REVIEW

Progress in Research on Biomarkers of Gestational Diabetes Mellitus and Preeclampsia

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Abstract: Gestational diabetes mellitus (GDM) and preeclampsia (PE) are common complications in pregnancy, with incidence rates of 1–5% and 9.4%, respectively, in China. Both these phenomena can cause adverse pregnancy outcomes and are extremely harmful to the mother and fetus. In this study, we observed that several predictive factors have important value in GDM and PE. Among the GDM group, abnormal levels of adiponectin (APN), C-reactive protein (CRP), and Leptin were observed. The coexistence of PE and GDM in the pregnant population is not uncommon. Ultimately, we discovered abnormal levels of factors such as Visfatin, Advanced oxidative protein product (AOPP), Fibroblast growth factor 21 (FGF21), and resistin in both GDM and PE groups. Particularly, the FGF21 factor holds significant importance in our research. Therefore, we need to complete the analysis and discussion of relevant predictive factors to enable early prediction and disease monitoring of GDM, PE, and other pregnancy-related disorders, ultimately contributing to the long-term health of pregnant women.

Keywords: gestational diabetes mellitus, preeclampsia, predictor of the GDM and PE

Introduction

Hyperglycemia in pregnancy is categorized as diabetes combined with pregnancy (pregestational diabetes mellitus, PGDM), newly discovered overt diabetes, and gestational diabetes mellitus (GDM). GDM refers to a class of diseases in which carbohydrate intolerance is first discovered during second trimester or the third trimester of pregnancy.[1]

Due to the special clinical status and abnormal function of maternal glucose and lipid metabolism,[2] researched showed that during gestation, the effect of progesterone and glucocorticoids on insulin sensitivity have been suggested to be relative for the increase of insulin resistance.[3] Meanwhile, on the contrary of normal pregnancy, when β-cell secretion is no longer sufficient to compensate for insulin compensate, it will lead to carbohydrate intolerance.[4] Both insulin resistance and insulin insufficiency will lead to the increase of maternal glucose, amino acids and lipids, thus forming GDM (see Figure 1).

For the diagnostic criteria of GDM, though 2-stage oral glucose tolerance test (OGTT) can improve the detection efficiency.[5] Nowadays, whether recognizing single or 2-stage OGTT test as golden standard still cannot reach a consensus. When it comes to single stage OGTT, the criteria are abnormal values for all pregnant women whose PGDM or GDM is not diagnosed after 24 to 28 weeks of pregnancy. GDM can be the diagnosis when 5.1mmol/L≤fasting blood glucose<7mmol/L,1hour≥10.0mmol/L, or 8.5mmol/L≤2hours<11.1mmol/L, after ingesting sugar.

Recently, the improvement of living standards has led to increased incidence rates, which are 7.6% in the US and 14.8% in China.[6,7] GDM has effects on the fetus, including abortion, premature birth, macrosomia and fetal malformation, growth restriction, distress and death.

Preeclampsia (PE) is a hypertensive disease associated with pregnancy that mainly occurs after 20 weeks of gestation, with symptoms such as hypertension, edema, and proteinuria. It is one of the complications of GDM. At present, the pathogenesis and etiology of PE have not been clarified. It is considered as a multifactorial disease. These include
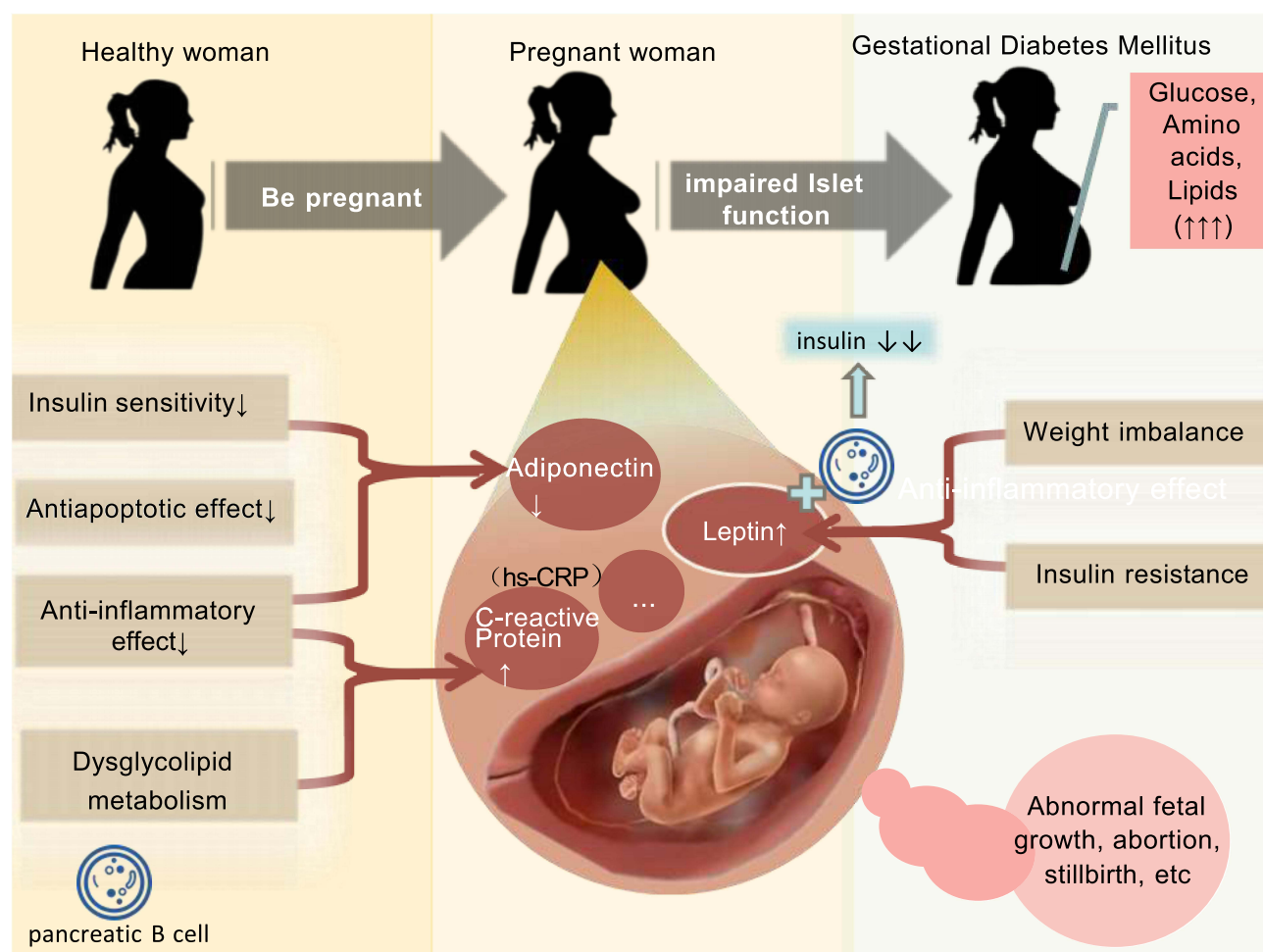
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Figure 1 Mechanisms of gestational diabetes mellitus.

abnormal uterine placental vascular structure, impaired extravillous trophoblast infiltration capacity, and increased vascular resistance, resulting in reduced blood flow to the placenta.[8] The excessive activation of inflammatory immunity results in the reduction of maternal immune tolerance to the embryo. At the same time, inflammatory mediators can lead to vascular endothelial injury, decrease the synthesis of vasodilating substances, promote vasospasm, and lead to the rise of blood pressure.[9] On the other hand, vascular endothelial cell injury activates platelets and coagulation factors, aggravating the hypercoagulation state of PE. In addition, PE has a familial predisposition, but the mode of inheritance is not clear.[10] Elevated blood pressure and proteinuria are the main diagnostic criteria of PE. Furthermore, the occurrence of abnormalities in the liver, kidney, and blood system laboratory indicators or symptoms before eclampsia, such as headache, dizziness, and upper abdominal pain can clarify the diagnosis of PE. The incidence of PE ranges from 2% to 8% worldwide.[11] PE is very harmful to the mother, in whom it can lead to cerebral edema, abnormal liver, kidney, and coagulation functions and massive bleeding, which can be life-threatening. The hazard of PE extends to the fetus, with the possibility of placental abruption, leading to fetal growth retardation and even death in the womb.

GDM and PE have similar risk factors and pathophysiological alterations, whereas GDM may be one of the risk factors for PE.[12] The incidence of PE has been shown to be higher in patients with GDM than in those without GDM.[13]

It is known that obesity is a risk factor of pregnancy complications. The study of Lewandowska showed that excessive pre-pregnancy maternal weight has important influence on the risk of pregnancy complications such as GDM and hypertension, which can cause adverse fetal outcomes.[14] Hillier's research also showed that first trimester GDM screening for pregnant people with obesity may improve GDM-associated outcomes.[15] Ke also found that maternal overweight was associated with adverse pregnancy outcomes in GDM.[16]

GDM with PE can aggravate the disease condition, whereas early detection, diagnosis, treatment can improve the prognosis and reduce treatment cost. The improvement of advances in medical technology has facilitated the discovery of an increasing number of predictors. So far, we have noticed biomarkers like adiponectin (APN), leptin, C-reactive protein (CRP), myokines, γ-glutamyltransferase (GGT), TNF-α, IL-6 and so on have strong relationship with GDM.[17,18] In this article, we will discuss the influence of APN, leptin and CRP on GDM (see Table 1).

Table 1 Predictors of Gestational Diabetes Mellitus (GDM), and Concurrent GDM with PE

	Predictive Factor	Introduction	Expression	Whether to Make a Prediction Curve and Results	Reference Documentation	Specimen
GDM	APN	APN is an endogenous bioactive polypeptide or protein secreted by adipocytes, important for the regulation of sugar and fat metabolism.	Low	I/A,(+)	[19–26]	Serum
	Leptin	Hormones secreted by adipose tissue are generally believed to be involved in the regulation of sugar, fat, and energy metabolism; reduce food intake; increase energy release; and inhibit adipocyte synthesis	High	I/A,(+)	[27–34]	Serum
	CRP	Cell molecule with multiple biological activities, synthesis site in the liver, induces insulin resistance through an inflammatory response	High	I/A,(+)	[35–42]	Serum
GDM merge PE	AOPP	Generated in response to plasma albumin with chloride under oxidative stress, can stimulate apoptosis	High	N/A	[43,44]	Placental tissue
	sFlt-1 to 25(OH)D ratio	sFlt-1 is reduced as an antiangiogenic factor, with further increases in vascular permeability and significant loss of albumin. Meanwhile, abnormal expression of 25 (OH) is also a form of vascular endothelial dysfunction	High	I/A,(+)	[45]	Serum
	Fibroblast growth factor −21 (FGF21)	FGF21 is an excellent predictive factor that can simultaneously predict the progression of both GDM and PE. However, when it comes to pregnant patients with PE, it is important to consider the specific tissues and organs from which the predictive factor blood samples are collected.	High	I/A,(+)	[46–50]	Serum
	resistin	Resistin is one of the strongly correlated predictive factors for GDM and PE. However, it is important to consider the individual characteristics of the patients, such as high BMI, existing abnormalities in pancreatic function, and metabolic dysfunction, which require careful consideration.	High	I/A,(+)	[51–54]	Serum

Abbreviations: APN, adiponectin; CRP, C-reactive protein; AOPP, advanced oxidative protein product; I/A(+), there is prediction curve and the result is positive; N/A, there is no prediction curve.

GDM Biomarkers

Adiponectin (APN)

Adiponectin (APN), which is mainly produced and secreted by adipocytes in adipose tissue, has pleiotropic effects on numerous organs, including the liver. The APN structure consists of the following four domains, the N-terminal signal peptide and hypervariable, collagen, and carboxy-terminal globular domains.[19] APN plays an important role in regulating glucose and lipid metabolism, which can promote the oxidation of plasma free fatty acids, improve sensitivity to insulin,[20] increase glucose uptake by peripheral tissues, and inhibit glucose output and glucose regeneration. APN can improve insulin resistance to a certain extent. As insulin sensitivity changes, blood sugar decreases. The level of APN decreases, the degree of insulin resistance increases, the body's sensitivity to insulin decreases, and blood glucose increases. Numerous studies have linked serum APN levels to GDM. The result of a study by Xueli and Pei on 84 pregnant women showed that APN levels were significantly lower in the serum of patients with GDM than in those without GDM.[21]

Study has shown that pregnant women with GDM have significantly lower APN levels than pregnant women without GDM, which is a good indicator for monitoring blood glucose during pregnancy.[22] Jinying et al showed that APN level was lower in the serum of patients with GDM than in those without GDM.[23] However, the specific values may vary with the pregnancy period, the degree of disease, the weight change in the past history, and even the differences in race.[24] The above factors should be taken into account in the early risk assessment.

In addition, APN also has a certain anti-apoptotic and anti-inflammatory mechanism on blood vessels.[25] Some studies have proved that the vascular endothelium in GDM patients is continuously damaged, which may also be related to the decline of APN level.[26]

Leptin

White adipose tissue is the main site of leptin synthesis and secretion regulation. The precursor of leptin consists of 167 amino acid residues with a 21-amino acid residue signal peptide at the N terminal. The precursor signal peptide is cut off in the blood to generate a peptide of 146 amino acids with a molecular weight of 16 KD, forming leptin. Leptin binds to leptin receptors on islet β cells, thereby inhibiting glucose-stimulated insulin secretion, this causes blood glucose to rise.[27] Numerous studies have found a clear correlation between leptin levels and GDM, such as that by Yang et al which showed the association between increased leptin concentration and GDM.[28] In a study of 120 pregnant women, Fang et al showed that leptin level was increased in the serum of patients with GDM.[25] Plowden et al showed pregnant women with high leptin level are more likely to experience adverse pregnancy outcome like GDM.[29] Xiao showed that pregnant women with GDM have higher leptin level.[30] Peltokorpi also showed that GDM patients have higher leptin level.[31] Therefore, leptin may have a predictive value in GDM.

Bawah et al reported that 1 out of 140 pregnant women showed increased leptin levels in the presence of GDM.[32] Furthermore, the leptin-predicted GDM area under the curve of the receiver operating characteristic (AUCROC) curve showed that leptin acted as a predictor of GDM. Florian et al reported that the leptin-predicted GDM AUCROC curve had a good predictive effect.[33] Thus, elevated levels of leptin may be a predictor of GDM in patients.

In addition, body mass index is also one of the important factors affecting leptin release, so it is necessary to consider that the number of fat cells in overweight or obese people is much greater than that in normal pregnant women, and may be accompanied by abnormal islet function.[34] Therefore, the content of leptin released may also interfere with the prediction of GDM.

C-Reactive Protein (CRP)

C-reactive protein (CRP) is a protein that is released by the liver, whose level rises sharply in the plasma when the body is infected or sustains tissue damage, and that can be produced within several hours following inflammation, while peaking at 8 hours. CRP elevation is common in late pregnancy, infections, inflammation, and burns. CRP opsonizes by activating complement, strengthening phagocytosis, and removing pathogenic microorganisms and damaged, necrotic,

and apoptotic tissue cells that invade the body. Elevated serum levels of CRP are indicative of chronic metabolic inflammation and may be associated with cardiovascular disease and insulin resistance (IR) in both men and women.[35]

Intravascular lipoprotein is an important component of human blood vessels, and the value of lipoprotein in pregnant women with potential for GDM is usually unbalanced. The pathological effect caused by chronic inflammation in the vascular endothelium gradually accumulates, resulting in further increase of CRP value. Meanwhile, the resulting chronic inflammation also further affects blood glucose metabolism. The equilibrium of blood sugar is further broken; Therefore, dysglycolipid metabolism may be one of the main causes of CRP induced GDM.[36]

Numerous studies have shown that CRP levels are closely related to GDM and that increased serum levels in early pregnancy increase the risk of GDM. Alamolhoda et al showed a statistically significant difference in CRP levels between the GDM and control groups.[37] In a study of 120 pregnant women, Liu et al found that serum CRP levels were significantly higher in the GDM group than in the normal group.[38] Yu et al showed that CRP may be related to the onset of GDM and that CRP levels were significantly increased in GDM patients.[39] The study of Amirian shows that, the CRP level in blood may be a potential predictor of GDM.[40] In a study by Durnwald et al, the CRP predicted GDM AUCROC curve results showed CRP to be a good predictor of GDM.[41]

Vecchie et al reported that women who had experienced adverse pregnancy outcomes were more likely to develop hypertension and get older, and the ROC curve analysis showed that CRP concentrations > 1.86 g/mL could accurately predict adverse outcomes.[42] Therefore, elevated serum CRP levels may predict GDM, with higher levels being indicative of a higher risk of GDM.

Biomarkers of PE Occurrence in GDM

The risk factors for GDM and PE are similar and have similar pathophysiological variations. GDM may be one of the risk factors for PE, and patients with GDM have been reported to show a higher probability of developing PE than those without GDM.[13] Study shows that GDM combined with PE significantly increases the likelihood of adverse pregnancy outcomes.[55] However, the relationship between GDM and PE needs further investigation. Therefore, the study of biomarkers is crucial.

Advanced Oxidative Protein Product (AOPP)

Oxidative stress (OS) refers to the imbalance between oxidant and antioxidant effects in the body, which tends to cause oxidation, leading to inflammatory infiltration of neutrophils. Furthermore, increased secretion of proteases and the production of a large number of oxidative intermediates, which is a negative effect of free radical production in the body, may be observed. Advanced oxidative protein product (AOPP) is mainly formed by the reaction of plasma albumin and chloride under oxidative stress, which can stimulate the respiratory burst of monocytes.[43] Furthermore, AOPP promotes the synthesis and release of inflammatory cytokines, causes systemic microinflammation, and participates in the episode of diseases such as chronic kidney disease, diabetes, and heart disease.

Numerous studies have shown that AOPP is associated with the occurrence of GDM combined with PE. A study in 130 pregnant women conducted by Shu et al found that AOPP expression level in placental tissue in pregnant women with GDM and PE was significantly increased and continued gradually increasing further with disease progression.[44] Therefore, AOPP correlates with the concurrent onset of GDM and PE, but further studies would be required to determine its usefulness as a biomarker.

Soluble Fms-Like Tyrosine Kinase-1 (sFlt-1) to 25(OH)D Ratio

Vascular endothelial growth factor (VEGF) has a soluble antagonist, sFlt-1, which plays an important role in maintaining vascular growth balance. The expression of sFlt-1 is an important predictor of other diseases associated with pregnancy, and recent studies have shown that this predictor is significantly associated with endothelial cell integrity. Changes in the number of sFlt-1 in poor vascular status and Vitamin D associated with endothelial dysfunction are also related predictors. In particular, significant changes in the value of sFlt-1/25(OH)D, which can further predict the appearance of GDM and PE.[45]

Fibroblast Growth Factor 21 (FGF21)

Fibroblast growth factor (FGF) is one of the important predictive factors in recent years. Its study on the mechanisms of gestational diabetes mellitus (GDM) and preeclampsia has significant significance. It is a peptide hormone synthesized by various organs. In recent years, the regulatory mechanisms of FGF in the human body have gradually been understood. FGF generally acts in conjunction with its receptor (FGFR).[46] FGF also regulates cell differentiation and proliferation. If there are fluctuations in FGF/FGFR values outside the normal range, it is highly likely to indicate pathological changes, with a higher possibility of being associated with cancer and kidney diseases.[47] Furthermore, FGF has many subtypes. In this discussion, we found a correlation between FGF-21 and human glucose metabolism, especially significant abnormal expression in studies of diabetic patients.[48,49] This substance can be used as one of the predictive factors and holds significant importance in the clinical treatment of GDM patients. However, this factor also undergoes partial changes during pregnancy-related preeclampsia. It is important to timely differentiate diagnostic criteria related to these diseases to avoid unnecessary misdiagnosis. Interestingly, some studies have reported no significant changes in FGF-21 during the pre-eclampsia period in the placenta.[50] Further research can verify the specificity of FGF21 expression in GDM, which holds certain significance in clinical exclusionary diagnosis.

Resistin

Resistin, also a factor expressed abnormally in the serum of patients with gestational diabetes mellitus (GDM) and preeclampsia (PE), plays a role in the pathogenesis as follows: Essentially, it is a small secreted protein that regulates glucose metabolism. Under normal conditions, it stably modulates the body's inflammatory response and enhances immune properties in conjunction with insulin. However, once its levels increase, it induces insulin resistance, partially losing the regulatory function of insulin in the body.[51] In terms of serum levels in pregnant women, pregnancy itself has a certain probability of altering the serum levels. However, if resistin levels are found to be significantly abnormal, it may indicate the possibility of pregnancy complications, particularly in the occurrence of high resistin expression before the onset of GDM and preeclampsia.[52] Resistin detected in GDM patients is closely related to metabolic function, and GDM patients with high resistin expression are often prone to metabolic disorders such as obesity during pregnancy. In investigations of serum levels in PE patients, resistin is one of the best predictive factors, providing a higher level of accuracy in prediction. In relevant experiments, resistin is seen as a significant monitoring factor, but it is necessary to exclude certain interfering factors in correlation tests.[32]

In addition, the research of Xie also found that, plasma soluble transferrin receptor(sTfR), ceruloplasmin(CP) and apolipoprotein E(ApoE) levels have potential clinical significance in early screening of GDM combined with PE.[53] Moreover, Xue promoted that high serum complement factors B concentration during mid-pregnancy is a potential biomarker of the risk of PE in patients with GDM.[54]

Conclusions

GDM is the most common complication in pregnancy, with a trend towards increased incidence with improving living standards in recent years. PE is also a common complication during pregnancy. GDM and PE are extremely harmful to both mother and fetus. Finding suitable predictors can help improve adverse pregnancy outcomes. APN, leptin, CRP are closely related to the onset of GDM, and in GDM patients, decreased APN levels, and increased leptin and CRP levels may be predictors of GDM. GDM combined with PE is also common in pregnancy, but there are few studies on the predictors of GDM combined with PE. Early in the disease, we can detect it with ultrasound, and we can find the difference on AOPP, sFlt-1/25(OH)D ratio, FGF21 and resistin compared with healthy pregnant women. Whether they can act as biomarkers needs further study.

Expectation

With the improvement of living standards, the incidence of GDM and PE is on the rise. Early diagnosis and early treatment can improve the prognosis, save treatment costs and reduce hospitalization costs. The ideal predictor should be detectable early in the disease, with high sensitivity and specificity. Several factors have been listed in this paper, which

are relatively easy to detect. However, the relationship between some factors and the prediction of disease has not been clarified. In the future, we should focus more on whether they have specificity for the detection and the assessment of prognostic effect. Furthermore, studies on these factors can broaden our knowledge about the predictors of GDM combined with PE, in order to carry out rigorous therapeutic regimen for such complications in pregnancy. And there are still many biomarkers waiting to be studied.

Statement

During the preparation of this work the authors used ChatGPT in order to Translate part of the article. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Statement of Ethics

This article does not contain any studies with human or animals performed by any of the authors.

Consent for Publication

Agreed to publish.

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Disclosure

The authors declare no conflicts of interest in this work.

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