**FERTILITY AND STERILITY®**
*VOL. 73, NO. 2, FEBRUARY 2000*

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

# Successful induction of ovulation using highly purified follicle-stimulating hormone in a woman with Kallmann's syndrome

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**Objective:** To describe a woman with Kallmann's syndrome who was treated successfully with highly purified FSH to achieve ovulation induction and pregnancy.

**Design:** Case report.

**Setting:** University hospital.

**Patient(s):** A 32-year-old woman with Kallmann's syndrome who had been treated with oral contraceptives to prime secondary sex characteristics and genital organs since the age of 16 years.

**Intervention(s):** Highly purified FSH was administered intramuscularly for a total dose of 3,825 IU.

**Main Outcome Measure(s):** Follicle number and diameter.

**Result(s):** Three follicles with a diameter of >1.7 cm and an endometrial thickness of 8 mm were observed. A clinical pregnancy, which subsequently was spontaneously aborted, was obtained.

**Conclusion(s):** In primed patients with Kallmann's syndrome, highly purified FSH may be a useful alternative to pulsatile GnRH or menopausal gonadotropins to achieve ovulation induction and pregnancy. (Fertil Steril® 2000;73:284–6. ©2000 by American Society for Reproductive Medicine.)

**Key Words:** Kallmann's syndrome, COH, anosmia, hypogonadism, ART

In 1856, Maestra de San Juan first reported the pathologic association of hypogonadism and absence of the olfactory system, and in 1944, Kallmann described the association as a genetic syndrome. The cause of the hypogonadism and anosmia that characterize the syndrome is a congenital, isolated GnRH deficiency resulting from aplasia of both GnRH-secreting cells and olfactory bulbs. Pituitary function usually is normal and adrenal and thyroid function is preserved. The incidence of Kallmann's syndrome in females is about 1:50,000, and the condition may be associated with some congenital abnormalities (e.g., cleft lip and palate, renal agenesis, cardiac anomalies, and abnormal platelet function).

Only a few pregnancies have been reported in the literature in patients with Kallmann's syndrome. Until now, ovulation induction has been achieved by the combined administration of human pituitary gonadotropins or hMG with hCG, or by the long-term administration of pulsatile GnRH through an infusion pump (1, 2).

This article describes a woman with Kallmann's syndrome who was treated with a combination of highly purified FSH and hCG to achieve ovulation induction and pregnancy.

## CASE REPORT

A 32-year-old hypogonadotropic woman presented to our Infertility Clinic for investigation and treatment. She was first seen at the age of 16 years and had presented with incomplete pubertal development, primary amenorrhea, and anosmia. She had very low serum levels of FSH, LH, and $E_2$. Her serum prolactin level was in the lower part of the normal range, whereas her adrenal and thyroid hormone levels were normal. The woman did not have color blindness, visual abnormalities, or other congenital abnormalities.

Plain skull roentgenograms and computed

Received June 1, 1999; revised and accepted September 8, 1999.

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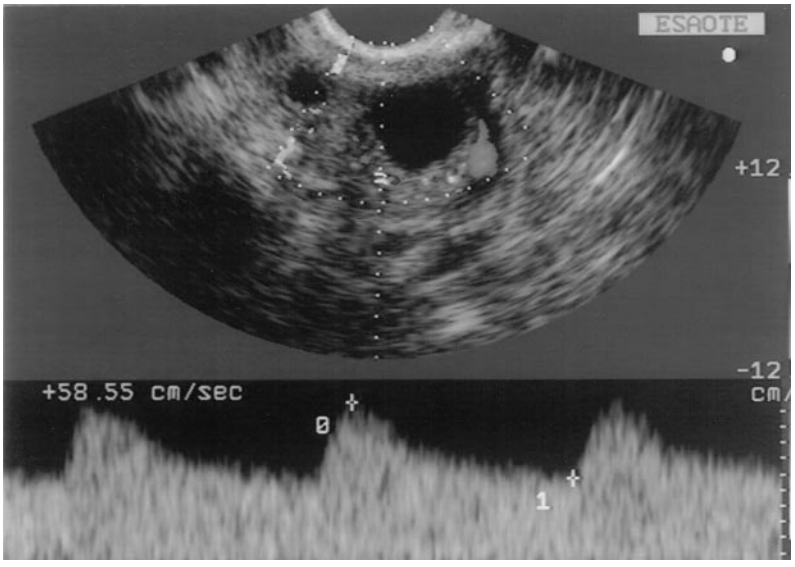
0015-0282/00/$20.00
PII S0015-0282(99)00535-X

**FIGURE 1**

A normally vascularized corpus luteum, in the right ovary, on Doppler analysis. Two similar corpora lutea were observed in the left ovary.




*Battaglia. Ovulation in Kallmann's. Fertil Steril 2000.*

tomography of the pituitary gland were normal. A normal 46,XX karyotype was present. Laparoscopy revealed normal pelvic structures with hypoplastic internal genitalia and patent tubes. An ovarian biopsy demonstrated primordial follicles near the ovarian surface. The clinical presentation suggested the diagnosis of Kallmann's syndrome and the patient underwent oral contraception for priming of her secondary sex characteristics and genital organs.

At the time of her presentation to our center, a physical examination revealed normal weight (body mass index = 22.7), normal breast development, and normal amounts of axillary and pubic hair. On day 3 of the menstrual cycle, after she had taken a combined monophasic oral contraceptive containing 20 $\mu$g of ethinyl $E_2$ and 150 $\mu$g of desogestrel (Mercilon; Organon Italia; Rome, Italy) daily for 21 days, the serum FSH concentration was 1.7 IU/L, the LH concentration was 1.1 IU/L, and the $E_2$ concentration was 90 pmol/L. At ultrasonographic examination, performed with the use of a 6.5-MHz transvaginal transducer (Au 4 Idea; Esaote, Milan, Italy), the uterine (64 mL), right ovarian (3.8 mL), and left ovarian (2.9 mL) volumes were below our reference ranges established in normally ovulating patients. Tubal patency was confirmed by color Doppler hysterosalpingography (3). Her partner was fertile according to World Health Organization standards.

To induce gonadotropin receptors at the ovarian level, a combined monophasic oral contraceptive (Mercilon; Organon Italia) was administered before ovarian stimulation was initiated. Ovulation induction first was attempted with an IV GnRH (0.8 mg, Lutrelef; Serono, Rome, Italy) delivered through a computerized infusion pump (Zyklomat pulse; Ferring, Milan, Italy). The pulse frequency was set at 1 pulse every 90 minutes and the GnRH dosage was increased progressively from 10 $\mu$g per pulse to a maximum of 30 $\mu$g per pulse. A single follicle was obtained; when it reached a mean diameter of $>$1.7 cm, 10,000 IU of hCG (Profasi; Serono) was administered intramuscularly. Intrauterine insemination was performed 36 hours after the injection of hCG. The patient did not conceive. Because of physical and psychologic discomfort, the patient refused to repeat the ovarian stimulation protocol with an IV GnRH.

After another month of oral contraceptive treatment, on the first day of the menstrual cycle, the patient underwent ovulation induction with highly purified FSH (Metrodin HP; Serono) because hMG was not commercially available in Italy. The total dose of Metrodin HP was 3,825 IU given over 23 days of stimulation. An endometrial thickness of 8 mm and three follicles with a mean diameter of $>$1.7 cm were obtained, after which 10,000 IU of hCG (Profasi; Serono) was administered intramuscularly.

Intrauterine insemination was performed 36 hours after the injection of hCG. Intramuscular injections of hCG (2,000 IU) were prescribed for luteal support on alternate days until serum $\beta$-hCG was assayed. Normally functioning corpora lutea, as evidenced by Doppler flow analysis, were obtained (Fig. 1) and a clinical pregnancy was diagnosed by ultra-

sonographic evidence of embryonic heart activity at 7 weeks. One week later, the pregnancy ended in miscarriage. The couple is now on a waiting list for IVF treatment.

## DISCUSSION

Infertility in women with Kallmann's syndrome is caused by inadequate hypothalamic secretion of GnRH and, consequently, a deficiency in the FSH and LH that are required for follicular recruitment and growth and luteal function. Fertility therapies, therefore, are designed to replace these hormones. Pulsatile GnRH, by restoring the release of both FSH and LH from the pituitary, may be considered the treatment of choice. It results in a unifollicular cycle and has an acceptable pregnancy rate and a low rate of multiple pregnancy (1). Pituitary and menopausal gonadotropins, with fixed doses of FSH and LH, have been the alternative therapy for ovulation induction (2). To our knowledge, the case reported herein is the first published case in which highly purified FSH was used, in conjunction with IUI, to achieve a pregnancy in a woman with Kallmann's syndrome.

Over the last 15 years, a preparation of highly purified urinary FSH has been available for clinical use. The purification techniques have resulted in a product with a high purity (>95% of the protein content is FSH) and a very low residual content of LH (<0.1 IU per 1,000 IU of FSH). The relative importance of LH in the follicular phase and its role in follicular growth and maturation is uncertain.

There is some evidence to suggest that exogenous LH is not necessary for adequate folliculogenesis during controlled ovarian hyperstimulation, and that the clinical effectiveness of gonadotropin preparations correlates with the amount of FSH administered (4). However, Shoham et al. (5) demonstrated that treatment with FSH alone did not result in follicular $E_2$ secretion and concluded that LH is fundamental for ovulation induction. Our data contradict those of Shoham et al. (5) and show that FSH alone is adequate for the recruitment and growth of primordial follicles and that an adequate amount of estrogen, as demonstrated by the thickness of the endometrium, can be induced.

We believe that the maturational effect of oral contraceptives on the pituitary and uterus is important in determining ovarian sensitivity to gonadotropins through the induction of specific receptors at the ovarian level. Further, it may be that theca cells require very low levels of LH to produce androgens, which then are aromatized to estrogens by the granulosa cells, and the administration of hCG allows normal luteinization.

In conclusion, although treatment with pulsatile GnRH or hMG seems more reasonable, our results indicate that, in primed patients with Kallmann's syndrome, the use of highly purified FSH may be a viable alternative for ovulation induction and pregnancy.

### References


1. Crowley WF Jr, McArthur JW. Stimulation of the normal menstrual cycle in Kallmann's syndrome by pulsatile administration of luteinizing-releasing hormone. J Clin Endocrinol Metab 1980;51:173–5.
2. Chryssicopoulos A, Gregoriu O, Papadias C, Loghis C. Gonadotropin ovulation induction and pregnancies in women with Kallmann's syndrome. Gynecol Endocrinol 1998;12:103–8.
3. Battaglia C, Artini PG, D'Ambrogio G, Genazzani AD, Genazzani AR, Volpe A. Color Doppler hysterosalpingography in the diagnosis of tubal patency. Fertil Steril 1996;65:317–22.
4. Howles CM, Loumaye E, Giroud D, Luyet G. Multiple follicular development and ovarian steroidogenesis following subcutaneous administration of a highly purified urinary FSH preparation in pituitary desensitized women undergoing IVF: a multicentre European phase III study. Hum Reprod 1994;9:424–30.
5. Shoham Z, Balen A, Patel A, Jacobs HS. Results of ovulation induction using human menopausal gonadotropin or purified follicle-stimulating hormone in hypogonadotropic hypogonadism patients. Fertil Steril 1991;56:1048–53.