

## Insulin like growth factor 1 (IGF-1) and IGF binding proteins in obese pregnant women and their babies: Potential effects on placental function and fetal growth

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### Abstract

**Introduction:** The placenta expresses significant amounts of insulin and IGF1 receptors at distinct locations on both fetal and maternal surfaces. This makes the IGF1 and the insulin receptor accessible to fetal and/or maternal insulin, IGF1 and IGF2. IGFs are involved in the receptor-mediated regulation of placental growth and transport, and placental angiogenesis. Maternal obesity during gestation mediates significant changes in the metabolism of mothers, placentas as well as fetal growth.

**Objectives:** In obese women. the role of the insulin like growth factor system IGFs, IGF receptors, IGF-binding proteins (IGFBPs) and IGFBP proteases during gestation, and their effect on placental growth and fetal anthropometric changes need further clarification. In this update we reviewed the literature on the detected changes in the maternal and fetal IGFs in relation to placental growth and function and to fetal growth and newborn size in pregnant obese mothers. Eighteen research articles fitted the criteria of this update.

**Results:** Twenty-three research papers were including 2817 pregnant obese and non-obese women (controls) and their babies were selected and reviewed. Results showed that obesity and excessive nutrient intake during gestation increase maternal IGF1 and decreases IGFBP1. Increased maternal IGF1 and/or its availability due to decreased IGFBP1 can increase the size (weight) and development of the placenta, stimulate mTOR signaling which stimulates protein synthesis, mitochondrial function, and upregulate specific placental amino acid transporter isoforms (amino acids transport), GLUT-1, (glucose transport) and possibly lipid transport to the fetus which can induce fetal IGF1 secretion and lead to overgrowth.

**Conclusions:** In obese women during pregnancy, increased level of IGF1 and/or its availability due to decreased IGFBP1 can increase the size (weight) and development of the placenta, stimulate mTOR signaling which stimulates protein synthesis, mitochondrial function, and upregulate placental transport of amino acids, glucose and possibly fatty acids.

**Keywords:** Obesity; BMI; Pregnancy; Placenta; Fetus; Newborn; Growth; IGF1; IGFBP; mTOR

### 1. Introduction

The interaction between maternal nutrition and hormones and placental growth and development including hormones play a major part in the control of fetal nutrition and growth. (1)

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The placenta is a highly active endocrine organ during gestation, secreting a variety of hormones with physiological effects in the mother and fetus. It controls the transfer of maternal nutrients to the fetus and modulate fetal growth through many mechanisms.

Emerging evidence suggests that the placenta actively responds and orchestrates the nutritional and metabolic signals from the mother and the fetus. (2)

The syncytiotrophoblast, is a very specialized multinucleated epithelial layer which cover the surface of the chorionic villi. It produces many hormones, and controls nutrient transport from the maternal to fetal circulations. Most solutes are transferred actively or passively across the two polarized plasma membranes of the syncytiotrophoblast, an apical microvillous membrane in direct contact with the maternal blood, and a basal membrane facing the fetal capillaries. An extensive panel of cellular signaling pathways in the syncytiotrophoblast controls and integrates placental growth and function in response to maternal and fetal signals. (3-5)

The apical microvillous membrane of the syncytiotrophoblast expresses numerous hormone receptors, such as insulin and IGF-I, consistent with regulation of placental function by maternal hormones. It has been shown that insulin and IGF-I secreted from the maternal liver stimulates placental growth and transport functions. (6-8)

The insulin-like growth factors (IGFs), insulin-like growth factor binding proteins (IGFBPs), and the IGFBP proteases are involved in the regulation of somatic growth and cellular proliferation. IGF-I is one of the key metabolic signals notifying the placenta about the nutritional status of the mother. For example, maternal nutrient restriction is typically associated with low circulating IGF-I, whereas conditions characterized by overnutrition are associated with elevated serum IGF-I. (9-10)

IGF-1 availability in the maternal circulation and at the maternal-fetal interface is primarily regulated by IGF binding proteins such as IGFBP-3 and IGFBP1. (11,12)

Data about the interaction between maternal, placental, and fetal IGF1/IGFBP in obese mothers in relation to fetal growth and newborn size needs illumination.

### *Aim of the study*

To review research papers published in Pubmed, Google scholar, Research gate, and Scopus in the past 20 years, on the maternal, placental and fetal/infantile/ IGF1/IGFBP-1 in relation to birth size in pregnancies associated with maternal obesity.

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## **2. Results and discussion**

Twenty-three research papers were selected and reviewed (n = 2817 pregnant obese and non-obese women (controls) and their babies were studied).

Serum concentrations of IGF-I, IGF-II, IGF-binding protein (IGFBP)-1, IGFBP-3 and IGFBP-3 protease activity were assessed in 23 women before conception, at weeks 8, 14, 20, 32 and 35 of pregnancy and 2 weeks postpartum. Birth weight was negatively correlated with IGFBP-1 at gestational week 20 and 35. One third of the variability in fetal weight was explained by maternal IGF-I in combination with IGFBP-3 protease activity, measured at gestational week 32. (13,14)

Hills FA et al, reported that maternal IGF-I levels increased in 55 obese pregnant women and showed a significant positive correlation with maternal weight (P = 0.0033) but was not correlated with birthweight. The maternal IGFBP-1 levels showed a negative correlation with birthweight, maternal weight, placental weight and maternal glucose level. (15)

Lappas M measured IGF1, IGFBP-1, IGFBP-6 and IGFBP-rP1 in maternal and cord plasma from women with normal glucose tolerance (NGT) (30 non-obese and 36 obese) and GDM (44 non-obese and 26 obese) at the time of term elective cesarean section. Maternal plasma concentrations of IGFBP-1, IGFBP-6 and IGFBP-rP1 were significantly lower in NGT obese compared with NGT non-obese women. In cord plasma, IGFBP-1-3 and IGFBP-rP1 concentrations were significantly lower in NGT obese compared with NGT non-obese women. Maternal BMI had significant correlations with cord plasma IGFBP-1 concentrations and fetal birthweight. Pre-existing maternal obesity and GDM are associated with

lower IGFBP levels in maternal and cord plasma. Authors suggested that alterations in circulating IGF and IGFBPs may alter birthweight and/or neonatal adiposity. (16)

Geary MP et al studied a cohort of 987 normal pregnancies. After adjustment for gestational age, parity, and maternal height, they found that cord plasma concentrations of IGF-I and IGFBP-3 along with sex explained 38.0% of the variability in birth weight, 25.0% in birth length, and 22.7% in head circumference. (17)

Patel N et al, studied 343 obese mother-offspring pairs and found that maternal IGF-1 was positively correlated, and IGFBP-1 was inversely correlated to birth weight in infants from obese mothers. There was a positive linear relationship between cord IGF-1 and neonatal birth weight z scores, skin fold thickness (SFT) (subscapular and triceps SFT) and mid upper arm and abdominal circumferences. (18)

Kimyon C G et al, studied 142 pregnant women at gestational week 11<sup>o</sup>-13<sup>6</sup>. They reported that the first trimester IGFBP-1 levels were significantly lower in the mothers with large for date (LGA) neonates. Maternal IGFBP-1 levels at delivery were negatively correlated with neonatal birth weight. (19)

Yang et al analyzed 332 blood samples from 114 expectant mothers at different gestational ages (GA) without adverse medical history. They reported that maternal serum IGF-I during pregnancy was significantly correlated to GA, maternal BW and maternal BMI. (20).

Verhaeghe J et al, studied 289 women, who were pregnant with a single fetus, between 24- and 29-week gestational age (GA). They detected that maternal IGF-I levels were mainly determined by maternal body weight (BW), placental growth hormone (PGH), and insulin, while IGFBP-1 concentrations were negatively determined by maternal BW, IGF-I, and insulin. Birth weight, and the ponderal index were strongly related to maternal BW, but not to maternal PGH, IGF-I, or IGFBP-1 levels. (21)

In 27 obese pregnant women, Wardana ZS et al, found that birthweight was positively correlated with maternal body mass index, umbilical vein glucose and insulin. Umbilical vein glucose levels were positively correlated with placental weight and maternal BMI. Women entering pregnancy obese had higher circulating concentrations of IGF-1 and insulin, and more pronounced insulin resistance, compared with pregnant women with normal BMI. A positive correlation of IGF-1 levels with fasting blood glucose (FBG) was detected in obese women. (22)

In 100 pregnant women, Mokkal K et al, detected an inverse correlation between the maternal concentration of IGFBP-1 and maternal weight. Nutritional status and diet contributed to the levels of IGFBP-1. (23)

Baumann et al, hypothesized that IGF-I could be responsible for the stimulation of GLUT1 expression and, can promote the feto-maternal glucose transport that plays a role in the development of fetal macrosomia. Their in-vitro study outcomes indicated that the treatment of primary syncytial cells with increasing concentrations of IGF-I resulted in the increased expression of GLUT1 protein, promoted the transepithelial glucose transport and stimulated the glucose uptake into cells. (24)

Acosta O et al, determined the expression of GLUT-1 and -9 (Western blot) and glucose uptake (radiolabeled glucose) in isolated syncytiotrophoblast microvillous and basal plasma membranes from 33 placentas. They reported that birthweight was positively correlated with maternal BMI, basal plasma membranes GLUT-1 expression, umbilical vein glucose, and insulin. Umbilical vein glucose levels were positively correlated with placental weight and maternal BMI, but not with maternal fasting glucose. They suggested that increased placental size, not increased glucose transport, promotes glucose delivery to these fetuses. (25)

Borges MH et al, reported that the circulating fetal IGF-I, basal membrane GLUT1 expression and glucose transporter activity were correlated with birth weight, in 28 non- diabetic women. Placental weight was correlated significantly with fetal IGF1 level. (26)

Jansson N et al, measured the activity and protein expression of the amino acid transporter systems A and L in syncytiotrophoblast microvillous plasma membranes of 23 Swedish non-diabetic obese pregnant women. They detected up-regulation of microvillous plasma membrane system A activity and protein expression in obese women. The activity of placental insulin/IGF-I and mTOR signaling was positively correlated to birth weight. They proposed that this effect may be mediated by activation of insulin/IGF-I and mTOR signaling pathways, which are positive regulators of placental amino acid transporters. A similar study in mice supported their findings. (27,28)

Mazurkiewicz D et al, studied 157 mother-newborn pairs and reported that more frequent consumption of sweet and salty snacks, fruit and fruit juices may promote greater weight gain in pregnancy and higher newborn birth weight. A significant relationship was only found between the concentration of IGF-1 in the mother's blood and the Ponderal index of the newborn. (29)

Garcia-Santillan JA et al analyzed the placental nutrient transporter protein expression in small (SGA, n = 14), adequate (AGA, n = 18), and large (LGA n = 10) gestational age term for newborns from healthy or obese mothers (LGA-OB, n = 9) and their association with maternal fatty acids, metabolic status, placental triglycerides, and neonatal outcomes. GLUT1 was higher in LGA and lower in SGA and positively correlated with maternal HbA1c and placental weight (PW). Protein transporters SNAT2 was lower in SGA, while SNAT4 was lower in LGA-OB. Fatty acid transport protein 1 FATP1 was lower in SGA and higher in LGA. SNAT4 correlated negatively and FATP1 correlated positively with the placental weight and birth anthropometry. (30)

Mexitalia M et al, studied the association between cord blood IGF1 and changes in fetal weight gain (ultrasonographic measurement) in 52 pregnant mothers during the third trimester. Results indicated that maternal BMI and a higher IGF-1 cord blood level were correlated with larger weight gain during the third trimester and bigger birth weight.(31)

In 152 lean and overweight (OW) pregnant women with or without GDM, OW significantly increased the placental mRNA expression of genes involved in lipid metabolism (FAT/CD36, FATP1, FATP4, FATP6, and PPAR- $\alpha$ ), elevated placental lipid content (triglyceride, cholesterol), enhanced placental mTORC1-rpS6 and ERK1/2 signalling, increased cord blood insulin levels and birth weight. Neonatal birth weight was positively correlated with maternal pre-BMI. (32)

Bret K E et al, measured Gene expression in placenta samples obtained from lean (n = 11) and obese (n = 10) women. Weight gain during gestation (GWG) in excess of the upper limit of the body mass index (BMI) specific guidelines was correlated with increased expression of Sodium-Coupled Neutral Amino Acid Transporter 1 (SNAT1). In another study, a strong positive correlation was observed between total sugar intake and glucose transporter 1 (GLUT1). (33,34)

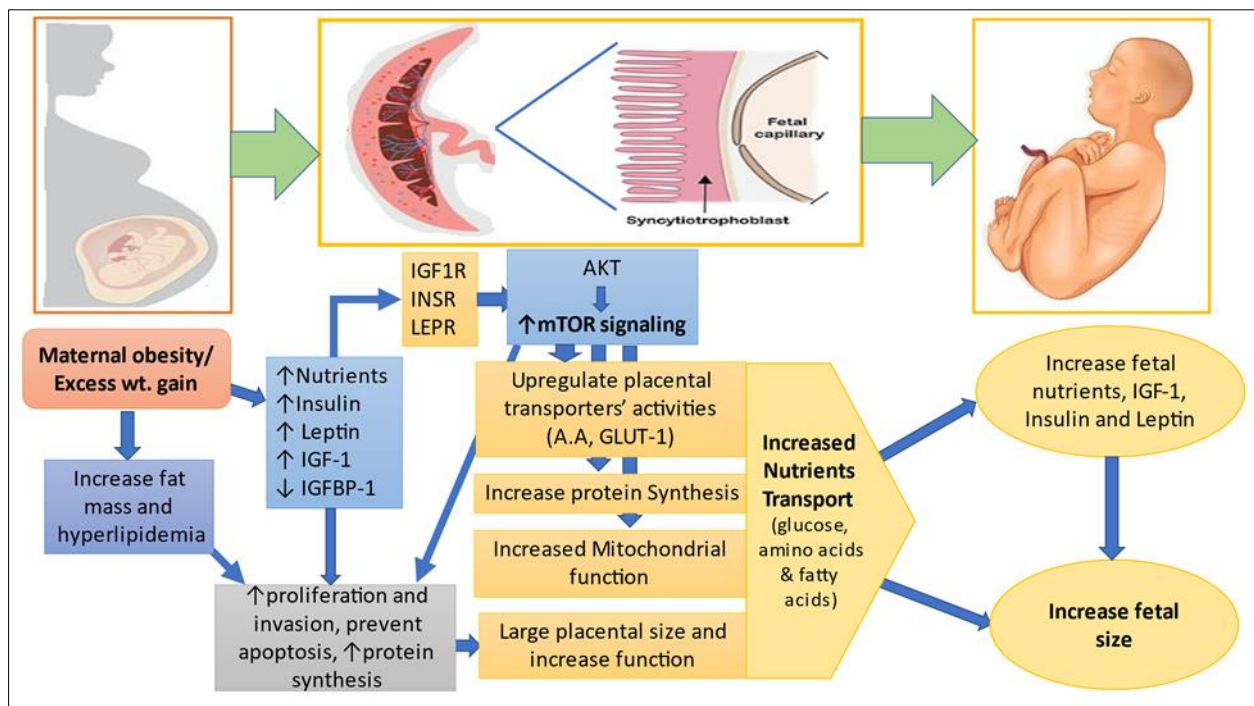
Martino et al reported that gene expression for markers of placental energy sensing and oxidative stress, were primarily affected by maternal obesity. SIRT-1 (a positive regulator of nuclear receptors that function as cholesterol sensors and regulate cholesterol and lipid homeostasis) and UCP2 were both upregulated. (35)

The significant findings of the reviewed studies can be summarized in the following key points:

- Women entering pregnancy obese had higher circulating concentrations of IGF-1.
- Maternal plasma concentrations of IGFBP-1, IGFBP-6 and IGFBP-rP1 were significantly lower in NGT obese compared with NGT non-obese women. Maternal IGFBP-1 levels showed a negative correlation with birthweight, maternal weight, placental weight, maternal glucose level and gestational age.
- Maternal IGF-I levels were mainly determined by maternal body weight (BW), placental growth hormone (PGH), and insulin, while IGFBP-1 concentrations were negatively determined by maternal BW, IGF-I, and insulin.
- Pre-existing maternal obesity was associated with lower IGFBP levels in maternal and cord plasma.
- A positive correlation of IGF-1 levels with FBG was detected in obese women.
- Frequent consumption of sweet and salty snacks, fruit and fruit juices is suggested to promote greater weight gain in pregnancy and higher newborn birth weight.
- Maternal IGF-1 was positively correlated, and IGFBP-1 was inversely correlated to birth weight in infants from obese mothers.
- Nutritional status and diet contributed to the levels of IGFBP-1.
- Increased concentrations of maternal IGF-I resulted in the increased expression of GLUT1 protein, promoted the transepithelial glucose transport and stimulated the glucose uptake into cells.
- Maternal overweight significantly increased the placental mRNA expression of genes involved in lipid metabolism, elevated placental lipid content, enhanced placental mTORC1-rpS6 and ERK1/2 signalling, and increased cord blood insulin levels and birth weight.
- Up-regulation of microvillous plasma membrane system A activity and increased placental protein expression occur in obese women.
- Placental weight was correlated significantly with fetal IGF1 level.
- The activity of placental insulin/IGF-I and mTOR signaling was positively correlated to birth weight.
- GLUT1 was higher in large babies and positively correlated with maternal HbA1c and placental weight.
- Protein transporters SNAT4 is lower in large babies born to obese mothers.

- Maternal BMI had significant correlations with cord plasma IGFBP-1 concentrations and fetal birthweight.
- Cord plasma, IGFBP-1-3 and IGFBP-rP1 concentrations were significantly lower in NGT obese compared with NGT non-obese women.
- Cord plasma concentrations of IGF-I and IGFBP-3 along with sex explained 38.0% of the variability in birth weight, 25.0% in birth length, and 22.7% in head circumference.
- Umbilical vein glucose levels were positively correlated with placental weight and maternal BMI.
- Circulating fetal IGF-I, basal membrane GLUT1 expression, and glucose transporter activity were significantly correlated with birth weight.

Collectively, these findings suggest that obesity and obesogenic diets modify placental phenotype in connection with changes in IGFs system and has important contribution to fetal growth. In the placenta of obese women, the expression of IGF signalling machinery (IGFR, INR, AKT, mTORC1) and different nutrient transporters have significant changes. These changes seem to depend on the level of maternal body fat mass, gestational weight gain and BMI as well as excess nutrients intake. Taken together, these findings suggest that obesity and obesogenic diets alter placental phenotype in association with changes in placental IGFs system and fetal growth. (Figure 1)



**Figure 1** The mechanistic link between maternal obesity, placenta and fetal overgrowth/increased infant adiposity

We propose that the mechanistic link between maternal obesity, fetal overgrowth/increased infant adiposity involves specific alterations in the placenta including increased mTOR signaling. Increased IGF-1, insulin, leptin, and nutrient levels and low IGFBP1 in the maternal circulation are important factors in the activation of placental mTOR signalling, a positive regulator of important placental functions, including glucose, amino acid transport and mitochondrial biosynthesis. These changes are suggested to stimulate the transport of nutrients (glucose, amino acids, and fatty acids) to the fetus, which significantly increase fetal growth and/or fat mass.

IGF-1, insulin-like growth factor 1; IGF1R = insulin-like growth factor receptor, INSR = insulin receptor, LEPR = leptin receptor, mTOR, mechanistic target of rapamycin.

### 3. Conclusion

In obese mothers and those who gain excessive weight during pregnancy, and increased nutrient intake appear to increase maternal IGF1 and decreases IGBP1. Increased maternal IGF1 and/or its availability due to decreased IGFBP1 can increase the size (weight) and development of the placenta, stimulate mTOR signaling which stimulates protein synthesis, mitochondrial function, and upregulate specific placental amino acid transporter isoforms (amino acids

transport), GLUT-1, (glucose transport) and possibly lipid transport to the fetus which can induce fetal IGF1 secretion and lead to overgrowth.

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## Compliance with ethical standards

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### *Disclosure of conflict of interest*

There is no conflict of interest among authors.

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