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EARLY PREDICTION AND EMERGING BIOMARKERS OF GESTATIONAL DIABETES MELITUS: A REVIEW

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ABSTRACT

Gestational Diabetes Mellitus (GDM) is a metabolic disorder occurring during pregnancy, often associated with various complications for the mother and the baby. Complications of GDM include pre-eclampsia, foetal macrosomia, neonatal hypoglycemia, and the risk of developing type 2 diabetes. Conventional screening for GDM, i.e., the oral glucose tolerance test performed between 24 and 28 weeks of gestation, detects GDM relatively late. However, the recent studies have emphasised the search for new biomarkers for the early detection of GDM. Such markers would enable the application of preventive measures for the complications of GDM.
The metabolic and hormonal biomarkers of GDM include fasting glucose, fasting insulin, lipid profile, leptin, and adiponectin, which reflect the changes occurring in the early stages of GDM. Inflammatory and placental biomarkers, i.e., C-reactive protein (CRP), interleukins (IL-6), Tumor necrosis factor-alpha (TNF-alpha), placental growth factor, and human placental lactogen, can provide a better insight into the condition. Genetic and molecular biomarkers, i.e., genetic polymorphisms of the TCF7L2, MTNR1B, and KCNQ1 genes, and microRNAs, would identify the women at increased risk of GDM. The use of multiple markers may improve the accuracy of early predictions and enable more effective personalised interventions, such as lifestyle changes, dietary advice, and glucose monitoring. Further studies are necessary to validate such findings in a diverse group of people and to utilise advanced technology in this field. The early identification of high-risk pregnancies using markers is a promising approach to improve outcomes in mothers and newborns.

Conclusion

Foramen magnum morphometry serves as a useful supplementary method for determining an individual's sex; however, it is not particularly effective for estimating their age in adulthood. To enhance its utility across diverse populations, standardized measurement protocols and validation are required for each group.

1.Introduction

Gestational Diabetes Mellitus is a metabolic disorder that is defined as the presence of glucose intolerance that is first detected during pregnancy(1). It is one of the most common complications that pregnant women face. Recently, the incidence of this condition has been rising significantly(2). This condition is currently one of the major concerns faced by pregnant women. Therefore, it is crucial to manage this condition effectively.

GDM, or gestational diabetes mellitus, is caused mainly due to the insulin resistance that is observed during pregnancy. During pregnancy, the placenta secretes hormones that include human placental lactogen, oestrogen, and progesterone(3). These hormones induce insulin resistance. In the presence of insulin resistance, the level of insulin that is secreted from the pancreatic beta cells is not sufficient to maintain the blood glucose levels at the required level. As a result, hyperglycaemia is observed, which leads to the onset of GDM(4). Screening is conducted between the 24th and 28th weeks of pregnancy. In this condition, the level of glucose tolerance is tested. However, this screening may not be conducted early. Therefore, the identification of biomarkers that may be used to predict the condition is one of the recent concerns(5).

2. Pathophysiology of Gestational Diabetes Mellitus

The pathophysiology of GDM is multifactorial in nature, and it involves the complicated interaction between hormonal, metabolic, and genetic abnormalities. During pregnancy, insulin resistance in maternal tissues is an essential adaptation to ensure glucose availability for the developing foetus(6). This insulin resistance is mainly mediated by placental hormones, such as human placental lactogen, progesterone, oestrogen, and cortisol, which counteract insulin action in peripheral tissues, such as muscle and fat(7).

Normally, the compensatory action of pancreatic β-cells overcomes insulin resistance by increasing insulin secretion, thus maintaining normoglycemia(8). However, in women with GDM, the compensatory action of pancreatic β-cells is impaired due to β-cell dysfunction and β-cell mass, leading to hyperglycemia in the mother, which not only affects the mother but also influences foetal outcome. Hyperglycemia in the mother is also associated with low-grade inflammatory responses, oxidative stress, and abnormal levels of adipokines, such as decreased levels of adiponectin and increased levels of leptin(9). Genetic predisposition is also one of the factors that play an important role in the pathogenesis of GDM. Genetic variants in genes that regulate insulin secretion and glucose metabolism, such as TCF7L2, MTNR1B, and KCNQ1, are associated with the pathogenesis of GDM(10).

3.Limitations of Current Screening Methods

In the present context, screening for Gestational Diabetes Mellitus (GDM) is conducted between 24 and 28 weeks of gestation by means of an oral glucose tolerance test (OGTT)(11). Although OGTT has been established to be the gold standard for diagnosing gestational diabetes, it has several limitations that affect its efficiency. Firstly, the OGTT for diagnosing gestational diabetes is conducted relatively late in pregnancy, which may allow the effects of hyperglycaemia to affect foetal development(12).

In addition to this, OGTT has several limitations in terms of its convenience, as it requires blood to be taken several times over a period of 2 to 3 hours. It has also been observed that the reproducibility of OGTT results may vary depending upon factors like diet, exercise, and stress levels, which can lead to inconsistent diagnoses of gestational diabetes and complicate the management of the condition(13). There has also been much debate about the criteria to be followed in diagnosing gestational diabetes, as the criteria proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG), the American Diabetes Association (ADA), and the World Health Organization (WHO) differ(14). Therefore, it has become necessary to establish early, reliable, and non-invasive methods to predict gestational diabetes mellitus, which can prevent the development of metabolic disturbances(15).

4.Metabolic and Hormonal Biomarkers for Early Prediction

Early diagnosis of gestational diabetes mellitus (GDM) plays a critical role in reducing complications for both mother and foetus. Various biomarkers, both metabolic and hormonal, have been proposed to be effective for assessing the risk of GDM(16). Various metabolic biomarkers, such as fasting glucose, fasting insulin, and lipid profile, are known to be effective for assessing the risk of GDM. An elevated fasting insulin level and high HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) values are known to be associated with an increased risk of GDM. Dyslipidaemia, such as elevated triglycerides and cholesterol levels, can be considered an early biomarker for GDM(17).

The use of hormonal biomarkers, such as adipokines, has been proposed to be effective for assessing the risk of GDM. Hormones such as leptin, which are responsible for insulin resistance, are known to be elevated in early pregnancy in pregnant women with GDM(18). Conversely, hormones such as adiponectin, which are responsible for insulin sensitivity, are known to be reduced. Other hormones such as resistin, ghrelin, and human placental lactogen are known to be involved in glucose and lipid metabolism(19). The combination of metabolic and hormonal biomarkers could be advantageous in the prediction of early GDM. The inclusion of these biomarkers in clinical practice could prevent pregnancy complications and improve the outcome for both the mother and the child(20).

5. Inflammatory and Placental Biomarkers

Inflammation and placental function have emerged as key players in the pathogenesis of Gestational Diabetes Mellitus (GDM). Several inflammatory and placental function biomarkers have also been studied for early prediction of GDM. Chronic inflammation is often seen in women who develop GDM(21). Elevated C-reactive protein, interleukin-6, and tumour necrosis factor-alpha in early pregnancy have also been linked with insulin resistance and an increased risk of developing GDM(22).

The placenta plays an important role in the pathogenesis of GDM by secreting various hormones that affect maternal carbohydrate metabolism, such as human placental lactogen and placental growth factor, which can influence insulin sensitivity and glucose regulation(23). Various placental function biomarkers, such as placental growth factor, soluble fms-like tyrosine kinase-1 (sFlt-1), and human placental lactogen (hPL), have also been studied as early predictive biomarkers for GDM. An abnormal level of these biomarkers may lead to early placental dysfunction, resulting in hyperglycaemia(24). The use of inflammatory and placental function biomarkers, along with various metabolic and hormonal biomarkers, may improve the accuracy of early GDM predictions. This may help in reducing the risk of adverse pregnancy outcomes(25).

6.Genetic and Molecular Biomarkers

Genetic and molecular factors are found to play an important role in the development of Gestational Diabetes Mellitus (GDM), and recent studies have been conducted to identify genetic markers that could be used to predict GDM in early stages of pregnancy. Genetic variants in the TCF7L2, MTNR1B, and KCNQ1 genes are among the genetic factors associated with impaired insulin secretion and glucose metabolism(26).

Apart from genetic factors, epigenetic changes, such as DNA methylation and histone acetylation, are also found to play an important role in the pathogenesis of GDM. Epigenetic changes are found to regulate gene expression in pancreatic β-cells and peripheral tissues, leading to insulin secretion and insulin resistance without any changes in the underlying DNA sequence(27). Molecular markers, such as microRNAs, are also found to play an important role in predicting GDM in early stages of pregnancy. MicroRNAs, also known as circulating microRNAs, are found in the plasma of pregnant women in early stages of pregnancy and are associated with the development of GDM(28).

The integration of genetic and molecular biomarkers with metabolic and hormonal markers may improve early risk stratification for personalised interventions(29). The early identification of high-risk pregnant women with these biomarkers has the potential to improve pregnancy outcomes by reducing adverse maternal and foetal complications(30).

7. Clinical Applications, Challenges, and Future Perspectives

The identification of early biomarkers for Gestational Diabetes Mellitus (GDM) has significant clinical implications. This finding would enable clinicians to identify women at risk of GDM as early as the first trimester of their pregnancy(31). This step would, in turn, enable clinicians to institute timely interventions, thereby reducing the risk of complications, such as macrosomia, pre-eclampsia, and neonatal hypoglycemia, associated with GDM. However, several challenges face the use of these biomarkers. Firstly, several of these biomarkers have yet to be validated, and the differences in laboratory procedures and cut-off values for them reduce their reproducibility(32). Another challenge in using these biomarkers for the early identification of GDM is their associated cost and accessibility, particularly for women living in disadvantaged settings. However, the use of multiple biomarkers for the early identification of GDM is a complex process, as it requires careful consideration of the validation status, laboratory variability, and the economic and logistical barriers faced by women in disadvantaged settings(33).

Future research should aim to conduct prospective multicentre studies to further validate predictive biomarkers and create reliable early screening panels. The integration of traditional markers with new technologies, such as the application of 'omics techniques and machine learning algorithms, may further increase the accuracy of prediction(34). These techniques have the potential to revolutionise the management of GDM, reduce the risks associated with complications, and improve the metabolic health of both the mother and the child(35).

Table 1: Hematological Biomarkers Associated with Gestational Diabetes Mellitus

Hematological Marker	Category / Function	Sample Type	Gestational Timing	Clinical Significance	References
Hemoglobin (Hb)	Oxygen-carrying capacity	Blood	1st trimester	Elevated Hb may indicate increased risk of GDM; related to oxidative stress	(36)
Hematocrit (Hct)	Blood viscosity	Blood	1st trimester	Higher Hct linked to insulin resistance	(37)
White blood cell count (WBC)	Inflammatory marker	Blood	1st trimester	Elevated WBC indicates low-grade inflammation associated with GDM	(38)
Neutrophil / Lymphocyte ratio (NLR)	Inflammation / immune balance	Blood	1st trimester	Higher NLR observed in women who develop GDM	(39)
Platelet count (PLT)	Coagulation / inflammation	Blood	1st trimester	Altered PLT counts may reflect inflammatory changes	(40)
Mean platelet volume (MPV)	Platelet activation	Blood	1st trimester	Increased MPV linked to GDM and endothelial dysfunction	(41)
Red cell distribution width (RDW)	Erythrocyte size variability	Blood	1st trimester	Elevated RDW associated with insulin resistance and GDM	(42)

DISCUSSION

Early prediction of Gestational Diabetes Mellitus (GDM) with the help of biomarkers has become a significant area of research, as the conventional screening tests often reveal the condition at the end of pregnancy(43). Metabolic and hormonal markers, including fasting blood glucose, insulin, lipid levels, leptin, and adiponectin, indicate early metabolic changes and insulin resistance. These biomarkers have shown promise, as they offer early insights into the condition of women at risk. Inflammatory markers, including CRP, IL-6, and TNF-α, indicate the role of inflammation in insulin resistance. Placental biomarkers, including placental growth factor and human placental lactogen, point towards the role of the placenta in the pathophysiology of GDM(44).

Genetic and molecular biomarkers, including genetic variants of the TCF7L2, MTNR1B, and KCNQ1 genes, and circulating miRNAs, have shown promise as they identify the inherent predisposition to the condition(45). These biomarkers may be used along with metabolic and hormonal markers to provide a more comprehensive understanding of GDM and enhance diagnostic accuracy(46). However, the field is still challenged with the lack of standardisation of biomarkers, validation of markers, and their availability. Further research is required to combine the use of biomarkers with machine learning techniques and omics approaches to improve the predictive power of the markers(47).

CONCLUSION

Gestational Diabetes Mellitus (GDM) still poses a serious problem in the health care of mothers and babies, as the condition is becoming more prevalent and complications are arising. Moreover, current screening practices, usually done in the second trimester, often reveal the condition when the symptoms have already begun. Current research, on the other hand, suggests that various metabolic, hormonal, inflammatory, placental, genetic, and molecular biomarkers may have predictive value for GDM.

The inclusion of these biomarkers in the management of pregnant women may help in the early intervention of the condition, including diet, lifestyle, and management strategies. However, there are still challenges, including the validation, cost, and lack of standardisation of these biomarkers. Future research, including the use of these biomarkers in large populations, along with the use of technology such as omics and machine learning, may improve the predictive accuracy of the condition. Using biomarkers to identify high-risk pregnant women early may improve maternal and foetal health and reduce the risk of future metabolic complications for both the mother and the baby.

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