Editorial Articles

Ovulation disorders: Part I
Anovulation associated with estrogen deficiency

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Summary

Purpose: To describe the diagnosis and treatment of anovulatory disorders associated with estrogen deficiency.

Methods: Anovulation with estrogen deficiency was divided into two types: association with low vs. high serum gonadotropin levels. Treatments included bromocriptine or cabergoline for hyperprolactinemia and gonadotropins for normal prolactin levels. When gonadotropins were low, lowering the elevated serum FSH to restore down-regulated FSH receptors in the few remaining follicles with either ethinyl estradiol or GnRH agonists or antagonists was used. High serum FSH was followed by either close observation for spontaneous follicular maturation or low dose gonadotropin stimulation. Progesterone supplementation, especially by vaginal use, was given in the luteal phase.

Results: Though success in ovulation induction and pregnancies was greater in women with low FSH than high FSH, pregnancies following ovulation induction were nevertheless achieved even in women in apparent menopause.

Conclusions: The use of ethinyl estradiol as opposed to other estrogen drugs has the advantage of not being able to be measured by most serum assays for estradiol allowing the physician to detect endogenous follicular development and thus determining when follicular maturation has been achieved. Even in the presence of marked diminished ovarian egg reserve, eggs from chronically younger women are superior in quality to women aged ≥ 45.

Key words: Amenorrhea; Serum FSH; Estrogen deficiency; Ovulation induction.

Ovulation disorders

Ovulation disorders can be divided into several categories: 1) anovulation, 2) luteinized unruptured follicle syndrome, 3) premature luteinization, 4) luteal phase defect with release of the egg from an immature follicle, 5) luteal phase defects with a mature follicle.

Anovulation

Ovulation consists of developing a mature dominant follicle of 18-24 mm average diameter by ultrasound usually associated with the granulosa theca cells secreting sufficient estradiol (E2) to raise the serum E2 level > 200 pg/ml, a luteinizing hormone (LH) surge and to a lesser degree a follicle stimulating hormone (FSH) surge which enables the rupture of the egg from the follicle, and then finally, the remainder of the follicle minus the egg begins to secrete progesterone (P) in addition to estradiol with dominance of the granulosa cell.

In most instances, whatever the etiology for the anovulatory process, the final common denominator is insufficient FSH to allow maturation of the follicle. The exception would be in the circumstance when there is diminished egg reserve and the baseline day 3 serum FSH is elevated. In this circumstance the reason for failure to ovulate may be that the FSH receptors in the granulosa theca cells have been down-regulated because of the chronically elevated serum FSH, or the remaining follicles are just of lesser quality.

Anovulation with low FSH and estrogen deficiency

Severe suppression of serum FSH may lead to amenorrhea or oligomenorrhea. Etiologic factors include hyperprolactenimia from a microprolactinoma of the pituitary or less commonly from a pituitary macroprolactinoma, isolated gonadotropin deficiency, weight loss, or inadequate body fat, severe stress, or panhypopituitarism. Thus evaluation of a woman with amenorrhea and estrogen deficiancy should include a fasting 8:00 a.m. serum prolactin, free thyroxin level, thyroid stimulation hormone and serum cortisol. General health studies such as complete blood count, liver enzymes, serum calcium, and kidney function tests are also advised.

Frequently the woman fails to get a menstrual flow following progesterone withdrawal, e.g., medroxyprogesterone acetate 10 mg x 10 days. If one is facile with vaginal cytology, parabasal cells and small intermediate cells may predominate. Generally a magnetic resonance imaging (MRI) study of the pituitary and suprasellar structures are performed.

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The presence of a macroadenoma without prolactin hypersecretion should prompt the consideration for surgical removal to prevent encroachment of the optic chiasm or even further extension that could lead to visual impairment (e.g., bitemporal hemianopsia), blindness or death. Similary a pituitary macroprolactinoma should be given the same consideration. However, there are times when surgery could be dangerous and another consideration is treating with bromocriptine or cabergoline which can shrink macroprolactinomas [1]. In the presence of hypogonadotropic hypogonadism, if the sella tursica appears normal, one should still be aware of the possibility of suprasellar lesions, e.g., a craniopharyngeoma. Suprasellar calcification may suggest a craniopharyngeoma or MRI can detect it.

The prolactin hormone itself suppresses gonadotropins. Thus if a pituitary microadenoma is present, and if the serum prolactin level is high enough, the woman may have hypogonadotropic hypogonadism and estrogen deficiency. The treatment could be bromocriptine or cabergoline and then wait to see if normal ovulation is restored or just use human menopausal gonadotropins (hMG). With hypogonadotropic hypogonadism there is a need for LH so recombinant FSH preparations would not be nearly as effective. Though one could use recombinant FSH with either recombinant LH or dilute hCG, e.g., 100 IU daily, one may question why do it that way instead of just using human menopausal gonadotropin (hMG) which contains both LH and FSH.

Sometimes side-effects, e.g., nausea, vomiting, light headedness, or nasal stuffiness precludes the use of bromocriptine or cabergoline so hMG is used from the outset. Since ovulation induction may take several weeks to months with bromocriptine, some women prefer to get started with bromocriptine, yet initiate ovulation with hMG hoping for a quick pregnancy. However if there is no success in one to two cycles then perhaps they can eliminate parenteral therapy and just use bromocriptine. Gonadotropins are expensive if not covered by insurance. Sometimes the bromocriptine or cabergoline does not induce ovulation but restores a better estrogen environment, i.e., allows progression to at least the antral follicle stage and the woman may now respond to clomiphene citrate which is a lot less expensive.

A previous study found that women treated with gonadotropins have persistent luteal phase defects despite the achievement of ovulation [2]. Miscarriages have been considerably reduced by adding progesterone support in the luteal phase [2, 3].

With insufficient gonadotropin function, patients achieving follicular maturation with gonadotropins are unable to generate a sufficient LH surge to allow oocyte release from the follicle. Thus this surge is generally supported by the injection of human chorionic gonadotropin (hCG) and oocyte release typically occurs 36 hours later.

In the absence of a pituitary tumor or hypothalamic lesion one can see hypogonadotropism as an isolated defect or associated with panhypopituitarism where there may be associated hypothyroidism or adrenal insufficiency.

Anovulation, estrogen deficiency and elevated gonadotropins

In most infertility centers the treatment for this entity would simply be egg donation. However, we published a study in 1984 showing that women with hypergonadotrophic amenorrhea and estrogen deficiency who failed to respond to gonadotropins alone were able to respond to exogenous gonadotropins once the serum FSH had been suppressed [4]. The hypothesis for suppressing FSH first was that there may be pre-antral and/or antral follicles still present that could respond to exogenous or even endogenous gonadotropin were it not for the possibility that the FSH receptors in the follicle were down-regulated by the chronically high serum FSH levels [4]. In this pilot study three of the five women treated were made to ovulate and all three who ovulated had successful pregnancies [4]. A follicular response to exogenous gonadotropins despite high endogenous gonadotropin levels and estrogen deficiency could be interpreted that the woman was making defective gonadotropins but had plenty of follicles remaining just waiting for proper gonadotropin stimulation. However, the fact that these women failed to stimulate with exogenous gonadotropin, supports the concept that it is needed to first restore FSH receptors in the granulose-theca cells by first suppressing the high endogenous levels of gonadotropin [4].

It could be argued that maybe this therapy works by estrogen having a direct effect on the follicles making them more sensitive to gonadotropins. However, this seems not nearly as likely a mechanism as the proposed hypothesis since successful ovulation in the face of hypergonadotropism and estrogen deficiency was also demonstrated by restoring sensitivity to human menopausal gonadotropins (hMG) after lowering FSH with leuprolide acetate [5].

Gonadotropin therapy is expensive but for those women who are in alleged premature menopause who can now ovulate the expense is worth it (many insurance companies do not pay for fertility drugs or at least injectable fertility drugs). Thus for those women who do not respond it could be an expensive treatment without results. We considered that if we could monitor the serum E2 we could start gonadotropins only if a rise in serum E2 could be seen. In fact if the E2 was rising we could determine if some women could develop a dominant follicle driven by endogenous gonadotropin and eliminate the need for expensive FSH injections. Most estrogens, however, will contribute to the serum E2 measurement. However, ethinyl estradiol does not cross-react with 17 beta-estradiol and thus with its use a rise in serum E2 indicates recruitment of a follicle.

Using ethinyl estradiol 20-50 μg per day to lower elevated serum FSH, and theoretically restore down-regulated FSH receptors in the granulso-theca cells so that sensitivity to FSH would be restored, in 91 consecutive cases of hypergonadotropic amenorrhea and estrogen deficiency, ovulation was achieved in 34 of 311 cycles (10.9%) and at least once in 34 of 91 (37.3%) women [6]. Pregnancies were achieved in 19 of 91 (20.8%) and live deliveries in eight of 91 (8.8%)

[6]. The mean serum FSH was 70.3 mIU/ml for those who ovulated vs 66.5 mIU/ml for those who did not ovulate and was 69.1 mIU/ml in those who conceived [6]. The mean age of those who became pregnant was 33.4 vs 34.8 for the poor-responders but there were no pregnancies in women ≥ 43. The two best prognostic features were shorter duration of amenorrhea (2.2 years for those who conceived vs 4.8 years in those who did not) and younger age [6].

The majority of the women in the 1990 study used gonadotropins once there was a rise in serum E2 [6]. Over the last several years the technique has been further modified to allow maximum follicle development by endogenous gonadotropins once the FSH receptors have been restored following suppression of elevated gonadotropins with minimal or no gonadotropin stimulation [7].

Both by ultrasound and direct observation during C-section delivery, the majority of these cases had a marked diminished egg reserve rather than a "gonadotropin resistant" gonad [8, 9]. Successful pregnancies have been achieved with hypergonadotropic amenorrhea with estrogen deficiency with a serum FSH as high as 164 mIU/ml [10]. One 40-year-old woman with a serum FSH of 123 mIU/ml successfully conceived and delivered a baby with her own eggs despite failing to conceive four times using donor eggs [11].

Again aggressive use of progesterone in the luteal phase is key in the treatment once ovulation occurs. Usually oral estradiol is also used in the luteal phase to help keep FSH suppressed to allow a better chance of recruitment of another follicle in a succeeding cycle with an adequate length to the follicular phase. Women with elevated FSH are more prone to a short follicular phase and a better chance for success occurs if one can delay ovulation to day 11 or later [12, 13].

In our IVF program in women who had at least two embryos transferred but were ≥ age 45 there was only one live pregnancy in 130 embryo transfers of two or more embryos. Though a pregnancy was recorded in a 45-year-old in ovarian failure in two treatment cycles by suppressing her elevated serum FSH (43 mIU/ml) with ethinyl estradiol, in general, most of the pregnancies have been recorded in younger women [14, 15]. Certainly these younger women with hypergonadotropic amenorrhea with estrogen deficiency have even fewer oocytes left than the group of women ≥ 45 that were described with at least two embryos transferred. Some of the 45-plus year-olds even had normal day 3 serum FSH levels. One hypothesis to explain this paradox is that depletion of oocytes as age advances involves selection of the best oocytes when younger so that only inferior oocytes remain in women of older reproductive age. Perhaps some factor, possibly related to mitrochondrial DNA, is present which allows advancement of primordial follicles to pre-antral follicles and this same factor is responsible for inhibiting embryo apoptosis of the subsequent embryo that is formed and which may occur after blastocyst formation. Thus, based on demonstrating reasonably good pregnancy rates in younger women with elevated serum FSH with or without IVF-ET compared to older women with or without elevated day 3 serum FSH levels, the data suggest that younger women with elevated FSH have better quality eggs than women in the older reproductive group [15, 16]. The data, in fact, favor the hypothesis that in younger women there is a destructive process that destroys geographical areas of the ovaries. However, the remaining follicles, though much lower in number and possibly comparable in quantity to much older women, from a quality standpoint, are equivalent to their aged matched peers. Though some women with premature ovarian failure may undergo an acceleration of normal atresia and thus go through an acceleration of the normal process to reach menopause, these women must be in a minority based on the reasonably good pregnancy rates found in women up to age 42 with elevated serum FSH [17].

Of course some will argue that other data suggest that elevated serum FSH levels are associated with terrible pregnancy rates even in younger couples who respond to stimulation [18]. So how can we explain the apparent conflicting data? Data has been presented that the controlled ovarian hyperstimulation regimen itself with IVF or even just the use of follicle maturing drugs can have an adverse effect on embryo implantation [19-21]. In women with normal baseline serum FSH the adverse effect may actually be at the endometrial level and could be related to premature trophoblast invasion [22]. It has been shown that giving follicle maturing drugs to a woman with decreased egg reserve can induce temporary reversible menopause by down-regulating FSH receptors [23]. The possibility exists that even if the FSH receptors are not so shut down that the follicles fail to respond at all to FSH, there may be some important factor that is not being secreted causing an embryo that has less implantation potential.

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