CASE REPORT

Successful Pregnancy in a Woman with Hypogonadotrophic Hypogonadism Using Low Dose hCG After Priming with Recombinant FSH in an IVF Cycle

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Abstract

In this case report, we present a 34-year old woman with hypogonadotrophic hypogonadism in which we used low dose human chorionic gonadotrophin (150 IU/day) as luteinizing hormone supplement after priming with recombinant follicle stimulating hormone in an assisted reproduction cycle. Twenty-five oocytes were retrieved, 14 oocytes underwent intracytoplasmic sperm injection and 13 were fertilized and all of them cleaved. Four embryos were transferred on day 2. The result was a twin pregnancy. The patient had an uneventful pregnancy and at 38th weeks of gestation delivered two healthy female and male infants weighing 3015 g and 2876 g, respectively. As a conclusion, low dose human chorionic gonadotrophin administration in the late follicular phase of the ovulation induction cycle may be an effective way to provide luteinizing hormone like activity in hypogonadotrophic patients. Randomized controlled studies are needed to support this conclusion.

Keywords: low dose human chorionic gonadotrophin, hypogonadotrophic hypogonadism, ovulation induction, assisted reproduction

Özet

Hipogonadotrofik Hipogonadizmi Olan Bir Kadında IVF Siklusunda Rekombinant FSH ile İndüksiyon Sonrası Düşük Doz hCG ile Elde Edilen Başarılı Gebelik

Otuz dört yaşında ve hipogonadotrofik hipogonadizme bağlı primer infertilitesi olan bir hastaya yardımcı üreme tekniği sırasında ovülasyon indüksiyonu için rekombinant folikül stimüle edici hormon (recFSH) ile indüksiyon sonrası luteinizan hormon (LH) desteği amacıyla düşük doz insan koryonik gonadotropini (150 IU/gün) uygulaması yapılmıştır. Yazımızda bu olguyu sunuyoruz. Hastadan 25 oosit elde edildi, 14'üne sitoplazma içine sperm enjeksiyonu uygulandı, 13'ü döllendi ve bunların hepsinde klivaj elde edildi. İkinci günde transfer edilen 4 embriyo ikiz gebelikle sonuçlandı. Hastanın gebeliği sorunsuz geçti ve 38. gebelik haftasında 3015 g kız ve 2876 g erkek sağlıklı bebek doğurtuldu. Sonuç olarak, yumurtlama sürecinin geç folikül süresinde uygulanan düşük doz insan koryonik gonadotropini, hipogonadotropik hastalarda luteinizan hormon aktivitesini elde etmede etkili bir yöntem olabilir. Bu sonucu desteklemek için rasgele yöntemli, kontrollü çalışmalara gerek vardır.

Anahtar sözcükler: düşük doz insan koryonik gonadotropini, hipogonadotrofik hipogonadizm, ovülasyon indüksiyonu, yardımcı üreme tekniği

Introduction

Hypogonadotrophic hypogonadism (HH) is one of the rare etiologies for female infertility, but ovulation induction with gonadotropins lead to successful conceptions in most cases.

The treatment is simply to replace the absent endogenous hormones either by urinary gonadotropins having luteinizing hormone (LH) activity (e.g. hMG) or by pulsatile GnRH pump. The necessity of LH supplementation is not questioned in these patients treated with exogenous follicle stimulating hormone (FSH), because both hormones are

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required for optimal follicular growth and steroidogenesis. With the introduction of recombinant gonadotropins, in recent years urinary products are being used less and they are being removed from the market. The available LH compound used in HH patients now is recombinant LH. There are also some reports about using low dose hCG as a substitution of LH both for ovulation induction (1) and GnRH agonist assisted reproductive technology (ART) cycles (2). In this case, we report a patient with HH who has been successfully treated with low dose hCG after priming with recombinant FSH in an ART cycle.

Case Report

Mrs. F.T.H, 34-year old, was admitted to our IVF clinic with the complaint of of infertility for 3 years. Serum hormone measurements determined the following results; FSH: 0.4 IU/ml, LH: 0.1 mIU/L, estradiol: <9 pg/ml, prolactin: 6.1 ng/ml, thyroid stimulating hormone: 2.51 mIU/ml, free tri-iodothyronine: 4.52 pg/ml and free tetraiodothyronine: 1.3 pg/ml. Hysterosalpingography was normal. The partner's semen analysis showed oligoasthenospermia ($9.6x10^6$/ml sperm count and 15% progressive motility). Before coming to our department, the patient had received one cycle of ovulation induction with IUI and one cycle of IVF/ICSI treatments which had been unsuccessful, and which had been followed by a frozen embryo transfer cycle which did not result in pregnancy. The patient was accepted to our ART program with the diagnosis of severe oligoasthenospermia and anovulatory infertility due to female HH. In the first treatment cycle ovulation induction was started with 4 ampules of human menapousal gonadotrophin (Humegon 300 IU FSH and 300 IU LH, Organon Pharmeceuticals, Istanbul, Turkey). Twenty-three oocytes were collected 36 hours later, fifteen of which were at metaphase II and underwent ICSI, all fertilized and 12 cleaved. Four embryos were transferred on day 3. However, the patient did not get pregnant.

The second treatment cycle commenced 4 months later. Since HMG was not commercially available at that time, it was decided to use low dose hCG as a substitution for LH, after priming with recombinant FSH in a dose of 300 IU/day was started on cycle day 3 and the dosage was increased to 600 IU/day on cycle day 12, since there was not adequate response. When the leading follicle reached 12 mm on day 17 of the cycle 150 IU/day hCG (1500 IU Pregnyl [Organon Pharmeceuticals, Istanbul, Turkey] ampule was diluted) was added to this regimen. On cycle day 20, hCG in a dose of 10,000 IU was administered and 25 oocytes were retrieved 36 hours later, 14 of which were metaphase II. These 14 oocytes underwent ICSI and 13 were fertilized and all of them cleaved. Four embryos were transferred on day 2. Luteal phase was supported with Crinone gel (Serono Pharmeceutical Company, Istanbul, Turkey). The pregnancy test which was performed two weeks later was positive and pelvic ultrasound showed 2 gestational sacs. The patient had an uneventful twin pregnancy and at 38^{th} weeks of gestation delivered two healthy female and male infants weighing 3015 g and 2876 g, respectively.

Discussion

Ovulation induction for HH patients requires concomitant administration of both FSH and LH to achieve optimal therapeutic results. LH is necessary for theca cell androgen synthesis which serves as a substrate for the aromatase enzyme to convert into estrogen by granulosa cells. Once ovarian follicles reach a diameter of 10-12 mm, their granulosa cells begin to express LH receptors and become receptive to LH stimulation. After this stage both FSH and LH are equally effective to support granulosa cell function, hCG has intrinsic LH activity, has a longer plasma half life then, does LH and occupies the LH receptors in a more prolonged and stable way. Several studies have demonstrated that administration of urinary hCG in a low dose fashion is as effective as administration of LH (3,4). The minimal essential dose of hCG as a surrogate LH and the starting day of hCG is still a matter of debate. Filicori et al. (5) reported that supplementation of FSH (150 IU/day) with hCG 50 IU/day in patients undergoing controlled ovarian stimulation can improve treatment parameters without untoward effects such as premature luteinization or hyperandrogenism. There have also been studies in which larger amounts of LH (300-750 IU/day of recombinant LH) or hCG (up to 200 IU/day) have been used to support the late stages of folliculogenesis (6,7). The FSH administration is reduced or discontinued with the goal of selectively stimulating the final growth and maturation of larger ovarian follicles while inhibiting the development of small follicles (8,9). These studies have been in small groups of normogonadotrophic patients, but in each of these studies, adding low doses of hCG improved ovulation induction outcome and did not cause premature luteinization. The presented case, here, was a hypogonadotrophic patient who definitely required LH supplementation. In this group of patients it has been shown that there is a therapeutic benefit of adding exogenous LH in a daily dose of 75 IU when the endogenous serum LH level is ≤1.2 IU/L (10). The serum LH level in our patient was 0.1 IU/L which necessitated LH supplementation. However, hCG was used instead of recombinant LH which yielded similar number of oocytes compared to the previous cycle where HMG was used. In this case, we have demonstrated that in a patient with HH, low dose hCG supplementation induces adequate follicular response after priming with recombinant FSH. Although the patient responded well in the previous cycle with HMG, she did not respond to recombinant FSH preparation in the beginning of the stimulation protocol. There are some reports about using recombinant FSH only preparations for ovulation induction in HH patients, but success rate is often very limited. Therefore, adding LH either as in a recombinant form or as in this case, in the form of low dose hCG is mandatory in HH patients. In conclusion, administration of low dose hCG beginning in the late follicular phase of the ovulation induction cycle may be an economical way and an alternative to recombinant LH to provide LH like activity in HH patients.

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