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Research Letter

Successful pregnancy in a woman with Kallmann's syndrome using human menopausal gonadotropin followed by low-dose human chorionic gonadotropin in the mid-to-late follicular phase

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Kallmann's syndrome is characterized by hypogonadotropic hypogonadism and anosmia [1]. It is a rare disorder, occurring in only one per 50,000 women [2]. Induction of ovulation in women with hypogonadotropic hypogonadism requires follicle-stimulating hormone (FSH) for follicular growth, and both FSH and luteinizing hormone (LH) to induce optimal follicular steroidogenesis and ovulation. Numerous reports of achieving successful pregnancies in women with Kallmann's syndrome have appeared in the literature. Recent evidence suggests that low-dose human chorionic gonadotropin (hCG) can also be used to mimic LH actions on developing follicles in a more sustained and stable manner, permitting the progression of folliculogenesis when the LH/hCG receptors begin to be expressed in the granulose cells of larger ovarian follicles [3]. More specifically, serum levels of hCG during human menopausal gonadotropin (hMG) administration were inversely correlated with the occurrence of small preovulatory follicles [4]. We describe here a woman with Kallmann's syndrome who was treated with a combination of hMG and low-dose hCG to achieve ovulation induction and successful pregnancy.

A 29-year-old woman was referred to our hospital for investigation and treatment of infertility. She was first seen at the age of 19 years with a complaint of primary amenorrhea, having presented without any secondary characteristics and anosmia. She had very low serum gonadotropin and estrogen levels, and inadequate responses to repeated gonadotropin-releasing hormone (GnRH) tests. In addition, olfactory magnetic resonance imaging (MRI) revealed olfactory tract agenesis. She was diagnosed with Kallmann's syndrome and had irregularly taken oral contraception since then. When she later presented to our reproductive center at 29 years old, physical examination revealed her to be overweight (body mass index = 27.6 kg/m^2), at Tanner stage 3 for breast development, and at Tanner stage 2 for pubic and axillary hair. The serum level of FSH and LH concentration was < 0.5 IU/L, and the estradiol (E2) concentration was 13 pmol/L. Her serum prolactin and thyroid-stimulating hormone levels were within normal range. The patient complained of anosmia. She did not have color blindness, visual abnormalities, or any other congenital abnormalities. Her husband's semen analysis was normal.

To induce the gonadotropin receptors at the ovarian level, we administered hormone therapy with estrogen and progesterone to reprogram the menstrual cycle before ovarian stimulation. Follicular stimulation was initiated with human menopausal gonadotropin (Menopur, Ferring Pharmaceuticals Ltd, Germany) at a dose of 150 IU/day for 6 days starting on Day 1 of her menstrual cycle. On cycle Day 6,100 IU of recombinant human FSH (Puregon, Organon Laboratories Ltd, Cambridge, UK) was introduced, because an adequate follicular development and serum level of E2 had not been achieved. After 23 days of treatment, the patient had only one dominant follicle that had reached a diameter of > 1.6 cm. There was an appropriate endometrial thickening of 13 mm and a serum E2 level of 1117 pmol/L. On Day 24, 5000 IU of hCG (Profasi, Serono, Italy) was administered intramuscularly for ovulation. The total dose of FSH was 1800 IU, which was given over 18 days of stimulation. Intrauterine insemination (IUI) was performed 36 hours after the injection of hCG. On the day following the IUI, micronized progesterone at 400 mg daily was started to provide luteal phase support. Unfortunately, the woman did not become pregnant and suffered from withdrawal bleeding 2 weeks later.

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Table 1
Methods of ovulation induction in women with previously diagnosed Kallmann's syndrome since 1990.

Year (reference no.)	Stimulation	No. of follicles sized > 1.6 cm on hCG day	Max. E2 level (pmol/L)	No. of pregnancies (patients)
1992 (11)	Leuprolide acetate followed by hMG	[a]	[a]	1 (1)
1995 (2)	Pulsatile GnRH or hMG	[a]	[a]	9 (3)
1996 (12)	Recombinant FSH and LH	1	760	1 (1)
1998 (13)	hMG	Mean 2.5	Mean 1540.6	5 (3)
2000 (14)	Highly purified FSH	3	[a]	1 (1)
2001 (15)	hMG	[a]	[a]	1 (1)
2005 (16)	hMG	2	[a]	1 (1)
2007 (17)	hMG pretreated with testosterone patch	1	348	0 (1)
2007 (18)	hMG	1	235	1 (1)
Case	hMG followed by low-dose hCG	4	1952	1 (1)

FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; hMG = human menopausal gonadotropin; LH = luteinizing hormone.
[a] Information not available.

The patient commenced a second cycle of treatment using the same dose of hMG (150 IU/day). During the ovarian stimulation, we monitored the follicular growth and serum E2 concentration. After 20 days of treatment, 200 IU of hCG per day were added, and after Day 27, 112.5 IU/day FSH (Gonal F, Serono Laboratories, Rome, Italy) were added. After 35 days of stimulation, an endometrial thickness of 13 mm, four follicles with a mean diameter of > 1.6 cm, and a serum E2 level of 1952 pmol/L were obtained. Trigger ovulation was administered with 5000 IU hCG, followed by an IUI 2 days later. The total dose of FSH was 900 IU, which was given for 8 days. The patient conceived and an ultrasound scan confirmed a viable twin intrauterine pregnancy. Two healthy infants weighing 2685 g and 2355 g were delivered via cesarean section at a gestational age of 36 weeks.

Kallmann's syndrome, a disorder characterized by hypogonadism resulting from hypogonadotropism and anosmia, was first reported as a genetic syndrome by Kallmann et al. in 1944 [1]. The incidence of the condition in women is approximately 1:50,000 [2]. It may be associated with some congenital abnormalities, including midline defects (e.g., cleft lip, palate, and transverse facial cleft), renal abnormalities (agenesis), color blindness, neurosensorial deafness, and platelet dysfunction.

Infertility in women with Kallmann's syndrome results from inadequate hypothalamic secretion of GnRH characterized by very low FSH and LH. Consequently, these hormones need to be replaced and ovulation induction is necessary to achieve pregnancy. Various ovulation induction treatments have been attempted for infertile women with this syndrome, such as using pulsatile GnRH, FSH and LH, or hMG [5−10]. In the literature, few pregnancies in women with Kallmann's syndrome have been reported since 1990 (Table 1) [2,11−18]. To our knowledge, the case reported herein is the first published case in which low-dose hCG was used in the mid-to-late follicular phase, in conjunction with an IUI, to achieve pregnancy in a woman with Kallmann's syndrome.

Although ovulation induction using purified FSH or recombinant FSH for infertile women with Kallmann's syndrome has been previously attempted, these gonadotropins may produce an inadequate estradiol level, require more ampoules of menotropin, and result in fewer preovulatory follicles and a reduced occurrence of ovulation. We therefore selected low-dose hMG initially for triggering ovulation induction. The main difference in ovulation induction approach between the first and second cycle was making use of hCG in the mid-to-late follicular phase. With our patient, low-dose hCG was used in mid-to-late follicular phase of the second cycle and resulted in a higher E2 level (1952 vs. 1117 pmol/L), more larger preovulatory follicles, and fewer small preovulatory follicles. We also had more dominant follicles and higher E2 levels compared to the previous case reports (Table 1).

Early follicular phase prevalence of FSH is essential to follicle recruitment, whereas later LH increments are critical for dominant follicle selection and maturation at a time of declining FSH levels [19]. The granulosa cells (GC) of the larger follicles (roughly following achievement of a 10-mm diameter) become responsive to LH through the expression of LH/hCG receptors induced by FSH and estrogens [20], thus making them sensitive to LH activity stimulation. Filicori et al. [3] demonstrated that the administration of low-dose hCG in the last 3−4 days of ovarian stimulation was associated with a more estrogenized intrafollicular environment, fewer small preovulatory follicles, higher fertilization rates, and no signs of premature luteinization. A recent study obtained similar results when assessing the use of selective hCG in the late follicular phase in a larger series [21].

In our case, the effect of using low-dose hCG in the late follicular phase was the same as in previous studies. For this reason, we believe that low-dose hCG may play a role in inducing a higher hyperestrogenized environment and attaining follicular growth synchronization.

In conclusion, administering hMG in combination with a low-dose of hCG in the mid-to-late follicular phase may be used in women with Kallmann's syndrome for ovulation induction and pregnancy.

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