Induction of spermatogenesis in hypogonadotrophic hypogonadism

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Summary
A young male who presented with isolated bihormonal gonadotrophin deficiency is described. Basal levels of LH and FSH were low and there was no response to clomiphene citrate or LHRH. The remaining anterior pituitary function was intact. The administration of a combination of human menopausal gonadotrophin and human chorionic gonadotrophin caused testicular maturation with spermatogenesis and full androgenization. The patient was able to father a child.

Introduction
There have been a number of reports of the successful induction of spermatogenesis in male patients with the syndrome of isolated bihormonal gonadotrophin deficiency (IGD) (Johnsen, 1966; Johnsen and Christiansen, 1968; Macleod, 1970; Martin, 1967; Paulsen, Hespeland and Michaels, 1970; Rabinowitz and Spitz, 1975). This is usually achieved by treatment with human menopausal gonadotrophins (HMG) or human pituitary FSH together with human chorionic gonadotrophin (HCG) (Johnsen and Christiansen, 1968; Macleod, 1970; Martin, 1967; Paulsen et al., 1970). However, the number of reports are few and most of them antedate the era of radio-immunoassay, and the availability of dynamic tests of pituitary function.

In this report a patient with well documented IGD is described. The patient fathered a child after successful treatment with a combination of HMG and HCG which caused testicular maturation with spermatogenesis, and androgenization.

Case report
The patient was first seen at the Endocrine Clinic in 1971 when he was aged 20 years. He complained of lack of sexual development with absence of body and facial hair. He was depressed and felt that he was a source of acute embarrassment to his family. He admitted to very occasional erections, but had had no ejaculations. Past history and systematic enquiry were non-contributory. There were three other siblings in the family, one male and two females, who had all undergone normal pubertal development between the ages of 12 and 13 years.

The patient had eunuchoid body proportions. The ratio of upper segment to lower segment was 86 : 91 cm. He was sexually infantile, lacking facial or axillary hair and with minimal pubic hair. His penis and testes were small and prepubertal, and there was mild gynaecomastia. Offaction and visual fields were within normal limits.

Chest and skull X-rays were normal and his bone age corresponded to 14 years. Chromosomal analysis revealed the normal male XY pattern. Urine 17-ketosteroids and 17-hydroxycorticoids, routine haematological and biochemical blood tests, serum thyroxine and 131I uptake were all normal. Basal plasma cortisol was 15 μg/dl. In response to insulin-induced hypoglycaemia there was elevation of serum growth hormone (GH) to 31 ng/ml and of plasma cortisol to 23 μg/dl. TSH levels rose to 9 μu./ml following the administration of 200 μg thyrotrophin releasing hormone (TRH) by intravenous injection. Prolactin (PRL) levels increased from 10 to 16 ng/ml following TRH. In six normal male control subjects (aged 18–24 years) the peak (±s.d.) TSH and PRL responses to 200 μg TRH were 11·0±5·1 μu./ml and 25·8±6·2 ng/ml respectively.

Basal levels of both LH and FSH were below 3 μi.u./ml (2nd IRP HMG) which is at the limit of
sensitivity of both the LH and FSH radioimmunoassays. Testosterone levels were low and ranged from 0.5 to 1.0 ng/ml. The patient was given 150 mg clomiphene citrate/day for 5 days and the hormonal response was evaluated during the ensuing 3 weeks. LH, FSH and testosterone levels did not show any elevation (Fig. 1). The patient was unresponsive to the intravenous administration of 100 μg luteinizing hormone releasing hormone (LHRH).

He was subsequently challenged on different occasions with 200 μg and 300 μg LHRH and with three repeated pulses of LHRH at 30-min intervals. In all these tests, levels of both LH and FSH remained undetectable. Testicular biopsy showed immature tubules lined with undifferentiated germinal epithelium and Sertoli cells. There were scattered immature Leydig cells in the interstitium (Fig. 2).

In November 1971, treatment was commenced with HCG and HMG (menotrophins, Pergonal 500). According to the manufacturer’s literature, each ampoule of HMG contains 75 i.u. FSH and 75 i.u. LH. He was initially given 5000 HCG once and two ampoules of HMG three times each week. There was a dramatic clinical response. The patient’s voice deepened and he developed facial and body hair. There was a progressive increase in the size of his penis and of his testes, and he now had frequent erections and emissions. His mental state markedly improved. In March 1972, the HCG dosage was increased to 5000 i.u. twice weekly and HMG regimen was continued. However, gynaecomastia worsened, and he developed a left-sided varicocele. For these reasons the weekly dosage of gonadotrophins was reduced to 5000 i.u. HCG and three ampoules of HMG. Serum testosterone levels increased progressively reaching 12 ng/ml by September, 1972. A testicular biopsy, repeated 8 months after the start of therapy, showed impressive maturation of the tubules with an increase in tubular diameter, and the presence of spermatocytes and mature Leydig cells. When re-evaluated two months later his penis measured 9 cm, and both testes measured 3 × 2.5 cm. Because of shortage in the supply of HMG, therapy was discontinued, and parenteral testosterone enanthate 200 mg was administered every three weeks. This was continued for a further two years during which his clinical improvement was maintained.

Treatment with weekly injections of 5000 i.u. HCG and 75 i.u. of HMG was recommenced in April, 1975. Two months later this dosage schedule was increased to a twice-weekly regimen. LH levels ranged from 32 to 200 mi.u./ml which reflected cross-reaction with the administered HCG. Values of FSH were between 3 and 6 mi.u./ml (normal male values in the authors’ laboratory are 11-2 mi.u./ml ± 5-4 s.d.). Testosterone levels increased progressively to 10 ng/ml, and oestradiol-17β levels increased to 45 pg/ml (Fig. 3).

The patient was married in November 1975. Intercourse was reported to be frequent and normal. In January 1976 his wife conceived, and, at term, was delivered of a healthy girl. Semen analysis revealed an ejaculate of 3 ml, with a sperm count of 16 × 10⁶/ml and a motility of 60%. In March 1976 therapy with HMG was withheld but HCG was continued. As of June 1976 spermatogenesis had been maintained, and the count at that time was 14 × 10⁶/ml.

Discussion

The patient fulfills the criteria for the diagnosis of isolated bihormonal gonadotrophin deficiency (IGD). Secretion of GH, ACTH and TSH was normal. Although there was a PRL response to TRH, this was somewhat decreased when compared with controls. This phenomenon has been noted previously in male subjects with IGD (Yamaji et al., 1977). Repeated determinations of LH and FSH were undetectable or at the limit of sensitivity of the radioimmunoassay. The patient was unresponsive to clomiphene and to the administration of repeated pulses of LHRH. While this suggests that the gonadotrope itself is defective, it does not exclude a lesion at the level of the hypothalamus since LHRH influences both synthesis and release of the gonadotrophins (Rabinowitz and Spitz, 1975; Schally, Kastin and Arimura, 1971; Zarate et al., 1973). Moreover, chronic LHRH deprivation may render the gonadotrope unresponsive (Roth et al., 1972). Indeed, in patients with IGD, long-term priming with LHRH often converts the LHRH 'non-responder' to responder status (Hashimoto et al., 1975; Mortimer et al., 1974; Yoshimoto, Moridera and Imura, 1975; Reitano, Caminos-Torres and Snyder, 1975).
There are a few reports of successful therapy with long term clomiphene citrate (Hamilton et al., 1973) and there are also important new observations of responsiveness to chronic LHRH therapy (Mortimer et al., 1974). In this patient, in view of his apparent LHRH non-responsiveness, a combination of HMG and HCG was employed. It is of interest that conception occurred at a time when the sperm count was $16 \times 10^6$/ml.

In summary, using a combination of HCG and HMG, androgenization and spermatogenesis have been induced in a male patient with documented IGD.

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**References**


Case reports


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