Case Report

Leptin Level Correlates with Ovarian Response and Oocyte Quality in a Woman with Anorexia Nervosa: Case Report

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Abstract

We report a case of a 33-year-old patient with HA secondary to AN, in which leptin was used to monitor dietary compliance to demonstrate the importance of leptin levels to assess dietary compliance in an infertile woman with hypothalamic amenorrhea (HA) related to anorexia nervosa (AN) and to demonstrate the correlation between leptin levels and ovarian response with HA due to AN. Ovarian response and embryo quality were extremely poor when the leptin level was in the low normal range for her body mass index (BMI) (6.4ng/mL), and both markedly improved when levels increased to the mid-normal range for her BMI (13.0 ng/mL) with increased caloric intake. Conception resulting in live birth was achieved with gonadotropin ovulation induction when the leptin level was 17.8ng/mL. In conclusion, monitoring of dietary compliance with serum leptin levels in women with AN may be a powerful tool to encourage behavior modification, and increased levels of predicted success with fertility treatments in a woman with AN.

INTRODUCTION

Hypothalamic amenorrhea (HA) accounts for greater than 30 percent of cases of amenorrhea in women of reproductive age [1]. It is characterized by the absence of menstrual cycles due to the suppression of the hypothalamic-pituitary-ovarian (HPO) axis. Hypothalamic dysfunction is evidenced by low basal levels of gonadotropins despite low estrogen levels. This disruption in the HPO axis is usually secondary to chronic energy deficiency from stress, excessive exercise or inadequate caloric intake [2]. Amenorrhea is in fact one of the cardinal features of anorexia nervosa (AN) [2]. Although the precise neuroendocrine mechanisms that mediate the HPO axis are yet to be elucidated, previous studies have shown that leptin plays a significant role in modulating this equilibrium.

Leptin is a protein encoded by the obese gene (Ob) in adipocytes. Leptin levels have been associated with weight and body fat in normal, obese, and anorexic patients. Anorexic patients have lower basal plasma leptin levels compared to normal or obese patients [3]. The decreased leptin levels in undernourished women are thought to disrupt the integrity of the HPO axis. For example, treating leptin-deficient rodents with leptin reverses infertility [4]. In addition, treating women with hypothalamic amenorrhea with subcutaneous leptin has also reversed infertility, as shown by the resumption of menses with ovulatory cycles and increased estradiol levels [5,6].

We report a case of a 33-year-old patient with hypothalamic amenorrhea secondary to anorexia nervosa who presented desiring fertility via in vitro fertilization (IVF). The aim of the study is to illustrate a case in which leptin was used as marker to track compliance with increased caloric intake after other measures had failed, and to describe a remarkable correlation between the serum leptin level and ovarian response to gonadotropin stimulation.

CASE REPORT

A 33-year old G4P2002 woman with hypothalamic amenorrhea as a consequence of anorexia nervosa presented to Carolinas Medical Center Women’s Institute in 2005 for evaluation and treatment of infertility. She and her husband reported unprotected intercourse for 6-years. She had oligomenorrhea since menarche at age 15, which was first attributed to long-distance running (8-10 hours per week) and then anorexia nervosa. She had recently been amenorrheic except while on fertility medications prescribed at another fertility center. In addition, her husband had severe oligospermia. They had two children from prior assisted reproductive technology (ART) cycles.
Their body mass index (BMI) was 15.5 during the initial visit, increased from 14.7 after a self-reported 5-pound weight gain. During the initial visit and afterwards, the patient was counseled about the importance of adequate nutrition, and was seen in conjunction with a therapist and a nutritionist. Testing included basal FSH 2.8 mIU/mL, LH < 0.5 mIU/mL, estradiol (E2) 14 pg/mL, thyroid stimulating hormone (TSH) 0.5 uIU/mL, free T4 0.9 ng/dL, and prolactin 15.5 ng/mL. Transvaginal ultrasound showed antral follicle count was 11, hysterosalpingogram was normal, and semen analysis volume was 2.4 mL, density 4.0 million/mL, motility 25%, with rapid motility 1.3% and 4% normal forms by strict morphology. IVF with intracytoplasmic sperm injection (ICSI) was recommended.

She underwent her first IVF cycle in July 2005 using a long oral contraceptive (OCP) leuprolide protocol, and underwent stimulation with 450 international units (IU) of recombinant FSH daily plus 150 IU of recombinant LH starting on stimulation day four. Her peak E2 was 1,386, four oocytes were retrieved and underwent ICSI; one fertilized normally and was transferred but pregnancy did not occur. At the failed cycle review, she admitted that her food consumption was suboptimal for IVF and she provided assurance that she would improve.

In September, 2005, a second IVF cycle was attempted using an antagonist protocol and 900 units of human menopausal gonadotropin (hMG) daily with the antagonist initiated four days before hCG administration. This resulted in a peak estradiol of 893, recovery of three oocytes, all three were injected, two fertilized, and one cleaving embryo was transferred resulting in a chemical pregnancy with peak hCG 289 mIU/mL.

We hypothesized that the poor response to high-dose ovarian stimulation was related to suboptimal nutritional status and poor compliance with eating in spite of counseling and therapy, and obtained a leptin level to assess her compliance. Her leptin level immediately after the second cycle was 6.4 ng/mL (normal range for her BMI 2.1 to 29), and she was advised that we would attempt another cycle only when her leptin level increased.

Two months later, her leptin level rose to 15 ng/mL, and in January 2006 she underwent another high-dose hMG/antagonist cycle, but this time her peak estradiol reached 3,341 pg/mL, seventeen oocytes were retrieved, eleven fertilized, three cleaving embryos were transferred. She did not conceived, and one good-quality blastocyst cryopreserved. She attempted a fourth IVF cycle months later; this time her leptin level was 13, and peak estradiol was 5,380, nineteen oocytes were retrieved, thirteen fertilized with ICSI, and two blastocyst embryos were transferred but pregnancy did not occur.

After four failed cycles of IVF and one frozen transfer, she pursued gonadotropin ovulation induction with donor insemination. Her leptin level was 17.8. Treatment was initiated with hMG 75 units daily for 5 days, and increased to 150 units after estradiol level fell from 34 ng/mL on stimulation day 1 to 25 ng/mL on day 5. After 5 days of hMG 150 units, her estradiol was 363 ng/mL, and by stimulation day 14 her estradiol was 1,599 pg/mL, the lead follicle measured 15mm, she was administered hCG and IUI with donor sperm performed 36 hours later, leading to a twin intrauterine pregnancy that ultimately self-reduced to a single IUP. She carried the pregnancy to term and gave birth to a 5 pound 12-ounce healthy baby by cesarean delivery for breech presentation.

**DISCUSSION**

In this case, we used leptin as an objective way to monitor her caloric intake, and saw a remarkably improved response to ovarian stimulation (Table 1), and embryo development as her food consumption and leptin levels increased, ultimately resulting in a live birth with low-dose gonadotropin ovulation induction. Since leptin is reflective of energy stores in the body, it is logical to use leptin as a marker for compliance with diet in women with anorexia nervosa desiring fertility.

Hypothalamic amenorrhea results from aberrations in the pulsatile release of gonadotropin-releasing hormones (GnRH), which suppresses the hypothalamic-pituitary-ovarian axis. HA has most commonly been associated with 1) stress-related factors, 2) excessive exercise, and 3) poor nutrition/underweight [7]. Anorexia nervosa (AN) is characterized by behaviors including chronic self-starvation and severe weight loss [3]. The emotional stress and decreased body fat in women with AN predispose them to suppression of the HPO axis, which clinically manifests as amenorrhea, one of the cardinal features of AN.

The treatment of HA in women desiring fertility is highly specialized, and should be directed at correcting the underlying cause of amenorrhea – primarily by increasing nutrition and caloric intake. However, monitoring of AN by assessing serial weights can be challenging, as some may “cheat” by placing heavy items in clothing, or by fluid loading before a “weigh-in.” Ovulation induction drugs such as clomiphene citrate and letrozole are ineffective for women with AN, since their mechanisms of actions rely on a functional HPO axis [8].

Women with HA usually respond to ovarian stimulation with gonadotropins or pulsatile GnRH. However, treatment with gonadotropins can be very difficult, because of the high cost of medications and monitoring as well as a narrow margin of effectiveness where a small increase in dose can shift one from non-responsive to an excessive response. Moreover, these traditional ovulation induction methods do not address the underlying factors for the hypothalamic disturbance [6].

Leptin levels are low in women with HA due to AN. Since circulating leptin levels reflect the amount of energy stores in fat as well as acute changes in energy intake, low leptin levels are indicative of a state of energy deficiency [5]. A prospective, open-label study done by Welt et al. (2004), showed that administering leptin to women with HA for three months improved reproductive function, shown by increased mean LH levels, follicular diameter, number of dominant follicles, and estradiol levels Chou et al. [1], also showed leptin administration to improve reproductive function with recovery of menstruation and marked increases in estradiol and progesterone levels in those given leptin compared to their placebo-treated counterparts [5].

There is little clinical data exploring the use of leptin levels for infertile women with eating disorders, but animal studies have shown that leptin is an important hormone that affects oocyte maturation and embryo development. Leptin enhances
bovine oocyte meiotic maturation in vitro [9,10] and enhances embryonic developmental capacity [10,11]. Leptin also enhances porcine and murine oocyte maturation and pre-implantation blastocyst development [12,13]. In humans, estradiol appears to be an important regulator of leptin production, and leptin levels increase in both underweight and in healthy women while undergoing gonadotropin ovulation induction [14,15]. In women with normal gonadotropin levels undergoing IVF, leptin levels correlate with oocyte fertilization and are higher in in follicular fluid in oocytes that fertilized compared to non-fertilized oocytes [15,16]. Although leptin appears to play an important role, excessive levels may be harmful; high fasting leptin levels are associated with poor IVF outcomes, and obesity may have a detrimental effect on oocyte maturation [17].

It has been over a decade since we initiated treatment of this patient, and while some of the management is clearly dated, such as the use of excessive doses of gonadotropins and the transfer of far too many embryos, the lessons learned from this case are highly relevant and likely apply to other women with amenorrhea related to anorexia nervosa. Women with insufficient caloric intake may experience impaired response to fertility treatments, even ovulation induction with HMG, and this may result in poor egg and poor embryo quality. Improving the nutritional status, as assessed by rising leptin levels, may be beneficial to improve ovarian response and oocyte quality, as well as the improving the health of the patient and her fetus during pregnancy.

The physicians in our practice have consistently referred to this case when encountering a woman with a low BMI and an unexpectedly poor ovarian response. There appears to be a very important correlation between leptin level and ovarian response. We hope this case report will encourage further investigation.

In conclusion, this case illustrates the potential value in monitoring leptin levels to assess caloric consumption in an infertile woman with anorexia nervosa. The rise in leptin levels served as a sensitive marker of weight gain and improved nutrition. Ovarian response and embryo quality were extremely poor when the initial levels were low, were markedly improved when levels improved, and live birth was achieved from HMG ovulation induction. It appears that monitoring of serum leptin levels in women with AN may be a powerful tool for explaining a poor ovarian response in women with AN, and predicting an improved response to ovarian stimulation in women with HA.

REFERENCES


