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PATHOPHYSIOLOGICAL ASPECTS OF INSULIN RESISTANCE IN GESTATIONAL DIABETES MELLITUS: A LITERATURE REVIEW

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Summary

Gestational diabetes mellitus (GDM) is a significant metabolic disorder characterized by impaired insulin sensitivity during pregnancy. This review explores the key pathophysiological mechanisms of insulin resistance in GDM, including dysfunction of insulin signaling pathways (IRS/PI3K/Akt), activation of inflammatory cascades (JNK, SOCS), and the role of adipokines (leptin, adiponectin, resistin). Hormonal factors such as placental lactogen, estrogens, progesterone, and thyroid hormones, which influence metabolic homeostasis and contribute to insulin resistance, are also discussed. Special attention is given to the link between adipokine imbalances, impaired lipolysis, elevated free fatty acids, and microangiopathy. The heterogeneity of GDM and its increasing burden necessitate further research to enhance understanding and management.

Keywords: *Gestational Diabetes Mellitus (GDM); Insulin Resistance; Insulin-Signaling Pathways (IRS/PI3K/Akt); Adipokines (Leptin, Adiponectin, Resistin); Placental Lactogen (hPL).*

1. Introduction

Gestational diabetes mellitus is defined as hyperglycemia first detected during pregnancy with glucose concentrations lower than those of manifest diabetes. Approximately 14% of pregnant women worldwide are affected, though prevalence varies based on risk factors, screening methods, and diagnostic criteria [1]. The incidence of GDM is rising alongside increasing obesity and type 2 diabetes (T2D). Between 30% and 70% of GDM cases are diagnosed early (before 20 weeks of gestation), and early-onset GDM is associated with worse pregnancy outcomes compared to late-onset GDM (diagnosed at 24-28 weeks) [1].

GDM increases the risk of adverse maternal and fetal outcomes, including premature rupture of membranes (PROM), preterm labor, postpartum hemorrhage, low birth weight, macrosomia, and fetal distress [2]. A prospective cohort study of 694 pregnant women reported higher rates of gestational hypertension, PROM, and intrauterine and postpartum bleeding in GDM cases [3]. Polyhydramnios, often multifactorial, is linked to maternal glycemic disturbances. Excess maternal glucose transfer through the placenta leads to fetal hyperglycemia and hyperosmolar diuresis, increasing urine output, amniotic fluid volume, and risks of PROM and preterm birth [4].

GDM poses both short- and long-term health risks. Short-term fetal complications include macrosomia, shoulder dystocia, birth trauma, neonatal hypoglycemia, increased neonatal intensive care unit (NICU) admissions, and hyperbilirubinemia [5,6]. Long-term risks include a higher prevalence of obesity and cardiometabolic disorders in offspring during childhood and adulthood [5].

Insulin resistance, exacerbated by pregnancy-related hormonal changes, is the central pathophysiological feature of GDM. Given the global diabetes epidemic, the heterogeneity of GDM, and advancements in medical technology, further investigation into its mechanisms is essential.

2. Molecular Mechanisms of Insulin Resistance in GDM

2.1. Adaptation of Insulin Signaling Pathways

During normal pregnancy, insulin sensitivity decreases physiologically to ensure adequate glucose supply to the fetus. However, dysregulation of metabolic pathways and signaling cascades can lead to excessive insulin resistance, contributing to gestational diabetes mellitus. The key pathways involved in insulin resistance include:

- **IRS/PI3K/Akt Pathway**: Reduced activity of insulin receptor substrates (IRS-1/IRS-2) impairs phosphorylation and activation of phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt), reducing glucose uptake by cells [7].
- **JNK and SOCS Signaling**: Chronic inflammation in GDM activates c-Jun N-terminal kinase (JNK) and increases the levels of suppressors of cytokine signaling (SOCS), both of which inhibit insulin signaling [8].

The **PI3K/Akt pathway** regulates essential cellular processes, such as glucose homeostasis, lipid metabolism, protein synthesis, and cell proliferation. Dysregulation of this pathway contributes to obesity, type 2 diabetes (T2D), and GDM. Its proper function is critical for maintaining metabolic balance and energy homeostasis.

Tight regulation of the PI3K/Akt pathway ensures cellular homeostasis through several mechanisms:

- **RTK Activation**: Receptor tyrosine kinases (RTKs), transmembrane proteins, bind ligands (e.g., hormones and growth factors). This binding induces autophosphorylation, initiating downstream signaling cascades, including PI3K/Akt activation [8].
- **PI3K Activation**: RTKs activate PI3Ks, lipid kinases that phosphorylate phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 recruits pleckstrin homology (PH) domain-containing proteins, including Akt, to the cell membrane, where it acts as a second messenger [8].
- **Akt Activation**: Akt is activated through phosphorylation at two critical sites, Thr308 by phosphoinositide-dependent kinase 1 (PDK1) and Ser473 by

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the mammalian target of rapamycin complex 2 (mTORC2). This activation is crucial for the downstream effects of Akt, including the inhibition of glycogen synthase kinase-3β (GSK3β), stabilization of β-catenin, and modulation of extracellular matrix synthesis [8].

- **Negative Regulation by PTEN**: PTEN, a lipid phosphatase, antagonizes PI3K signaling by dephosphorylating PIP3, preventing excessive activation of the PI3K/Akt pathway [8].
- **Negative Feedback Loops**: SOCS and IRS proteins inhibit upstream signaling components, protecting the pathway from overactivation. SOCS modulate cytokine signaling through the JAK/STAT pathway, while IRS proteins mediate insulin and growth factor signaling, ensuring dynamic regulation in response to extracellular stimuli [8].
- In GDM, chronic inflammation exacerbates JNK activation and SOCS expression, further disrupting insulin signaling and contributing to insulin resistance [8].

2.2 Role of Adipokines

Adipokine imbalances, including leptin, adiponectin, and resistin, contribute to insulin resistance in gestational diabetes mellitus (GDM). Reduced adiponectin levels in pregnant women correlate with increased insulin resistance, while impaired lipolysis and lipotoxicity drive hyperproduction of free fatty acids (FFAs) [9]. Leptin, adiponectin, and resistin, primarily secreted by adipose tissue, exhibit pro- and anti-inflammatory properties and influence chronic inflammation, metabolic homeostasis, and tumorigenesis [9].

Leptin is crucial in immune regulation, cell proliferation, and growth factor-related effects. However, its primary function is modulating energy expenditure via hypothalamic hunger suppression. In obesity, leptin sensitivity may be impaired, leading to its overproduction [9]. Adiponectin, in contrast, enhances insulin sensitivity, regulates lipid metabolism, inhibits cell growth, and increases following weight loss. Resistin, secreted by adipose tissue macrophages, induces insulin resistance at high concentrations and contributes to hyperglycemia, adipocyte proliferation, and obesity [9].

Leptin upregulates matrix metalloproteinases 2 and 9 and is a tissue inhibitor of metalloproteinase 1 in endothelial cells, promoting extravascular matrix remodeling and atherosclerosis, potentially contributing to vascular calcification [10]. Adiponectin negatively correlates with lipid levels, correcting glucose and lipid homeostasis disturbances, reducing inflammation, and enhancing insulin sensitivity. Resistin significantly affects insulin function and promotes adipocyte proliferation, further exacerbating obesity [10].

Serum levels of resistin, leptin, and FFAs are significantly higher in patients with type 2 diabetes (T2D) compared to healthy individuals. Additionally, resistin and leptin levels are elevated in individuals with microangiopathy. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and glycated hemoglobin (HbA1c) is markedly increased in T2D and microangiopathy patients. Resistin and leptin positively correlate with FFAs and HOMA-IR, while adiponectin negatively correlates with these parameters but positively with high-density lipoprotein cholesterol (HDL-C). Resistin also positively correlates with leptin but negatively with adiponectin, reinforcing the association between these adipokines and insulin resistance, T2D, and microvascular complications [10].

3. Hormonal Factors Influencing Insulin Resistance

3.1 Role of Placental Hormones

Human placental lactogen (hPL) significantly influences glucose metabolism by stimulating lipolysis and increasing circulating FFAs, which inhibit peripheral glucose uptake and exacerbate insulin resistance [11]. hPL is a potent stimulator of pancreatic β-cell proliferation during pregnancy, likely via prolactin receptor activation. It also inhibits β-cell apoptosis through Akt phosphorylation and protects against glucolipotoxicity via the Janus kinase-2/signal transducer and activator of transcription-5 (JAK2/STAT5) pathway and anti-apoptotic Bcl-XL expression [11]. Preclinical studies suggest hPL facilitates maternal β-cell adaptation, potentially preventing insulin resistance [11]. However, clinical studies reveal inconsistencies: no clear association exists between hPL levels and GDM. In type 1 diabetes (T1D), hPL levels are lower in early pregnancy (possibly reflecting delayed placental development) and higher in late pregnancy (potentially due to increased placental mass). Limited data exist for other metabolic conditions. hPL levels positively correlate with placental and birth weight in diabetic pregnancies, but its relationship with maternal metabolism remains complex and unresolved, warranting further investigation for diagnostic and prognostic utility [12].

3.2 Steroid Hormones in Insulin Resistance Development

Estrogen and progesterone influence insulin resistance via the IRS1/PI3K pathway and GLUT4 expression regulation. Early pregnancy increases insulin sensitivity to enhance adipocyte glucose uptake, preparing for later energy demands [13]. However, as pregnancy progresses, surges in estrogen and progesterone promote insulin resistance [14]. Progesterone may exert toxic effects on β-cells through oxidative stress-induced apoptosis, while abnormal steroid hormone levels (e. g., estradiol and progesterone) in GDM correlate with insulin resistance onset and progression [15]. Steroid metabolites also regulate fat distribution and muscle mass [15]. Altered insulin signaling disrupts GLUT4 translocation, reducing glucose uptake by 54% in GDM compared to normal pregnancy [13]. Rising progesterone levels from the first to third trimester suppress PI3K by downregulating IRS-1, inhibiting GLUT4-mediated glucose transport [17]. High estrogen concentrations further diminish insulin activity [17]. Human placental growth hormone (hPGH) and pituitary growth hormone exhibit diabetogenic effects, contributing to hyperinsulinemia, reduced glucose uptake, impaired glycogen synthesis, and diminished insulin suppression of hepatic gluconeogenesis [18]. In the third trimester, elevated cortisol, TNF-α, and cytokines further disrupt insulin signaling, inducing resistance [19]. Pre-existing insulin resistance and β-cell dysfunction may heighten postgestational diabetic complication risks.

3.3 Role of Thyroid Hormones

Monitoring thyroid hormone levels during pregnancy is critical, as thyroid dysfunction is the second most common endocrine disorder after GDM [20]. Human chorionic gonadotropin (hCG) in early pregnancy increases thyroxine (T4) and triiodothyronine (T3) secretion by 50%, reducing thyroid-stimulating hormone (TSH) levels [21]. Thyroid hormones impair glucose uptake by affecting GLUT4 expression, with insulin resistance negatively correlating with T4 and positively with T3 [21]. Thyroid disorders are linked to increased metabolic syndrome and diabetes risks [21]. Both hypothyroidism and hyperthyroidism contribute to diabetes via complex pathophysiological mechanisms. Thyroid hormones regulate energy expenditure, enhance glucose and fatty acid oxidation in muscle and liver, stimulate adipose tissue lipolysis, and support healthy body weight, suggesting a protective role against diabetes [22]. A negative correlation between T4 and HOMA-IR indicates that low T4 reduces tissue insulin sensitivity, accelerating insulin resistance [23]. Thyroid hormones regulate glucose homeostasis via direct effects on pancreatic cells, GLUT4 expression in muscle and adipose tissue, and hepatic gluconeogenesis/glycogenolysis enzyme genes (e.g., glucose-6-phosphatase, phosphoenolpyruvate carboxykinase [PEPCK], pyruvate carboxylase) [24].

The negative T4-insulin and positive T3-insulin correlation may reflect placental transport of iodothyronines to the fetus and increased type 2 iodothyronine deiodinase activity, converting T4 to T3, mainly when T4 is low. Placental deiodinase expression further reduces maternal T4 and elevates T3, though the precise mechanisms remain unclear [24]. Serum T3 levels are higher in GDM patients than controls, within the euthyroid range [25]. In euthyroid pregnant women with insulin resistance, an inverse correlation exists between T4 and glycated hemoglobin, suggesting reduced T4 lowers peripheral insulin sensitivity, impairing glucose utilization and contributing to hyperglycemia and hyperinsulinemia [24]. These interrelationships may explain T3 and T4 correlations with insulin resistance.

4. Conclusions

1. Reduced insulin receptor substrates (IRS-1/IRS-2) activity disrupts PI3K/Akt phosphorylation, impairing glucose uptake. Chronic inflammation further inhibits insulin signaling via c-Jun N-terminal kinase (JNK) activation and increased suppressors of cytokine signaling (SOCS) levels.

2. Imbalances in adipokines, particularly decreased adiponectin, contribute to insulin resistance. Impaired lipolysis and elevated free fatty acids (FFAs) also exacerbate metabolic dysfunction.

3. Placental lactogen stimulates lipolysis, raising FFA levels and reducing glucose uptake by peripheral tissues. Estrogens, progesterone, and thyroid hormones influence insulin resistance through IRS1/PI3K signaling and GLUT4 regulation.

4. Altered thyroid hormone levels during pregnancy impact GLUT4 expression, impairing glucose uptake. Increased insulin resistance is associated with lower T4 and higher T3 levels.

5. The development of insulin resistance in GDM results from disrupted PI3K/Akt signaling, JNK activation, SOCS upregulation, adipokine imbalance, and hormonal modulation, highlighting the complex interplay of metabolic and endocrine factors.

5. Clinical Implications and Future Perspectives

Understanding the pathophysiology of insulin resistance in gestational diabetes mellitus (GDM) is crucial for developing effective therapeutic approaches and improving clinical outcomes. Future research should focus on early detection by identifying genetic and epigenetic markers, enabling timely preventive interventions. Considering individual metabolic characteristics, genetic predisposition, and environmental factors, a personalized treatment approach could enhance therapeutic effectiveness. An important direction is the exploration of innovative therapeutic strategies, including using antioxidants and anti-inflammatory agents to reduce insulin resistance, oxidative stress, and inflammation. Long-term follow-up of maternal and offspring health remains essential, as GDM increases the risk of type 2 diabetes in mothers and affects the metabolic health of offspring. Emphasizing preventive measures during pregnancy and the postpartum period is critical to curbing the rising prevalence of diabetes and its associated complications.

Conflict of Interest. The authors declare that there are no actual or potential conflicts of interest related to the preparation and publication of this article.

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ПАТОФІЗІОЛОГІЧНІ АСПЕКТИ ІНСУЛІНОРЕЗИСТЕНТНОСТІ ПРИ ГЕСТАЦІЙНОМУ ЦУКРОВОМУ ДІАБЕТІ: ОГЛЯД ЛІТЕРАТУРИ

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Резюме.

Гестаційний цукровий діабет (ГЦД) є значним метаболічним порушенням, що розвивається внаслідок порушення інсулінової чутливості під час вагітності. У цьому огляді розглянуто ключові патофізіологічні механізми інсулінорезистентності при ГЦД, включаючи дисфункцію сигнальних шляхів інсуліну (IRS/PI3K/Akt), активацію запальних каскадів (JNK, SOCS) та роль адипокінів (лептину, адипонектину, резистину). Обговорюються гормональні фактори, такі як плацентарний лактоген, естрогени, прогестерон та тиреоїдні гормони, що впливають на метаболічний гомеостаз і сприяють розвитку інсулінорезистентності. Особлива увага приділена зв'язку між адипокіновм дисбалансом, порушенням ліполізу, підвищеним рівнем вільних жирних кислот та мікроангіопатією. Гетерогенна природа ГЦД та актуалізація проблеми у зв'язку з тенденцією до зростання обумовлюють необхідність подальших досліджень для удосконалення підходів до його розуміння та лікування.

Ключові слова: гестаційний цукровий діабет (ГЦД); інсулінорезистентність; шляхи передачі інсулінового сигналу (IRS/ PI3K/Akt); адипокіни (лептин, адипонектин, резистин); плацентарний лактоген (hPL).

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