

Live Delivery in a 46.5-Year-Old Woman in Overt Menopause by Restoring Follicular Sensitivity to Follicle Stimulating Hormone (FSH)

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ABSTRACT

For almost 40 years, there have been several publications where ovulation induction has occurred by lowering elevated serum follicle stimulating hormone (FSH) to up-regulate down-regulated FSH receptors on granulosa-theca cells thus restoring follicular sensitivity to endogenous gonadotropin resulting in live deliveries. The majority of case reports used ethinyl estradiol to lower FSH. The advantage of ethinyl estradiol is that it does not add to the serum estradiol and thus allows the physician to better determine follicular maturation. To date the oldest woman to have ovulation induction and live delivery despite menopause was aged 45. A 46.5-year-old woman with 9 months of amenorrhea with a serum estradiol <15 pg/mL and a serum FSH of 117 mIU/mL was given ethinyl estradiol 20 micrograms daily. She attained a mature follicle on day 44 and conceived with natural intercourse with vaginal progesterone supplementation in the luteal phase. She delivered a full-term healthy chromosomally normal baby. Interestingly, she also had a successful live delivery when we treated her with progesterone in the luteal phase at age 42 when her day 3 serum FSH was 47 mIU/mL. Besides a luteal phase defect, she failed to release the egg from the follicle first naturally then with 10,000 units of human chorionic gonadotropin (HCG) but finally did release and conceived with the novel use of granulocyte colony stimulating factor, which was used again at age 46.5. Live deliveries are uncommon in women aged 46 even with regular menses and normal egg reserve. Precedents are important in medicine. Thus, this case represents the oldest woman with documented menopause to conceive naturally.

Keywords

Advanced reproductive age, Ethinyl estradiol, FSH receptor up-regulation, Ovarian failure, Ovulation induction.

Introduction

In 1984 a technique was described in which some women in apparent menopause were made to ovulate by restoring sensitivity of remaining follicles to follicle stimulating hormone (FSH) by up-regulating down-regulated FSH receptors on the granulosa theca cells [1]. The up-regulation of FSH receptors was accomplished by lowering elevated serum FSH levels through negative feedback by estrogen for release of FSH either by the pituitary or by inhibiting FSH production by inhibiting gonadotropin release hormone (GnRH) either by a GnRH agonist or by an antagonist [2-5]. In a series of 100 consecutive women given 4 months of this FSH

receptor up-regulation technique, 35% ovulated at least one time in 4 cycles of treatment and 20% became pregnant [6]. Advanced age seemed to be a greater negative factor to achieve a live baby than diminished oocyte reserve (DOR) [7]. Nevertheless, live deliveries have been achieved in women of very advanced reproductive age of 45 and 46 with DOR both with and without IVF-ET [8-10]. There has even been one woman age 45 who appeared to be in overt menopause who was made to ovulate using this FSH receptor up-regulation technique with ethinyl estradiol and delivered a healthy baby [11,12].

A case is presented of a 46.5 old woman who was in apparent overt menopause who was made to ovulate by this FSH up-regulation technique and successfully delivered a healthy baby that was chromosomally normal.

Case Report

Ethinyl estradiol (EE) 20 micrograms was given to a woman age 46.5 who had amenorrhea for 9 months, and who was in overt menopause, as evidenced by failure to have menses following 10mg medroxyprogesterone acetate x 13 days. In addition, the patient had a serum estradiol (E2) of <15 pg/mL, a serum FSH of 117 mIU/mL, and a serum anti-mullerian level of <0.09 ng/mL.

She was treated with EE to lower serum FSH levels rather than E2 because the former does not contribute to the total serum E2 level, and thus allows the treating physician to detect when a follicle has been recruited by rising serum E2 levels. A rising E2 would dictate the addition of pelvic sonography to help determine when a mature dominant follicle was achieved (18mm average diameter with serum E2 >200pg/mL). If a mature follicle were achieved, 1mg granulocyte colony stimulating factor (G-CSF) would be given the day before an injection of 10,000 unit's human chorionic gonadotropin (HCG) to help the oocyte release.

At age 42 she had been treated for infertility and was found to have the luteinized unruptured follicle syndrome. She failed to release the oocyte with either HCG or leuprolide acetate but was successful with HCG when granulocyte-colony stimulating factor (G-CSF) was added (and delivered a healthy baby despite a day 3 serum FSH of 47 mIU/mL). Progesterone vaginal suppositories 200mg twice daily was supplemented in the luteal phase.

After 44 days of EE she was able to attain a mature follicle (E2 of 273 pg/mL, follicular size 18.8mm average diameter). She released the oocyte, conceived and successfully delivered a full-term healthy baby.

Discussion

When the patient was 42 with marked diminished oocyte reserve, she had regular menses and seemed to make a mature follicle (serum E2 >200pg/mL, average follicle diameter >18mm). However, in the first cycle of observation, when she attained a mature follicle, and had a normal post-coital test, she failed to release the egg from the follicle as evidenced by the follicle failing to shrink by at least 5mm by 3 days from the luteinizing hormone (LH) surge [13,14].

In the next two cycles she similarly failed to release the egg despite 10,000 IU human chorionic gonadotropin (HCG) in cycle 2 and 15,000 units hCG and 150 IU FSH in cycle 3. In cycle 4 she similarly failed to release the oocyte from the follicle despite 1mg leuprolide acetate at 12-hour intervals x 3 when peak follicular maturation was reached. Some studies suggest that the use of a GnRH a can correct the luteinized unruptured follicle (LUF) syndrome even when hCG has failed [15,16].

Her next recommendation was to have the egg manually retrieved and perform IVF-ET. She could not afford the procedure and asked if there was still some experimental protocol that could be used

to help release her eggs. She was the first case in which a 1mg injection of G-CSF was given a day before hCG in cycle 5. She released the egg, conceived, and delivered a healthy baby. Her case was included in a series of recalcitrant LUF cases that released oocytes with the addition of G-CSF [17].

Thus, when she finally attained a mature follicle, she was once again treated with 1mg of G-CSF and again released the oocyte, with the help of progesterone supplementation once the egg released, she had a successful live delivery [18,19].

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