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Pregnancy in a Woman With Congenital Generalized Lipodystrophy:

Leptin's Vital Role in Reproduction

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Abstract

BACKGROUND—Congenital generalized lipodystrophy is a rare disorder characterized by scant adipose tissue, profound leptin deficiency, and severe insulin resistance, resulting in multiple metabolic derangements, including hyperandrogenism, anovulation, and impaired fecundity.

CASE—A young woman with congenital generalized lipodystrophy receiving leptin therapy experienced menarche, conceived spontaneously, and delivered a liveborn male neonate.

CONCLUSION—Adipose tissue is important to normal female reproductive function. Leptin in particular appears to play a key role in adipose-mediated regulation of fertility.

Congenital generalized lipodystrophy, or Berardinelli-Seip syndrome, is a rare disorder involving pathologic paucity of adipose tissue leading to impaired ability to store triglycerides and reduced adipokine levels. Congenital generalized lipodystrophy results in several significant metabolic disturbances, including severe insulin resistance, dyslipidemia, and ectopic fat accumulation.[1] Women with congenital generalized lipodystrophy are also frequently infertile.[2] They have hyperandrogenism, oligomenorrhea or amenorrhea, and polycystic ovaries, giving them the diagnosis of polycystic ovary syndrome. Insulin resistance is suspected to be the main cause of excessive ovarian androgen production in these patients. In addition, inadequate leptin levels in women with congenital generalized lipodystrophy lead to a loss of the ultradian rhythm of gonadotropins. Anovulation in women with congenital generalized lipodystrophy, therefore, is likely due to the combined effect of irregular luteinizing hormone (LH) stimulation and androgenic effects on the ovaries.

Leptin administration corrects metabolic[3,4] and endocrine abnormalities[2,4] in patients with congenital generalized lipodystrophy without any change in fat mass. Among several other beneficial effects, leptin treatment reduces insulin resistance, lowers androgens, and establishes a regular ultradian rhythm of gonadotropin secretion.[5,6]

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Owing to impaired fecundity, pregnancy is extremely rare in women with congenital generalized lipodystrophy.[7,2] This report documents a conception and pregnancy in a patient with congenital generalized lipodystrophy receiving recombinant leptin.

CASE

We report a patient with congenital generalized lipodystrophy secondary to a mutation in the AGPAT2 gene. This mutation interrupts conversion of lysophosphatidic acid into phosphatidic acid. Lipodystrophy associated with this mutation is believed to be caused by impaired triglyceride synthesis or a decrease in bioavailable phosphatidic acid or phospholipids. The mutation is inherited in an autosomal recessive fashion.[1] This mutation is associated with nearly complete absence of adipose tissue, insulin resistance, acanthosis nigricans, hepatomegaly and steatosis, hypertriglyceridemia, and amenorrhea. The patient first was seen at the National Institutes of Health when she was 14 years old. Before initiation of recombinant leptin therapy, she required 1,200 units of insulin daily to maintain euglycemia. Her hemoglobin A1c (Hb A_{1c}) level was 11.7% (normal 4–5.9%), serum insulin was 599 microunits/mL, and triglyceride level was markedly elevated at 1,355 mg/dL (normal less than 150 mg/dL) (Table 1). She had not yet experienced menarche. Despite her significant insulin resistance, this patient did not have hirsutism. Later that year, she was entered into an experimental trial of recombinant leptin therapy.[2,3] She was started on an initial pediatric dose of 0.04 mg/kg/d, and the dose was increased gradually to normalize her metabolic parameters. After starting leptin treatment, the patient's Hb A_{1c} level dropped to 7.4% and her triglyceride level fell dramatically. Her insulin requirement disappeared, and her serum glucose was controlled on metformin alone (Table 1). Her ovarian volumes also decreased markedly after initiating leptin treatment, from 28.4 cc to 17 cc on the right and 27.22 cc to 8.5 cc on the left. This marked decrease in ovarian volume typically has not been seen after leptin therapy.[2] Menarche occurred at age 17. The patient had regular monthly cycles and conceived spontaneously at age 23. Just before conception, she had a normal Hb A_{1c} level of 5.7% and triglyceride level of 75 mg/dL.

Once pregnancy was confirmed, the patient's metformin was stopped but leptin was continued at 0.13 mg/kg/d divided into two daily doses. Although leptin was an experimental hormonal drug in this setting, the decision to continue therapy was based on its positive effects in nonpregnant women, the likelihood that leptin would not be teratogenic, and the goal of maintaining the most ideal metabolic control during pregnancy. The patient's preconception weight was 62.8 kg, and she gained 22 kg during the course of her pregnancy. During the first half of pregnancy, the patient's glucose targets were attained without insulin therapy. However, her blood glucose values began to rise, and insulin was instituted at 24 weeks of gestation. During the latter half of pregnancy, the patient required up to 90 units of regular insulin three times daily to maintain moderate control of her serum glucose. Her diabetes management was carried out at another institution, and we do not have information on the day-to-day blood glucose levels. The information that we have suggests that the blood glucose values were close to pregnancy targets in the first 24 weeks but deviated modestly from those targets throughout the remainder of the pregnancy. The patient's Hb A_{1c} level was 5.8% at 33 weeks of gestation. Whether increasing her insulin dose in the last trimester would have reduced the tendency toward macrosomia cannot be determined precisely.

The patient was induced at 37 weeks for hydramnios and delivered a liveborn 4,200-g, 56-cm male neonate vaginally. The delivery was complicated by cephalopelvic disproportion with shoulder dystocia. The neonate ultimately was delivered vaginally but experienced postpartum respiratory distress and Erb's palsy. His respiratory distress responded to immediate therapy. By 18 months of age, he had gained full function of his left upper

extremity and no longer required physical therapy. The child's growth and development otherwise has been normal.

The patient's blood sugars normalized after delivery, and her glucose levels were 70–110 mg/dL off of insulin. The patient continued on her usual leptin dose (0.13 mg/kg/d) without interruption. She resumed menstruation approximately 3 months after stopping breastfeeding.

COMMENT

Congenital generalized lipodystrophy is a rare disorder, with an estimated incidence of only 1 in 10 million.[8] However, the reproductive derangements witnessed in association with this disorder and the remarkable improvement in symptoms with leptin therapy support a significant role for adipokines, and leptin in particular, in regulating reproductive function in the general female population.[6]

Leptin deficiency contributes to anovulation and infertility through two mechanisms: 1) insulin resistance and hyperandrogenism and 2) absence of an ultradian rhythm of gonadotropin secretion. Exogenous leptin administration can ameliorate these effects and restore fertility.

Reports of pregnancies in women with familial partial lipodystrophy who exhibit less pronounced loss of adipose tissue have suggested an increased risk of gestational diabetes, preeclampsia and eclampsia, intrauterine growth restriction, and intrauterine fetal death.[9,10] The complications experienced by this patient were similar to, although perhaps less extreme than, those previously reported and likely resulted from insulin resistance and hyperglycemia. However, we have observed 12 partial lipodystrophy patients, nine of whom had one or more pregnancies with favorable outcomes (unpublished observations).

Leptin is an adipokine with multiple functions, including regulation of appetite and energy expenditure, fatty acid metabolism, pancreatic beta cell function, and reproduction.[11] Mice deficient in leptin are obese and infertile. They undergo normal secondary sexual development but fail to ovulate. Forcing these animals to normal weight through dietary restriction does not restore fertility. However, administration of exogenous leptin enables ovulation and pregnancy.[12] Humans with mutations in the leptin gene are obese and have hypogonado-tropic hypogonadism.[8,13] Women with hypothalamic amenorrhea have lower leptin levels than do controls matched for age, weight, and body fat.[14] Leptin administration to such women has been shown to restore ovulatory menstrual cycles.[6]

Leptin acts at many points along the reproductive axis. It indirectly augments LH release through kisspeptin action on gonadotropin-releasing hormone receptors in the hypothalamus and directly through stimulation of pituitary LH secretion.[15,16] There is also evidence that leptin influences follicle, oocyte, and embryo development as well as endometrial receptivity.[14,18]

In contrast to patients with isolated leptin deficiency, who are typically obese, patients with congenital generalized lipodystrophy have pathologically low levels of adipose tissue. Nonetheless, both conditions are characterized by low leptin levels and infertility. Despite the hyperinsulinemia seen in patients with both disorders, there also seems to be a significant hypothalamic component to their anovulation. Unlike women with polycystic ovary syndrome, patients with congenital generalized lipodystrophy and isolated leptin deficiency are hypoestrogenic, with blunted LH response to gonadotropin-releasing hormone in the youngest patients.[4,8] This finding is consistent with leptin's known role in augmenting LH response through kisspeptin action in the hypothalamus and direct

stimulation of the pituitary. The fact that women with both isolated leptin deficiency and leptin deficiency due to congenital generalized lipodystrophy display similar patterns of infertility, despite markedly different body compositions, provides further support for leptin's significant influence on female reproductive function. Indeed, the markedly excess amount of adipose tissue in women with isolated leptin deficiency is insufficient to support normal reproductive function.[8] However, in a patient with congenital generalized lipodystrophy who has virtually no adipose tissue, leptin replacement alone is sufficient to restore ovulation and fertility.

Although leptin was able to restore reproductive function in this patient, her obstetric outcome was suboptimal. Although this patient's condition is quite rare, the challenge faced in controlling her blood glucose underlines both the increased insulin resistance characteristic of all pregnancies and the amplified difficulty in managing serum glucose in patients with significant baseline insulin resistance. Multiple daily blood sugar measurements with aggressive increases in insulin dosing and even hospitalization for enhanced glucose monitoring may be necessary to maintain normal glucose levels in patients with significant insulin resistance. Indeed, optimal blood sugar control should be a central focus of care because it has been shown to be associated with improved obstetric outcomes.[19]

In conclusion, in this patient with virtually absent adipose tissue, leptin replacement was sufficient to restore normal reproductive function. Moreover, leptin therapy did not appear to be teratogenic in this case and may have improved this patient's metabolic control during pregnancy. Nonetheless, the patient's obstetric outcome was, in part, suboptimal. Should other women with congenital generalized lipodystrophy conceive in the future, their blood glucose levels should be managed aggressively and planned cesarean delivery should be considered. This case suggests a key role for leptin specifically, rather than adipose tissue in general, in female reproduction.

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Table 1

Endocrine Parameters in a Patient With Congenital Generalized Lipodystrophy Before Starting Leptin, After Initiation of Leptin Therapy, Preconception, and Postpartum

	2000 (Initial Presentation)	2001 (On Leptin)	2008 (Preconception)	2009 (7 wk Pregnant, On Leptin)	2010 (Postpartum, On Leptin)
Hb A_{1c} (%) (4.8–6.4)	11.7 (↑)	7.4 (↑)	5.7	5.6	7.6 (↑)
Random glucose (mg/dL)	373 (↑)	—	107	101	119
Insulin (microinternational units/mL) (6–27)	599 (↑)	—	7.6	11	22.4
IGF1 (ng/mL) (143–859)	146	364	216	155	—
Triglycerides (mg/dL)	1,355 (↑)	303	75	63	401 (↑)
Cholesterol (mg/dL)	303 (↑)	156	145	133	166
AST (units/L) (9–34)	75 (↑)	Normal	29	28	86 (↑)
ALT (units/L)(6–41)	58 (↑)	Normal	26	7	75 (↑)
SHBC (nmol/L) (18–114)	5.3	9	22	74	33
Free testosterone (ng/dL) (0.1–2.4)	5.6 (↑)	—	1.7	0.7	1.3
FSH (units/L)	3	4	5	0.1	5.4
LH (units/L)	3	5	9	5.6	8.2
DHEA	1,100	1,600	1,300	—	—
TSH (0.4–4)	1.2–10	0.9	0.26 (↓)	0.23 (↓)	0.79
Free thyroxine (ng/dL)	1.3	0.7	1.5	1.5	1.1

Hb A_{1C}, hemoglobin A1c; IGF1, insulin-like growth factor 1; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SHBG, sex hormone binding globulin; FSH: follicular stimulating hormone; LH, luteinizing hormone; DHEA, dehydroepiandrosterone; TSH, thyroid-stimulating hormone; —, value was not measured at that time.

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