MSI Journal of
Medicine and Medical Research (MSIJMMR)

Volume: 3, Issue: 3 (Sep-Dec 2026)
Published by *MSI Publishers*
ISSN 3049-1401 (Online)

Received: 18-08-2026
Accepted: 01-10-2026
Published: 19-10-2026

Review Article: Fetal Insulin: The Double-Edged Sword of Intrauterine Growth and Adult Metabolic Risk

Authors Details

Rasha Hussain Kuba[1*]
Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq.

Lina A. Salih[2]
Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq.

Email: rasha.hussain@sc.uobaghdad.edu.iq

ABSTRACT: While extensive studies observe the impact of hyperglycemia on the health of both mothers and their children, this article review specifically highlights the significance of role of fetal insulin resistance (FI) in intrauterine environment during fetal growth and the offspring's long-term health.

Recent studies highlight that insulin has fundamentally different functions in fetal development compared to adult homeostasis, where fetal insulin primarily serves as an anabolic growth factor, while adult insulin acts as a metabolic regulator.Unbalance in insulin action, during embryonic life, often is associated with disordered growth.This is associated with reduced levels of circulating Insulin growth factors (IGF's) which may be partly responsible for the growth failure.

During intrauterine life the placentaprevent cross the maternal insulin to the fetus, but in the other hand the maternal glucose does, the maternal hyperglycemia induces by placenta itself to increase insulin resistance in mother so more glucose will be available to fetus in this way more glucose will pass to feed the fetus, lead to exhaust premature pancreas to produce and secrete elevated insulin.

Elevated levels of fetal insulin (fetal hyperinsulinemia) promotes the growth of fetus also forces fetal tissue to convert the excessive amounts of glucose into triglyceride in fetal

DOI: *10.5281/zenodo.23590893*

liver and adipose tissue. After the baby is born, the supply of maternal glucose stop, yet the baby's elevated insulin production persists this led to rapid decline in blood sugar (hypoglycemia) with no good fetal care management this condition will cause many immediate complications or even later in life.

Introduction

Insulin is an essential polypeptide hormone; it consists of 51 amino acids. This hormone has a vital biological activity like cytological glucose homeostasis, supporting the growth of cells, and in metabolism of biological process. The production and release of insulin are affected by circulating glucose concentration [1].

The process of glucose metabolism is started by the consumption of food, which results in a simultaneous rise in insulin production and secretion from the pancreatic β- cells and in return a reduction in glucagon secretion from pancreatic α- cells, to restore blood glucose levels to the normal range [2]. After secretion of insulin, it circulates through the body and inters hepatocytes, which are stimulated to transform glucose into glycogen for storage. Additionally, some other tissues like, skeletal muscle cells and adipocytes, which are important targets of circulating insulin, they absorb glucose to release energy and store the additional glucose, thus lowering the blood glucose levels and back to baseline. [3].

Fetal Insulin Dynamics

The study of fetal insulin hypothesis is not a newconcept in the medical sciences, but with the progressive scientific ways and more frequent fetal defects the articles focused on much information.

Fetal insulin has a main role in the regulation of prenatal growth during the fetal stage [4]. It functions as an anabolic hormone especially in the final trimester. This hormone help the cellular absorption of glucose, amino acids, and other nutrients, in that way facilitating tissue proliferation, protein synthesis, and fat accumulation [5] insulin promotes the shift of glucose into glycogen for energy storageand promotes fat accumulation, helping the fetus grow and build body mass [6 fetal insulin acts on placenta receptors to control nutrient transport [7].During Pregnancy Fetal liver insulin degradation is low until third trimester, meaning the placenta take a significant role in insulin turnover. At third trimester the

 DOI: *10.5281/zenodo.23590893*

human placental lactogen (HPL) facilitate maternal insulin resistance through produce of insulin-like growth factors (IGFs) in the fetus, which is ensuring increased glucose availability for the fetus [8].

Fetal Insulin and Placenta Interactions

The surfaces of the placenta that are exposed to the two blood circulations differ; specifically, trophoblast cells of the maternal circulation, and endothelial cells are in contact with the fetal circulation. Both types of cells exhibit elevated levels of insulin receptors [9].

Insulin receptors are found on both sides of the placenta, but their location shifts to support fetal demand. The placenta exhibits elevated levels of insulin receptors (IRs) during early pregnancy these receptors are located on the maternal-facing cyncytiotrophoblast; as pregnancy progresses to term, they become concentrated on the fetal-facing endothelial cells [10]. These receptors cooperate with fetal insulin, promoting fetal development and nutrient transfer, while also expressing insulin-related genes like (Insulin-like growth Factor Binding Protein 1) *IGFBP1*is a key gene the primary function is bind the circulating insulin-like growth factor (IGFs) and finely regulate their bioavailability, determining how much of the growth factor is free to activate cell-surface receptors and drive tissue growth [11]. Insulin receptors are primarily found on the cyncytiotrophoblast, which is the outer layer of the placenta that faces maternal blood. These receptors play a vital role in nutrient absorption and placental metabolism during the early stages of pregnancy. The concentration of insulin receptors diminishes on the maternal-facing side but shows a significant increase on the fetal vascular endothelium, marks a dynamic transition in how the placenta responds to maternal and fetal metabolic signals throughout pregnancy [12]. This distribution shows that the placenta is responsive to the mother' s insulin during the early stages of gestation, while at term, it is more greatly influenced by fetal insulin [13]. The large molecular weight of maternal insulin prevents it from crossing the placenta and being consumed by the embryo. Instead, the fetus is required to produce its own insulin to manage blood glucose levels. The fetal pancreas starts producing insulin as early as the 10th to 12th week of gestation. [14]. By the second/third trimester, the developing fetal endocrine pancreas produces both insulin and glucagon. These hormones do not cross the placenta and must be metabolized within the fetal-placental unit [15].

 DOI: *10.5281/zenodo.23590893*

In a developing fetus, the placenta has the ability to transport the glucose of motherthis process is essential for regulating glucose level as the primary energy source. During late gestation, the metabolism of glucose in the fetus is critical for the growth of embryonic liver, heart, adipose tissue, and skeletal muscles. Three important features that play a major role in fetal glucose homeostasis include; the concentration of maternal glucose, the transport of glucose from the mother to the placenta under the need of glucose utilized by the fetus and, lastly, the production of insulin by the fetal pancreas [16].

Fetal insulin production progressively rises throughout the prenatal period unbalanced in glucose levels support insulin secretion; but persistent hyperglycemia reduces insulin sensitivity and glucose tolerance [17]. Congenital abnormalities, prenatal macrosomia, and stillbirth are among the negative effects on the fetus in pregnant women with persistently high blood glucose levels [18].

After birth, cutting of the umbilical cords simultaneously, insulin levels fall, which allows the liver to shift from storing energy (anabolism) to producing energy (catabolism)combined with massive surge in adrenaline/noradrenaline, glucagon, and cortisol [19]. The liver of the newborn must promptly transition from the placental supply to the self-regulation of blood glucose, primarily via liver glycogenolysis gluconeogenesis [20].

Fetal Insulin Predict Adult Outcomes

The fetal period is a fundamental phase in utero which determines the lifelong health outcomes of the offspring. According to the fetal insulin hypothesis, genetic variants related to insulin that influence insulin sensitivity or secretion in the fetusoften leading to low birth weightmay increase the risk of developing diabetes in adulthood [21].

The fetal insulin hypothesis suggests that insulin secretion and resistance, which are genetically predetermined and exist from conception later influence intrauterine growth. This also clarifies the connection between reduced birth weight and the onset of type 2 diabetes in adulthood, as seen in epidemiological research [22]. Prenatal pancreatic insulin secretion is stimulated by the increasing blood glucose levels of mother, which in turn raises fetus's glucose levels. The first releasing of insulin hormone occurs between weeks 7 and 8 of embryonic life, and the human pancreas begins to mature four weeks after

 DOI: *10.5281/zenodo.23590893*

conception. Insulin can be found in amniotic fluid starting at 12 weeks, which, as demonstrated by high link between cord blood insulin levels at delivery and amniotic fluid insulin at 31 weeks, is an excellent indicator for fetal serum insulin [23]. Research on both human and animals has shown a link between prenatal insulin and fetal obesity. There different functions for insulin one of them is the enhancement of adipose tissue growth, which may describes the positive correlations between insulin and leptin levels in infants who are large for gestational age.

This underscores the impact of prolonged hyperinsulinemia in the fetus on the expansion of white adipose tissue and the synthesis of leptin in adipose tissue [24].Long exposure to high glucose levels put the premature fetal pancreas under high metabolic stress, resulting in both structural and functional alterations in pancreatic beta-cells. This early stress may lead to a reduced ability to generate sufficient insulin, increasing the risk of impaired glucose tolerance and Type 2 diabetes in the offspring and restricted fetal growth which is linked to reduced insulin secretion (lower first-phase insulin) and increased insulin resistance in later life [25].Overstimulation of the beta-βcells can effect on the action of mitochondria through produce high levels of reactive oxygen species (ROS) which attack the pancreatic cells itself [26].

Throughout fetal development, the nutrients easily cross the placenta, prompting the fetal pancreas to produce elevated concentrations of insulin; hyperinsulinemia this condition may directly influences epigenetic programming in the intrauterine environment via DNA methylation and histone acetylation of the fetus [27].

The epigenetic modifications lead to alteration in the expression of some genes related to metabolic activity of fetus especially which control the appetite (like the hypothalamic *POMC* gene) and glucose metabolism (like *IRS1* and *IGF2*) [28].

As shown in figure 1. Changes in the mother's intrauterine environment are the first step towards the fetal origin of beta-cell malfunction, which impacts placental function, involving molecules like miRNAs. These changes hold the potential to influence the programming of various organs such as the reduction of functional beta-cell mass in the offspring [29].

 DOI: *10.5281/zenodo.23590893*

Due to the high plasticity of the epigenome in early fetal development, protective care underlines the importance of maternal BMI before pregnancy and rigorous glycemic management.

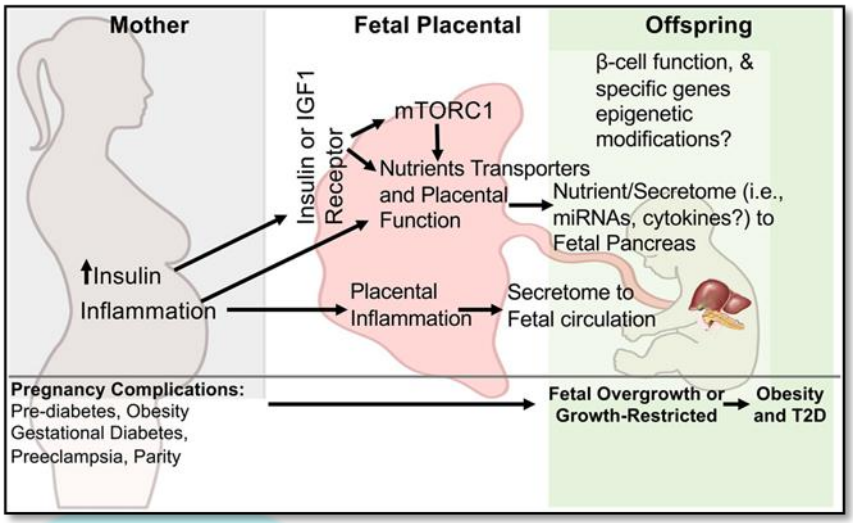

Figure 1. Factors influencing fetal pancreas development and function [29]

Future Insights in Fetal Insulin Research

The way of an individual's metabolic health begins to take character during perinatal phase, continuing to the lactation period. Maternal metabolic health status play vital roles in heath programs of offspring, the developing type 2 diabetes in adulthood, which is part of the endocrine disorders of Pancreatic beta-cells, which are sensitive to nutrients at early development [30].

The Developmental Origins of Health and Disease (DOHaD) concept suggests that the intrauterine periods, and immediately after birth is critical for influencing how the developing offspring's tissue are programmed. Consequently, if essential metabolic tissues such as the pancreas are incorrectly programmed during these important vital periods, it may lead to long-lasting effects on the health history and susceptibility of the offspring to overweight and type 2 diabetes in adulthood [31].

There are multiple complications in prenatal like:mother malnutrition and gestational diabetes have been related to adverse metabolic effects in the offspring, including elevated glycemia, overweight, insulin resistance, and diminished pancreatic beta-cell mass all of which are significant factors in the onset of type 2 diabetes and cardiovascular disease [32].

DOI: *10.5281/zenodo.23590893*

Conclusion

Pregnancy outcomes and the long-term of offspring are both impacted by the metabolic health of the mother. Gestational diabetes, hypertensive diseases, and unfavorable newborn outcomes such as macrosomia, hypoglycemia, and jaundice, however, these factors could be accelerated by postnatal environmental effects, including dietary habits and availability of calories. So the focus on these processes is crucial for improving the health of both mothers and their offspring.

References

1. Alarcon, C., Lincoln, B., and Rhodes, C.J. (1993). The biosynthesis of the subtilisin-related proprotein convertase PC3, but no that of the PC2 convertase, is regulated by glucose in parallel to proinsulin biosynthesis in rat pancreatic islets. J. Biol. Chem., 268:4276–4280. doi: 10.1016/S0021-9258(18)53606-1.

2. Kaufman, B.A., Li, C., and Soleimanpour, S.A. (2015). Mitochondrial regulation of beta-cell function: Maintaining the momentum for insulin release. Mol. Asp. Med., 42:91–104. doi: 10.1016/j.mam.2015.01.004.

3. Szablewski, Leszek. (2024). Changes in cells associated with insulin resistance. International journal of molecular sciences 25.4, 2397.

4. Hivert M-F, Backman, H., Benhalima, K., Catalano, P., Desoye, G., Immanuel, J., McKinlay, C. J. D., Meek, C. L., Nolan, C. J., Ram, U., Sweeting, A., Simmons, D., and Jawerbaum, A.(2024). Pathophysiology from preconception, during pregnancy, and beyond. Lancet 404(10448):158–174.

5. Gladych-Macioszek, A., Ozegowska, K., Radzicka-Mularczyk, S., Sibiak, R., Desoye, G., and Wender-Ozegowska, E. (2025). Insulin-Like Growth Factors, Binding Proteins and Their Role in Pregnancy in Patients With Diabetes. Journal of diabetes research, 3330482. https://doi.org/10.1155/jdr/3330482

6. Karcz, K., and Królak-Olejnik, B. (2024).Impact of Gestational Diabetes Mellitus on Fetal Growth and Nutritional Status in Newborns. Nutrients, 16(23), 4093. https://doi.org/10.3390/nu16234093

 DOI: *10.5281/zenodo.23590893*

7. Milincic, M., Cirkovic, A., Ivanovic, K., Dugalic, S., and Gojnic Dugalic, M. (2025). Trimester-Specific Serum Lipid Profiles in Gestational Diabetes Mellitus: A Systematic Review, Meta-Analysis, and Meta-Regression. Medicina (Kaunas), 61(7):1290. doi: 10.3390/medicina61071290. PMID: 40731919; PMCID: PMC12300116.

8. Rassie, K., Giri, R., Joham, A. E., Teede, H., and Mousa, A. (2022). Human Placental Lactogen in Relation to Maternal Metabolic Health and Fetal Outcomes: A Systematic Review and Meta-Analysis. International journal of molecular sciences, 23(24), 15621. https://doi.org/10.3390/ijms232415621

9. Hiden, U., Maier, A., Bilban, M., Ghaffari-Tabrizi, N., Wadsack, C., Lang, I., Dohr, G., and Desoye, G. (2006). Insulin control of placental gene expression shifts from mother to foetus over the course of pregnancy. Diabetologia, 49(1):123-31. doi: 10.1007/s00125-005-0054-x. Epub 2005 Dec 13. PMID: 16344925.

10. Hiden, U., Glitzner, E., Hartmann, M., and Desoye, G. (2009). Insulin and the IGF system in the human placenta of normal and diabetic pregnancies. Journal of anatomy, 215(1), 60–68. https://doi.org/10.1111/j.1469-7580.2008.01035.x

11. LeRoith, D., Holly, J. M. P., and Forbes, B. E. (2021). Insulin-like growth factors: Ligands, binding proteins, and receptors. Molecular metabolism, 52, 101245. https://doi.org/10.1016/j.molmet.2021.101245

12. O'Tierney-Ginn, P., Presley, L., Myers, S., and Catalano, P. (2015). Placental growth response to maternal insulin in early pregnancy. *The Journal of clinical endocrinology and metabolism*, *100*(1), 159–165. https://doi.org/10.1210/jc.2014-3281

13. Tumminia, A., Scalisi, N. M., Milluzzo, A., Ettore, G., Vigneri, R., and Sciacca, L. (2021). Maternal Diabetes Impairs Insulin and IGF-1 Receptor Expression and Signaling in Human Placenta. Front. Endocrinol., 12:621680. doi: 10.3389/fendo.2021.621680.

14. Nteeba, J., Varberg, K. M., Scott, R. L., Simon, M. E., Iqbal, K., and Soares, M. J.,(2020). Poorly controlled diabetes mellitus alters placental structure, efficiency, and

 DOI: *10.5281/zenodo.23590893*

plasticity. BMJ Open Diabetes Res Care., 8(1):e001243. doi: 10.1136/bmjdrc-2020-001243. PMID: 32595139; PMCID: PMC7322553.

15. Ahmadi, S. M.

16. Perez, M. L. and Guardia, C. M. (2025). Secretion of placental peptide hormones: functions and trafficking. Front. Endocrinol., 16:1584303. doi: 10.3389/fendo.2025.1584303

17. Halloran, K. M., Hoskins, E. C., Stenhouse, C., Moses, R. M., Dunlap, K. A., Satterfield, M. C., Seo, H., Johnson, G. A., Wu, G., and Bazer, F. W. (2021). Pre-implantation exogenous progesterone and pregnancy in sheep. II. Effects on fetal-placental development and nutrient transporters in late pregnancy. J Anim Sci Biotechnol., 12(1):46. doi: 10.1186/s40104-021-00567-1. PMID: 33827696; PMCID: PMC8028684.

18. Hay WW. (2006). Placental-fetal glucose exchange and fetal glucose metabolism. Trans Am Clin Climatol Assoc., 117:321-39; discussion 339-40.

19. Schaefer-Graf, U., Napoli, A., and Nolan, C. J. (2018). Diabetic Pregnancy Study Group. Diabetes in pregnancy: a new decade of challenges ahead. Diabetologia., 61(5):1012-1021.

20. Kajino, M., Fujita, A., Nishizawa, R., Shimokawa, S., Kawakami, T., Inaba, Y., and Sai, Y. (2025). Neonatal hypoglycemia triggered by maternal ritodrine administration is caused by inhibition of gluconeogenesis in the neonatal liver in rodents. Biochemical and Biophysical Research Communications, 153075.

21. Huerta-Cervantes, M., Peña-Montes, D. J., López-Vázquez, M. Á., Montoya-Pérez, R., Cortés-Rojo, C., Olvera-Cortés, M. E., and Saavedra-Molina, A. (2021). Effects of Gestational Diabetes in Cognitive Behavior, Oxidative Stress and Metabolism on the Second-Generation Off-Spring of Rats. Nutrients., 13(5):1575. doi: 10.3390/nu13051575. PMID: 34066827; PMCID: PMC8150291.

22. Yan, Y-S., Feng, C., Yu, D-Q., Tian, S., Zhou, Y., Huang, Y-T., Cai, Y-T., Chen, J., Zhu M-M, and Jin, M. (2023). Long-term outcomes and potential mechanisms of offspring

exposed to intrauterine hyperglycemia. Front. Nutr. 10:1067282. doi: 10.3389/fnut.2023.1067282.

23. Hughes, A. E., Hattersley, A. T., Flanagan, S. E., and Freathy, R. M. (2021). Two decades since the fetal insulin hypothesis: what have we learned from genetics?. Diabetologia, 64(4), 717–726. https://doi.org/10.1007/s00125-021-05386-7]

24. Desoye, G. and Nolan, C. J. (2016). The fetal glucose steal: an underappreciated phenomenon in diabetic pregnancy. Diabetologia, 59: 1089–1094. (https://doi.org/10.1007/s00125-016-3931-6).

25. Tamai, J., Ikenoue, S., Akita, K., Hasegawa, K., Otani, T., Fukutake, M., Kasuga, Y., and Tanaka, M. (2025). Association of Cord Blood Metabolic Biomarkers (Leptin, Adiponectin, IGF-1) with Fetal Adiposity Across Gestation. International journal of molecular sciences, 26(14), 6926. https://doi.org/10.3390/ijms26146926.

26. Dludla, P. V., Mabhida, S. E., Ziqubu, K., Nkambule, B. B., Mazibuko-Mbeje, S. E., Hanser, S., Basson, A. K., Pheiffer, C., and Kengne, A. P. (2023). Pancreatic β-cell dysfunction in type 2 diabetes: Implications of inflammation and oxidative stress. World journal of diabetes, 14(3): 130–146. https://doi.org/10.4239/wjd.v14.i3.130.

27. He, R., Sun, H., Liu, H., and Li, J. (2025). The relationship between novel inflammatory markers SII, SIRI, MHR, UHR and insulin resistance in patients with type 2 diabetes: based on a retrospective analysis. Front. Endocrinol. (Lausanne).,16:1648823. doi: 10.3389/fendo.2025.1648823. PMID: 40995589; PMCID: PMC12454046.

28. Schiera, G., Macajone, G., Volpes, S., Greco, L., Di Liegro, C. M., Serio, G., Caradonna, F., and Naselli, F. (2026). Maternal Overnutrition and Fetal Programming: Long-Term Metabolic, Cognitive, and Epigenetic Consequences. Cells, 15(4), 366. https://doi.org/10.3390/cells15040366.

29. Hufnagel, A., Dearden, L., Fernandez-Twinn, D. S., and Ozanne, S. E. (2022). Programming of cardiometabolic health: the role of maternal and fetal

 DOI: *10.5281/zenodo.23590893*

hyperinsulinaemia. J Endocrinol., 253(2):R47-R63. doi: 10.1530/JOE-21-0332. PMID: 35258482; PMCID: PMC9066586.

30. Jo, S., and Alejandro, E. U. (2023). RISING STARS: Mechanistic insights into maternal-fetal cross talk and islet beta-cell development. J. Endocrinol., 259(3):e230069. doi: 10.1530/JOE-23-0069. PMID: 37855321; PMCID: PMC10692651.

31. Lecoutre, S., Maqdasy, S., and Breton, C. (2021). Maternal obesity as a risk factor for developing diabetes in offspring: An epigenetic point of view. World journal of diabetes, 12(4), 366–382. https://doi.org/10.4239/wjd.v12.i4.366.

32. Heindel, J. J., Balbus, J., Birnbaum, L., Brune-Drisse, M. N., Grandjean, P., Gray, K., Landrigan, P. J., Sly, P. D., Suk, W., Cory Slechta, D., Thompson, C., and Hanson, M. (2015). Developmental Origins of Health and Disease: Integrating Environmental Influences. Endocrinology., 156(10):3416-21. doi: 10.1210/EN.2015-1394. Epub 2015 Aug 4. PMID: 26241070; PMCID: PMC4588819.

33. Markopoulou, P., Papanikolaou, E., Loukopoulou, S., Galina, P., Mantzou, A., and Siahanidou, T. (2021). Increased circulating endothelial progenitor cells (EPCs) in prepubertal children born prematurely: a possible link between prematurity and cardiovascular risk. Pediatr Res., 90(1):156-165. doi: 10.1038/s41390-020-01190-y. Epub 2020 Oct 10. PMID: 33038874.

 DOI: ***10.5281/zenodo.23590893***