Review

Early Identification of the Maternal, Placental and Fetal Dialog in Gestational Diabetes and Its Prevention

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Abstract: Gestational diabetes mellitus (GDM) complicates between 5 and 12% of pregnancies, with associated maternal, fetal, and neonatal complications. The ideal screening and diagnostic criteria to diagnose and treat GDM have not been established and, currently, diagnostic use with an oral glucose tolerance test occurs late in pregnancy and produces poor reproducibility. Therefore, in recent years, significant research has been undertaken to identify a first-trimester biomarker that can predict GDM later in pregnancy, enable early intervention, and reduce GDM-related adverse pregnancy outcomes. Possible biomarkers include glycemic markers (fasting glucose and hemoglobin A1c), adipocyte-derived markers (adiponectin and leptin), pregnancy-related markers (pregnancy-associated plasma protein-A and the placental growth factor), inflammatory markers (C-reactive protein and tumor necrosis factor- α), insulin resistance markers (sex hormone-binding globulin), and others. This review summarizes current data on first-trimester biomarkers, the advantages, and the limitations. Large multi-ethnic clinical trials and cost-effectiveness analyses are needed not only to build effective prediction models but also to validate their clinical use.

Keywords: gestational diabetes; biomarkers; early prediction; pregnancy complications

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1. Introduction

Gestational diabetes mellitus (GDM) is defined as a condition in which carbohydrate intolerance develops during pregnancy [1]. GDM complicates between 5 and 12% of pregnancies, with prevalence varying significantly by region, race, and diagnostic criteria [2].

GDM is associated with maternal, fetal, and neonatal complications [3,4], as well as with a significant risk to develop type 2 diabetes mellitus (T2DM) and cardiovascular complications in the future for both the mother and her offspring [5,6].

Despite decades of research, the ideal screening and diagnostic criteria to diagnose and treat GDM have not been established and are still under debate [7,8]. Currently, the gold standard for diagnosing GDM is the oral glucose tolerance test (OGTT), which involves fasting, is time-consuming and exacting for both patients and physicians, and produces poor reproducibility [9]. Furthermore, universal screening occurs between 24 to 28 weeks of gestation, leaving little time for intervention and treatment once GDM is diagnosed.

Therefore, in recent years, significant research was undertaken to develop a simple, rapid, non-fasting blood test that could identify women with GDM. Identifying such a first-trimester biomarker that predicts GDM in pregnancy will enable not only the nullification for the need for universal screening in all pregnant women but also the possibility of early intervention to improve pregnancy and long-term outcomes.

The purpose of this review is to discuss the importance of early GDM prediction, to summarize current data on first-trimester biomarkers which have been evaluated in recent years as potential predictors of GDM, and to illustrate future directions and research.

2. Pathophysiology of GDM

The pathogenesis of GDM is multifactorial and complex. During pregnancy, insulin sensitivity decreases by up to 70% in the third trimester, with placental hormones significantly contributing to this process [10]. GDM develops when a relative pancreatic β -cell dysfunction leads to insufficient maternal insulin levels to sustain increasing demands. The exact cause for this β -cell dysfunction is unclear, with described mechanisms include inflammatory pathways, genetic abnormalities, hormone-mediated and autoimmune disorders [11].

GDM predisposes both the mother and baby to a wide variety of complications during pregnancy but also in the postpartum period and later in life. During pregnancy, women with GDM are at a higher risk for hypertensive disorders of pregnancy [12]. Regarding labor and delivery, GDM is associated with significantly higher rates of induction of labor, operative delivery, obstetric anal sphincter injury, and cesarean section [13,14]. Later in life, up to 70% of women with GDM will develop T2DM within 25 years after pregnancy, with higher rates of metabolic syndrome and cardiovascular disease [6,15,16].

The fetus of the mother with GDM has an increased risk for macrosomia, shoulder dystocia, and birth trauma [17]. In the postpartum period, the neonate is at risk for neonatal hypoglycemia and hyperbilirubinemia [18,19]. Studies have demonstrated that exposure to maternal diabetes in utero affects fetal programming and is associated with significant morbidities later in life, including childhood and adult-onset obesity and diabetes, as well as cardiovascular complications [5,20].

3. Importance of GDM Prediction

The Hyperglycemia Adverse Pregnancy Outcomes (HAPO) study demonstrated that the relationship between adverse outcomes and maternal glucose levels is a continuum and therefore already exists even below the threshold that is considered diagnostic for GDM [19]. Similarly, recent data suggest that a 3-h OGTT with only one pathological value is associated to risks comparable to those of women with two or more pathological values on OGTT, thus regarded as GDM [21,22]. Multiple studies have shown that proper diagnosis and intervention of GDM with lifestyle modifications (dietary and physical activity) or pharmacological treatment can significantly reduce the frequency of adverse pregnancy outcomes [23,24]. Therefore, early prediction of GDM has the potential to detect and treat women earlier in pregnancy, limit the fetal and maternal exposure to impaired glucose metabolism, decrease pregnancy complications, and perhaps affect fetal programming, thereby reducing the prevalence of T2DM for both the mother and offspring [25].

4. Predicting GDM by Maternal Risk Factors

Clinical and historic risk factors can be used individually or in combination to identify women with an increased risk of developing GDM (Table 1).

Table 1. Clinical risk factors with corresponding odds ratios for gestational diabetes mellitus.

Risk Factor	Odds Ratio
1. Ethnicity: Asian, Middle Eastern, Hispanic, Latino, African American, and Indigenous	2.32 [26]
2. Maternal age ≥ 35 years	3.54 [27]
3. Pre-pregnancy BMI >25 kg/m ²	2.14 [28]
4. Polycystic ovary syndrome	2.32 [29]
5. GDM in a previous pregnancy	5.9 [26]
6. Previous delivery of macrosomic baby (birth weight >4000 gr or >90 th centile)	1.54 [26]
7. Family history of diabetes (1st degree relative)	1.36 [26]
8. Multiple pregnancy	1.13 [30]
9. Assisted reproductive technology	1.26 [31]

BMI—body mass index and GDM—gestational diabetes mellitus.

These include, among others, advanced maternal age, increased body mass index (BMI), ethnicity, family history of diabetes, and history of GDM or macrosomia in a previous pregnancy [26–31]. However, while some studies showed that a combination of maternal risk factors can allow for successful early screening [32,33], others have demonstrated minimal efficacy [34,35] and are limited by variation between ethnic groups in the association of different risk factors (e.g., BMI), alongside a lack of significant external validation in clinical practice. More importantly, these models are targeted mostly to identify women who have some degree of glucose intolerance that preceded pregnancy rather than predicting the development of GDM later in pregnancy.

5. Predicting GDM Using Individual Biomarkers

Due to the increased prevalence of GDM and the poor reproducibility of the OGTT, extensive research in recent years attempted to identify biomarkers that could aid in GDM prediction. In fact, a recent review found 589 different biomarkers evaluated for association with GDM [36]. Tested biomarkers include glycemic-related markers, adipokines, growth factors, pregnancy-related proteins, inflammatory markers, different hormones, coagulation factors, nucleic acids, glycoproteins, complement components, and many others (Figure 1).

Figure 1. Overview of tested biomarkers. CRP—C-reactive protein; IL-6—interleukin 6; PAPP-A—pregnancy-associated plasma protein A; PLGF—placental growth factor; SHBG—sex hormone-binding globulin; and TNF- α —tumor necrosis factor α .

In this review, we chose to focus on the main biomarkers that were evaluated as GDM predictors (Table 2).

Table 2. Potential biomarkers for gestational diabetes mellitus.

Biomarker	Function	Suggested Involvement in GDM Pathophysiology
Adiponectin	Modulation of glucose and fatty acid metabolism. Involvement in inflammation, apoptosis, and angiogenesis.	Low levels associated with decreased insulin sensitivity and GDM
Leptin	Regulation of energy balance and expenditure. Role in hormone regulation and immunity.	High leptin levels cause hyperinsulinemia and increase insulin resistance
PAPP-A	Increase bioavailability of IGF-1 and promotes somatic growth. Involvement in wound healing and bone remodeling.	Decreased levels contribute to an increase in insulin resistance
PLGF	Vascular endothelial growth factor-like protein. Role in angiogenesis and placentation.	High PLGF levels promote the abnormal vascular network in placentas of GDM pregnancies
TNF- α	Inflammatory cytokine involved in the regulation of immune cells, inflammation, and autoimmune diseases.	Increased levels impair insulin signaling and beta-cell function, leading to insulin resistance and GDM
CRP	Acute-phase reactant. Role in tissue injury, inflammation, and infection.	High levels associated with insulin resistance and systemic inflammation
IL-6	Circulating inflammatory cytokine. Role in immune response regulation, inflammation, and hematopoiesis.	Increased secretion by adipocytes and placental cells, leading to a chronic inflammatory process and insulin resistance
SHBG	Glycoprotein that binds androgen and estrogen.	Decrease SHBG levels associated with hyperinsulinemia and GDM

GDM—gestational diabetes mellitus; PAPP-A—pregnancy-associated plasma protein A; IGF-1—insulin growth factor 1; PLGF—placental growth factor; TNF- α —tumor necrosis factor α ; CRP—C—reactive protein; IL-6—interleukin 6; and SHBG—sex hormone-binding globulin.

The “ideal GDM marker” would be simple to obtain, fast, inexpensive, and, most importantly, clinically useful, with a high positive predictive value. The optimal biomarker will predict GDM development before it occurs and therefore will allow for early intervention and improved outcomes for the short and long term, thus making it cost-effective.

6. Predicting GDM by Early Glycemic Markers

Overt diabetes can be diagnosed in the first trimester by using one of several glycemic measures: fasting glucose ≥ 126 mg/dL, post-load glucose ≥ 200 mg/dL, or hemoglobin A1c (HbA1c) $\geq 6.5\%$, and is then considered as pregestational diabetes [37,38]. A number of studies have tried to assess whether these glycemic markers can be used in the first trimester to predict the risk for GDM development later in pregnancy.

6.1. Fasting Glucose

In 2010, the International Association of Diabetes and Pregnancy Study Group recommended different thresholds for diagnosis and classification of hyperglycemia in pregnancy based on the results of the HAPO study [39]. The panel recommended the use of first-trimester fasting glucose above 92 mg/dL to diagnose early GDM; however, this approach was criticized due to a lack of evidence [38,40]. Although not established as a diagnostic marker, several studies have demonstrated an association between first-trimester fasting glucose and GDM development in late pregnancy. Mashiah et al. showed strong, graded associations between fasting glucose levels in the first trimester and GDM development, macrosomia, and cesarean section [41]. Other studies have shown that elevated first-trimester fasting glucose levels have sensitivities of 47–75% and specificities of 52–77% for the prediction of GDM later in pregnancy [42,43], making the predictive value of fasting glucose similar to the risk factor of BMI [42]. Nevertheless, a definitive clinically useful cut-off for first-trimester fasting glucose has not been established and results show an insufficient predictive value for this marker.

6.2. HbA1c

HbA1c is used to estimate average blood glucose over the lifespan of a red blood cell (~120 days). HbA1c does not require fasting and is used in non-pregnant populations to

diagnose and monitor both pre-diabetes and diabetes [44]. Several studies demonstrated that a first-trimester HbA1c in the pre-diabetic values (5.7–6.4%) is correlated with GDM manifestation in late pregnancy and associated with adverse pregnancy outcomes [45–47]. Although a significant risk factor for GDM, the low sensitivity of HbA1c in this range makes it a poor test to identify women who will develop GDM [46]. HbA1c levels are also subjected to pregnancy changes and possibly require pregnancy-specific reference ranges [48]. Finally, Osmundson et al. conducted a randomized control trial which showed that treatment of women with early (before 14 weeks' gestation) pre-diabetic HbA1c (5.7–6.4%) did not reduce the risk of GDM later in pregnancy, except in non-obese women [49]. In summary, current evidence does not support the use of HbA1c as an effective early predictor for GDM.

7. Predicting GDM by Adipokines

Adipokines are cytokines that are produced by the adipose tissue and play a fundamental role in the development of metabolic morbidities, including diabetes. As such, a number of them were evaluated as biomarkers for GDM prediction [50,51]. Mainly, adiponectin and leptin were investigated, with evidence showing altered levels in GDM pregnancies. Others, including resistin [52], visfatin [53], and retinol-binding protein 4 [54], were inconsistently associated with GDM.

7.1. Adiponectin

Adiponectin is a protein secreted primarily by the adipose tissue but also by the brain, skeletal muscle, and placenta [55]. Adiponectin augments insulin sensitivity and low levels of adiponectin are associated with obesity, T2DM, hypertension, and coronary artery disease [56,57]. In normal pregnancy, maternal adiponectin secretion progressively declines probably due to decreased insulin sensitivity [58].

Previous studies have demonstrated that low levels of adiponectin in the first trimester are associated with GDM development later in pregnancy [53,59,60]. A meta-analysis by Iliodromiti et al. suggested that early pregnancy adiponectin levels have a moderate predictive value for GDM, similar to that of clinical risk factors [61]. In summary, adiponectin may play a role in the pathophysiology of GDM and has the potential for a promising predictive biomarker. Further research is needed to further establish the true value of adiponectin in GDM prediction.

7.2. Leptin

Leptin regulates energy intake, suppresses appetite, and enhances the insulin effect with both central and peripheral effects [62]. Leptin is also expressed by placental cells and levels increase up to three-folds in pregnancy likely due to placental secretion and an increase in fat tissue; however, its exact role in pregnancy remains unclear [63,64]. Evidence regarding the association between leptin levels and GDM is inconsistent, with some studies demonstrating higher leptin levels in women who subsequently develop GDM [50,65], whereas others showed no difference [66,67]. Future prospective studies are required to determine leptin predictive ability in GDM while adequately addressing the confounding influence of BMI and gestational weight gain on leptin levels in pregnancy.

8. Predicting GDM by Pregnancy-Related Proteins

8.1. Pregnancy-Associated Plasma Protein A (PAPP-A)

PAPP-A is a metalloproteinase that increases the bioavailability of insulin-like growth factor 1 (IGF-1) by its cleavage from IGF binding protein-4 [68]. In pregnancy, PAPP-A is secreted by trophoblast cells and used as a first-trimester screening test for aneuploidy, as well as a predictor of placental disorders such as preeclampsia and fetal growth restriction [69]. It has been hypothesized that PAPP-A has a role in regulating glucose levels in pregnancy, with low levels associated with insulin resistance and GDM.

Nonetheless, previous studies have yielded conflicting results. A number of studies reported low first-trimester PAPP-A levels in women who eventually developed GDM [70–73]. Additionally, a large systematic review and meta-analysis by Donovan et al. concluded that women who are diagnosed with GDM have lower first-trimester levels of PAPP-A, even though a high degree of between-study heterogeneity was noted [74]. Other studies failed to demonstrate differences in PAPP-A levels in pregnancies with GDM compared to normal pregnancies [75,76] and Syngelaki et al. showed that the performance of screening for GDM by maternal factors was not improved by the addition of PAPP-A [77]. Future prospective studies are required to establish the clinical utility of this biomarker.

8.2. Placental Growth Factor (PLGF)

PLGF is an angiogenic protein highly expressed in the placenta [78]. PLGF is widely used in aneuploidy screening in the first trimester, with low levels associated with placental-mediated disorders, mainly preeclampsia and fetal growth restriction [79].

Several studies have shown that elevated PLGF levels in early pregnancy are associated with GDM development [80,81]. However, other studies have demonstrated no differences in PLGF levels between women who developed GDM and controls [82,83]. Additionally, a large prospective cohort study from the UK showed that even though early PLGF levels were higher in women with GDM, the addition of PLGF to a prediction model that includes maternal factors did not improve the predictive ability [77]. Therefore, current evidence does not support the use of PLGF as an effective biomarker for GDM.

8.3. First-Trimester Combined Test (FTCT)

The FTCT is an effective screening tool for fetal aneuploidy, which includes the combination of maternal age, ultrasound measurement of fetal nuchal translucency, and the serum markers-free β -human chorionic gonadotropin and PAPP-A. As an early, routinely implemented test, which includes pregnancy-related proteins, the FTCT has the potential to be used as a tool for the prediction of GDM. Visconti et al. showed that an FTCT result of $<1:10,000$ was significantly associated with GDM development later in pregnancy, but with low accuracy [84], and other studies failed to demonstrate this association [76,85]. Based on current evidence, it is unclear whether the use of low PAPP-A solely (in absolute levels or in multiples of the median) contributes to GDM prediction better than the entire FTCT.

9. Predicting GDM by Inflammatory Markers

9.1. Tumor Necrosis Factor- α (TNF- α)

TNF- α is an inflammatory cytokine that is produced by placental cells and has been suggested as a mediator for insulin resistance in pregnancy [86]. While some studies showed an association between elevated levels of TNF- α in the first trimester and GDM development later in pregnancy [87,88], others failed to demonstrate this effect [67,89]. Furthermore, adding TNF- α to a screening model did not improve the prediction of GDM over maternal clinical characteristics [90]. In summary, even though TNF- α probably has a role in the pathogenesis of insulin resistance and GDM, the actual predictive value of this biomarker is yet to be established.

9.2. C-Reactive Protein (CRP)

CRP is an acute-phase protein secreted and released in response to tissue injury, inflammation, and infection [91]. Evidence regarding the association between levels of CRP or high-sensitivity CRP and GDM is inconsistent, with multiple studies showing high first-trimester levels in women who eventually develop GDM [92–95] and some studies not [90,96]. A possible confounder is the fact that CRP levels in pregnancy correlate with BMI and a prospective study by Wolf et al. concluded that the association between increased CRP and GDM was attenuated when BMI was included in the model [97]; the same effect was reported by others as well [98,99]. A recent systematic review by Amirian et al.

discussed conflicting evidence and concluded that more studies are needed for CRP to be used as an indicator for GDM [100].

9.3. Interleukin 6 (IL-6)

IL-6 is a circulating inflammatory cytokine secreted by adipocytes as well as by macrophages, endothelial cells, pancreatic cells, and placenta cells [101]. IL-6 is involved in the regulation of immune response regulation, inflammation, and hematopoiesis [102], but also has a significant role in obesity and insulin resistance [103]. A systematic review and meta-analysis by Wang et al. concluded that IL-6 is a strong predictor of developing T2DM [104].

Previous studies showed an association between high levels of IL-6 and GDM [105–107]; however, these studies were limited by the gestational age at which IL-6 levels were measured, the population assessed, and by controlling for confounders such as BMI. Other studies failed to demonstrate a difference in IL-6 levels between GDM and normal pregnancies [108,109]. Nevertheless, a study by Hassiakos et al. showed that first-trimester IL-6 levels were a significant predictor of GDM development later in pregnancy and adding IL-6 to a prediction model that included maternal characteristics yielded an improved prediction [110]. A systematic review by Amirian et al. concluded that IL-6 levels are significantly higher in pregnant women with GDM than in healthy pregnant women and therefore the evaluation of this marker as a GDM predictor can be investigated [111]. In summary, although IL-6 has the potential to be a good biomarker for GDM in the future as demonstrated in T2DM, current evidence does not support it as such. Larger prospective studies are needed to assess IL-6 function in GDM as well as to adjust for obesity as a confounder and to obtain serial IL-6 measurements for the identification of trimester-specific ranges.

10. Predicting GDM by Insulin Resistance Markers

Several studies have suggested that GDM is associated with an increase in insulin resistance [112,113] and therefore markers of insulin resistance were evaluated as potential biomarkers for GDM. Evaluation of first-trimester fasting insulin and the corresponding Homeostatic Model Assessment of Insulin Resistance as GDM predictors yielded limited predictive values [114,115] and still require fasting. Sex hormone-binding globulin (SHBG) showed better results as a possible GDM predictor.

SHBG

SHBG is a glycoprotein produced mainly by the liver, binds androgen and estrogen, and has an inverse relationship with insulin levels [116]. Low levels of SHBG prior to pregnancy [117,118] and in the first trimester [92,119,120] were found to be correlated with GDM development later in pregnancy. Nanda et al. showed that adding SHBG to a clinical risk prediction model improved its accuracy [121]. However, in other studies this association was not found [122] or was no longer significant after adjusting for BMI, ethnicity, and family history [96]. Hence, even though SHBG is a very promising marker for early diagnosis of GDM, with even pre-pregnancy predictability, further studies are required to establish its role.

11. Early Prediction to Improve Maternal, Placental and Fetal Dialog

GDM is regarded as one of the “great obstetrical syndromes”. The underlying concept hypothesizes that GDM has many underlying etiologies that adversely interact with the maternal–fetal unit and initiate subclinical pathology, which progresses to clinical manifestation that also results in fetal involvement [123].

According to this hypothesis, the placenta has a crucial role in the development of GDM and in mediating the metabolic effect on the fetus with a direct effect on pregnancy outcomes. Thus, for example, the placenta acts as a buffer of glucose levels for the fetus. Placental dysfunction will lead to over or under-transfer of glucose to the fetus. Moreover,

the disruption of normal placental development is most profound if it occurs early in gestation, such as in pregestational diabetes. Considering early disruption of the placenta occurs at a time of structural evolution and vasculature development, major placental dysfunction leading to hypertensive disorders and abnormal fetal growth may ensue. Indeed, studies reveal that maternal diabetes is associated with histological changes in the placenta. Madazli et al. compared the histology of 22 placentas from women with well-controlled GDM to 22 placentas from non-diabetic women that served as a control and found a six-fold increase in villous immaturity and chorangiosis, as well as a three-fold increase in ischemic changes in the placentas of women diagnosed with GDM [124].

While pregestational diabetes is associated with marked structural changes in the placenta, subtle functional changes are more prevalent with later-onset GDM [125,126]. Although subtle, these changes are associated with increased intervillous diffuse distance, and may predispose the fetus to acute and chronic changes in gas as well as in other nutrients' exchange [125,126], thus making the fetus more vulnerable and turning the placenta from being protective to a potential source of adverse fetal outcome. Whether tight control of glucose levels abolishes the placental changes and pregnancy adverse outcomes is controversial. Jones et al. observed various degrees of changes in the syncytiotrophoblast, cytotrophoblast, trophoblastic basement membrane, and fetal vessels in diabetic women regardless of diabetic severity [127]. Moreover, Daskalakis et al. reported on an evaluation of a large number of placentas by a pathologist who was blinded to maternal glycemic status. The authors showed that GDM was associated with villous immaturity, chorangiosis, villous fibrinoid necrosis, and nucleated red blood cells regardless of maternal glycemic status [125].

First-trimester GDM biomarkers that originate in the placental tissue, such as PAPP-A and TNF- α , support the hypothesis that the impaired placenta is an early mediator to adverse fetal outcomes. The prediction of abnormal glucose maternal–fetal metabolism at early pregnancy and quick intervention may prevent placental remodeling and ensure the protective nature of the placenta.

12. Future Directions

As individual first-trimester markers showed a modest predictive value for GDM, early pregnancy screening models combining biomarkers with demographic and clinical risk factors were evaluated [32,90,110,121,128,129]. Current evidence demonstrates minimal improvement of GDM prediction in combining models compared to prediction based on maternal risk factors and therefore the search for the optimal model is still ongoing.

In recent years, significant progress has been made in the field of metabolomics, which is the study of small-molecule metabolites in cells, tissues, and organisms. Metabolomic studies using mass spectrometry and nuclear magnetic resonance spectroscopy have already identified small-molecule metabolic products of lipids, carbohydrates, and amino acid metabolites, with suggested possible mechanisms in T2DM [130,131]. Using the same methods, metabolomics is a promising approach for investigating the metabolic pathways associated with the pathogenesis of GDM, as well as for detecting biomarkers of GDM, and future studies will assess their predictive value [132].

Epigenetic modifications—chromosomal changes that do not involve alterations in the DNA sequence—may have a role in GDM pathogenesis [133,134]. Animal models have demonstrated that maternal exposure to high-fat diets is associated with increased fetal epigenetic modifications associated with metabolic dysregulation [135,136]. More recent data in humans showed an association between maternal GDM and changes in DNA methylation of the offspring, measured in blood samples from the umbilical cord, the placenta, or peripheral blood [134,137–139]. Future research will focus on whether epigenetic changes, especially DNA methylation, occur before GDM development and if epigenetic signatures can be used as predictive markers of GDM [140].

13. Conclusions

Currently, GDM is usually diagnosed during the third trimester when unfavorable metabolic conditions might have already affected the fetus. Multiple biomarkers have been assessed as potential first-trimester predictors of GDM, including glycemic markers, adipokines, pregnancy-related proteins, inflammatory markers, and others. Most studies evaluating these markers were small retrospective studies that yielded limited results. As the prevalence of GDM continues to rise correspondingly with obesity rates worldwide, the need for an effective predictive biomarker for GDM is increasing. In order to translate current findings to a pragmatic clinical practice, future studies must not only find biomarkers predictive for GDM but must also assess their reproducibility in large multi-ethnic clinical trials and cost-effectiveness analyses. The identification and validation of such novel biomarkers has the potential to significantly improve the diagnosis and outcomes of GDM for mothers, newborns, and society as a whole.

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