Successful pregnancy in a 45-year-old woman with elevated day 3 serum follicle stimulating hormone and a short follicular phase

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Summary

Purpose: To determine if a successful pregnancy is possible in a woman aged 45 with elevated day 3 serum follicle stimulating hormone (FSH), a short follicular phase, and failure to attain a mature follicle before ovulating.

Methods: Ethinyl/estradiol (20 μg daily) was given from day 2 of the menstrual cycle until follicular maturation was attained. Progesterone support of 200 mg twice daily progesterone vaginal suppositories were given in the luteal phase.

Results: A mature follicle was attained on day 12 with a serum estradiol of 335 pg/ml. Successful pregnancy and delivery were attained.

Conclusions: This is the third reported case of a successful pregnancy in a woman ≥ 45 years old with hypergonadotropism, and the first one reported that was also complicated by a short follicular phase.

Key words: Short follicular phase; Hypergonadotropism; Advanced age.

Introduction

Successful pregnancies and deliveries are rare in women 45 and over but they have been recorded. Most occur in grand multiparas who have been very fertile in the past but some occur even in those who defer having a child until later [1]. The majority of these women conceive quickly and have favorable circumstances such as persistence of adequate oocyte reserve as evidenced by lower day 3 serum follicle stimulating hormone (FSH) levels. Some inherited cytoplasmic factor that can inhibit cytoplasmic senescence has been hypothesized [1].

As menopause approaches, leave in a state of paucity of ovarian follicles, which is manifested by a rise in the day 3 serum FSH levels [2]. These remaining follicles are considered weaker and more prone to having extra chromosomes and defective cytoplasmic mitochondria [3]. Though some researchers believe that an elevated day 3 serum FSH predicts poor quality oocytes no matter what the age [4-7], others support the concept that this merely predicts a paucity of follicles in younger women without a marked reduction in oocyte quality [8]. The explanation given to explain the age differences is that the older reproductive aged women has gone through a natural selection process so the best oocytes have already come forth, whereas in the younger woman the etiology for the reduced number of follicles is a destructive process leaving the same proportion of good quality oocytes as her age peers with a normal amount of follicles remaining.

Thus, it would be expected that the combination of advanced age and elevated day 3 FSH would rarely lead to a successful outcome. This would be especially true for nulligravidas. However, anecdotally some successes have been recorded in a menstruating 46-year-old nulligravida with elevated day 3 FSH and in a 45-year-old who was in overt ovarian failure [9, 10].

A short follicular phase has also been associated with infertility [11, 12] which is frequently, but not always, related to a high serum FSH driving faster follicular maturation.

A case is presented where a 45-year-old woman with an elevated day 3 serum FSH and a short follicular phase was able to achieve a pregnancy and deliver a normal baby.

Case Report

A 45-year-old woman married to a 47-year-old man presented with a 3-year history of primary infertility. She stated that her menstrual cycles had shortened since around the time of marriage going from 28 days to approximately 25 days and occasionally 22 days. Her day 3 serum FSH was 16.1 mIU/ml with a serum estradiol (E2) of 67 pg/ml. She ovulated by day 9 in two consecutive cycles without attaining either an 18 mm diameter follicle or a serum E2 of ≥ 200 pg/ml.

She was treated with ethinyl/estradiol, 20 μg twice daily. This delayed peak follicular maturation until day 12 when she attained a follicle with a mean diameter of 18 mm associated with a serum E2 of 335 pg/ml and the luteinizing hormone which had been 5.5 mIU/ml on day 3 increased to 25.9 mIU/ml. The follicle demonstrated collapse two days later and she was started on progesterone vaginal suppositories of 200 mg twice daily. She conceived this cycle and delivered a full-term normal baby. She stayed on the progesterone therapy for the first trimester.

Discussion

Ethinyl estradiol has been used to induce ovulation in women with hypergonadism, estrogen deficiency, and in whom resistance to gonadotropin therapy has been

Revised manuscript accepted for publication February 10, 2004

demonstrated [13]. The theory is that the high levels of circulating FSH down-regulates the FSH receptor and that lowering the serum FSH through negative feedback at the pituitary level allows restoration of these FSH receptors and improves sensitivity of the follicles to both endogenous and exogenous FSH. The aforementioned 45-year-old woman in apparent menopause made a mature follicle and ovulated merely by using ethinyl estradiol [10]. Ethinyl estradiol alone without any exogenous gonadotropin allowed the formation of follicles in a 42-year-old gonadotropin resistant woman in imminent ovarian failure with blocked fallopian tubes. This allowed the retrieval of a single oocyte and successful pregnancy following embryo transfer [14].

Any estrogen can suppress FSH. However, the advantage of ethinyl estradiol is that it does not cross-react with estradiol immunologically, thus allowing one to determine the full extent of follicular maturation when measuring serum estradiol. It has been used to improve cervical mucus without contributing to the serum E2 level as a short course after follicular maturation was close to maturity [15], or in combination with human menopausal gonadotropin [16], or after stopping clomiphene up to the time of follicular maturation to counteract the advantage effect of this drug on cervical mucus [17].

Ethinyl estradiol has also been used to induce ovulation in hypergonadotropic women with gonadotropin resistance by restoring down-regulated FSH receptors either by itself [10, 14, 18] or in conjunction with low-dose gonadotropin [19-22].

Ethinyl estradiol has been used to lengthen the follicular phase both to improve fertility [11, 12] and for religious reasons. In the case presented here, the ethinyl/estradiol served a double purpose: to delay follicular maturation and to allow a mature follicle to form. It has also been used to inhibit premature luteinization [23].

There is no question that the large majority of women with high day 3 serum FSH at age 45 will not achieve successful pregnancy. Of course donor oocytes would result in a much higher pregnancy rate. However for some couples for personal or religious reasons (in this case the couple were orthodox Jews) the couple would be willing to try as long as they know that there are previous precedents. The case represents the third reported case of successful pregnancy in a woman ≥ 45 years old with elevated day 3 serum FSH levels.

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