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CASE REPORT

Successful induction of ovulation and completed pregnancy using recombinant human luteinizing hormone and follicle stimulating hormone in a woman with Kallmann's syndrome

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The induction of ovulation in women with hypogonadotrophic hypogonadism requires follicle stimulating hormone (FSH) for follicular growth and both FSH and luteinizing hormone (LH) to induce optimal follicular steroidogenesis. The development of human recombinant FSH and LH means that individually tailored doses of both hormones can be used with the aim of inducing unifollicular ovulation. This report describes the use of recombinant human FSH and LH for the induction of ovulation and conception in the second cycle of treatment, and subsequently a successfully completed pregnancy in a woman with Kallmann's syndrome.

Key words: hypogonadotrophic hypogonadism/ovulation induction/pregnancy/recombinant human FSH/recombinant human LH

Introduction

The development of molecular genetic technology has led to the production of recombinant human follicle stimulating hormone (r-hFSH) and luteinizing hormone (r-hLH). These gonadotrophin preparations are >95% pure. Studies using these highly purified gonadotrophins have shown that both gonadotrophins are necessary for normal follicular function. Although only FSH is required for follicular growth, LH is necessary for adequate steroid production from developing follicles as well as for follicular rupture following the LH surge. A significant proportion of hypogonadotrophic patients do not appear to have the minimum amounts of endogenous LH required to achieve optimal follicular development and steroidogenesis therapy with FSH alone, whether it is the highly purified urinary FSH preparations or r-hFSH (Couzinet *et al.*, 1989; Shoham *et al.*, 1991). Therefore these patients require the addition of LH for satisfactory follicular development.

Case report

A 31 year old hypogonadotrophic woman presented to the infertility clinic for investigation and treatment. She had presented with incomplete pubertal development and primary amenorrhoea at the age of 18 years. The clinical presentation strongly suggested the diagnosis of Kallmann's syndrome, in that she had hypogonadotrophic hypogonadism and anosmia. There were no other midline defects. A computerized tomography (CT) scan of the pituitary gland showed a pituitary cyst, which was found consistently in subsequent CT scans. Following diagnosis, the patient commenced oestrogen replacement therapy. In June 1992, aged 31 years, she presented with shortness of breath, swelling of the ankle and indigestion. She was diagnosed as having sarcoidosis with lung and eye involvement. She had no polyuria, polydipsia or other symptoms to suggest hypothalamic/pituitary sarcoid. She began taking 30 mg/day prednisolone (Prednesol; Glaxo, UK) with the good resolution of symptoms. At presentation, the patient was using the oral contraceptive Logynon (ethinyl oestradiol 30–40 μg/day and levonorgestrol 50–125 μg/day) (Schering Health, UK) and the dose of prednisolone had been decreased to 3 mg/day.

A physical examination revealed mild obesity (body mass index 25.4), normal breast development and axillary and pubic hair (Tanner stage 5). Anosmia was confirmed. Visual fields were full to confrontation.

By 1 month after stopping using Logynon, the serum FSH concentration was 2.2 IU/l, the LH concentration was <1.0 IU/l and the oestradiol concentration was 140 pmol/l. A progestagen withdrawal test was negative. Prolactin and thyroid-stimulating hormone concentrations were normal at 56.0 and 1.1 mIU/l respectively. Haematological, renal and liver function tests were all normal. A vaginal ultrasound scan of her ovaries and uterus showed a small uterus (transverse diameter 21 mm) and small inactive ovaries (right ovarian volume 2.45 cm^3, left ovarian volume 1.13 cm^3).

A semen analysis of the patient's partner was normal.

Ovulation induction

The treatment protocol was established as part of a multicentre trial to determine the effective dose of r-hLH to support r-hFSH in ovulation induction in hypogonadotrophic women. Ethical Committee approval was obtained from Parkside Health Authority, London, UK, and treatment commenced after written informed consent was obtained from the patient. Treatment was started with daily s.c. injections in the abdominal wall of 150 IU r-hFSH (Gonal-F®; Ares Serono, Aubonne, Switzerland) and 75 IU r-hLH (LHadi®, Ares Serono, Aubonne, Switzerland). Ovarian follicular response and endometrial

growth were monitored by ultrasound scans every 2–3 days. FSH, LH and oestradiol concentrations were measured at each visit. Two cycles of treatment were completed. After 9 days of treatment in her first cycle she had developed a dominant follicle (average diameter 17 mm) in the right ovary. There were three smaller follicles (13–14 mm) in the left ovary. There was an appropriate endometrial thickening of 11 mm and a serum oestradiol concentration of 780 pmol/l. Human chorionic gonadotrophin (HCG; 10 000 IU; Profasi®; Ares Serono) was given i.m. on day 10. Luteal phase support of 2500 IU HCG i.m. was given 7 days after the first HCG injection. The serum progesterone concentration measured 6 days after the first HCG injection was 20 nmol/l, followed by a withdrawal bleed 6 days later.

The patient commenced a second cycle of treatment using the same dose of r-hFSH (150 IU/day), but the dose of r-hLH was increased to 225 IU/day. After 9 days of treatment, a single dominant follicle (average diameter 17 mm) had developed in the left ovary. The endometrium was 13 mm thick and the oestradiol concentration was 760 pmol/l on the day that 10 000 IU HCG were administered. Luteal phase support was given as in the first cycle. The mid-luteal progesterone concentration was 40 nmol/l. The patient conceived and an ultrasound scan confirmed a viable singleton intrauterine pregnancy.

Apart from a few days of light perivitelline vaginal bleeding in week 8, the pregnancy was uneventful until week 35. The patient developed itchiness of the skin and then jaundice. Her liver function tests were abnormal but ultrasound of the liver and biliary tract was normal. A diagnosis of intrahepatic cholestasis of pregnancy was made. Because of the increasing derangement of liver function tests, labour was induced at 37 weeks. Delivery was by Caesarean section because of failure to progress in labour. A healthy female infant weighing 3096 g was delivered. There was a full resolution of liver function post-partum.

Discussion

The successful induction of ovulation in women with hypogonadotrophic hypogonadism and intact pituitary function has been achieved with pulsatile gonadotrophin-releasing hormone (GnRH) therapy or human menopausal gonadotrophin (HMG) therapy. Pulsatile GnRH therapy has been the treatment of choice because it restores the pulsatile release of both gonadotrophins from the pituitary. This results in predominantly unifollicular cycles and satisfactory pregnancy rates. The treatment is associated with low rates of multiple pregnancy and is not complicated by ovarian hyperstimulation syndrome (Homburg *et al.*, 1988; Balen *et al.*, 1994).

However, for patients who do not respond adequately to pulsatile GnRH or those with pituitary disease, HMG therapy given by once daily injection has been the only alternative treatment for ovulation induction. Urine-derived HMG preparations contain a fixed dose of FSH and LH. The use of HMG is associated with an increased risk of multifollicular development, with the potential complications of multiple pregnancy and ovarian hyperstimulation syndrome.

The development of r-hLH used in addition to r-hFSH provides another therapeutic option for patients who are hypogonadotrophic. The successful induction of ovulation using this regimen in a patient with hypogonadotrophic hypogonadism was first reported in 1994 (Hull *et al.*, 1994). Because the two preparations are given separately, the dose of each gonadotrophin can be tailored to the individual's requirements and achieve the goal of unifollicular cycles. With our patient, in the second cycle a higher dose of r-hLH (225 IU) was used and this was associated with the development of a single dominant follicle. However, there was follicular development in the first cycle of treatment using the lower dose of 75 IU r-LH. It remains unclear as to whether the higher dose of r-LH was the minimum effective dose required. It is possible that the patient would have responded in the second cycle by continuing with the same dose of r-LH. By titration of both gonadotrophin doses for individual patients, the potential complications seen with HMG therapy (i.e. multiple pregnancy and ovarian hyperstimulation syndrome) may be reduced with r-hLH and r-FSH therapy.

The patient's pregnancy was complicated by intrahepatic cholestasis. This is a rare but well recognized benign complication of pregnancy. The condition, as with our patient, resolves spontaneously after delivery. It is often reported to recur in subsequent pregnancies but is not associated with the development of chronic liver cell disease. It is unlikely that the development of intrahepatic cholestasis was related to gonadotrophin used to induce ovulation.

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