimes for religious reasons, e.g., Orthodox Jewish women, intercourse is not allowed until one week after the cessation of menses, after a ceremonial bath referred to as a mikvah. Some of these women are very fertile but fail to achieve a pregnancy because they are ovulating before they can have intercourse. Sometimes they are actually ovulating on the day of the mikvah or even shortly thereafter, however the mucus may have receded several hours after the luteinizing hormone (LH) surge but before oocyte release.

There is evidence that a short follicular phase is associated with infertility even if a mature dominant follicle is attained [15, 16]. This seems to apply both to women whose short follicular maturation time may be related to diminished oocyte reserve and thus higher early follicular phase FSH driving follicular maturation quicker, and to women who appear to have adequate oocyte reserves [16]. This may be related to inadequate time exposure to estradiol with failure to generate sufficient endometrial progesterone receptors [16]. Lengthening the follicular phase with ethinyl estradiol has resulted in improvement of pregnancy rates [16].

Sometimes ethinyl estradiol can be used from day 2 to day 8 or so, then stopped, and follicular maturation ensues naturally or sometimes a low dose of gonadotropins is needed to stimulate the follicles.

Premature luteinization

A rise of LH before full maturation of the dominant follicle (i.e., 18-24 mm in size with a serum estradiol > 200 pg/ml) leading to a rise in serum progesterone above 2 ng/ml is referred to as premature luteinization [17]. In the normal ovulatory cycle in the late follicular phase estradiol has a positive feedback effect on LH release from the pituitary gland causing this hormone to rise. However, in pharmacologic dosages, estrogen will suppress LH. Thus frequently a condition, e.g., polycystic ovarian syndrome is treated with oral contraceptives to allow the pharmacologic dosage of ethinyl estradiol to lower the chronically elevated LH so as to reduce the production by the ovaries of excess androgens. Ethinyl estradiol can be used in cases of premature luteinization to keep the gonadotropins suppressed and then the follicle can be matured by using exogenous gonadotropins [18].

One could of course try to treat premature luteinization with GnRH agonists or antagonists. These agents are 100 times as expensive as ethinyl estradiol.

Final comments

Ethinyl estradiol has many uses in treating infertile couples. However, it is unlikely that any pharmaceutical company will rekindle an interest in commercial production because it is the common practice for most physicians to simply do IUI and not worry about postcoital tests. Furthermore, most physicians are not aware that apparent menopause can be temporarily reversed and will simply recommend donor oocytes. Nevertheless, for those treating physicians who have interests in these areas compounding pharmacies can easily make the ethinyl estradiol. I am not aware of another estrogen product that does not measure in the assay for estradiol.

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