World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Maternal, placental, and fetal Insulin-Like Growth Factor-I (IGF-1) and IGF Binding proteins (IGFBPs) in Diabetic pregnancies: Effects on fetal growth and birth size.

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World Journal of Advanced Research and Reviews, 2023, 17(02), 287–295

Publication history: Received on 01 January 2023; revised on 09 February 2023; accepted on 11 February 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.17.2.0251

Abstract

Introduction: During gestation, IGF1 secretion and availability in the maternal blood and at the maternal-fetal interface is mainly regulated by IGF-binding proteins (IGFBP) such as IGFBP-1 synthesized by the decidua. Data about the interaction between maternal, placental, and fetal IGF1/IGFBP in relation to fetal growth and newborn size during diabetic pregnancy (gestational Diabetes (GDM) and Type 1 DM (T1DM) is not clear.

Aim of the study and Methods: We reviewed the research papers published in Pubmed, Google scholar, Research gate, and Scopus in the past 20 years on the relationship between maternal, placental, and fetal/infantile/ IGF1/IGFBP-1 in relation to birth size in pregnancies associated with maternal diabetes.

Results: Twenty-eight research papers were selected and reviewed (patients' number = 1902). In GDM pregnancies, higher maternal IGF1 levels and/or its availability due to lower IGFBP1 levels can increase the size (weight) and functions of the placenta. These include the upregulation of specific placental amino acid transporter isoforms and GLUT-1, stimulation of mTOR signaling which stimulates protein synthesis, increasing mitochondrial functions, and accelerating nutrient transport which significantly contributes to fetal growth and newborn birth size. On the other hand, in pregnant women with T1DM, lower maternal IGF1 is associated with subsequent underweight placenta and lower birthweight.

Keywords: IGF1; IGFBPs; Diabetes; GDM; Placenta; fetal growth; Birth weight

1. Introduction

The regulation of normal human fetal growth includes several multidirectional interactions between the mother, placenta, and fetus. (1) During gestation, the mother must adapt her body systems to provide sufficient nutrients and oxygen essential for the growth and development of her baby in utero. Improper adjustment of maternal physiology during gestation can lead to fetal complications. (2)

Maternal adaptations to pregnancy are primarily mediated by the placenta, the biological interface between the mother and fetus. The placenta is a highly active endocrine organ during gestation; secreting various hormones with physiological effects in the mother and can control the transfer of maternal nutrients to the fetus and consequently modulate fetal and neonatal growth. (3-6)

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In many studies maternal weight, BMI, fat content, and blood glucose level have been correlated positively with infant birth weight. The maternal insulin-like growth factor (IGF) system has been proposed to be a significant mediator between maternal nutritional status and fetal growth. (7,8)

The insulin-like growth factors (IGFs), IGF1 and IGF2, are 7.5 kDa single-chained polypeptides that stimulate growth in utero and postnatally. They affect the metabolism, mitogenesis, survival, and differentiation of a wide variety of cell types by binding to IGF receptors (IGF1R and IGF2R), insulin receptors (INSR) and a hybrid IGF1R–INSR receptors with varying affinity. (9)

Maternal IGF1 is affected by nutritional status, and it facilitates maternal retention of nutrients. (10) IGF1 can stimulate placental growth and protein synthesis and stimulates nutrient transfer. (11) IGF1 actions are adjusted by 6 binding proteins. In the circulation, most IGF is bound to binding proteins (IGF binding proteins (IGFBP)-1–6). These IGFBPs are capable of both inhibiting (e.g., IGFBP-1) and enhancing (e.g., IGFBP-3) IGF1 biological activities. In addition, during pregnancy, maternal proteases degrade IGFBP-3 (12-14) which lessens its affinity for IGF1 and can enhance the metabolic activities of IGF-I in the placenta and consequently may modify fetal growth. On the other hand, IGFBP-1 binds only about 2 % of serum IGF1 (15), and shares in the short-term regulation of IGF activity, and glucose metabolism. (16).

The IGF1/IGFBP family has been suggested to play an important role in driving maternal adaptations and fetal growth and development in health and during illness. (17,18) Maternal diabetes mellitus (gestational diabetes GDM, T2DM, and T1DM can adversely affect the maternal physiological adaptation, placental growth, and functions and subsequently fetal growth. (19,20) In diabetic pregnancies, data about the interaction between maternal and fetal IGF1/IGFBP in relation to placental growth and functions and to fetal growth and newborn size still needs clarification.

This review examines the recent literature about changes in maternal, placental, and fetal IGF1/IGFBP in pregnant women with diabetes in relation to placental size and functions as well as to fetal growth and newborn size.

Aim of the study

To review research paper published in Pubmed, Google scholar, Research gate, and Scopus in the past 20 years on the relation between placental IGF1/IGFBP-1 and fetal/infantile/childhood growth in pregnancies associated with maternal diabetes. Inclusion criteria included "pregnancy", Diabetes, gestational diabetes (GDM), T1DM, T2 DM, obesity, IGF1, IGFBP, birth size, placenta size, BMI, macrosomia, SGA, fetus, growth factors. Exclusion criteria: Other maternal disorders (preeclampsia, hypertension, other endocrine and systemic diseases, anemia, malnutrition, and genetic disorders).

2. Results and Review

Twenty-eight research papers fitted the inclusion criteria and were reviewed (n = 1902 pregnant women).

Zhao Y studied 527 GDM patients in comparison to 527 healthy pregnant women (NGT). The GDM group had higher BMI, fasting blood glucose, blood glucose level at 1 h, 2 h after meal, and AUCG than the NGT group. IGF1 and Growth/differentiation factor 15 (GDF-15) levels (a member of the transforming growth factor (TGF)-beta family, which is released as a response of oxidative stress and inflammation) were higher in the GDM group vs the NGT group. IGF1 levels were positively correlated with maternal FBG and with GDF15 level. (21)

Grissa O, et al, studied 30 women with GDM and their 30 macrosomic babies. Serum concentrations of IGF-I, IGFBP3, epidermal growth factor (EGF), and fibroblast growth factor 2 (FGF-2) (which promotes endothelial cell proliferation and angiogenesis) were higher in GDM women and their macrosomic babies as compared to their respective controls (n = 30). (22)

Luo ZC, et al reported that maternal and fetal IGF-I levels were significantly higher in GDM vs nondiabetic pregnancies. In women with GDM (n = 307), maternal plasma IGF1 concentrations increased by an average of 55.4% between 24–28 and 32–35 weeks of gestation. The maternal IGF-I levels were correlated with placental weight and birth weight. Each SD increase in maternal IGF-I level at 24–28 weeks was associated with a 75-g increase in birth weight, a 20-g increase in placental weight, and 1.91-fold higher odds of macrosomia. (23)

Kimyon C G et al, studied 142 pregnant women at gestational week 11° to 13⁶. All fetuses were imaged through ultrasonography. The maternal IGFBP-1 level during the first trimester was significantly lower in the mothers with LGA neonates versus SGA neonates. (24)

In 67 pregnancies complicated with T1DM, and 28 with GDM, Gibson JM et al detected that cord serum highly phosphorylated IGFBP-1 concentrations were lower in both groups vs controls (n = 62). (25) In diabetic pregnancies, Loukovaara et al, described suppression of highly phosphorylated IGFBP-1 (hp) forms with higher affinity for IGF-I than low phosphorylated (lp) forms which were linked with stimulated fetal growth. (26)

In a prospective study by Higgins MF et al, maternal samples were obtained from 25 non-diabetic and 25 T1DM mothers at 36 weeks gestation. Cord blood was obtained after delivery. Maternal IGF-I was lower in T1DM and maternal and fetal serum IGFBP3 was higher in T1DM. (27)

Liu K et al reported that the level of IGF1 in 21 women with GDM was positively correlated with the level of HbA1C at the end of pregnancy and with neonatal weight. (28)

Anderlová K et al measured serum and cord blood levels of IGF system components in women with GDM (n = 39) and without GDM (n =22). Maternal serum levels of IGF1 and IGF2 did not differ between the GDM and non-GDM groups. However, levels of IGF-binding proteins (IGFBPs) were different. IGFBP4 levels were decreased during pregnancy and after delivery in women with GDM, while IGFBP7 levels were increased during pregnancy in women with GDM. Cord blood IGFBP3 and IGFBP7 levels were increased, while IGFBP4 levels were decreased in the GDM group compared with the non-GDM group. (29)

Dubietyte G rt al, studied 130 pregnant women with T1DM. Consecutive measurements showed an association of maternal IGF1 with fetal growth in T1DM pregnancy. Lower maternal IGF1 levels were associated with subsequent lower birthweight displayed markedly at the end of 2nd trimester. (30)

In 103 pregnant women with T1DM, Lauszus et al reported that maternal serum IGF-I increased with increasing birth weight until a plateau was reached in week 32. Birth weight was significantly associated with a higher level of serum IGF-I. (31) Mohsen AH et al, reported that infants of diabetic mothers (IDM) (n = 30) had significantly greater IGF1 levels compared to controls. Their IGF1 level was highly correlated with all neonatal anthropometric measures (weight, head circumference, abdominal circumference, and triceps skin fold thickness). (32)

Gupta MB studied babies born to mothers with both GDM and T2DM (n = 138), with significantly increased birth weight, and reported significantly reduced fetal IGFBP-1 concentrations in compared to non-diabetic controls (n =95). (33)

Lindsay RS et al, found that IGF1 level was significantly increased in the cord blood of infants of mothers with GDM vs. controls. (34) In all offspring, IGF1 levels were positively correlated, and IGFBP-1 levels were negatively correlated with birth weight. (35)

Yan-Jun L et al studied 84 insulin-treated diabetic mothers and their infants. They reported that IGF-I and IGFBP-3 concentrations in the cord serum of neonates born to diabetic mothers were higher than those of newborns of normal mothers. Fetal IGF-I and IGF-II were correlated with each other and with maternal HbA1C. Cord IGFBP-1 concentrations were significantly higher only in babies of mothers with IDDM. (36)

Roth S et al, stated that the levels of IGFI in cord serum from the macrosomic IDM were significantly higher than levels from either the non-macrosomic nondiabetic group or the non-macrosomic IDM group. There was a direct linear correlation between cord serum IGF-I and infant birth weight, independent of diabetes. (37) Chiesa et al, found that cord levels of IGF1 and IGFBP-3 (n = 153) were positively associated with all anthropometric indices (birth weight, length, head circumference, and ponderal index). Preterm growth-restricted babies displayed alteration in the GH-IGF axis (increased GH and low IGF1 and IGFBP-3 concentrations). (38) In 110 pregnant women with GDM, Lagiou P et al found that cord blood IGF1 was positively associated with birth weight and length, particularly among taller mothers. (39)

Tumminia A et al, studied placental tissues obtained from 20 T1D patients, 20 GDM patients, and 40 NGT women during pregnancy. In the placenta of T1D patients, IGF1 receptor (IGF1R) phosphorylation and insulin receptor (IR) isoform A (IR-A) expression were significantly increased compared to the NGT women. Moreover, IGF1R phosphorylation was significantly increased in the placenta of patients with peripartum glucose >90 mg/dl. An increased maternal blood

glucose level during pregnancy was associated with an increased IGF1R phosphorylation and IR-A expression in the placenta. Both these mechanisms can promote excessive fetal growth. (40)

Shang M et al studied placental tissues collected from 20 T1DM patients, 20 GDM patients, and 40 NGT women during pregnancy. They found that birth weights were positively correlated to maternal IGF1. The mRNA expression of three growth factor receptors, (IGF-IR, EGFR, and PDGFR-beta) was upregulated in the placenta of GDM women. The activity of placental IGFI and mTOR signaling was positively correlated with birth weight. (41)

Grissa, O et al, studied 30 women with GDM and their 30 macrosomic babies, and 30 healthy age-matched pregnant women, and their 30 newborns. The placental mRNA expression of the growth factors was either upregulated (FGF-2 or PDGF-B) or remained unaltered (IGFI and EGF) in the placenta of GDM women. The mRNA expression of three growth factor receptors, i.e., IGFIR, EGFR and PDGFR-β, was upregulated in the placenta of GDM women. (42)

In two studies, placental expressions of GLUT-1 were significantly higher in the GDM women and positively correlated to the maternal IGF1 levels in the GDM group. Increased phosphorylation of Akt and ERK 1/2 was found in the placenta of GDM women. (43,44) Balachandiran et al. observed significantly higher placental expressions of GLUT-1 in GDM women. They detected a positive correlation between the GLUT1 placental protein expression and maternal circulating IGF1 concentrations and the fetal birth weight in patients with GDM. Increased IGFI in women with GDM was suggested to enhance GLUT1 expression via the stimulation of placental insulin/IGF1 signaling, which might have affected fetal growth. (45)

Schaefer-Graf UM et al, reported a wide range of disturbances in lipid metabolism and suggested that maternal lipids seem to be the strongest determinant of fetal growth in GDM newborns. (46) Fatty acids traverse the placental membranes via several plasma membrane fatty acid transport/binding proteins (FAT, FATP, p-FABPpm, and FFARs) and cytoplasmic fatty acid-binding proteins (FABPs). Women with GDM have dyslipidemia characterized by high plasma triglycerides (TG) concentrations, low concentrations of high-density lipoprotein cholesterol, and increased low-density lipoprotein cholesterol. Therefore, their placenta appears to be exposed to an excess supply of lipids that may contribute to greater transplacental transport, and lipid storage. (47,48) Insulin and IGF1 are important regulators of fatty acid transfer by the placenta. New evidence also suggests important roles for nontraditional fatty acid transporters such as Mfsd2a which facilitates the placental transfer of the essential fatty acid docosahexaenoic acid (DHA) which is crucial for fetal neurodevelopment and of lipid transfer as a predisposing factor for childhood obesity. (49)

AMPK is an energy sensor that stimulates metabolism, improves insulin sensitivity, decreases inflammation, inhibits energy-consuming pathways, (e.g., fatty acid synthesis), and affects energy-generating pathways, e.g., glycolysis and glycogenolysis. Martino J et al, reported that obese women with GDM had higher estimated fetal weight at 34 gestational weeks. In the placenta of obese women with GDM, gene expression for AMPK was reduced, whereas the downstream regulator of mTOR, p70S6KB1 was raised. (50,51)

Summary of Key findings: (figure 1 and 2)

- Women with GDM had higher BMI, fasting blood glucose, blood glucose level at 1 h, 2 h after meal, and AUCG, IGF1, IGFBP3 and growth/differentiation factor 15 (GDF-15) than NGT women. IGF1 levels were positively correlated with maternal FBG and with GDF15 level.
- Each SD increase in maternal IGF-I level at 24–28 weeks was associated with a 75-g increase in birth weight, a 20-g increase in placental weight, and 1.91-fold higher odds of macrosomia.
- The maternal IGFBP-1 level during the first trimester was significantly lower in the mothers with LGA neonates versus SGA neonates. Cord serum highly phosphorylated IGFBP-1 concentrations were lower in GDM vs controls.
- Maternal IGF-I was lower in T1DM and maternal and fetal serum IGFBP3 was higher in T1DM. Consecutive measurements showed association of maternal IGF1 with fetal growth in T1DM pregnancy and lower maternal IGF1 levels were associated with subsequent lower birthweight.
- Maternal serum IGF-I increased with increasing birth weight until a plateau was reached in week 32. Increased birth weight was significantly associated with a higher level of infant serum IGF-I.
- The mRNA expression of IGF-IR was upregulated in the placenta of GDM women.
- Fetal IGF-I and IGF-II levels were correlated with each other and with maternal HbA1C.
- Infant of diabetic mothers (IDM) had significantly greater IGF1 and IGFBP3 levels and reduced IGFBP1 levels compared to nondiabetic group or the non-macrosomic IDM.

- Cord blood IGF1 and IGFBP-3 concentrations were positively associated with all anthropometric indices (birth weight, length, head circumference and ponderal index).
- In placenta from obese women with GDM, gene expression for AMPK was reduced, whereas the downstream regulator of mTOR, p70S6KB1 was raised.
- An increased maternal blood glucose level during pregnancy was associated with an increased IGF1R phosphorylation and IR-A expression in the placenta.
- Placental expressions of GLUT-1 were significantly higher in the GDM women and positively correlated to the maternal IGF1 levels and the fetal birth weight.

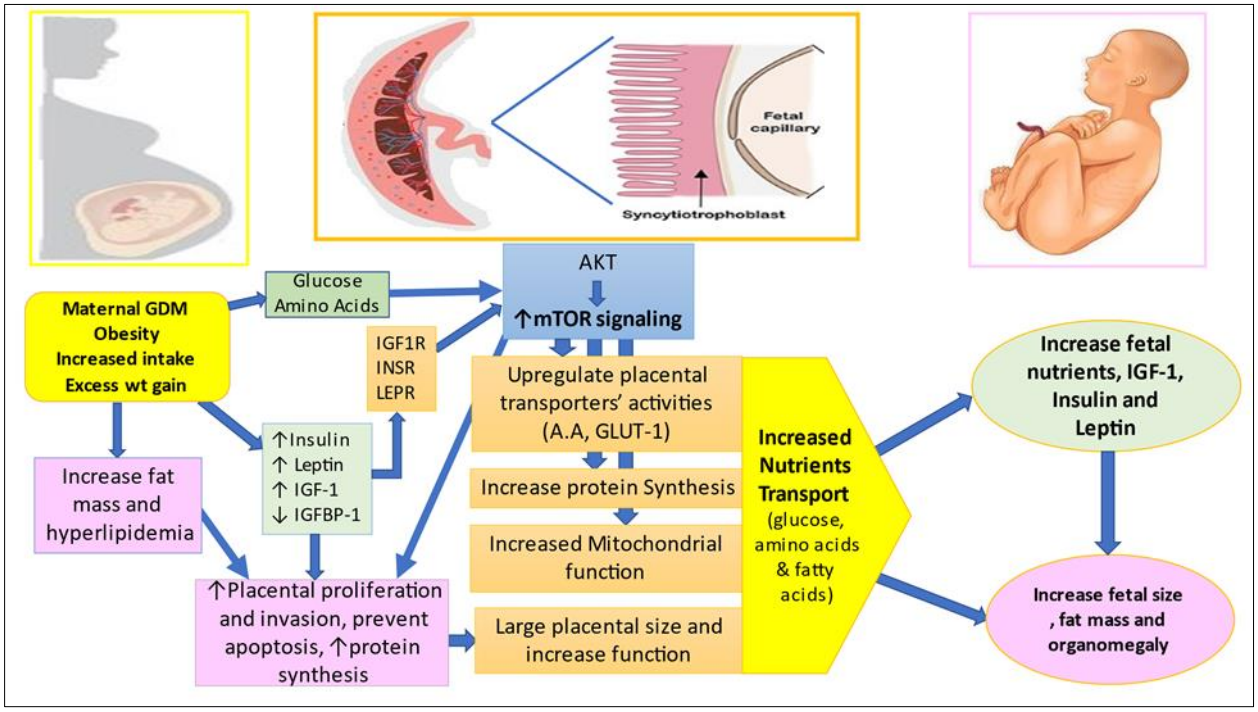

Figure 1 The mechanistic link between maternal diabetes, placenta and fetal overgrowth/increased infant adiposity

We propose that the mechanistic link between maternal gestational diabetes (GDM), and fetal overgrowth entails specific modifications in the placenta including increased mTOR signaling. Increased IGF1, insulin, leptin, and nutrient levels and decreased IGFBP1 in the maternal circulation are significant 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.

IGF1, insulin-like growth factor 1; IGF1R = insulin-like growth factor receptor, INSR = insulin receptor, LEPR = leptin receptor, AKT = protein kinase, mTOR= mechanistic target of rapamycin.

In GDM, increased IGF1, insulin, and decreased IGFBP1 in the maternal circulation are significant factors in the activation of placental mTOR signalling and transfer of nutrients to the fetus, with subsequent increased fetal growth. Whereas in mothers with T1DM, decreased IGF1, insulin, and increased IGFBP1 in the maternal circulation diminish mTOR activation and transfer of nutrients to the fetus with subsequent decreased fetal growth.

IGF1, insulin-like growth factor 1; mTOR= mechanistic target of rapamycin, LGA = large for gestational age, SGA = small for gestational age.

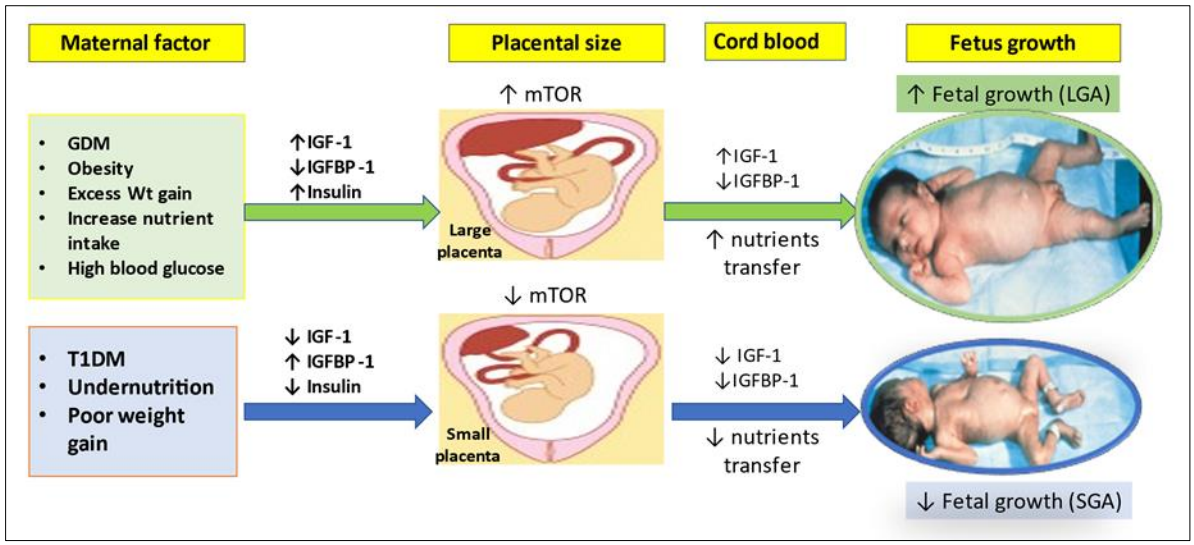

Figure 2 The link between maternal gestational diabetes (GDM) and T1DM, and placental and fetal size

3. Conclusion

In mothers with GDM increased nutrient intake, high blood glucose and increased weight appear to increase maternal IGF1and decreases IGBP1 levels. Increased maternal IGF1 and/or its availability due to decreased IGFBP1 can stimulate placental growth and functions, including mTOR signaling. mTOR stimulation increases protein synthesis, mitochondrial function, and upregulate specific placental amino acid transporter isoforms (amino acids transport), GLUT-1, (glucose transport) and possibly lipid (fatty acids) transporter to the fetus. Increased nutrients' transfer to the fetus can induce fetal IGF1 secretion and both can lead to overgrowth.

Compliance with ethical standards

Acknowledgments

We would like to express my very great appreciation to our diabetes educators: Ms. Nagwa El Darsy and Ms. Mona El Gamal for their valuable suggestions during the planning and development of this review article.

Disclosure of conflict of interest

There is no conflict of interest among all the authors.

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