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# Role of leptin in pregnancy: Consequences of maternal obesity

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ABSTRACT

Maternal obesity is associated with increased risks of pregnancy complications. Excessive fat mass, common to obese women, has the potential to influence production and secretion of adipose tissue derived proteins called adipokines. The adipokine leptin is involved in the regulation of multiple aspects of maternal metabolic homeostasis. In addition, leptin has been shown to be important for placentation and maternal–fetal exchanges processes regulating growth and development. In later stages of a healthy pregnancy, central leptin resistance occurs to allow increased nutrient availability for the fetus. Disruption of the signaling capacity of leptin associated with obesity is emerging as a potential risk factor leading to pregnancy complications as a result of aberrant fuel partitioning *in utero*. In this review we discuss the influence of obesity on the roles of leptin and leptin resistance at the central and placental level.



## 1. Introduction

The epidemic of obesity, a well-recognized worldwide phenomenon, has significant reproductive repercussions. Maternal obesity is associated with multiple pregnancy complications including gestational diabetes mellitus (GDM) and preeclampsia (PE) [1,2], macrosomia, fetal growth restriction (FGR), intrauterine fetal death and stillbirth [3,4]. In addition evidence also supports a link between maternal obesity and the development of offspring obesity later in life [5]. During pregnancy, these outcomes are believed to be caused by altered metabolic states and poor uteroplacental development. However, the postpartum consequences of maternal obesity on downstream offspring health are thought to be mediated by an abnormal intrauterine environment [6]. Interestingly, both adipose and placental tissues are potent endocrine organs capable of expressing and secreting leptin. In obese individuals and in pregnant women, there is an excess of adipose tissue resulting in altered expression patterns of leptin (Table 1) [7,8]. Maternal obesity is increasingly recognized to be associated with further dysregulation of adipose and placental tissue expression of leptin resulting in placental dysfunction, as well as maternal and fetal metabolic deregulation. In this review, we discuss the differential systemic and placental expression patterns of leptin associated with obesity, pregnancy and pregnancy complicated with obesity. Further, we provide a succinct overview of the potential role obesity plays in pregnancy complications and how this may alter fetal growth by highlighting current clinical and basic science research.

## 2. Leptin's endocrine function

Leptin is the most studied adipokine and is produced and secreted by white adipose tissue as well as the placenta [9]. The main endocrine function of leptin in the central nervous system is to maintain whole body energy homeostasis. It achieves this by acting as a satiety signaling peptide which suppresses the neuropeptide Y pathway of the appetite regulatory center in the hypothalamus [10]. It also decreases energy storage and increases energy mobilization in the periphery in an effort to achieve energy balance [11]. Gene deletion of a leptin and/or leptin receptor protein leads to aberrant postprandial appetite suppression resulting in constant hunger (i.e., attenuated satiety), over eating (i.e., hyperphagia) and ultimately severe early-onset obesity, resulting from an imbalance between caloric expenditure and excessive consumption [12].

Leptin target tissues/cells contain one or more of the leptin receptors isoforms. They are generated by splice variance of the OB–R (leptin receptor). The full length leptin receptor (OB–Rb) is membrane bound and is responsible for cell signaling through

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**Table 1**
Leptin expression patterns in obesity, pregnancy and pregnancy complications.

| | Maternal condition | | | | | | | Fetal condition | |
|---|---|---|---|---|---|---|---|---|---|
| | Non pregnant lean | Non pregnant obese | Healthy pregnancy | Gestational diabetes mellitus | Pre-eclampsia | Pre-eclampsia obese | Obese pregnancy | Macrosomia/(LGA) | SGA/FGR |
| **Maternal Serum** | | | | | | | | | |
| Non pregnant lean | | ↑ [7,8] | ↑ [24] | | | | | | |
| Healthy pregnancy | | | | ↑ [60] | ↑ [61] | | ↑ [58] | | |
| Pre-eclampsia lean | | | | | | ↑ [67] | | | |
| **Placenta** | | | | | | | | | |
| *Expressed by syncytiotrophoblast and villous vascular endothelial cells*[49] | | | | | | | | | |
| Healthy pregnancy | | | | ↑ [49,60] | ↑ [61–63] | | | | |
| AGA | | | | | | | | | ↓ [49] |
| **Fetal Serum** | | | | | | | | | |
| AGA | | | | | | | | ↑ [53,54] | ↓ [46] |

↑ Increase or ↓ decrease expression patterns.
Numbers indicates the references number from bibliography.
AGA: average for gestational age, LGA large for gestational age, SGA: small for gestational age, FGR: fetal growth restriction.

JAK-STAT signaling pathways [13]. OB–Rb is primarily found in the hypothalamus and is involved in satiety response [14]. There are three other membrane bound leptin receptor isoforms OB–Ra/OB–Rc/OB–Rd (short forms) which vary from the full length OB–Rb depending on the length of the intracellular domain. Their function also varies depending on the tissue in which they are localized and the length of the cytoplasmic tail. Various functions include leptin cellular internalization and signaling through the MAPK pathway [15,16]. The fifth OB–R isoform is a soluble form (OB–Re). This form does not contain the transmembrane domain or intracellular domains. *In vitro* studies have shown that a human derived OB–Re isoform can occur by post translational modification by proteolytic cleavage [17]. In rodents this isoform can also be generated by alternative splicing in such tissues as the liver and the placenta tissue [18,19]. In either cases OB–Re has the potential to reach circulation by either shedding from the membrane or by secretatory pathways. Once it has been released into the circulation it is capable of forming a complex with free leptin [20]. It is postulated that OB–Re can enhance signaling by reducing leptin clearance and degradation. It is also believed that an excess OB–Re can counteract the enhancing effects by blocking leptin's binding capacity to the membrane bound receptor [21].

## 3. Leptin and obesity

Obesity is associated with increased circulating free leptin concentration [7]. This increase positively correlates with BMI and fat mass [8]. In this situation, the paradoxical effects of increased leptin levels can be explained partly by a loss of signaling capacity to satiety centers which may occur as a result of leptin resistance. Higher rates of free leptin, bound leptin (bound with OB–Re) and OB–Re are secreted from subcutaneous adipose tissue from obese individuals when compared to their lean counterparts [20]. This increased secreted soluble OB–Re from adipose tissue must be incapable of reaching the circulation since lower levels of the OB–Re in serum of obese individuals have been reported [22,23]. Therefore, obesity is generally characterized by increased circulating levels of free leptin and lower levels of OB–Re.

## 4. Leptin and pregnancy

Maternal leptin serum levels steadily increase during the first and second trimesters and peak in late second or early third trimester [8,24]. These high levels are maintained throughout the remainder of gestation and decline drastically postpartum. This suggests a functional importance of leptin during pregnancy. In rats, hyperleptinemia in maternal circulation during healthy pregnancy leads to central leptin resistance, by down regulation of the OB–Rb in the ventromedial nuclei of the hypothalamus and increased circulating OB–Re, both leading to attenuated leptin signaling in the regulatory appetite center of the brain (Fig. 1) [11]. This central leptin resistance may act as a compensatory mechanism to meet the developing fetal energy needs akin maternal insulin resistance in later gestation. Interestingly, normal weight pregnant women and obese non pregnant individuals seem to have similar increases in circulating leptin levels compared with their counterpart non-pregnant or healthy controls. They also exhibit alterations in signaling of the appetite center of the brain, (i.e. both exhibiting a form of leptin resistance).

Leptin functions at the periphery as a paracrine/autocrine factor capable of modifying insulin sensitivity, tissue metabolism, stress response and reproductive functions [25]. The various reproductive functions of leptin include regulatory control of such processes as placental nutrient transport, placental angiogenesis, trophoblast mitogenesis and immunomodulation, all crucial events for fetal development and adequate placental function [26–29].

For example leptin's role in nutrient transport is evident in macronutrient exchange, particularly amino acid transport. In term placental explants from healthy pregnancy, leptin has been shown to enhance SNAT (System A sodium dependant neutral amino acid transport) activity, suggesting a role for leptin as a mediator of amino acid delivery to the fetus via the placenta [27]. The importance of SNAT in fetal growth regulation has been well demonstrated. In FGR complicated pregnancies the syncytiotrophoblast SNAT activity from microvillous membranes is decreased which

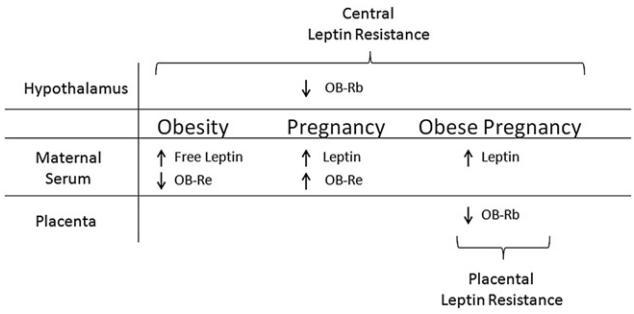


**Fig. 1.** Proposed leptin resistance at the central and placenta level (OB–Rb: leptin membrane bound signaling receptor, OB–Re: soluble leptin receptor).