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Preservation of fertility despite subnormal gonadotropin and testosterone levels after cessation of pulsatile gonadotropin-releasing hormone therapy in a man with Kallmann's syndrome*

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Idiopathic hypogonadotropic hypogonadism (IHH) is a clinical syndrome characterized by low or low-normal gonadotropin levels, subnormal T levels, and failure to undergo puberty, presumably due to an isolated deficiency of GnRH (1, 2). Idiopathic hypogonadotropic hypogonadism is not a single entity; it represents a spectrum of diseases ranging from absence of GnRH secretion with no detectable gonadotropin pulses to partial GnRH deficiency with evidence of sporadic pulsatile LH secretion, especially during sleep (1).

In most men with IHH, administration of pulsatile GnRH results in normalization of gonadotropin and T levels and, in many cases, in initiation and maintenance of spermatogenesis (1). In nearly all such men treated with GnRH, discontinuation of therapy results in a return to pretreatment status, with cessation of pulsatile gonadotropin secretion; however, Finkelstein et al. (2) described four men with IHH in whom LH pulses persisted 3 to 61 weeks after discontinuation of GnRH. In three of the men, T levels remained in the normal range. Sperm counts were not reported in these men. Recently, one of our patients with IHH and anosmia (Kallmann's syndrome) presented to us 1 year after discontinuation of pulsatile GnRH (and while receiving no other hormonal therapy) with persistent spermatogenesis and a successful pregnancy despite subnormal serum LH and T levels.

CASE REPORT

The patient was first seen in 1980 when he sought treatment for failure to go through puberty by age 23. Initial workup revealed normal thyroid function tests, PRL, and GH level, very low serum T level, and undetectable gonadotropins, without response to clomiphene citrate (CC) stimulation. His mother had a normal pregnancy and delivery, although she had received oral diethylstilbestrol during pregnancy. There was no family history of delayed puberty, infertility, anosmia, or congenital defects. Except for an umbilical hernia repair, he had an uneventful childhood. He was similar in height to his father and older brother. Gynecomastia had been present since adolescence. Occasional erections were noted beginning at age 16. He had developed sparse pubic hair over the previous 1.5 years, but he had no axillary hair. He had no sense of smell; anosmia was confirmed by formal testing. On physical exam, gynecomastia was present; the phallus measured 2 cm, the scrotum was prepubertal, and the testes measured 2.2×1.2 cm bilaterally. Repeat testing showed that serum gonadotropins were undetectable (LH < 0.8 mIU/mL [0.8 IU/L]

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and FSH < 1.3 mIU/mL [1.3 IU/L] in the assays used at that time). Serum T was 0.14 ng/mL (0.5 nmol/L; normal range in our laboratory: 2.90 to 8.65 ng/mL [10.0 to 30.0 nmol/L]). A wrist roentgenogram showed a bone age of 15 to 16 years.

The patient was begun on hCG, 2,000 IU IM three times weekly. Eighteen months later, while continuing hCG therapy, he and his wife conceived a child. Preparations containing FSH were not required. Over the next 8 years, he was treated intermittently with hCG, pulsatile GnRH, and T enanthate. When not receiving hCG or GnRH, his serum gonadotropins were very low or undetectable; however, three more children were conceived with hormonal therapy. After completing research protocols with pulsatile GnRH in January 1990, he was prescribed T enanthate. He was not seen again until April 1991, at which time he reported taking T shots irregularly during the first few months after discontinuing GnRH and essentially no injections during the 12 months before the clinic visit. He shaved twice a day and reported a good energy level despite frequent lack of sleep. He had noticed no change in libido or sexual function since discontinuing the pump. One month later, a fifth pregnancy was confirmed in his wife. The patient's seminal fluid showed a sperm count of 25×10^6/mL, with 70% motility at 1 hour and normal morphology. Serum LH was 2.1 mIU/mL (2.1 IU/L); FSH, 2.7 mIU/mL (2.7 IU/L) (normal ranges of LH and FSH in the current assay: LH, 2 to 12 mIU/mL, [2 to 12 IU/L]; FSH, 1.8 to 13 mIU/L [1.8 to 13 IU/L]); and T, 0.81 ng/mL (2.8 nmol/L). On repeat, the sperm count was 45.6×10^6/mL with 85% motility at 30 minutes; serum LH, FSH, and T were 2.2 mIU/mL (2.2 IU/L), 2.7 mIU/mL (2.7 IU/L), and 1.02 ng/mL (3.5 nmol/L), respectively.

To assess his hormonal secretory capacity, CC (50 mg twice daily) was administered for 7 days. Blood samples were collected every 10 minutes for 12 hours before and after 7 days of CC. Gonadotropin and T levels decreased slightly during CC (Table 1). Pulse analysis showed small but distinct LH pulses, which did not change in frequency during CC. The patient complained of progressive lethargy and moodiness over the preceding weeks; therefore, after completing CC, he began injections of T enanthate, 200 mg every 10 to 14 days. Two months later, serum LH was 0.9 mIU/mL (0.9 IU/L), FSH was <0.5 mIU/mL (<0.5 IU/L), and serum T was 7.49 ng/mL (26.0 nmol/L). He has continued regular injections, with an increase in energy level and general well-being. A healthy baby boy was delivered at 36 weeks gestational age because of severe pre-eclampsia in the mother. Haplotyping showed that father and son shared alleles at each human lymphocyte antibody locus tested.

Table 1 Serum LH, FSH, and T Levels and LH Pulse Frequency in the Patient Before and After 7 Days of CC, 50 mg Twice Daily

	Before CC	On CC	Normal range
Mean serum LH (mIU/mL)*	1.3	0.8	2.0–12.0
Mean serum FSH (mIU/mL)*	2.8	2.3	1.8–13.0
Mean serum T (ng/mL)†	1.66	1.30	2.90–8.65
Number LH pulses/12 h	8	10	4.0–8.0

* Conversion factor to SI units, 1.0.
† Conversion factor to SI units, 3.47.

DISCUSSION

Our patient presented with hypogonadotropic hypogonadism with anosmia (or Kallmann's syndrome) over an 11-year period, he remained hypogonadotropic and hypogonadal when not receiving hormonal therapy. At age 34, however, he returned with apparently normal spermatogenesis and low-normal FSH levels despite persistently low LH and T levels. He therefore represents a hitherto unreported syndrome of partial reversal of hypogonadotropic hypogonadism.

This patient differs from the men reported by Finkelstein et al. (2); after discontinuing pulsatile GnRH, those men maintained normal LH and T levels and normal pulsatile LH secretion, with higher than normal FSH levels; long-term treatment with GnRH appeared to stimulate increased pituitary responsiveness to small amounts of endogenously secreted GnRH or to stimulate the men's own ability to secrete GnRH. In our patient, we found evidence of pulsatile LH secretion, albeit of low pulse amplitude, suggesting that perhaps endogenous GnRH secretion was stimulated by treatment with exogenous hormones. Gonadotropin secretion was suppressed and LH pulse frequency was not increased during CC administration. This response is characteristic of prepubertal children, whereas the mature axis is stimulated by CC (3). Hypothalamopituitary function in our patient was therefore restored to a lesser degree than in those men studied by Finkelstein et al. (2).

In our patient, FSH levels 18 months after discontinuation of pulsatile GnRH were in the low-normal male range whereas LH levels were

persistently subnormal. This pattern is characteristic of early puberty. It is possible that, in this man, FSH responsiveness to small amounts of endogenous GnRH was enhanced by exposure to pulsatile exogenous GnRH, while LH responsiveness was largely unchanged. Alternatively, secretion of a separate FSH-stimulating factor could have been induced by treatment with exogenous GnRH. It is also possible that this man represents a variant of the "fertile eunuch" syndrome, in which FSH levels and spermatogenesis are relatively maintained despite markedly reduced Leydig cell function (4); this possibility is supported by the patient's ability to become fertile on hCG alone, without FSH-containing preparations. Several case reports exist of paternity in IHH patients receiving T replacement (5, 6). Because our patient stated that he had taken T only rarely since discontinuing GnRH therapy, a major stimulatory role of T is less likely in this case. We are unaware of any other patients with IHH who have maintained spermatogenetic capacity after long-term discontinuation of pulsatile GnRH or gonadotropin administration and without other hormonal therapy. It now appears, therefore, that in addition to a spectrum of presentations of the syndrome of IHH, there is also a spectrum of spontaneous partial recovery from this syndrome.

SUMMARY

A man with IHH and anosmia presented in 1980. He was successfully treated with various hormonal regimens; four children were conceived with hCG or pulsatile GnRH therapy. The patient discontinued GnRH after the fourth child was conceived, and testosterone enanthate injections were prescribed. However, he took the injections only briefly and 15 months later he demonstrated continuing spermatogenesis despite low serum FSH and LH levels. His wife successfully became pregnant. This case adds to the recognized range of recovery in IHH, with fertility despite stopping hormonal therapy and despite low serum gonadotropin and T levels.

Key Words: Hypogonadism, fertility, spermatogenesis.

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