Testosterone patch improves ovarian follicular response to gonadotrophins in a patient with Kallmann’s syndrome: A Case Report

Christopher S. Sipe and Bradley J. Van Voorhis

Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

To whom correspondence should be addressed at: Department of Obstetrics and Gynecology, 200 Hawkins Drive, University of Iowa Hospitals and Clinics, Iowa City, IA 52242-1080, USA. Tel: +1 319 384 6848; Fax: +1 319 353 6659; E-mail: brad-van-voorhis@uiowa.edu

Achieving ovulation in women with Kallmann’s syndrome requires both exogenous FSH and LH to successfully stimulate follicular maturation and ovarian steroidogenesis. We present a case of a woman with Kallmann’s syndrome, who had poor ovarian response to stimulation by exogenous gonadotrophins. When she was given testosterone by patch before initiation of gonadotrophins, her stimulation dramatically improved. Once we ceased to pretreat her cycle with testosterone, she again had a poor stimulation. This suggests that testosterone administration may be a useful adjunct in improving ovarian response to gonadotrophins in Kallmann’s syndrome patients.

Key words: follicular development/gonadotrophins/Kallman’s syndrome/ovarian response/testosterone

Introduction

Kallmann’s syndrome is a disorder characterized by hypogonadotropic hypogonadism and anosmia. Women with this syndrome typically present with primary amenorrhea and poor development of secondary sex characteristics. Initial treatment is aimed at restoring breast development and initiation of menstruation using estrogens and progestins. As GnRH is not produced, the anterior pituitary does not secrete gonadotrophins in the normal cyclical manner to promote follicular development, thus these patients are infertile. Numerous case reports exist of pregnancies achieved using either a GnRH pump to mimic hypothalamic secretion or gonadotrophin injections (Muller and Dellenbach, 1971; Jancke et al., 1983; De Mola et al., 1992; Sungurtekin et al., 1995; Kousta et al., 1996; Chryssikopoulos et al., 1998). Common observations in these reports are the need for both LH and FSH, as well as the long duration of ovarian stimulation typically required for the development of a mature follicle. Although prolonged high doses of FSH alone are able to induce folliculogenesis, a faster stimulation using lower doses of FSH can be observed when hCG or LH is added to the stimulation regimen. Presumably, LH stimulation of thecal cell androgen production is important for optimal follicular growth.

Recent evidence suggests that exogenously administered androgens can affect ovarian follicular response. Supplementing Rhesus monkeys with supra-physiologic levels of testosterone lead to a 10-fold increase in the number of pre-antral follicles (Vendola et al., 1998). Examination of granulosa cells in the testosterone-supplemented primate ovary revealed an up-regulation of FSH receptor mRNA (Weil et al., 1999). This suggests that androgens not only serve as a substrate for aromatase in estradiol (E2) production, but also may enhance follicular responsiveness to FSH. In further support of the observation made in primates, we present a patient with Kallmann’s syndrome in whom testosterone therapy was associated with improved ovarian responsiveness to gonadotrophin therapy.

Case report

A 26-year-old white female with Kallmann’s syndrome presented to our infertility clinic to discuss infertility treatment options. At the age of 21, she was initially seen at a local clinic with primary amenorrhoea, Tanner stage 1 breast development, Tanner stage 2 pubic hair pattern and anosmia. She was found to be hypogonadotropic with initial laboratory tests revealing an FSH level of 0.54 IU l⁻¹, LH <0.7 IU l⁻¹, TSH 1.41 IU ml⁻¹, prolactin 3.7 ng ml⁻¹ and E2 11 pg ml⁻¹. Chromosomal analysis was found to be normal. She was given a trial of Medroxyprogesterone (Provera®, Pharmacia Corp., St. Louis, MO, USA), but did not have a withdrawal bleed. She was then started on daily 1.25 mg conjugated estrogens (Premarin®, Wyeth Pharmaceuticals, Madison, NJ, USA) with cyclical Provera 10 mg for 10 days, which established monthly menses. Her past medical history was otherwise unremarkable. She reported having an older sister who began menstruating at age 11 and had spontaneously conceived a child.
When she presented to our clinic, she had Tanner stage 3 breast development and Tanner stage 4 pubic hair distribution with a BMI of 26.7 kg m$^{-2}$. She had menstruated cyclically while on oral contraceptive pills but had been amenorrhoeic for 6 months since stopping the pills. Her husband had a normal semen analysis and transvaginal ultrasonography revealed atrophic ovaries of <1 cc volume with a total of three antral follicles. Her baseline E$_2$ was 12 pg ml$^{-1}$ and her initial total testosterone level was 22 ng dl$^{-1}$ (normal female range 12–82 ng dl$^{-1}$). We discussed treatment options and initiated ovulation induction with menopausal gonadotrophins (hMG, Repronex, Ferring Pharmaceuticals Inc., Suffrin, NY, USA).

Ovulation induction

For her first gonadotrophin cycle, she was started on 75 IU of hMG each day for 6 days (cycle 1, Table I). At that time, her serum E$_2$ was <20 pg ml$^{-1}$ and the gonadotrophin dose was increased to 150 IU. Three days later, her E$_2$ level continued to be <20 pg ml$^{-1}$ and the induction cycle was cancelled. In the next cycle (cycle 2, Table I) she was started on 150 IU hMG for 9 days, but again her cycle was cancelled with an E$_2$ <20 pg ml$^{-1}$ on days 6 and 9. Owing to her poor response, we elected to pretreat the patient with a 2.5 mg testosterone patch (Androderm, Warner Pharma, Morristown, NJ, USA) daily for 12 days preceding her next initiation of gonadotrophins. During testosterone administration, her total testosterone level rose to 83 ng dl$^{-1}$, and she did not experience any problems with acne, hirsutism or change in libido. In the third cycle (cycle 3, Table I), she was again started on 150 IU of hMG, but this time her E$_2$ on day 6 had modestly risen to 40 pg ml$^{-1}$, so her dose was increased to 225 IU of hMG. By day 9, the E$_2$ was 285 pg ml$^{-1}$. An ultrasound performed the same day revealed four follicles 10–15 mm in mean diameter. She was continued on 225 IU until day 11 when she had one follicle >18 mm. Her endometrial stripe thickness was 6.8 mm. She was given 10 000 IU of hCG (Novarel, Ferring Pharmaceuticals Inc., Suffren, NY, USA) and had timed intercourse 2 days later. To support the luteal phase, she was given 2 mg Estrace orally three times a day and 50 mg progesterone in oil intramuscularly once a day until her pregnancy test.

Unfortunately, she did not become pregnant, but we elected to initiate another cycle (cycle 4, Table I) without testosterone priming to determine whether the prior successful induction was related to testosterone or if this was an effect of repeated cycles. She was started on 150 IU hMG; yet again on day 6, the dose was increased to 225 IU because of a low serum E$_2$ level. By day 9, she continued to have a low E$_2$ level, but wanted to continue. On day 13, she had a single 15 mm follicle and an E$_2$ level of 169 pg ml$^{-1}$ with an endometrial stripe thickness of 4.5 mm; she received 10 000 IU of hCG on day 14, but did not become pregnant.

She returned after a 4-month hiatus to try again. For her fifth cycle (cycle 5, Table I), we pretreated her once again with 12 days of 2.5 mg testosterone patch and then started her stimulation with 225 IU of hMG. Day 6 E$_2$ was low, but by day 9, it was 298 pg ml$^{-1}$, and she had a 16 mm and an 18 mm follicle. Ovulation was induced again followed by intrauterine insemination (IUI) 2 days later. Her endometrial stripe was 8.0 mm. She did not become pregnant and chose to undergo another cycle. We extended testosterone pretreatment to 14 days as she had not reported any side effects. Cycle 6 (cycle 6, Table I) was started with 225 IU and her E$_2$ levels were 61 pg ml$^{-1}$ on day 6 and 348 pg ml$^{-1}$ on day 9. Five follicles (14, 15, 16, 18 and 18 mm) were present on day 11 with an endometrial stripe of 8.3 mm, and she was given hCG followed by IUI 2 days later. Unfortunately, she did not achieve a pregnancy with the last cycle.

E$_2$ levels were determined by venous blood sampling using an E$_2$ test run on Roche modular E1 70 electro-chemiluminescence immunoassay with an inter-assay coefficient of variance (CV) 2.2–4.7% and an intra-assay CV 1.7–3.3%. Total testosterone levels were determined by venous blood sampling using a testosterone test run on Roche modular E1 70 electro-chemiluminescence immunoassay with an inter-assay CV 2.5–6.0% and an intra-assay CV 1.3–2.7%. Transvaginal ultrasonography was performed using an Acuson Sequoia with a 10 MHz vaginal probe. All ultrasounds were performed by gynaecologic ultrasonographers. All follicles >10 mm were measured in two perpendicular dimensions. The average of these measurements determined the follicle size for treatment decision and study results. A ‘mature’ follicle was defined as having a mean diameter of >15 mm, although the lead follicle had to be >18 mm before hCG was to be administered.

Discussion

Ovulation induction in women with Kallmann’s syndrome has been a clinical problem since the disorder was discovered in 1944 (Kallmann et al., 1944). Possible therapies include pulsatile GnRH or daily injections of gonadotrophins. At this time, GnRH is not commercially available in the USA. Women with Kallmann’s syndrome require prolonged stimulation

<table>
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<th>Cycle</th>
<th>Testosterone</th>
<th>Day 1 hMG dose (IU)</th>
<th>Day 6 E$_2$ (pg ml$^{-1}$)</th>
<th>Day 6 hMG dose (IU)</th>
<th>Day 9 E$_2$ (pg ml$^{-1}$)</th>
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<td>61</td>
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with a combination of FSH and LH. We now report that the addition of exogenous testosterone therapy was associated with an improved ovarian response to gonadotrophins in one woman who seemed particularly resistant to gonadotrophin stimulation.

There is evidence in the literature that androgens, either produced locally or given exogenously, can affect ovarian response to gonadotrophins. Women who have elevated testosterone levels [polycystic ovary syndrome (PCOS), androgen-secreting tumours or female-to-male transsexuals] develop polycystic ovaries and, at least in women with PCOS, the ovaries often seem to be more sensitive to gonadotrophin stimulation (Mason et al. 1994; Farhi and Jacobs, 1997). Two studies in Rhesus monkeys suggest that exogenous administration of testosterone leads to an increase in the number of pre-antral follicles and increases the mRNA expression FSH receptors in the ovary (Vendola et al., 1998; Weil et al., 1999). In women, the use of exogenous androgens in the form of dehydroepiandrosterone (DHEA) has been associated with improved follicular response to gonadotrophin stimulation (Casson et al., 2000). Because DHEA is a precursor to many other hormones, it is difficult to know the direct mechanism of action with this medication.

A recent published study using testosterone to pretreat women who had poor ovarian reserve (previous poor ovarian response to gonadotrophins, or day 3 FSH >12 IU l−1 and E2 >70 pg ml−1, and day 3 inhibin B <45 pg ml−1) found minimal differences in number of follicles recruited and no differences in outcomes when compared with those treated with placebo prior to an IVF cycle (Massin et al., 2006). In that study, the average total testosterone level was 53 ng dl−1 at baseline and rose to 155 ng dl−1 following a maximum of 20 days with 10 mg per day transdermal gel testosterone supplementation. These women may have had severely compromised ovarian responsiveness that was beyond salvage as evidenced by their increased FSH levels. Conversely, the lack of effect of testosterone in this study may be related to the normal testosterone levels at baseline. In other words, exogenous testosterone may only have an effect when women have low or low-to-normal baseline testosterone levels. It has been shown that women with low levels of testosterone (<20 ng dl−1) have lower pregnancy rates in IVF cycles while requiring more units of gonadotrophins. This could be helpful in patients with Kallmann’s syndrome or in women with low testosterone levels for other reasons. Further study for this use of testosterone is warranted.

Despite the benefits of testosterone in our patient, this remains a study of one patient. Unfortunately, the patient did not conceive, despite the improved ovarian response. There are several potential reasons why our patient did not conceive. Simple chance could have a role as we only produced three ovulatory cycles. We may not have found the optimal dose, duration and timing of testosterone supplementation. Implantation could have been adversely affected, but in two human studies that used testosterone pretreatment for IVF, pregnancies occurred and resulted in delivery, so any potential negative effect on implantation is not absolute (Balasch et al., 2006; Massin et al., 2006). The findings in this patient and other studies suggest that testosterone supplementation may improve follicular response to gonadotrophins. This could be helpful in patients with Kallmann’s syndrome or in women with low testosterone levels for other reasons.

References


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