CASE REPORT

Induction of spermatogenesis in isolated hypogonadotrophic hypogonadism with gonadotrophins and early intervention with intracytoplasmic sperm injection

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Idiopathic hypogonadotrophic hypogonadism (IHH) is a potentially correctable cause of male infertility. However, hormonal treatment is usually a slow process and artificial reproductive techniques such as intracytoplasmic sperm injection (ICSI) might be resorted to before full testicular response has been achieved. We report here an unusual variant of IHH of post-pubertal onset in which early intervention with ICSI was attempted. Our patient was 37 years old and presented with male infertility due to azoospermia and undetectable serum gonadotrophin concentrations. He had an apparently normal pubertal development, a testicular volume of 8 ml, normal pituitary-thyroid and pituitary-adrenal function, as well as normal computerized tomographic appearance of the sella region. A combination of human chorionic gonadotrophin (HCG) and menopausal gonadotrophins (HMG) was administered. Spermatozoa were first detected in the semen after 3 months and reached a concentration of $2 \times 10^6$/ml after 9 months. ICSI was attempted at this point; the spermatozoa had good fertilizing ability and three embryos were obtained and replaced. Unfortunately no pregnancy resulted. Treatment with 5000 IU HCG and 150 IU HMG three times per week was continued and sperm counts rose rapidly thereafter to reach $28.3 \times 10^6$/ml after 16 months of injections. His wife conceived naturally during this period and the pregnancy is now in the second trimester. This case illustrates the good prognosis of the rare patient with IHH of post-pubertal onset when treated with gonadotrophins, and suggests that ICSI procedures should be delayed until final testicular maturation is attained.

Key words: gonadotrophin/ICSI/male hypogonadotrophic hypogonadism

Introduction

Azoospermia due to hypogonadotrophic hypogonadism is a very rare but potentially curable cause of infertility (Natchigall et al., 1997). However, treatment in many of these cases may require several years of hormonal therapy (Lunenfeld et al., 1979) and, although pregnancy can occur when sperm counts are low, in many cases sperm concentrations do not reach ‘normal’ levels (Finkel et al., 1985). With the advent and purported success rates of intracytoplasmic sperm injection (ICSI) (Van Steirteghem et al., 1993), investigation and medical treatment of such men could be curtailed in favour of the latter procedure (Palermo et al., 1995). In this report we encountered a rare variant of hypogonadotrophic hypogonadism of post-pubertal onset where gonadotrophin therapy resulted in normalization of sperm concentration and spontaneous conception, whereas an earlier intervention with an ICSI procedure was not successful.

Case report

This 37 year old man was referred for primary infertility and azoospermia associated with low concentrations of follicle stimulating hormone (FSH). He did not need to shave his chin or upper lip and had sexual intercourse about once or twice a month. He had no deficiencies in smell nor any history of encephalitis or brain trauma. He did not notice anything abnormal with his sexual development at puberty and at the age of 20 years underwent a medical examination for military service and no deficiencies of secondary sexual development were noted. There was no family history of infertility or defective sexual development. He was 1.6 m tall and weighed 78 kg. There was no anosmia or visual field defects. He did not have gynaecomastia but had a prominent fat pad. Axillary hair was present and pubic hair was Tanner 4–5. The phallus was normal; and testes were normally descended, soft in consistency and each measured 8 ml. Serum FSH and luteinizing hormone (LH) were undetectable and testosterone was in the female range (0.59 ng/ml). Serum prolactin, cortisol, growth hormone and thyroid function tests were normal. His karyotype, with Giemsa banding, was a normal 46XY. Computerized tomographic scans of the pituitary, hypothalamus and suprasellar areas did not reveal any abnormal growths. Injection of gonadotrophin-releasing hormone (GnRH, Relisorm; Serono, Singapore) in the GnRH challenge test elicited a rise in gonadotrophin secretion indicating an intact pituitary response mechanism (Figure 1, inset).

Gonadotrophin treatment was initiated with i.m. human chorionic gonadotrophin 2000 IU (HCG, Profasi; Serono) and human menopausal gonadotrophins 75 IU (HMG, Pergonal; Serono) three times a week. Trough concentrations of testosterone, FSH and LH were measured at monthly intervals. Concentrations of the three hormones remained suboptimal and the thrice weekly doses of HMG and HCG were increased to 150

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IU and 5000 IU respectively, 7 months after the initiation of treatment. At this dose of gonadotrophins, testosterone and dihydrotestosterone (DHT) concentrations were maintained at the mid-range of normal Singapore males. He reported increased acne, pimples and hair growth on his shins: libido was also improved. Testicular size increased to 10 ml and his sperm count rose to ~2.0 × 10^6/ml after 9 months of injections (Figure 1). He was anxious to start infertility treatment and an ICSI procedure was decided upon. His wife was down-regulated with GnRH agonists and then follicular growth stimulated with gonadotrophins. Nine oocytes were collected by ultrasound-guided transvaginal route. The sperm concentration on that day was 1.9 × 10^6/ml. Five oocytes were injected intracytoplasmically with a single spermatozoon each and three good quality 4-cell embryos resulted, suggesting that spermatozoa were qualitatively normal. The embryos were replaced but no pregnancy resulted. Gonadotrophin treatment was continued and his serum androgen concentrations remained at the high end of normal range. After about 11 months of treatment his sperm counts rose to 6.5 and then to 28.3 × 10^6/ml after 16 months. Spermatozoa were 30–40% motile, and 40–47% of them were vital. His wife conceived spontaneously during this period and pregnancy is now well into the second trimester. Ultrasound examination of the fetus did not show any abnormality.

Discussion

Hypogonadotrophic hypogonadism secondary to pituitary or hypothalamic masses, infections, head trauma, adrenal, thyroid or chromosomal disorders were excluded in our patient (Winters, 1992). Normal pituitary function was observed in the GnRH challenge test. The diagnosis is therefore one of isolated hypogonadotrophic hypogonadism (IHH), which could be of a pre- or post-pubertal onset. The most common presentation of IHH is that of complete absence of pubertal development with minimal testicular growth (Matsumoto, 1994). The testes in such cases may be maldescended, testicular volume is usually <4 ml and treatment rarely results in complete normalization of sperm production. However patients with hypogonadism of adult or post-pubertal onset are rare (Whitcomb and Crowley, 1990). Patients with post-pubertal IHH have sufficient androgen production to initiate puberty and testicular growth and this condition represents an eminently treatable variant of male hypogonadism especially if the testicular size is >8 ml (Burrîs et al., 1988). Hormonal therapy could be with either gonadotrophins or GnRH (Schoefhol et al., 1991). We elected to use gonadotrophin therapy as it is less cumbersome compared with GnRH which has to be administered as a pulsatile infusion (Knobil, 1980). Moreover, GnRH does not significantly accelerate or augment testicular growth or hasten sperm production compared with gonadotrophins (Liu et al., 1988). Some authors favour the use of HCG to initiate spermatogenesis and to add HMG later if spermatogenesis is not sufficient (Finkel et al., 1985). Treatment in this case was with HCG and HMG as there is evidence that the combination regime is effective (Kliesch et al., 1994) and is required for all but the mildest form of IHH (Tachiki et al., 1995). The doses of both gonadotrophins were increased until trough testosterone production was optimal. This required 5000 IU and 150 IU of HCG and HMG respectively, both administered thrice weekly. Because the patient was anxious to proceed, ICSI was attempted when the spermatozoa counts reached 2.0 × 10^6/ml after some 9 months of therapy. Although good quality embryos were obtained and replaced, no pregnancy resulted. Gonadotrophin treatment was continued and, after 16 months, sperm counts reached normal values. During this period conception occurred naturally. In conclusion, this study illustrates the relevance and importance of complete evaluation of cases of male infertility to determine if treatable causes are present. Although the value of gonadotrophins in male infertility with normal pituitary function is still uncertain (Matorras et al., 1997), post-pubertal IHH responds well to gonadotrophin therapy and the chances of spontaneous pregnancy are excellent. Full testicular function should be allowed to develop before ICSI procedures are attempted.

References


Figure 1. Sperm counts following gonadotrophin therapy. The patient was treated with human menopausal gonadotrophin (HMG) and human chorionic gonadotrophin (HCG) at zero time and sperm counts assessed. An intracytoplasmic sperm injection (ICSI) procedure was performed as indicated but did not result in pregnancy. The patient’s wife conceived naturally when sperm counts rose to >15 × 10^6/ml. Inset: secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) after an i.v. bolus injection of 100 µg of gonadotrophin-releasing hormone (GnRH) at zero time. Both FSH and LH were undetectable before the administration of GnRH.

References


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