REVIEW ARTICLE

Biomarkers of Gestational Diabetes Mellitus: Mechanisms, Advances, and Clinical Utility

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Abstract

Gestational diabetes mellitus (GDM) continues to pose a significant challenge to maternal and fetal health, driving the need for advanced diagnostic and therapeutic strategies. Biomarker discovery has proven essential for early detection, mechanistic insights, and targeted interventions. This review provides an in-depth examination of biomarkers related to GDM, focusing on glucose metabolism, insulin resistance, inflammatory signaling, adipokines, oxidative stress markers, and genetic/epigenetic determinants. We also evaluate novel biomarkers emerging from omics technologies and their translational potential in clinical practice. Additionally, we explore the role of microRNAs and extracellular vesicles as emerging biomarkers that could offer new perspectives on GDM pathophysiology. Integration of these biomarkers into predictive models holds the potential to improve risk assessment and patient health outcomes.

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Introduction

Gestational diabetes mellitus (GDM), identified as glucose intolerance that arises or is first detected during pregnancy, impacts approximately 13% of pregnancies worldwide.[1,2] This definition overlooks the distinction that GDM does not include women previously diagnosed with type 1 or type 2 diabetes mellitus (T1D or T2D) prior to pregnancy, which is called "diabetes in pregnancy" (DIP), and this group is linked to higher rates of maternal and fetal complications.[3] FIGO recommends using the term "hyperglycemia in pregnancy" (HIP) to encompass both GDM and preexisting DIP.[4] In India, this prevalence is estimated to be between 15 and 18%, reflecting a growing public health challenge.[5–8] In Russia, GDM is also very frequent, with 13.6% of pregnant women estimated to have GDM.[9] GDM contributes significantly to adverse maternal and fetal outcomes.[10–12] GDM poses risks such as preeclampsia, fetal macrosomia, and long-term metabolic disturbances, including an increased predisposition to T2D in mothers.[12–15] Moreover, children of mothers with GDM are at a higher risk of developing obesity, T2D, and cardiovascular diseases (CVD) as they grow older.[16,17]

Addressing this issue effectively requires targeted interventions and best management strategies to reduce these risks and improve outcomes for both mothers and their children.

Several studies, such as the TOBOGM (Treatment of Booking Diabetes Mellitus) study,[18] the WINGS (Women in India with GDM Strategy) study,[19,20] and the STRIDE (STratification of Risk of Diabetes in Early pregnancy) study,[21] have provided valuable insights into screening, risk stratification, and management of GDM in India. The WINGS study demonstrates the effectiveness of structured screening programs and follow-up care in improving maternal and fetal outcomes, advocating for widespread implementation of GDM screening guidelines.[22] Additionally, the STRIDE study has been instrumental in providing a threshold for early pregnancy screening using HbA1c and routinely collected maternal data to identify a subgroup of women, in early pregnancy, who are at the highest risk of developing GDM. This has the potential to offer intervention to this subgroup for prevention.[21]

While these studies have enhanced screening and glycemic management strategies, there is still a need for more personalized approaches to treatment. The identification of reliable biomarkers is essential in addressing this gap, as these contribute to a better understanding of the pathophysiology of GDM and present opportunities for more focused therapeutic interventions.[23,24] An ideal biomarker for GDM would offer two primary benefits: it could significantly reduce unnecessary testing by efficiently identifying women at low risk, simplifying the prenatal care process. Additionally, it enables the early identification of women at higher risk, facilitating prompt intervention and targeted preventive measures. This review aims to consolidate current and emerging biomarkers of GDM (Table 1), emphasizing their mechanistic roles and clinical relevance, with a particular focus on their implications in the Indian and Russian context.

Glucose Metabolism Markers

Fasting Plasma Glucose

Fasting plasma glucose (FPG) is a key component in diagnosing GDM, defining a threshold of ≥92 mg/dL for diagnosis, indicating impaired glucose homeostasis.[25,26] Elevated FPG levels, reflecting hepatic insulin resistance and increased glucose production, are central to the pathophysiology of GDM.[27] However, various studies suggest that the optimal FPG cut point may vary. For instance, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study identified increased risks of adverse outcomes at lower FPG cut points, leading to recommendations for a threshold of ≥95 mg/dL.[12] Additionally, multiple studies found that different cut points, such as ≥90 mg/dL and ≥100 mg/dL, were linked with varying risks of complications,[28,29] underscoring the need

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Table 1: Biomarkers for GDM—timing, significance, and limitations

Biomarker	*Timing for test in GDM*	*Significance in GDM*	*Limitations*
Preconception or early pregnancy			
Genetic variants	Preconception or early pregnancy (genetic testing)	Can identify risk variants associated with GDM	Genetic predisposition alone does not predict GDM development; complex interaction with environment
Epigenetic modifications	Preconception or early pregnancy	Can show heritable changes in gene expression related to GDM	Experimental; not yet applicable in routine clinical practice
Early pregnancy			
Adiponectin	Early pregnancy	Low levels are associated with insulin resistance and GDM	Limited availability of assays; influenced by obesity and other metabolic conditions
Metabolomics	Early pregnancy	Profiles metabolic changes that may indicate risk for GDM	High cost; complex interpretation; still in research phase
Proteomics	Early pregnancy	Identifies protein markers that could predict GDM risk	Expensive; complex data analysis; not yet used in clinical practice
MicroRNAs	Early pregnancy	Potential biomarkers For GDM diagnosis and prognosis	Limited clinical use; requires further validation and standardization
Ficolin-3	Early pregnancy	A novel biomarker that may be linked to inflammation and insulin resistance in GDM	Early research; not validated for clinical use in GDM diagnosis or management
F2-isoprostanes	Early pregnancy	Sensitive marker of oxidative stress, may be elevated in GDM	High cost; difficult to standardize; nonspecific to GDM
Early to mid-pregnancy			
Insulin and C-peptide levels	Early to mid-pregnancy	Reflects insulin secretion and pancreatic beta-cell function	Variability in assays; not routinely used for diagnosis; limited by fasting and circadian changes
C-reactive protein	Early to mid-pregnancy	Marker of inflammation, which is elevated in GDM	Nonspecific marker of inflammation; elevated in other conditions
Leptin	Early to mid-pregnancy	Associated with insulin resistance and obesity, common in GDM	Influenced by body mass index and other metabolic conditions
Nesfatin-1	Early to mid-pregnancy	May regulate glucose metabolism and insulin sensitivity in GDM	Limited studies; unclear clinical utility in routine diagnosis
Fasting plasma glucose	Early pregnancy or at 24–28 weeks	Indicator of baseline glucose metabolism; commonly used for GDM diagnosis	May miss postprandial hyperglycemia; poor sensitivity in early GDM diagnosis
Mid-pregnancy			
Oral glucose tolerance test	24–28 weeks	Gold standard for diagnosing GDM based on glucose levels after a glucose challenge	Time-consuming; requires fasting; patient discomfort
Any time in pregnancy			
HOMA-IR	Any time in pregnancy	Assesses insulin resistance, which increases in GDM	Requires fasting insulin and glucose measurements; not routinely used in clinical practice
Malondialdehyde	Throughout pregnancy	Marker of oxidative stress, elevated in GDM	Not widely available; oxidative stress markers can be nonspecific
1,5-anhydroglucitol	Throughout pregnancy	Reflects short-term postprandial hyperglycemia; low levels indicate poor glucose control	Not commonly used in routine GDM diagnosis; expensive; not always correlated with other measures

for a multiparametric diagnostic approach. Integrating FPG with other measures, like the 75 gm oral glucose tolerance test (OGTT), enhances diagnostic accuracy and risk prediction for adverse maternal and fetal outcomes, including macrosomia and preeclampsia.[30] Therefore, a comprehensive approach that incorporates FPG alongside additional metabolic parameters ensures a more accurate assessment of glucose intolerance and informs effective intervention strategies.

Oral Glucose Tolerance Test

This is a diagnostic test that involves a 1-hour (≥180 mg/dL) and 2-hour (≥153 mg/dL) postglucose values rather than a biomarker, used for assessing specific health conditions.[25] The OGTT is still considered the gold standard for GDM diagnosis, as it effectively evaluates both insulin secretion and glucose metabolism over time. By assessing glucose levels at fasting, as well as 1-hour and 2-hour intervals following a 75 gm glucose load, the dynamic interplay between fasting and postprandial glucose excursions provides insights into beta-cell responsiveness and resistance to insulin in peripheral tissues. The glucose challenge-induced hyperglycemia reveals underlying impaired beta-cell function and insulin

resistance in the liver.[31] However, despite its utility, the OGTT has several drawbacks. One major limitation is the variability in glucose thresholds across different populations, complicating the establishment of a universal diagnostic standard.[32,33] Additionally, the test requires significant time (2–3 hours) and can cause discomfort due to nausea and vomiting, leading to poor patient compliance. Factors such as stress or illness can influence glucose readings, increasing the risk of false positives or negatives.[34]

Glycated Hemoglobin

In the context of GDM, HbA1c has been explored for both diagnostic and prognostic purposes. Mechanistically, HbA1c formation is driven by the nonenzymatic glycation of hemoglobin, with higher glucose concentrations leading to increased glycation.

Despite the dynamic shifts in glucose metabolism during pregnancy, HbA1c is not typically utilized for the diagnosis of GDM. Recent advances have highlighted its potential utility in identifying women at risk of adverse pregnancy outcomes, such as preeclampsia and macrosomia.[35] A recent study revealed that early pregnancy HbA1c levels, either alone or in combination with factors such as age, BMI, and family history, were strongly linked to the risk of developing GDM between 24 and 28 weeks. The adjusted risk ratios were 1.60 (95% CI 1.19–2.16) in India, 3.49 (95% CI 2.80–4.34) in Kenya, and 4.72 (95% CI 3.82–5.82) in the UK. Using a composite risk score model could potentially decrease the reliance on OGTTs by 50–64%. The HbA1c thresholds for diagnosing or ruling out GDM varied across regions, with rule-in and rule-out values of 5.4 and 4.9% in India, 6.0 and 5.2% in Kenya, and 5.6 and 5.2% in the UK.[21]

Clinically, HbA1c offers a practical advantage as it does not require fasting, making it a convenient marker for follow-up assessments in GDM management.[36] However, its sensitivity in predicting GDM remains lower compared to traditional oral glucose tolerance tests.[37,38] Certain conditions, like hemoglobinopathies (e.g., thalassemias, Hb variants) and iron-deficiency anemia, can interfere with accurate HbA1c measurement, which is more prevalent in regions like India.[39] Further research is required to confirm its role in early pregnancy screening and risk assessment.

Insulin Sensitivity and Secretion Markers

Homeostasis Model Assessment of Insulin Resistance

Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is a commonly used method for estimating insulin resistance by integrating fasting insulin and glucose concentrations, providing a surrogate marker for hepatic insulin sensitivity. In the context of GDM, elevated HOMA-IR values are indicative of significant insulin resistance, a hallmark of the disorder. This increase in insulin resistance reflects impaired insulin signaling, specifically to the insulin receptor and its downstream signaling pathways, including the AKT/PKB cascade, which is critical for glucose uptake and glycogen synthesis.[40] Research has demonstrated that in women with GDM, HOMA-IR levels are significantly elevated compared to those in normoglycemic pregnancies, highlighting the disruption in insulin receptor function and its downstream metabolic effects.[41] This impairment is further exacerbated by pregnancy-induced hormonal changes, including elevated placental hormones such as human placental lactogen (hPL) and progesterone, which impair insulin resistance during pregnancy.[42] Research also suggests that HOMA-IR may predict not only the severity of GDM but also the likelihood of postpartum metabolic complications.[43] Given its noninvasive and cost-effective nature, HOMA-IR is a valuable tool for assessing insulin resistance in GDM at any time during pregnancy, although its limitations, such as reliance on fasting measures alone, necessitate careful interpretation in clinical settings.

Insulin and C-Peptide Concentrations in Gestational Diabetes Mellitus

Elevated insulin and C-peptide levels in individuals with GDM reflect a compensatory response of the pancreatic beta cells to increased insulin resistance, a defining characteristic of GDM. Normally, insulin and C-peptide are released together from pancreatic beta cells in equal amounts, but C-peptide is considered a more reliable marker of endogenous insulin secretion because it has a longer half-life.[44] In GDM, insulin resistance rises significantly during the second and third trimesters, largely due to placental hormones like human placental lactogen (hPL), progesterone, and cortisol, which interfere with insulin's effects on target tissues.[45] As insulin resistance worsens, beta cells initially respond by ramping up insulin production to compensate, leading to elevated insulin and C-peptide concentrations in circulation.[46] However, in late pregnancy, the disproportionate rise in C-peptide compared to insulin suggests potential alterations in insulin clearance or changes in the kinetics of insulin secretion.[47] This variation might be attributed to enhanced hepatic insulin clearance, leading to elevated levels of circulating C-peptide in comparison to insulin. Furthermore, elevated C-peptide levels are often seen as a marker of beta-cell stress, indicating that while beta cells are compensating for insulin resistance, they are also under considerable strain, potentially leading to beta-cell dysfunction if this compensatory mechanism fails. From a pathophysiological perspective, the persistence of elevated C-peptide and insulin levels in GDM individuals suggests that while there is compensatory hyperinsulinemia, it is not always sufficient to address the insulin resistance, particularly in the postprandial state. This disruption in glucose regulation leads to hyperglycemia and increases the risk of negative maternal and fetal outcomes, such as macrosomia and neonatal hypoglycemia.[48] Moreover, understanding these shifts in insulin and C-peptide dynamics is critical for evaluating beta-cell reserve and functional capacity in GDM, which can have implications for long-term metabolic health. Monitoring both insulin and C-peptide levels, therefore, provides important insight into the underlying pathophysiology of GDM and its potential progression to future metabolic disorders.

Sex Hormone Binding Globulin

Sex hormone binding globulin (SHBG) has gained recognition as an early biomarker for GDM.[49] Low levels of SHBG in early pregnancy have consistently been linked to a higher risk of developing GDM during the 24–28-week gestational period. This association suggests that SHBG could serve as an early marker for GDM risk.[50] SHBG is crucial in regulating insulin sensitivity and glucose metabolism, with reduced levels reflecting insulin resistance, a defining characteristic of GDM.[51] Various studies have shown that combining early pregnancy SHBG measurements with other risk factors improves the prediction of GDM.[52] This composite risk scoring model can significantly reduce the need for OGTTs, especially in resource-limited settings, by stratifying women into risk categories. SHBG thresholds for diagnosing GDM vary across populations, and its sensitivity adds to its limitation,[53] but its inclusion in screening strategies provides a simple, reproducible, and efficient method for identifying women at high risk, enabling earlier interventions to enhance both maternal and fetal outcomes.

Quantitative Insulin Sensitivity Check Index

Quantitative insulin sensitivity check index (QUICKI) serves as an important indicator for evaluating insulin sensitivity in the context of GDM. QUICKI is calculated from fasting insulin and glucose levels and offers a dependable measure of insulin sensitivity,

which is frequently diminished in women with GDM.[54] Research indicates that lower QUICKI values during early pregnancy are predictive of GDM onset, as they signify underlying insulin resistance, a central factor in the pathophysiology of GDM.[41] When used alongside insulin secretion markers such as fasting insulin and C-peptide, QUICKI can improve the identification of women at high risk for developing GDM.[55] Its simplicity and efficiency make it a useful tool for early screening, especially in low-resource settings, reducing the dependence on more burdensome tests like the OGTT. Incorporating QUICKI into a composite risk score can also improve the prediction of adverse pregnancy outcomes related to GDM.

Urinary Markers

Urinary L-Tryptophan

Urinary L-tryptophan excretion has gained attention in the context of metabolic disorders, including GDM.[56] The urinary excretion of L-tryptophan and its metabolites, such as kynurenine, reflects disturbances in tryptophan metabolism, which are often linked to inflammatory and oxidative stress pathways.[57] In GDM, altered tryptophan metabolism could play a role in the development of insulin resistance and disrupted glucose regulation, with increased excretion potentially indicating a dysregulation in the kynurenine pathway.[58] This dysregulation can enhance oxidative stress and immune activation, further exacerbating the metabolic disturbances observed in GDM. Through targeted and untargeted metabolomic analysis, the integration of both plasma and urine metabolites enhanced the accuracy of GDM prediction, with an AUC of 0.99.[59] Monitoring urinary L-tryptophan and its metabolites could thus serve as a noninvasive biomarker for assessing metabolic stress and insulin resistance in pregnant women.

L-Urobilinogen

L-urobilinogen, a bile pigment derivative formed from the breakdown of hemoglobin, has been explored as a potential indicator in numerous metabolic disorders, including GDM. Its presence in urine reflects liver function and gut microbial activity, both of which can be affected by metabolic changes during pregnancy.[59] In GDM, altered glucose metabolism may influence liver function, potentially leading to elevated levels of L-urobilinogen.[60] Additionally, the dysbiosis of gut microbiota, commonly observed in GDM, could impact urobilinogen metabolism.[61] Increased urinary L-urobilinogen levels may thus serve as an indicator of hepatic or gut-related metabolic disturbances in GDM, presenting a possible noninvasive biomarker for the early diagnosis and monitoring of the disease. Additional research is needed to explore its precise role and diagnostic significance in the pathology of GDM.

Ceramides

Ceramides, a class of bioactive sphingolipids, have been implicated in insulin resistance and inflammation,[62] both of which are key features of GDM. Recent studies suggest that urinary ceramide levels may reflect underlying metabolic disturbances in GDM, as ceramides play a crucial role in lipid metabolism, cell signaling, and apoptosis. Elevated urinary ceramide levels in GDM individuals may indicate disrupted lipid homeostasis and play a role in the development of insulin resistance, a common feature of GDM.[59] Additionally, ceramides are linked to oxidative stress and inflammation, which further exacerbate glucose intolerance during pregnancy.[63] Measuring ceramide levels in urine may serve as a noninvasive biomarker for the early identification and progression of GDM, providing perspectives into the pathophysiology of the disease and prospective treatment targets for managing metabolic dysfunction in pregnant women. Further investigations are necessary to validate the diagnostic utility of urinary ceramides in GDM.

21-Deoxycortisol

21-deoxycortisol, a steroid intermediate in the biosynthesis of cortisol, has been studied in various metabolic and endocrine disorders.[64] In GDM, the hormonal and metabolic environment is significantly altered, often leading to disruptions in the hypothalamic-pituitary-adrenal (HPA) axis.[65] This disruption may result in abnormal levels of steroid intermediates like 21-deoxycortisol. Elevated levels of 21-deoxycortisol could indicate impaired steroidogenesis or dysregulation of adrenal function, both of which are relevant to the insulin resistance and glucose intolerance seen in GDM.[66] A recent study revealed that women who later developed GDM had elevated levels of 21-deoxycortisol during the first trimester, compared to those who did not develop the condition. The study's GDM prediction model, which incorporated multiple variables including 21-deoxycortisol, demonstrated a high specificity of 96.6% and sensitivity of 97.5%, indicating that early risk estimation based on these markers could provide an effective tool for preventing and managing GDM.[67] As a biomarker, 21-deoxycortisol in urine or plasma may provide insight into the hormonal imbalance characteristic of GDM, potentially offering a tool for early detection and risk stratification. Additional research is required to establish the significance of 21-deoxycortisol in the pathophysiology of GDM and its clinical utility as a diagnostic marker.

Cucurbitacin-C and Aspartame

Cucurbitacin-C is recommended during pregnancy due to its medicinal properties, and aspartame, a nonnutritive sweetener, has also been noted in dietary patterns. As urine composition is largely affected by dietary intake, analyzing maternal urine can help detect shifts in dietary patterns. A study found that aspartame and cucurbitacin-C were among the metabolites dysregulated in the urine of pregnant women with GDM.[59] However, these markers are not highly specific, and additional research is required to gain a more comprehensive understanding of the implications of these results.

Inflammatory Markers

C-Reactive Protein

C-reactive protein (CRP), a widely recognized systemic marker of inflammation, has garnered significant attention for its role in the development of GDM. Increased CRP levels are frequently observed in individuals diagnosed with GDM, reflecting subclinical inflammation that parallels the metabolic and hormonal changes occurring during pregnancy. This inflammatory state is not just a consequence of metabolic dysfunction but may actively contribute to it, creating a feedback loop that increases insulin resistance, a hallmark feature of GDM.[68] The relationship between CRP and GDM involves multiple complex mechanisms, particularly at the molecular level. CRP serves as an indicator of heightened immune activation, signifying systemic inflammation that impacts vascular function. A major pathway involved in this process is the activation of nuclear factor-kappa B (NF-κB), an essential transcription factor that controls the expression of various pro-inflammatory cytokines.[69] In GDM, NF-κB activation triggers the release of inflammatory mediators like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), all of which contribute to insulin resistance and endothelial dysfunction.[70,47] CRP, through its interaction with endothelial cells, promotes vascular inflammation, oxidative stress, and dysregulation of insulin signaling pathways. This pro-inflammatory environment enhances insulin resistance, making glucose regulation more challenging for the mother and increasing the risk of

adverse pregnancy outcomes. The risk of unfavorable pregnancy outcomes may increase for the mother.[71] However, the specificity of CRP as a diagnostic tool is limited, as it reflects generalized inflammation and is elevated in various conditions.[72] Nonetheless, its role in the inflammatory cascade central to GDM underscores the importance of targeting inflammation in therapeutic interventions.

Interleukin-6 and Tumor Necrosis Factor-Alpha

The pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are critical contributors to the impairment of insulin signaling in GDM. These cytokines promote insulin resistance by inducing serine phosphorylation of insulin receptor substrates (IRS), particularly IRS-1, which impairs the downstream signaling necessary for insulin action.[27,73] This disruption of insulin pathways is a core feature of GDM and exacerbates glucose intolerance. Increased levels of these cytokines in GDM point to a chronic low-grade inflammatory condition, often referred to as "meta-inflammation."[74] This inflammation also impairs adipose tissue function, which leads to the elevated release of free fatty acids, altered adipokine secretion, and lipotoxicity—all contributing to further insulin resistance and metabolic dysregulation. The dysfunction of adipose tissue further perpetuates the inflammatory cycle, exacerbating metabolic impairment.[75] This chronic inflammatory state not only worsens insulin resistance during pregnancy but may also have lasting implications, increasing the likelihood of cardiovascular complications in both the mother and her offspring.[71] Early interventions targeting inflammatory pathways could potentially mitigate these risks, leading to improved outcomes for women with GDM and their children. These interventions may also contribute to reducing the long-term metabolic consequences associated with GDM, such as the risk of developing type 2 diabetes in the mother.

Adipokines

Leptin

Leptin, an adipokine primarily produced by adipose tissue, plays a crucial role in regulating body weight by controlling appetite and energy expenditure through its central actions on the hypothalamus. However, its influence extends far beyond appetite regulation.[76] In GDM, elevated leptin levels are often observed, but they are typically accompanied by a diminished physiological response, a condition known as leptin resistance. This resistance impairs the hypothalamic regulation of energy balance, resulting in increased food consumption and decreased energy expenditure, both of which can exacerbate insulin resistance.[77] Leptin's role in glucose metabolism is also significant. It directly influences insulin sensitivity in peripheral tissues such as skeletal muscle, liver, and adipose tissue, enhancing glucose uptake and utilization. However, in leptin resistance, these beneficial actions are reduced, leading to increased blood glucose levels and insulin resistance.[78] Moreover, leptin has an impact on the hypothalamic-pituitary axis, which regulates hormones involved in glucose homeostasis. Leptin resistance disrupts this delicate hormonal balance, further impairing glucose metabolism and contributing to the development of GDM.[79] Given leptin's multifaceted role in energy homeostasis and glucose regulation, it is a critical factor in the metabolic disturbances observed in GDM. Leptin's involvement in both central and peripheral processes affecting insulin sensitivity and glucose metabolism underscores its potential as a target for therapeutic interventions in GDM. Continued research is necessary to explore leptin's role further, as understanding its exact mechanisms and therapeutic potential could offer new approaches to managing GDM and reducing the risk of its long-term complications.[80]

Nesfatin-1

Nesfatin-1, a novel adipokine, has gained significant attention for its diverse metabolic functions, particularly its role in regulating energy balance, maintaining glucose homeostasis, and enhancing insulin sensitivity. Initially discovered in the hypothalamus as a key regulator of satiety, nesfatin-1 has since been found to be expressed in several peripheral tissues, including adipose tissue, the pancreas, and the gastrointestinal tract.[81] This broader expression suggests that nesfatin-1 has systemic effects on metabolism, beyond just controlling hunger. In the context of GDM, emerging research indicates that nesfatin-1 plays a critical role in glucose metabolism.[82] Studies have shown that nesfatin-1 improves insulin sensitivity and enhances glucose uptake in peripheral tissues, which is essential for maintaining glucose balance.[83] Recent reports[84–86] have found that circulating nesfatin-1 levels are significantly lower in women with GDM, correlating with increased insulin resistance and dysregulated glucose metabolism. This pattern suggests that nesfatin-1 may be an important marker or even a potential therapeutic target in GDM management. Our recent study on nesfatin-1 demonstrated similar findings, where reduced levels of nesfatin-1 were associated with insulin resistance in GDM. This further underscores the role of nesfatin-1 in regulating glucose metabolism during pregnancy. Given its ability to modulate insulin sensitivity and glucose uptake, nesfatin-1 could hold promise not only as a biomarker for early detection of GDM but also as a potential therapeutic agent to improve glucose regulation and insulin sensitivity in affected women. These findings highlight the need for further investigation into the precise mechanisms by which nesfatin-1 influences metabolic processes in GDM, and how its modulation could offer new avenues for managing the condition.[84]

Additionally, nesfatin-1 has demonstrated anti-inflammatory properties, which may help mitigate the chronic low-grade inflammation characteristic of GDM.[87] These results indicate that nesfatin-1 could be a potential biomarker and therapeutic target for the management of GDM, warranting further investigation into its mechanistic pathways and clinical implications.

Adiponectin

Adiponectin, a key adipokine secreted by adipocytes, plays an essential role in modulating insulin sensitivity and exerting anti-inflammatory effects.[88,89] In GDM, low adiponectin levels are frequently observed, reflecting impaired adipocyte function and reduced insulin sensitization.[90] This reduction in adiponectin is particularly concerning given its metabolic benefits, such as enhancing glucose uptake and fatty acid oxidation, as well as inhibiting hepatic gluconeogenesis, which collectively help maintain metabolic balance.[91] Multiple studies have indicated that reduced adiponectin levels in GDM are linked to higher insulin resistance and a greater likelihood of progressing to T2D after pregnancy.[92,93] Research also suggests that the reduction in adiponectin levels in GDM may be linked to hypertrophied adipocytes, which become dysfunctional in the setting of obesity and insulin resistance. These hypertrophied adipocytes exhibit a dysregulated secretion of adiponectin, further exacerbating insulin resistance and contributing to metabolic imbalances.[27] A study conducted by Retnakaran et al.[94] revealed that women with GDM exhibited significantly reduced levels of circulating adiponectin when compared to healthy pregnant women, and this was linked with impaired glucose tolerance and elevated insulin resistance. Another study by Pheiffer et al.[95] highlighted that adiponectin levels in mid-pregnancy could help predict the onset of GDM, underscoring its role as an early biomarker for metabolic disturbances

in pregnancy. Adiponectin are inflammatory markers which may increase due to proinflammatory state. They gain importance only if they have predictive ability in early/prepregnancy singly or in combination. Thus, adiponectin serves as a valuable marker for assessing metabolic health in GDM and could offer potential avenues for early diagnosis and therapeutic intervention to improve maternal and fetal outcomes.

Resistin

Resistin, an adipokine primarily secreted by adipose tissue, has garnered growing attention for its potential role in the pathophysiology of GDM.[96] It is recognized as a contributor to insulin resistance, a defining characteristic of GDM. Research has shown that pregnant women with GDM exhibit significantly elevated levels of HOMA-IR, resistin, IL-6, and TNF-alpha, while adiponectin levels are notably reduced compared to those in healthy pregnant women.[97] Elevated resistin levels during the first trimester (hyperresistinemia) were strongly linked to a higher likelihood of developing GDM later in pregnancy.[98] Resistin demonstrated a high predictive value for GDM, with an AUC of 0.836, indicating its potential as a reliable early marker for identifying women at risk of developing the condition. However, the precise mechanisms connecting resistin to GDM are still not well understood, and additional research is required to clarify its exact function and potential as a biomarker or therapeutic target in managing GDM.

Visfatin, Omentin-1, and Ghrelin

Visfatin, omentin-1, and ghrelin are increasingly being recognized as important biomarkers in the context of GDM.[99,100] Visfatin, produced by visceral adipose tissue, is believed to affect glucose metabolism by exerting insulin-like effects. Increased levels in GDM have been associated with greater insulin resistance and metabolic dysregulation.[101] A meta-analysis revealed that omentin-1, an adipokine with anti-inflammatory and insulin-sensitizing effects, is generally decreased in individuals with GDM. Its reduced levels are linked to impaired glucose regulation, increased insulin resistance, and chronic inflammation, all of which play a role in the development of GDM.[102] Ghrelin, commonly known as the "hunger hormone," regulates appetite and energy homeostasis, and its levels tend to be dysregulated in GDM.[103] A study found that pregnant women with GDM and T2D exhibited significantly reduced ghrelin levels in comparison to healthy women ($p < 0.001$). Additionally, maternal proinsulin levels were lower in those with GDM ($p < 0.001$).[104] Preterm births in GDM showed higher maternal ghrelin ($p = 0.031$) and lower neonatal proinsulin ($p = 0.033$). These adipokines collectively reflect the intricate metabolic and hormonal alterations that occur in GDM, and their combined measurement may offer enhanced predictive value, enabling earlier intervention and better management strategies to improve maternal and fetal outcomes.

Oxidative Stress Markers

Malondialdehyde

Malondialdehyde (MDA) is a by-product of lipid peroxidation, commonly used as a marker for oxidative stress.[105] Elevated MDA levels have been observed in GDM, highlighting the critical role that oxidative stress plays in the development of this condition.[106] Increased oxidative damage not only contributes to the interruption of normal insulin signal transduction pathways but also worsens insulin resistance in critical metabolic tissues like the liver and skeletal muscle. The accumulation of MDA indicates heightened lipid peroxidation, which is linked to cellular stress and damage, further worsening the metabolic imbalances seen in GDM.[107] Studies have shown that oxidative stress impairs mitochondrial function in insulin-sensitive tissues, reducing their capacity for efficient glucose uptake and energy production.[108] Mitochondrial dysfunction disrupts the balance between reactive oxygen species (ROS) generation and the body's antioxidant defenses, triggering pro-inflammatory pathways that exacerbate insulin signaling impairment. The detrimental cycle of oxidative stress, mitochondrial dysfunction, and insulin resistance is a key contributor to the progression of GDM.[109] Lappas et al.[110] demonstrated that women with GDM exhibited significantly higher levels of MDA compared to healthy pregnant women, indicating that oxidative stress may play a key role in the metabolic dysfunction associated with pregnancy. As a result, addressing oxidative stress and mitochondrial dysfunction could present promising therapeutic strategies for enhancing insulin sensitivity and alleviating the negative metabolic effects of GDM.

F2-Isoprostanes

Endothelial dysfunction, mediated by oxidative stress, plays a crucial role in disrupting vascular homeostasis, which is essential for maintaining proper insulin signaling and glucose uptake.[111] The rise in F2-isoprostanes mirrors the oxidative damage to cell membranes and the resultant inflammatory responses that aggravate insulin resistance in GDM.[112] Studies have shown a strong link between increased F2-isoprostane levels and worsened insulin sensitivity, linking oxidative damage to metabolic dysfunction.[113] Furthermore, the heightened oxidative stress reflected by F2-isoprostanes is linked with increased risk in pregnancy outcomes, making them a potential biomarker for early detection and intervention in GDM.[105] By measuring F2-isoprostanes, researchers and clinicians can better understand the oxidative stress burden in GDM, offering insights into the molecular mechanisms underlying its progression and potential therapeutic strategies to mitigate its effects.

Placenta-derived Markers

Placenta-derived markers are essential for assessing both maternal and fetal health, particularly in complicated pregnancies such as those involving GDM and preeclampsia.[114] Follistatin-like 3 (FSTL3), a glycoprotein primarily expressed in the placenta, regulates several signaling pathways, including those of activin and myostatin, which are essential for placental development and function.[115] Studies have shown altered FSTL3 levels in pregnancies complicated by GDM and preeclampsia, suggesting its role in placental dysfunction.[116] Similarly, placental growth factor (PlGF) is vital for angiogenesis and vascular development in pregnancy.[117] Decreased levels of PlGF are strongly associated with placental insufficiency and are widely used as a marker for predicting preeclampsia.[118] These markers are critical for understanding the pathophysiology of pregnancy complications and can serve as potential therapeutic targets. Additionally, emerging markers such as placental exosomes, afamin, and fetuin-A provide further insight into placental biology.[119,120] Placental exosomes, which are extracellular vesicles released into the maternal circulation, play key roles in immune modulation and metabolic regulation during pregnancy.[121] Afamin, a vitamin E-binding glycoprotein, has been found to be elevated in cases of GDM, reflecting changes in metabolic and oxidative stress pathways. A meta-analysis showed that pregnant women with GDM had significantly elevated plasma afamin levels during the first trimester (SMD = 0.481, 95% CI: 0.280–0.682), but this difference was not observed in the later stages of pregnancy. In women with preeclampsia, afamin levels were elevated across all trimesters, with the highest levels observed in the second/third trimesters (SMD = 0.904, 95% CI: 0.570–1.239).[122] Fetuin-A, another glycoprotein, is involved in insulin resistance and inflammation, making it a

relevant marker in pregnancies affected by diabetes.[123] A study found that women who developed GDM had significantly reduced levels of maternal fetuin-A during the first trimester compared to those who did not (AUC = 0.337, $p = 0.013$). The optimal cutoff value for fetuin-A in predicting GDM was identified as <166 mg/dL. Additionally, a significant inverse correlation was found between fetuin-A and hs-CRP levels ($r = -0.21$, $p = 0.047$).[124] Moreover, fibroblast growth factors-21 (FGF-21) and FGF-23 are involved in metabolic processes and have been linked to altered placental function.[125] Ficolin-3, a protein involved in the innate immune response, has also been linked to the development of preeclampsia. In preeclamptic patients, plasma ficolin-2 and ficolin-3 levels were significantly lower compared to healthy pregnant (ficolin-2: 3.1 µg/mL, ficolin-3: 17.6 µg/mL) and nonpregnant women (ficolin-2: 3.7 µg/mL, ficolin-3: 18.2 µg/mL). Ficolin-2 levels showed a positive correlation with PlGF and an inverse correlation with sFlt-1, endothelial injury markers, and trophoblast debris,[126] highlighting the interplay between immune regulation and placental health. Collectively, these placenta-derived markers provide broad understanding of the multifaceted roles performed by the placenta in maintaining pregnancy and the potential disruptions caused by metabolic and vascular complications.

Emerging Biomarkers

Genetic and Epigenetic Markers

Genetic Variants

Multiple genetic variants have been strongly linked to the development of GDM. Notably, polymorphisms in the TCF7L2 (transcription factor 7-like 2) and PPARG (peroxisome proliferator-activated receptor gamma) genes are among the most studied (Fig. 1).[127] TCF7L2 is essential for regulating insulin secretion and maintaining glucose homeostasis, with gene variants frequently associated with decreased insulin secretion and an elevated risk of GDM.[128] PPARG is central to adipocyte differentiation and insulin sensitivity, and its variants have been associated with impaired insulin action, contributing to the metabolic dysregulation seen in pregnancy.[129] These findings underscore the genetic predisposition to GDM, particularly in individuals carrying risk alleles that impair beta-cell function and insulin signaling pathways. Beyond TCF7L2 and PPARG, other loci such as MTNR1B (melatonin receptor 1B), GCK (glucokinase), and IRS1 (insulin receptor substrate 1) have also been linked to GDM, further reinforcing the role of genetic predisposition in the disease.[130] Collectively, these genetic variants may interact with environmental factors such as nutrition, body mass, and physical activity levels, exacerbating the susceptibility to metabolic dysregulation during pregnancy. In three recent studies conducted by Kanthimathi et al.,[131] the genetic susceptibility to GDM was explored in a South Indian population, uncovering key associations with several gene variants. The initial study discovered two single nucleotide polymorphisms (SNPs) in the CDKAL1 gene, rs7754840 and rs7756992, which were associated with an elevated risk of developing GDM, with corresponding odds ratios of 1.34 and 1.45, respectively. The second study[132] focused on variations in the hexokinase domain containing 1 (HKDC1) gene, identifying that rs10762264 and rs4746822 were linked to a 1.24- and 1.34-fold increased risk of GDM. A third study[133] investigated gene variants associated with T2D and found that variants in HMG20A (rs7178572) and HNF4A (rs4812829), previously connected to T2D, also conferred significant risk for GDM, with risk alleles increasing susceptibility by 1.24 and 1.28 times, respectively, and up to 1.97 times when carrying two risk genotypes. These studies collectively highlight the shared genetic foundations of T2D and GDM in South Asians, providing valuable understanding into the genetic factors contributing to GDM susceptibility in this population.

In Russia, Popova et al.[134] conducted a study looking at the effect of gene-lifestyle interactions on GDM risk. They found that the association between certain lifestyle factors, such as sausage consumption, and GDM risk was influenced by genetic susceptibility loci. Specifically, they discovered an interaction between sausage consumption and the number of risk alleles in MTNR1B (rs10830963) and GCK (rs1799884), suggesting that dietary habits may differentially impact GDM risk based on genetic background. These results highlight the significance of taking both genetic and lifestyle factors into account when evaluating the risk of GDM. Identifying these genetic markers provides an opportunity for personalized risk evaluation and targeted interventions for those at elevated risk of developing GDM. Apart from studying associations of SNPs with GDM, several genome-wide association studies (GWAS) have focused specifically on exploring the genetic factors associated with GDM.[135] These studies have confirmed the associations with GDM of previously linked to T2D genes MTNR1B, TCF7L2, CDKAL1, and CDKN2A-CDKN2B, along with MTNR1B exhibiting the highest significance. Additionally, a recent study by Zhen et al. revealed 14 novel loci that were significantly associated with four commonly measured glycemic traits.[136]

Epigenetic Modifications

Epigenetic changes, especially DNA methylation and histone modifications, control the expression of crucial genes responsible for glucose metabolism, insulin sensitivity, and inflammation. DNA methylation refers to the addition of methyl groups to cytosine residues in the DNA sequence, leading to gene silencing or altered gene expression, while histone modifications affect chromatin structure and gene accessibility.[137] Environmental factors like maternal obesity, diet, and intrauterine exposures during pregnancy can trigger these epigenetic changes. Research has shown that pregnant women with GDM exhibit specific

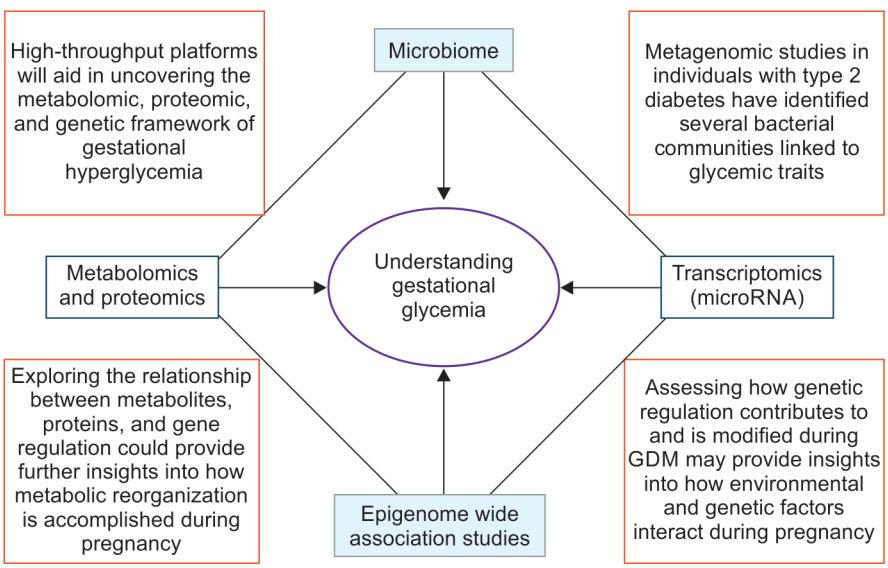

Fig. 1: Biomarkers to understand the disease biology of GDM

epigenetic profiles, with altered methylation patterns in genes associated with glucose transport (e.g., SLC2A4 encoding GLUT4) and insulin signaling (e.g., IGF2 and LEP).[138] Epigenetic changes resulting from GDM can extend well beyond pregnancy, potentially contributing to the higher likelihood of metabolic disorders in the offspring of affected mothers. This suggests that these epigenetic modifications may not only impact the mother's metabolism but also increase her children's susceptibility to conditions like insulin resistance and obesity in the future. According to a study conducted by Popova et al.,[139] examining genomic expression in the human umbilical vein endothelial cells (HUVECs) from newborns showed an elevated leptin-to-adiponectin ratio. Additionally, newborns of mothers with GDM show a reduced expression of angiopoietin-like protein 4 in their umbilical cord blood when compared to those from the control group. Achieving target glycemic levels was associated with the normalization of the elevated leptin-to-adiponectin ratio in the umbilical cord blood. In another study by the same authors,[140] a correlation between TRIB1 gene expression in HUVECs and the duration of intrauterine hyperglycemia exposure was observed. It is known that the TRIB1 gene affects plasma lipid concentrations and is associated with the risk of developing ischemic heart disease. Epigenetic alterations have the potential to function as biomarkers for the early detection of GDM and may also present novel targets for therapeutic intervention.[141] Gokulakrishnan et al.[142] presented their findings at the 60th Annual Meeting of the European Association for the Study of Diabetes (EASD), where they highlighted that DNA methylome profiling identified a set of seven CpG sites with strong predictive value for GDM in Indian women. The CpGs identified from first-trimester blood samples were found to be significantly hypermethylated in women who subsequently developed GDM compared to those who maintained normal glucose levels. The study employed machine learning classifiers to validate the predictive power of these CpGs, achieving high sensitivity (92%) and specificity (86%) in early GDM detection (unpublished data). The CpGs were also correlated with glucose levels and linked to pathways such as insulin resistance, AGE-RAGE signaling, and Th1/Th2 cell differentiation, highlighting their potential utility in GDM prevention and personalized treatment strategies. The reversibility of some epigenetic changes holds promise for interventions that could mitigate the risk of GDM and its long-term effects on offspring health, emphasizing the importance of understanding both genetic and epigenetic contributions to GDM pathophysiology.[143]

MicroRNAs

MicroRNAs (miRNAs) are short, noncoding RNA molecules that control gene expression at the posttranscriptional level and have been increasingly recognized for their role in metabolic diseases, including GDM. MicroRNA profiling in women with GDM has identified dysregulated miRNAs involved in insulin sensitivity, glucose metabolism, and inflammatory pathways.[144] For example, miRNAs like miR-29a, miR-222, and miR-330 have been found to be dysregulated in GDM, possibly influencing insulin signaling and inflammatory pathways.[145] These miRNAs may serve as upstream regulators of gene expression changes that contribute to the metabolic derangements observed in GDM. Beyond their role in disease development, miRNAs show potential as biomarkers for GDM. Their stability in bodily fluids such as blood and urine makes them attractive candidates for noninvasive testing. Targeting specific miRNAs could also represent a novel therapeutic strategy for improving insulin sensitivity and reducing inflammation in GDM.

Metabolomics

Advances in metabolomics have provided new insights into the metabolic alterations associated with GDM. Metabolomic profiling allows for an in-depth examination of small molecules and metabolites present in biological samples, offering a snapshot of metabolic changes in response to physiological states such as pregnancy. In GDM, studies have revealed disruptions in amino acid metabolism. Elevated levels of branched-chain amino acids (BCAAs), such as leucine, isoleucine, and valine, have been observed in women diagnosed with GDM.[146] These elevated levels may reflect impaired insulin sensitivity, as BCAAs have been shown to influence insulin signaling pathways. Furthermore, alterations in lipid metabolism have also been observed, with elevated levels of specific ceramides and triglycerides indicating lipid dysregulation in GDM.[147]

These metabolomic signatures not only reflect the metabolic stress of pregnancy but also suggest potential early biomarkers for GDM risk. For example, a unique metabolic profile characterized by elevated levels of acylcarnitines, fatty acids, and amino acids has been linked to a higher risk of GDM, even before clinical diagnosis.[148] This suggests that metabolomic profiling could be used for early screening and risk stratification in pregnant women, enabling preventive strategies to mitigate the progression of GDM.

Proteomics

Proteomics has emerged as a powerful tool for understanding the molecular mechanisms underlying GDM by identifying protein dysregulation in plasma and placental tissues. Proteomic analyses have uncovered significant alterations in proteins involved in insulin signaling, inflammation, and oxidative stress. For instance, proteins associated with insulin resistance, such as insulin receptor substrate 1 (IRS1) and glucose transporter type 4 (GLUT4), exhibit altered expression in GDM, providing insights into the mechanisms driving hyperglycemia in pregnancy.[149] Placental proteomics has also revealed changes in proteins involved in nutrient transport, mitochondrial function, and cellular stress responses, shedding light on how GDM affects placental function and, consequently, fetal development.[150] These proteomic discoveries enhance our knowledge of GDM pathophysiology and present promising biomarkers for early diagnosis and potential therapeutic targets.

1,5-Anhydroglucitol (1,5-AG) and Fructosamine

1,5-AG is a naturally occurring polyol that has gained recognition as a potential biomarker for short-term glycemic control.[151,152] 1,5-AG levels are typically lower due to hyperglycemia. Elevated glucose levels interfere with the renal reabsorption of 1,5-AG, resulting in greater urinary excretion,[153] particularly in the late stages of pregnancy when postprandial hyperglycemia becomes more pronounced.[154] Given its sensitivity to short-term fluctuations in glucose levels, 1,5-AG could complement traditional markers like HbA1c in providing glycemic control in women with GDM. Additionally, 1,5-AG may aid in the early detection of GDM and offer a useful tool for monitoring the effectiveness of interventions aimed at improving glycemic control during pregnancy.

Fructosamine, which reflects the nonenzymatic glycation of circulating proteins such as albumin, globulins, and lipoproteins, has become a viable alternative to HbA1c testing in cases where HbA1c may be unreliable.[155] Fructosamine levels measured in the second trimester have been shown to be an unreliable indicator of gestational glucose tolerance and postpartum glycemic outcomes.[156]

Microbiome

Dysbiosis during early pregnancy, in conjunction with the host's immune system, can impact the development of GDM later on. Numerous studies have identified differences in gut microorganisms

between pregnant women with GDM and those with normal glucose levels.[62,157,158] In women with GDM, there was an observed increase in the abundance of microbial species such as *Ruminococcus*, *Klebsiella variicola*, *Prevotella*, *Rothia*, *Desulfovibrio*, *Fusobacterium*, the *Eubacterium hallii* group, and *Blautia*. Conversely, there was a decrease in populations of *Eubacterium* spp., *Bifidobacterium* spp., *Akkermansia*, *Bacteroides*, *Parabacteroides*, *Dialister*, *Marvinbryantia*, *Faecalibacterium*, and *Anaer osporobacte*.[62,157,158] A recent study by Pinto et al. identified an altered gut microbiome and elevated levels of proinflammatory cytokines in women who later developed GDM. The researchers further validated that changes in microbial composition linked to GDM during the first trimester contributed to inflammation and insulin resistance >10 weeks prior to the GDM diagnosis. This was demonstrated through fecal microbiota transplantation (FMT) experiments. They later implemented a machine learning method to accurately predict GDM by using clinical data, microbial profiles, and inflammatory markers from the first trimester.[159] Thus, the gut microbiome seems to play a role in the development of GDM by promoting inflammation, with interleukin-6 possibly playing a role in this process. Potential markers for GDM, such as specific microbiota, could be used for early diagnosis and targeted therapy, which may help in preventing the condition.

Other Markers

In GDM, several biomarkers are crucial for diagnosis and management. Vitamin D levels are considered important as deficiencies are associated with greater risk of GDM and may impact insulin sensitivity.[160] Although, some studies provide conflicting results concerning the role of Vitamin D in GDM.[161–163] Glycosylated fibronectin helps assess placental function, with elevated levels indicating potential complications such as preterm birth or restricted fetal growth.[164] The soluble (pro) renin receptor, a component of the renin-angiotensin system, could potentially act as an early marker for gestational GDM due to its link with insulin resistance.[165,166] Ferritin levels, reflecting iron status, are crucial as both deficiency and overload can affect glucose metabolism and increase GDM risk.[167] While not primary markers, glucagon levels can influence glucose regulation, and elevated PAI-1 levels indicate insulin resistance and increased thrombotic risk.[168] Adipocyte fatty acid-binding protein (AFABP) levels can highlight metabolic stress associated with GDM.[169]

Biomarkers to Distinguish "Early Gestational Diabetes Mellitus" from "Late Gestational Diabetes Mellitus"

FPG combined with other markers in machine learning models shows some limitations in accurately identifying early GDM, as adding more predictors did not significantly improve the model's discriminant power.[170] GDM has traditionally been diagnosed between 24 and 28 weeks of pregnancy, and this is referred to as "Late GDM."

More recently, GDM is being diagnosed before 20 weeks and even before 14 weeks of gestation. This is referred to as "Early GDM."[171,172] It would be useful if biomarkers for Early GDM and Late GDM are developed, as this will lead to better identification of the two forms of GDM.

Future Perspectives

It is important to note that all of the aforementioned studies have used glucose levels from OGTT conducted after 24 weeks of gestation. A key direction for future research would be to investigate the genetic factors influencing glycemic traits in early pregnancy (before 20 weeks) and to compare the genetic profiles of early-onset GDM with those of late-onset GDM. Additionally, maternal ethnicity may contribute to heterogeneity, leading to both phenotypic and genotypic differences among women with GDM.[173] Existing GWAS studies did not include Indian and Russian women. Polygenic scores (PGSs) predominantly developed from European populations have demonstrated significantly higher accuracy in White Europeans than in South Asians.[174] Consequently, multi-ancestry GWAS data are crucial for creating ancestry-specific PGSs to help mitigate health disparities. The most impactful biomarkers should be integrated into mathematical models predicting GDM and validated on independent cohorts.

Clinical Implications

In the realm of clinical implications, there is growing potential for the practical application of specific biomarkers to detect high-risk GDM at an early stage. Biomarkers with enhanced specificity and sensitivity can significantly improve day-to-day clinical practice by empowering clinicians to make more informed decisions and implement timely interventions. Emerging biomarkers have shown promise in enhancing early risk stratification. Incorporating these biomarkers into routine screening could greatly improve personalized patient management, potentially reducing the complications associated with GDM.

Looking ahead, the development of a clinical predictive model that integrates these biomarkers with traditional risk factors—which include family history, advanced age, and higher BMI—offers a promising avenue. Such a predictive algorithm, tailored for early GDM detection, could help clinicians identify high-risk individuals well before traditional screening methods indicate abnormalities. This approach has the potential to form the basis for future research, informing new clinical guidelines and fostering more precise and effective strategies for GDM management. By integrating biomarker research into clinical practice, we can improve the early detection of GDM and tailor interventions. Biomarkers also hold potential for monitoring postpartum progression to T2D, providing a continuum of care for women at risk.

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