CASE REPORT

A man with hypogonadotropic hypogonadism successfully treated with nasal administration of the low-dose gonadotropin-releasing hormone analog buserelin

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Objective: To report a patient with hypogonadotropic hypogonadism of hypothalamic origin successfully treated with nasal administration of a low-dose gonadotropin-releasing hormone (GnRH) analogue.
Design: Case report.
Setting: A reproductive medical center.
Patient(s): A 37-year-old man with anejaculation and infertility.
Intervention(s): Nasal administration of a low-dose GnRH analogue, buserelin.
Main Outcome Measure(s): Semen analysis and serum levels of gonadotropins and testosterone after nasal buserelin use.
Result(s): The patient's laboratory examination showed low serum levels of gonadotropins and testosterone. After being diagnosed with hypogonadotropic hypogonadism, 15 μg of buserelin acetate spray was administrated in each nostril three times a day (total: 90 μg/day). This therapy improved semen parameters and serum gonadotropin and testosterone levels. After approximately 1 year of this treatment, the patient's serum gonadotropin and testosterone levels remained in the normal range and semen analysis showed normozoospermia. The patient and his wife were treated with intracytoplasmic sperm injection, resulting in pregnancy.
Conclusion(s): A low-dose buserelin nasal spray appears to be an effective and well-tolerated therapeutic option for patients with hypogonadotropic hypogonadism of hypothalamic origin. (Fertil Steril® 2009;92:1169.e1–e3. ©2009 by American Society for Reproductive Medicine.)

Key Words: Hypogonadotropic hypogonadism, GnRH analogue, buserelin

Hypogonadotropic hypogonadism results from the absence of gonadotropins, which means the condition is due to either the lack of the hypothalamic decapeptide gonadotropin-releasing hormone (GnRH) or a problem with the pituitary gland. Treatment of hypogonadotropic hypogonadism may be initiated for two purposes: androgenization and fertility. The induction of puberty, secondary sex characteristics, and spermatogenesis in men with hypogonadotropic hypogonadism can be successfully achieved using gonadotropins (1–6) or pulsatile GnRH (7–9). In hypothalamic disorders, pulsatile GnRH or gonadotropins can be used alternatively, but patients with pituitary insufficiency can only be treated with gonadotropins. However, prolonged continuous therapy is necessary to achieve satisfactory outcomes. Pulsatile GnRH therapy is not an ideal treatment because of the need for daily injections using a portable infusion pump. Currently, the basic therapy for male patients with hypogonadotropic hypogonadism consists of gonadotropins. This gonadotropin therapy needs two to three injections a week at a hospital clinic. Thus, a less cumbersome treatment is needed.

This report describes a 37-year-old man with postpubertal onset hypogonadotropic hypogonadism of hypothalamic origin successfully treated with nasal administration of a low-dose GnRH analogue, which resulted in normalization of sperm concentration and intracytoplasmic sperm injection (ICSI) pregnancy.

Received February 22, 2009; revised May 24, 2009; accepted May 27, 2009; published online July 9, 2009.
H.I. has nothing to disclose. A.Y. has nothing to disclose. H.S. has nothing to disclose. M.T. has nothing to disclose. N.W. has nothing to disclose. T.N. has nothing to disclose.
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CASE REPORT

The patient, a 37-year-old man, was referred to our clinic for anejaculation and primary infertility of 10 years. He had

otherwise always been in excellent health, had no deficiencies in smell, and no history of encephalitis or brain trauma. There was no family history of infertility or defective sexual development. His wife was 35 years old, and her transvaginal sonographic examination showed multiple uterine myomas.

His physical examination revealed normal development of secondary sexual characteristics. Both testes were normally descended in the scrotum, but they were very small (5 mL each). The epididymides were also small, without presenting dilatations. The vasa deferentia were both palpable, and no varicoceles were detected. Laboratory investigation showed that serum follicle-stimulating hormone (FSH) level was 0.44 mIU/mL (reference range: 3.9–12.0 mIU/mL), testosterone level was 0.21 ng/mL (reference range: 3.0–10.6 ng/mL), and prolactin level was 9.11 ng/mL (reference range: 5.0–35.0 ng/mL). Serum luteinizing hormone (LH) was at undetectable level (reference range: 1.5–8.0 mIU/mL). The patient's karyotype, with Giemsa banding, was a normal 46,XY, and no deletions in AZFa, AZFb, or AZFc were observed (10). Semen analysis could not be performed at this time because of anejaculation.

The GnRH analogue treatment was initiated with 90 μg a day of buserelin acetate nasal spray (Suprecur; Sanofi Aventis, Tokyo, Japan). Because one spray of unaltered Suprecur contained 150 μg of buserelin acetate, it was diluted to 10% of the original concentration with sterile saline. Thus, 15 μg (one spray) of buserelin acetate was administrated in each nostril three times a day. After we had obtained informed consent, we started the therapy with the above regime while we intended to titrate empirically the dosage of the analogue by assessing hormonal levels. It is interesting that we found the initial dose was effective in this case on stimulating gonadotropin secretion without down-regulation; therefore, we maintained the dosage throughout the treatment period.

Twenty-six days after starting treatment, the patient's serum FSH, LH, and testosterone levels had increased to 13.14 mIU/mL, 7.28 mIU/mL, and 5.45 ng/mL, respectively. Furthermore, after 105 days, he was able to ejaculate (the analysis of the semen revealed only one nonmotile sperm after centrifugation); after 158 days, his sperm count had risen to 1.4 $\times$ 10^6/mL. The GnRH analogue treatment was continued, and after approximately 1 year of this treatment, his serum FSH, LH, and testosterone levels remained in the normal range, and the semen analysis revealed normozoospermia (Table 1).

After the achievement of normozoospermia, the couple failed to conceive after several cycles of natural intercourse, after which they sought medical intervention. The patient's wife was treated with two cycles of intrauterine insemination (IUI) and six cycles of ICSI, but no pregnancy followed. The couple initially did not want any surgical treatment on the uterine fibroids; however, they finally made the decision to undergo myomectomy after the six ICSI failures. The patient's wife underwent myomectomy, and 16 uterine myoma nodules were removed. After the operation, the couple was treated with three more cycles of ICSI, and the latest cycle resulted in pregnancy. The outcome was a caesarean section delivery of a 2480 g healthy female infant without congenital abnormalities at 37 weeks' gestation.

DISCUSSION

Male infertility due to hypogonadotropic hypogonadism, characterized by oligozoospermia (or azoospermia) and low serum levels of gonadotropin and testosterone, is very rare, accounting for approximately 1% to 2% of cases (11). For patients with hypogonadotropic hypogonadism, hormone therapy using gonadotropins has been reported to be successful in inducing spermatogenesis. However, to achieve satisfactory outcomes, long-term hormone therapy (for 2 or more years) is needed. It has been reported that spermatogenesis

TABLE 1

Serum hormone levels and semen parameters during the gonadotropin-releasing hormone analogue therapy.

	Days[a]												
Parameter	0	26	91	105	134	158	220	245	386	413	654	1104	1575
LH (mIU/mL)	<0.10	7.28	3.39	—	2.70	—	3.24	—	2.68	—	—	—	—
FSH (mIU/mL)	0.44	13.14	13.26	—	13.06	—	14.83	—	5.41	—	—	—	—
T (ng/mL)	0.21	5.45	4.63	—	2.10	—	1.33	—	5.17	—	—	—	—
PRL (ng/mL)	9.11	15.86	18.74	—	12.75	—	23.14	—	25.79	—	—	—	—
Vol. (mL)	—	—	—	1.1	—	1.5	—	1.8	—	3.0	1.8	2.0	2.5
Conc. ($\times 10^6$/mL)	—	—	—	1 sperm[b]	—	1.4	—	1.9	—	25.3	34.8	50.0	59.0
Motil. (%)	—	—	—	0	—	46.7	—	31.6	—	50.0	44.3	53.4	39.5

Abbreviations: Conc., sperm concentration; FSH, follicle-stimulating hormone; LH, luteinizing hormone; Motil., sperm motility; T, testosterone; PRL, prolactin; Vol., semen volume.

[a] Days after the treatment started.

[b] Analyzed pellet after centrifugation.

Iwamoto. Buserelin therapy for hypogonadism. Fertil Steril 2009.

has been achieved after several months of hormonal treatment (1–6). Furthermore, in some trials, treatment was maintained as long as 42 (12) or 56 months (13). Because gonadotropin therapy involves two to three injections weekly at hospital clinic, this treatment is often replaced by testosterone after puberty. Although androgenization can be obtained with testosterone substitution, fertility cannot be achieved.

It also has been reported that continuous infusion of pulsatile GnRH was effective in treating hypogonadotropic hypogonadism of hypothalamic origin (7–9). However, its advantage over gonadotropins remains uncertain (8, 14, 15). Furthermore, because of the need for daily injections using a portable infusion pump, this therapy is not ideal. Because hormone treatment for hypogonadotropic hypogonadism necessitates long periods of drug intake, a simpler treatment is required.

Many GnRH analogues have been synthesized, and the use of GnRH analogues in medical treatment for male infertility due to hypogonadotropic hypogonadism has been reported in the literature (16). Continuous administration of GnRH analogues is thought to decrease gonadotropin secretion by down-regulation of the pituitary GnRH receptor. To induce spermatogenesis in men with hypogonadotropic hypogonadism, the dose and frequency used to administer the GnRH analogue play an important role in the success of the regimen. Excessive doses may induce a down-regulation of the pituitary and gonadal receptors, and low doses may be ineffective. Because of the difficulty in determining the effective dose, GnRH analogues have not been successful for treating patients with hypogonadotropic hypogonadism (8).

In the present case, we elected to use low-dose nasal GnRH analogue therapy, as it is less cumbersome compared with gonadotropin injections. To have a GnRH analogue stimulatory effect without hypophyseal down-regulation, buserelin acetate was administered at 90 μg a day in the form of 15 μg of buserelin acetate administrated in each nostril three times a day. Matsumiya et al. (17) reported that for the treatment of normogonadotropic oligoasthenozoospermia, 15 μg of buserelin acetate administrated once a day was effective to induce successful spermatogenesis without hypophyseal down-regulation, so we decided the dose and frequency of buserelin acetate considering our case was hypogonadotropic hypogonadism. This therapy improved the serum FSH, LH, and testosterone levels and semen parameters for a long period of time. In addition, this therapy has several advantages in that the nasal spray can be performed easily at home, and the therapy is not painful, and thus patient adherence to the protocol is improved.

Although the successful titration of the buserelin acetate was obtained from the initial dose, it took a total of nine ICSI cycles (6 cycles before the myomectomy) to achieve a successful conception in this case. Uterine fibroids appeared to be responsible at least partially for the repeated implantation failures.

Low-dose buserelin nasal spray appears to be an effective and well-tolerated therapeutic option for patients with hypogonadotropic hypogonadism of hypothalamic origin. The dosage and frequency of the GnRH analogue is critical to the success of the regimen.

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