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Obesity and Female Fertility: The Bridging Role of Leptin

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Abstract

Leptin secretion is a requirement in order for both of energy balance and reproductive capacity to be preserved. That is because leptin plays an important role in appetite regulation and balance of body weight. Leptin binds to leptin receptor in the cells of the hypothalamus. This stimulates an intracrine signaling pathway that drives down-regulation of the receptors expression involved in appetite increase. It is clearly set that leptin impairs production of sex steroid hormones in granulosa cells. In addition, alterations noted in follicular fluid from obese women include increased androgen activity and decreased human chorionic gonadotropin levels by other studies. Likewise, adiponectin levels are inversely correlated with levels of insulin, which by inhibiting the production of hepatic sex hormone binding globulin, because increased levels of androgens. On meeting with the fertility problems that arise among these women, scientists must understand the pathophysiology of adipose signaling on reproductive function.

Keywords: Adipocytokines; Leptin; Fertility; Obesity; Appetite

Introduction

Obesity has expanded from the developed world, being a cause of morbidity and mortality globally [1]. In 2014, more than 1.9 billion adults, 18 years and older, were overweight. According to World Health Organization update, of these over 600 million were obese. These figures have been raised up to 700 million in 2015 [2]. An enormous increase has been observed in the prevalence of obesity and its subsequent metabolic complications, including Type 2 diabetes, dyslipidaemia, and cardiovascular disease. Even a percentage of U.S. children exceeding 40% are now considered overweight or obese [3]. Obesity arises due to equilibrium disorder between intake and consumption of energy. A simpler definition would be as follows: 'reduction of energy consumption in respect to energy intake causes an increased supply of the excess energy in the form of triglycerides in adipose cells, giving rise to an increased fat mass and finally giving position to obesity [4]. Obesity, therefore, is associated with poor quality of life [5], high risk of comorbidities, and the reduction of life expectancy by up to 20 years [6]. Chronic low-grade inflammation [7] and dysfunctional adipose tissue with its altered secretion of adipocytokine patterns seems to be the key in the progression of obesity-related disease [8]. Recently has been recognized that the obesity epidemic redounds to increasingly fertility difficulties. Obese young women and men were less likely to have their first child by 47 years of age than were their normal–weight counterparts. Obesity also predicted a lower probability of having more than one child, particularly for women [9]. In order to investigate the effect of obesity on female fertility, an overview of the literature is held here.

Models of obesity and subfertility; the bridging role of leptin

Human leptin is a protein, originally discovered in white adipocytes. Secretion of leptin is directly proportional to the total amount of fat mass in the body. The initial conceptualization of the role of leptin as an obesity hormone has evolved since 1994, when leptin itself was discovered by Friedman. Prior to its discovery, the effects of leptin were observed in 1950, by studying mutant obese mice [10,11]. Ultimately, several strains of laboratory mice were homozygous for single-gene mutations that cause them to become leptin deficient. They are categorized as follows: ob/ob mice, those having mutations in the gene for the hormone leptin, and db/db mice, those having mutations in the gene that encodes the receptor of leptin. When ob/ob mice are treated with leptin, they restore normal body weight by losing excess fat mass.

In the experiment by Ruth B.S. Harris and colleagues, lean and genetically obese ob/ob mice were infused with doses of recombinant human leptin up to the 10 μg/day for 7 days on defining genotypic differences in response and determining which responses to leptin were observed. Leptin expression was substantially higher in adipose tissue from ob/ob mice than in that from lean mice. In contrast to the other organs, leptin significantly reduced liver weight in obese mice starting at the 1 μg/day dose and reaching a maximal effect with 10 μg/day. Liver lipid was reduced at all doses of leptin, and liver glycogen content was decreased by 2 μg/day. Within genotypes, a significant effect on 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) concentrations in the hypothalamus and brain stem was indicated, with both compounds being present at higher concentrations in obese than in lean animals [12]. The design of this experiment did not allow us to determine the effectiveness of leptin treatment, since we could not possibly identify which responses in the mice were direct effects of leptin and which were secondary to the state of negative energy balance induced by leptin.

As to recent research, leptin-deficient ob/ob mice develop obesity and impaired ventilatory responses. Whether leptin replacement improves chemorespiratory responses to hypercapnia in ob/ob mice and if these effects were due to changes in body weight or to the direct effects of leptin in the central nervous system was examined by Bassi et al. [13]. Animals were allowed to recover for 7 days before intracerebroventricular daily microinjections of leptin and ventilation measurements were performed. To test whether the effect of ICV leptin replacement on pulmonary ventilation was due to peripheral actions of leptin caused by potential spill over into the systemic circulation, they

included an additional group of ob/ob mice that received leptin peripherally (10 μg/day via subcutaneous injections) for four consecutive days. As a consequence of leptin replacement, the obese ob/ob mice lost approximately 10-20% of their body weight which could have been contributed to the improvement in ventilatory function. To account for the effect of obesity in causing the respiratory deficit in obese ob/ob mice and to determine the role of weight loss in contributing to improved ventilatory responses to hypercapnia during leptin treatment, they investigated the responses to hypercapnia in lean, pair-weighted, ob/ob mice. The results from these experiments showed that the major cause of the impaired ventilatory response in ob/ob mice is leptin deficiency rather than obesity, and that weight loss in obese ob/ob during leptin treatment does not play a major role in mediating the effects of leptin to improve ventilatory responses to hypercapnia [13].

On addressing the issue of leptin replacement in ob/ob mice thoroughly by going back and forth, Ahima et al. [14] earlier showed that preventing the starvation-induced fall in leptin with exogenous leptin substantially blunts the changes in gonadal, adrenal and thyroid axes in male mice, and prevents the starvation-induced delay in ovulation in female mice. They implicated a role for leptin in the neuroendocrine response to fasting, putting forward for the first time the parameter of reproductive function in the frame of the leptin trailer and the balance of energy homeostasis.

In fact, leptin deficient ob/ob [11] and db/db mice [15], presenting with severe obesity and elevated insulin levels along with hypothalamic hypogonadism, offer breeding ground for studying the overlapping of symptoms between metabolic and reproductive pathophysiology. Along with these traits, the mutant rodents showed a pickup of endocrinologic disorders: Infertility due to hypothalamic hypogonadism, hyperinsulinemia associated with insulin resistance, hypercorticosteronemia, mild hypothyroidism and lower circulating growth hormone [16]. Moreover, leptin induces weight loss and progression to puberty when administered in leptin–deficient mice [17,18]. Therefore, in the evolution process, leptin is the primordial neurohormone modulating both energy balance and reproductive function. Dietary–induced obese models apply to human obesity. Like human, dietary–induced obesity is a polygenic trait which combines the contribution of genetic influence to the environmental one; thus, resistance to the endocrine effects of circulating leptin and insulin is strongly related to adherent increases in their circulating concentration levels following increased dietary–intake [19]. Furthermore, concurrent to the emergence of the phenotype of hyperleptinemic obese mutant mice, was the fact that chronically elevated levels of leptin may also be associated with hypothalamic infertility, suggesting that leptin resistance impairs GnRH pulsatile secretion and energy balance closing the vicious cycle of obesity [20].

Findings of hypothalamic infertility in dietary–induced obese mice implicate obesity–associated hyperleptinemia in turn responsible for hypothalamic hypogonadism, through increased hypothalamic neuropeptide Y–ergic tone [21]. Notwithstanding, leptin appears to be neurotrophic during the critical neonatal period of hypothalamic development [22]. Also, disordered nutrition of mouse pups during lactation is associated with perturbations in hypothalamic development, disrupting reproductive function in later adulthood [23].

Of note is, that adipocyte genesis and body composition are dependent on estradiol influence through regulation of leptin function [24]; namely, higher doses of estradiol inhibited adipogenic markers mRNA expression of leptin and PPARγ2, but low doses promoted leptin expression in ovariectomized rats [24]. There do exist a 'two-way' inverse relationship to the quantitative expression of leptin and estradiol in animal models of obesity and subfertility. The correlation of leptin with the secretion of other hormones even in normal circumstances is rather more complicated, especially in a particular period for women's reproduction such as pregnancy. Serum leptin and cortisol values were significantly higher, while those of prolactin and progesterone were significantly lower in the mother at the time of spontaneous vaginal delivery [25].

What is the fertility response to obesity?

The relative risk of anovulatory infertility is 2.7 in obese women at age 18 [26], while in ovulatory women presenting with fertility problems the chance of spontaneous conception decreases by 5% [27] for each unit increase in the BMI. Once obese women are pregnant, their risk of pregnancy complications is significantly higher than their lean counterparts [28]. In addition [29], many of the adjunct effects of obesity, including gestational diabetes and pre-eclampsia, occur as a result of increased levels of insulin and therefore insulin resistance; markers of cellular inflammation, neopterin and kynurenine/tryptophan ratio were determined early in pregnancy and related to pre-pregnancy BMI; A high pre-pregnancy BMI is the principal regulator for the inflammatory status in early pregnancy [30].

The mechanisms by which obesity increases subfertility have not been thoroughly explicited. Alterations noted in follicular fluid from obese women include increased insulin, glucose and lactate, increased androgen activity, increased C–reactive protein, and decreased human chorionic gonadotropin levels [31,32]. Studies have in vitro clearly set that leptin impairs steroidogenesis in granulosa cells [33,34] and such an impairment could also have an impact on follicular development, oocyte quality, and ovulation in obese women [35]. In humans, leptin receptors have been established on granulosa and theca cells, oocytes, preimplantation embryos and the endometrium [36,37]. There is also evidence that follicular leptin levels correlate with BMI [38,39] and a decrease in the serum levels of adiponectin [40].

In fact, leptin acting through the receptors on the theca and granulosa cells inhibits production of sex steroids in the ovary [41,42]. The inverse correlation of adiponectin to insulin ratio [40] causes elevation of androgen levels [39]. In addition, insulin acting via insulin like growth factor 1 (IGF 1) enhances luteinizing hormone –mediated increases in ovarian androgens [43]. On the other hand, peripheral conversion of androgens to estrogen in adipose tissue inhibits gonadotrophin secretion [39]. Increased androgens in turn contribute to 'apple' and not 'pear' shaped obesity [44,45]; thus, a vicious circle evolves, where abdominal fat accumulation increases insulin resistance and androgen production, with hyperandrogenemia promoting hyperinsulinemia and so forth [46,47].

The strongest consequence of obesity on fertility is anovulation. Polycystic Ovarian Syndrome (PCOS) related to obesity, being a well-known cause of ovulatory dysfunction, is furthermore exacerbated by increased insulin resistance and hyperinsulinemia [48,49]. In 65% of patients with PCOS, obesity shares one common denominator to anovulation [50]. Most of the studies have shown that BMI is the regulator for all the correlations seen between leptin and other parameters in women with PCOS [51].

On the correlation over obesity and disturbance of fertility, several retrospective studies have shown a negative impact of overweight and obesity in women on the outcome of in vitro fertilization (IVF)

[52-55]. The ongoing pregnancy rate and live birth rate is however consistently decreased especially due to an increase in miscarriages in women with obesity [56-58]. What should be verified? Leptin-resistin correlation and associations with TNF-α may be helpful during the interpretation of IVF outcome [59]. In any case, obesity during pregnancy contributes not only to abnormal fetal development and subsequent increased neonatal morbidity and mortality but also to increased morbidity during childhood, adolescence and adulthood, viz. 'developmental origins of adult disease' [60].

The preservation of the unbalanced forces: obesity and reproductive dysfunction

This challenge will require contribution disciplines, not only from clinicians but also from comparative biologists. A multidisciplinary approach is the ultimate hope for the 'cure' of obesity. There is little doubt that women who are trying to conceive should prevent obesity and attempt to attain a normal BMI. In obese women and even more significantly, in women suffering from PCOS, a 5–10% weight loss should be the initial therapeutic approach [61]. The hypocaloric diet promotes a decrease in BMI, percentage of body fat, and leptin concentrations, which improves oocyte development and pregnancy rate [62]. The endocrine changes seen after Roux–en–Y gastric bypass though at early stages are countering anovulation [63]. The ability of metformin versus sibutramine to restore ovulation further emphasizes the role of insulin resistance in ovulatory dysfunction [64]. Furthermore, a significant positive correlation was found between serum leptin and BMI values before and after administration of diazoxide, an insulin– reducing compound, as well as between leptin, insulin and insulin like growth factor binding protein in women having presented PCOS [65].

Of interest is, that the inositol can reduce insulin resistance, improve ovarian function, and reduce androgen levels in women with PCOS and is used lately solely therapeutically in order to alleviate hyperandrogenemia symptoms, having actually no side effects [66]; two inositol isomers, myo-inositol and D-chiro-inositol have been proven to be effective in PCOS treatment, by improving many features of the metabolic syndrome [67]. Perhaps, the fertility problems that arise among obese women need understanding of the impact of adipose signaling on reproductive function, emphasizing on the preconception management.

Is leptin used in the preservation of unbalanced forces? Leptin is an approved treatment for generalized lipodystrophy, a severe metabolic disorder, and has also shown potential for the treatment of diabetes. In addition, leptin restores reproductive capacity particularly in patients with central amenorrhea [68].

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