Editorial Articles

The concept and treatment methodology for inducing ovulation in women in apparent premature menopause

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Summary

Purpose: To provide the concept and details of the methodology of inducing ovulation in women in apparent menopause. *Methods:* A recent case is discussed and other previous publications described illustrating how to induce ovulation and achieve pregnancies despite what appears to be menopause. The various methods of lowering serum follicle stimulating hormone (FSH) and restoring down-regulated FSH receptors in granulosa theca cells of the follicle are described. *Results:* The newly reported case had two successful pregnancies after having a trisomy 15 in her first pregnancy. *Conclusions:* Women aged 42 and younger in apparent menopause have a reasonably good chance of ovulation induction and pregnancy by adhering to the tenets discussed, especially including lowering the elevated FSH in some way (the easiest and cheapest with ethinyl estradiol), using minimal or no gonadotropins, and supporting the luteal phase with progesterone.

Key words: Ovarian failure; FSH receptor; Gonadotropin suppression.

A technique was described in 1984 in which women in apparent menopause based on amenorrhea with estrogen deficiency, failure to menstruate despite progesterone withdrawal, and resistance to follicular stimulation by gonadotropin stimulation were made to ovulate by lowering the elevated gonadotropins by using pharmacologic dosages of estrogen [1]. The theory of why the estrogen helps to induce ovulation even when high-dose gonadotropins or high endogenous gonadotropins fail is that the pharmacologic dosage of estrogen, by lowering the high serum level of follicle stimulating hormone (FSH), allows a restitution of down-regulated FSH receptors in the granulosa-theca cells which previously regressed related to the chronic high levels of FSH exposure.

Initially, this technique involved staying on a pharmacologic dosage of estrogen until the serum FSH fell into the normal range when it would be maintained while gonadotropins would be injected and follicular maturation would be monitored [1]. The main estrogen used was ethinyl estradiol because it does not measure in the assay for serum estradiol [2]. At that time gonadotropins were not reimbursed by insurance companies, in general, and thus those women who were not going to demonstrate follicular maturation would be spending a lot of money without even a chance for pregnancy.

Observation of follicular monitoring with ultrasound, serum estradiol and serum FSH demonstrated that women would recruit a follicle or follicles simply by lowering the serum FSH [2]. Sometimes, these follicles would progress to dominant follicles (defined as reaching an average diameter of ≥ 17 mm with a serum estradiol (E2) ≥ 175 pg/ml). Others did better with a small boost of gonadotropins [2]. For maximal cost effectiveness this modification is the predominant technique used to try to initiate ovulation in a woman who seems to be in menopause (usually prematurely).

One may question the technique as to whether it was the proposed mechanism that was operational, i.e., restoration of down-regulated FSH receptors in granulosa-theca cells, which was responsible for the ovulation or whether the ovulation was merely fortuitous and independent of therapy. There have been anecdotal cases of ovulation and pregnancy without any treatment [3] or just with estrogen replacement therapy [4-6]. However, the occurrence of premature menopause is estimated at 1% of all women during their reproductive years [7]. The study describing the modified technique evaluated 91 women with premature ovarian failure defined as having > 12 months of amenorrhea, failure to have withdrawal menses following ten days of 10 mg medroxyprogesterone acetate, a serum E2 < 25 pg/ml and a serum FSH > 35 mIU/ml. Yet despite these criteria using the technique described about 20% of the treated cycles resulted in ovulation and 38% of the women ovulated at least once [2]. Furthermore, about 20% conceived [2]. This is much higher than would be expected by chance alone (1 in 6,500) considering the paucity of publications related to spontaneous conception [3-6].

It may be questioned whether the eggs of these women with apparent premature ovarian failure, but who are made to ovulate, may be qualitatively different than women of advanced reproductive age in menopause. The possibility exists

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that the women responding to pharmacologic ethinyl estradiol therapy with or without mild stimulation with exogenous gonadotropins may not suffer from a paucity of eggs but in fact have a plethora of eggs that are resistant to gonadotropins and somehow the estrogen restores their sensitivity to FSH. However, in contrast to that theory, and in support that there is actually a paucity of eggs even in younger women with premature ovarian syndrome, is the demonstration of ovulation and pregnancy in some women who have basically only streaked gonads left as demonstrated in one woman at the time of C-section and another woman during a laparoscopy prior to treatment [8, 9]. In fact, the serum FSH for the woman who had the C-section was 124 mIU/ml [8]. Furthermore the ovaries generally appear to be small by ultrasound and show usually no antral sized follicles and few if any pre-antral sized follicles.

Even if there is a deficiency of follicles, the possibility exists that it is not the effect of ethinyl estradiol lowering the serum FSH which is the operating mechanism but perhaps estrogen somehow other than lowering the FSH and restoring FSH receptors restores the sensitivity of the few remaining follicles to FSH. This mechanism seems less plausible than the theory of the need to lower the serum FSH to attain the right circumstances for recruitment of the follicle. This is supported by the induction of ovulation in similar circumstances by merely lowering the elevated serum FSH by using the gonadotropin releasing hormone (GnRH) agonist leuprolide acetate [2, 10]. Similarly ovulation induction with hypergonadotropic amenorrhea has been achieved using the GnRH antagonist cetrorelix [11]. Furthermore, it has been demonstrated that one can create an apparent menopausal state by further raising the already elevated day 3 serum FSH in a menstruating woman and create an estrogen deficiency state resistant to endogenous gonadotropin or clomiphene citrate therapy only to restore ovulation even with multiple follicles simply by withdrawing clomiphene citrate [12].

More support for the consideration that these women do not have the gonadotropin resistant gonad with a plethora of follicles versus a paucity of follicles with acquired gonadotropin resistance is by watching the progression of the condition in the same patient. For example, one 37-year-old woman who came with regular menses of 26-30 days conceived the first month that she and her husband tried but had a miscarriage. Chromosome analysis of the fetus showed a trisomy 15.

Further evaluation by her consulting reproductive endocrinologist determined that her day 3 serum FSH was elevated over 15 mIU/ml. Though she had conceived the very first cycle that she attempted to conceive, she was advised by that reproductive endocrinologist that her eggs were from a quantitative and qualitative standpoint "old" and that conception again would be highly unlikely, and even if it did occur, a repeat trisomy would be likely. In support of this argument she was referred to a recent study by an excellent IVF facility that had failed to have any successful live deliveries at any age of the woman despite the transfer of normal appearing embryos following IVF-ET if the serum FSH was > 15 mIU/ml [13]. The woman was advised to consider using donated oocytes.

She came to us for a second opinion and I advised her that from our experience her eggs might be quantitatively similar to women over the age of 45 (an age where pregnancies rarely occur), but from a qualitative standpoint they should be more compatible with her age peers of age 37. She was advised that in contrast to data showing atrocious pregnancy rates following IVF-ET in women with elevated day 3 serum FSH given traditional controlled ovarian hyperstimulation [13-15], we have been able to achieve very high pregnancy rates when using much lower dose FSH protocols and to avoid adding exogenous FSH when the serum FSH is already elevated [16, 17].

Since she conceived the very first cycle that she tried I did not think in vitro fertilization was necessary. I advised her that based on her regular menses my approach would be to determine whether she attains a mature follicle (average diameter 18-24 mm associated with a serum E2 > 200 pg/ml) and if so to only use vaginal progesterone supplementation in the luteal phase. If the oocyte released before follicular maturation was attained, in the succeeding cycle small dosages of exogenous FSH (such as 75 IU) would be given from the mid to late follicular phase when the serum FSH level would be decreased by the rising level of endogenous estradiol [18, 19].

On her initial visit she was actually a couple of days late for her menses so serum beta-hCG and serum progesterone were obtained. The serum beta-hCG was positive at 433 mIU/ml and the serum progesterone level was appropriate at 55.1 ng/ml. However since her vaginal cytology showed an inadequate progesterone effect based on the number of superficial cells seen she was placed on vaginal progesterone support during the first trimester. She had a full-term live delivery by C-section.

She returned a few months after delivery at age 40 to consider having another baby. She began weaning and her menses had not resumed. By vaginal cytology she now showed predominantly parabasal cells and she was clearly estrogen deficient. Her serum E2 was < 10 pg/ml and her serum FSH was increased to 21 mIU/ml. An ultrasound failed to demonstrate any pre-antral or antral sized follicles.

She was started on 20 mcg of ethinyl estradiol every day and then changed to every other day when the FSH dropped too low to < 1. After 21 days there still were no pre-antral or antral follicles seen on ultrasound. After 41 days taking ethinyl estradiol, 20 mcg every other day, there were two follicles seen at 6 and 4 mm. The serum E2 was still < 10 pg/ml (note that ethinyl estradiol is not measured in the serum 17 beta estradiol assay). One week later the serum E2 rose to 40 pg/ml and finally on the 57th day the serum E2 reached 270 pg/ml with a 15.7 mm follicle. However two days prior the serum E2 was 153 pg/ml with a 12 mm follicle as the serum LH was 26 mIU/ml and the serum P was 0.8 ng/ml. However with the 15.7 mm follicle the LH rose to 39 mIU/ml and the serum P rose to 1.0 ng/ml. The follicle reached 23.7 mm but the serum P was 3.3 ng/ml. Eventually the follicle collapsed but she did not conceive. One

possible reason for failing to conceive on this cycle besides possibly not selecting a normal egg was premature luteinization [20].

During her preceding luteal phase the ethinyl estradiol was switched to oral estradiol to allow exposure to the potential conceptus to a natural estrogen. She was also supplemented with progesterone vaginal suppositories, 200 mg, twice daily. With the ensuing menses she had a baseline serum E2 on day 3 of < 10 pg/ml and her serum FSH was 4 mIU/ml having been kept down by the combination of endogenous and exogenous E2 and P during the preceding luteal phase.

The plan was to carefully observe her again and depending on how well she was responding she might be given a boost of 75 IU exogenous FSH and possibly started on cetrorelix if the serum E2 approached 100 pg/ml and a follicle approached 14 mm. Her only medication was ethinyl estradiol every other day. By day 11 there was a 15.7 mm follicle seen with a serum E2 of 165 pg/ml. However since the serum LH was only 5 mIU/ml and thus lower than the earlier level on day 6 of 11 mIU/ml, and because the serum P was only 0.5 ng/ml (less than the 0.7 ng/ml level on day 5) it was elected not to boost with exogenous FSH or start cetrorelix. On day 12 the serum E2 was 264 pg/ml and the follicle size averaged 18.7 mm. The patient was given 10,000 IU of human chorionic gonadotropin and a repeat ultrasound two days later showed egg release by demonstrating follicular collapse. The ethinyl estradiol was stopped and she was supplemented again with estradiol and progesterone. She conceived that cycle. Chorionic villis sampling was performed and no chromosome abnormalities were found. She has successfully completed the first trimester.

I selected this recent case to first illustrate that the women with apparent ovarian failure are not those with ovarian failure with gonadotropin resistant follicles but merely less follicles. Obviously when our patient had regular ovulatory cycles with a high serum FSH she did not demonstrate any gonadotropin resistance despite increased FSH. She clearly showed that she could respond to her own endogenous gonadotropins. Her case was selected to show the evolution of ovarian failure from regular menses in one year to estrogen deficiency and amenorrhea the next year.

She also demonstrated the technique of lowering elevated serum FSH with ethinyl estradiol with the theory that remaining follicles acquire a resistance to FSH by the chronically elevated FSH down-regulating FSH receptors in granulosa theca cells.

Pregnancy is a state where because of the high levels of estrogen and progesterone the serum FSH and LH are suppressed. Our patient's progression from regular menses to ovarian failure while she was pregnant shows that suppression of follicular development with oral contraceptives or GnRH agonists are probably ineffective in preventing further atresia of follicles. The fact that she conceived three of the four times she had unprotected intercourse despite elevated serum FSH lends credence to the fact that oocytes from women with elevated serum FSH are not qualitatively poor; their eggs will frequently result in pregnancy. Two of three pregnancies being chromosomally normal dispels the concept that even if she were to conceive it would most likely be a trisomy.

It could be argued that one cannot state for sure in the case described above that recruitment of the follicle could have been spontaneous and not related to the suppression of serum FSH by ethinyl estradiol. Whether it was related to the ethinyl estradiol therapy or not, careful monitoring allowed detection of the follicle and thus proper timing of intercourse, and proper timing of luteal phase support with progesterone. Other cases clearly demonstrate the need for lowering the serum FSH in some way, e.g., the 25-year-old with two years of amenorrhea and estrogen deficiency as evidenced by failure to menstruate upon progesterone withdrawal treatment whose first three serum FSH levels measured were 144.9, 145.6, and 164.2 mIU/ml. She ovulated in six of the next ten cycles treated exclusively with ethinyl estradiol and had a chemical pregnancy in cycle 9 and a live delivery resulted from cycle 10 [21]. Another case supporting the theory is a 37-year-old woman whose serum FSH had been 120 and 123 mIU/ml with a serum E2 of 20 pg/ml who had not had a menstrual period for almost three years. Her endometrial thickness was only 2 mm. She was made to ovulate with just ethinyl estradiol alone in two of three treatment cycles. She elected to try donor oocytes in her part of the country 3,000 miles away. She failed to conceive after four donor egg cycles yet had spontaneous ovulation again two years later at the age of 40 following estrogen suppression of the elevated serum FSH and conceived and delivered a healthy live baby [22].

Eventually the oocytes become depleted or at least no longer recruited. Two women in apparent ovarian failure were able to induce ovulation and successfully conceive with in vitro fertilization for tubal factor problems [23, 24]. However, neither were able to ovulate again after their deliveries.

It is difficult to gauge, however, how fast a woman will develop ovarian failure once the serum FSH is elevated. We previously reported the case of a woman with tubal factor and increased day 3 serum FSH who had successful pregnancies following three of four IVF-ET cycles over an 8-year time span [25]. Ten years after her first high FSH she still menstruates about once a month. Another unreported case with elevated serum FSH had three successful pregnancies among a couple of miscarriages with an 8-year span between pregnancies and did not require IVF-ET.

Previously we also reported successful pregnancies in two women 45 and 46 years old with elevated serum FSH and even reported a successful pregnancy in a 45-year-old woman in apparent menopause [26-28]. Nevertheless we have had only one successful pregnancy in over 200 egg retrievals in women 45 or older even with normal serum FSH. Advanced age possibly related to the natural selection over the years of the follicles with the most apoptosis inhibiting factor forebodes a much less optimistic chance of successful conception.

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