

# Routine blood tests in early pregnancy: their development and value in the early diagnosis of gestational diabetes mellitus

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DOI: [10.31083/j.ceog.2021.02.2273](https://doi.org/10.31083/j.ceog.2021.02.2273)

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Submitted: 26 August 2020 Revised: 20 October 2020 Accepted: 06 November 2020 Published: 15 April 2021

With the change in China's second-child fertility policy, the numbers of older pregnant women and high-risk pregnancies have significantly increased, and the incidence of gestational diabetes mellitus (GDM) is likely to rise. GDM can cause a variety of adverse pregnancy outcomes, seriously threaten the safety of perinatal mothers and infants, and affect the long-term health of mothers and their offspring. Currently, the GDM screening period is between 24 to 28 weeks of pregnancy, but there are some shortcomings in screening at this time, since because of late diagnosis, the best time for intervention and treatment for some high-risk pregnant women may be delayed. Studies have shown that early prediction and early diagnosis of GDM is of great significance to improve pregnancy outcomes, so it is important to investigate early pregnancy prediction indexes of GDM to improve the screening efficiency for GDM and improve the management of GDM. It has been found that blood cell parameters, inflammatory factors, fat metabolism indices and liver enzyme metabolism markers have specific early predictive value for GDM. The application of these parameters combined with significant independent risk factors in the early prediction and early diagnosis of GDM will be of great value in the prevention and treatment of GDM and the prognosis of mothers and infants. This article reviews the development of routine blood test parameters during pregnancy and their value in the early diagnosis of GDM.

## Keywords

Gestational diabetes mellitus; Routine blood test; Early diagnosis

## 1. Introduction

GDM is a disease consisting in any degree of glucose intolerance with onset during pregnancy. It can cause adverse pregnancy outcomes such as abortion, macrosomia, dystocia, neonatal hypoglycemia, and neonatal respiratory distress syndrome. The vast majority of pregnant women with GDM have no obvious symptoms in the first trimester of pregnancy. In China, the 75 g oral glucose tolerance test (OGTT) is performed between the 24th and 28th week of pregnancy for diagnosis of GDM. However, there are some shortcomings in screening at this time, since because of late diagnosis, the intervention and treatment for some high-risk pregnant women may be delayed. Also, the glucose tolerance test has some shortcomings, such as numerous blood sampling and a complex, time-consuming operation with poor patient

compliance. Most scholars believe that early diagnosis and early intervention for GDM would help to improve maternal and infant outcomes and reduce pregnancy risks. Therefore, it would be of great value to bring together the risk factors for GDM with related blood tests to better predict GDM in the early stage of pregnancy. Studies have shown that early examination at 10–14 weeks of pregnancy may achieve the purpose of early detection and early treatment of GDM, using indicators such as body mass index (BMI), C-reactive protein (CRP), glycosylated hemoglobin (HbA1c), red blood cells (RBC), hemoglobin (Hb), white blood cells (WBC) and platelets (PLT), lipid metabolites, liver metabolites, etc. [1–4]. Other factors, such as leptin, adiponectin, androgen and sex hormone binding protein, may have value in early prediction of GDM, but at present these serological indexes are not necessary for clinical examination [5]. Although there is no completely reliable method for early diagnosis and prediction of GDM, the analysis of some of the above blood test parameters may have clinical significance for early identification of GDM, and are easy for patients to accept. If these indicators can be combined, and linked to other risk factors, this may prove more effective in prediction of the occurrence of GDM, and enable early detection, early diagnosis and early treatment. My search methods: routine analysis of blood and GDM fasting blood-glucose and GDM and so on in pubmed and CNKI. This article reviews the relationship between these blood-based parameters and GDM.

## 2. The relationship between routine blood analysis and GDM

Routine blood analysis is a procedure that pregnant women expect, the technology is mature, and it is one of the free antenatal examination items provided by the state. Routine blood analysis can simply and accurately assess the woman's health and nutritional status.

### 2.1 The relationship between WBC count and GDM

At present, the etiology and pathogenesis of diabetes has not been fully elucidated. In addition to insufficient insulin secretion by islet  $\beta$ -cells, and peripheral insulin resistance, most studies have shown that inflammation also plays an im-

portant role in the occurrence and development of the disease. Therefore, inflammatory factors may have value in the early prediction of diabetes. Reported studies have shown that insulin sensitivity is related to the peripheral blood WBC count. WBC, as one of the most common indicators of inflammatory response, can activate inflammatory signal pathways through structural recognition receptors when the body is stimulated by infection and chemical changes, thus causing insulin resistance (IR) [6]. Yang YX *et al.* [7] found that there was a positive correlation between the WBC count before 14 weeks of pregnancy and the incidence of GDM, and calculated that the range (95% confidence interval) of values of WBC for pregnant women before 14 weeks of pregnancy was  $5.12\text{--}11.83 \times 10^9/\text{L}$ . Pattanathaiyanon *et al.* [8] studied the WBC count of 1145 early pregnant women and found that the levels of WBC in patients with GDM were significantly higher than those in normal pregnant women, so they concluded that WBC count may be an independent risk factor for the occurrence of GDM. Zhao LL *et al.* determined that there was a significant correlation between WBC count and the occurrence of GDM. When the WBC of pregnant women with GDM was  $7.965 \times 10^9/\text{L}$ , the diagnostic sensitivity was 79.4% and the specificity was 31.3%. Through the assessment of the steady-state insulin evaluation model, it was found that the insulin resistance index was positively correlated with WBC and that the WBC count in early pregnancy can indicate the occurrence of GDM; this factor is expected to become one of the predictors of GDM [9].

## 2.2 The relationship between Hb and GDM

Hb is an index used to evaluate the physiological status and anemia of pregnant women during prenatal examination. In the past, a high Hb level was considered an indicator of good nutritional status in pregnant women, but some studies have found that the Hb level was a good predictor of pregnancy complications [10]. Lao *et al.* found that the incidence of GDM in pregnant women with a high Hb level in early pregnancy ( $\text{Hb} \geq 130 \text{ g/L}$ ) was as high as 18.7%, which was significantly higher than in the  $\text{Hb} < 130 \text{ g/L}$  group (10.9%). Further logistic regression analysis confirmed that a high Hb level during pregnancy was an independent risk factor for GDM [11]. Some studies have suggested that when the  $\text{Hb} \geq 130 \text{ g/L}$  or  $\text{Hb} \geq 150 \text{ g/L}$  in the first trimester of pregnancy, the risk of developing GDM in GDM pregnant women is 1.27 and 2.06 times higher than that in normal Hb women [10]. Through retrospective analysis, Gao *et al.* [12] also considered that there was a significant correlation between a high Hb level in early pregnancy ( $\text{Hb} \geq 130 \text{ g/L}$ ) and the occurrence of GDM. But there are also studies that hold the opposite view. Tarim *et al.* [13] found that the incidence of GDM in  $\text{Hb} \geq 122 \text{ g/L}$  group was significantly higher than that in  $\text{Hb} < 122 \text{ g/L}$  group, but a high Hb level was not found to be an independent risk factor for GDM, using logistic regression analysis. Chen *et al.* [14] consider that high Hb ( $\text{Hb} > 130 \text{ g/L}$ ) does not increase the risk of GDM.

## 2.3 The relationship between PLT and GDM

There are different opinions on the relationship between PLT parameters and GDM, though there are few relevant studies. It is generally believed that as pregnancy progresses, the body gradually tends to a hypercoagulable state, and GDM patients may also have changes in their blood coagulation system due to disorders of glucose and lipid metabolism. Wang DN *et al.* showed that the PLT, mean platelet volume (MPV) and platelet distribution width (PDW) of their GDM group were  $(181.70 \pm 57.78) \times 10^9/\text{L}$ ,  $(9.56 \pm 1.06) \times 10^9/\text{L}$  and  $(16.56 \pm 1.28) \times 10^9/\text{L}$  respectively, which were significantly higher than those in normal pregnant women. However, it is unclear that the normal reference range of platelet parameters is altered by GDM; the increase in MPV, the increase in platelet volume, the enhancement of platelet activity, and the activation of the coagulation system, resulting in platelet consumption, may all reflect the pregnant body being in a relatively hypercoagulable state [15]. Some studies have found that platelet activation, aggregation and bleeding tendency in patients with GDM are higher than those in normal pregnant women, which may be one of the reasons for postpartum hemorrhage in patients with GDM [16].

Routine blood analysis is a necessary item of early pregnancy assessment. In the past, we may have only paid attention to routine blood analysis to evaluate the nutritional status of pregnant women, but have ignored the early manifestations of other diseases. The above studies suggest that routine blood parameters may be of significance in the early detection of GDM, and is worthy of further study.

## 3. The relationship between fasting blood glucose (FPG) and GDM

FPG is the most commonly used detection index for diabetes, since it reflects the islet  $\beta$ -cell and its basic insulin secretion function. However, the OGTT test is time-consuming, laborious and increases the glucose load of potential GDM pregnant women. FPG decreases physiologically in the first trimester and gradually stabilizes after 14 to 16 weeks of pregnancy. Yang L *et al.* [17] assessed 11477 pregnant women with  $\text{FPG} < 7.00 \text{ mmol/L}$  at 8 and 12 weeks of pregnancy and OGTT was performed at 24 and 28 weeks of pregnancy, of which 1535 were diagnosed with GDM. The median FPG of GDM pregnant women in the first trimester was  $4.89 \text{ mmol/L}$ , which was significantly higher than that of normal controls ( $4.75 \text{ mmol/L}$ ). When FPG of 4.88, 5.10 and  $5.60 \text{ mmol/L}$  were taken as cutoff values in early pregnancy, the diagnostic sensitivity was 0.523, 0.334 and 0.618, and the specificity was 0.645, 0.811 and 0.983, respectively. With  $\text{FPG} \geq 5.60 \text{ mmol/L}$  in the first trimester, the incidence of GDM increased significantly in the second and third trimester, which deserves further study. Ozgu-Erdinc *et al.* [18] also suggested that there is a significant correlation between FPG and the occurrence and development of GDM. As an early predictor of GDM, FPG has a high sensitivity, but a slightly lower specificity. Therefore, FPG in early pregnancy

cannot be directly used as a diagnosis of GDM but can be used as an independent risk factor for GDM in early pregnancy, especially for pregnant women with FPG  $\geq 5.60$  mmol/L in early pregnancy. Early intervention, diet control, proper exercise and other measures may improve perinatal outcome.

#### 4. The relationship between HbA1c and GDM

HbA1c is a metabolite of Hb and glucose in the blood. Its synthesis is slow and irreversible. The concentration of blood glucose in the environment of red blood cells is proportional to the synthesis rate of HbA1c, while the lifespan of red blood cells is only about 120 days. HbA1c only reflects the blood glucose level of pregnant women for about three months. Fong *et al.* [19] conducted a 2-year retrospective cohort study on the application of HbA1c to early prediction of GDM. The results showed that 27.3% of the patients with 5.7% to 6.4% of HbA1c developed into GDM, while only 8.7% of those with HbA1c  $< 5.7\%$  were diagnosed as GDM. Multivariate analysis showed that the difference was statistically significant, suggesting that HbA1c can be used as one of the early predictors of GDM. The study of Ru ZX also found that there was a significant correlation between the level of HbA1c in early pregnancy and the occurrence of GDM [20]. Xu JN *et al.* [21] showed that BMI and HbA1c increased significantly in early pregnancy in patients with GDM, which may be related to the occurrence of GDM. Combined screening of BMI and HbA1c in early pregnancy could be of clinical significance for early identification of GDM.

#### 5. The relationship between C-reactive protein (CRP) and GDM

CRP is an inflammatory marker synthesized by the liver and can be used as an important predictor of endothelial damage, cardiovascular events, obesity and neonatal infection. There is a correlation between blood CRP levels and blood glucose in the third trimester of pregnancy [22, 23]. Although there is no clear consensus on the pathogenesis of GDM, studies have shown that cytokine-mediated inflammation is closely related to GDM [24]. CRP is an acute phase reactive protein related to metabolic diseases. Oxidative stress mediated by insulin resistance will promote the synthesis of CRP, while the inflammatory response mediated by CRP will further promote insulin resistance. Both stimulate each other and participate in the occurrence and development of GDM [25]. Some studies have shown that the levels of CRP and HbA1c in patients with GDM are significantly higher than those in healthy pregnant women, and high levels of CRP and HbA1c are positively correlated with the occurrence of GDM [26]. The studies of Liao W and others have shown that there is a significant correlation between the levels of BMI, CRP, and HbA1c in pregnant women and the occurrence of GDM, and the analysis of these indexes could help to predict the occurrence of GDM at an early stage [27]. A prospective cohort study of CRP in pregnant women with impaired glucose tolerance (IGT) and normal glucose tolerance, con-

ducted by Berggren [28], showed that the levels of CRP in pregnant women with IGT were higher, and there was a positive correlation between CRP and blood glucose levels, indicating that the maternal inflammatory response had been established in early pregnancy, and those women with higher CRP were more likely to develop GDM. However, after correcting for BMI, this correlation was not significant, so it was considered that CRP cannot accurately predict the occurrence of IGT in the third trimester of pregnancy.

#### 6. The relationship between serum ferritin (SF) and GDM

Iron is one of the important trace elements in the human body and an important component of red blood cells. Iron deficiency anemia is most likely to occur during pregnancy. Some scholars believe that a high concentration of Hb may be related to iron reserve level, because iron overload and its accompanying oxidative stress are important components of the pathogenesis of Type 2 DM and many other diseases, which can affect the synthesis and decomposition of insulin, enhance lipid oxidation, reduce the utilization of glucose in tissues, and increase hepatic gluconeogenesis, resulting in IR with the liver as an intermediate [29]. SF is an important indicator of human iron reserve, and the normal value for an adult female is 10–150  $\mu\text{g/L}$ . When studying the levels of HbA1c and SF in pregnant women during pregnancy, it was found that the levels of HbA1c and SF in the normal pregnant group were significantly lower than those in the GDM group, while the incidence of GDM in the high level SF group was twice as high as that in the normal pregnant group [30]. Zein *et al.* [31] suggested that the level of serum ferritin in early pregnancy was related to the level of blood glucose at 1 h and 2 h after taking glucose in OGTT test, suggesting that a high serum ferritin level in early pregnancy can be used as a predictor of IGT in non-anemic pregnant women. Some scholars believe that iron deficiency anemia in pregnant women can significantly reduce the risk of GDM, and iron deficiency anemia may be a protective factor for GDM [32].

#### 7. The relationship between parameters of lipid metabolism and GDM

Adipose tissue is one of the most important endocrine organs in the human body, which can synthesize and secrete a variety of adipose factors with important metabolism-related functions. Insulin in the middle and third trimester of pregnancy can regulate blood lipid levels by reducing lipase activity. Increased insulin resistance in GDM patients leads to enhanced fat mobilization, and the interaction between placental estrogen, progesterone and placental prolactin leads to an abnormal increase of blood lipid levels [33].

##### 7.1 Adiponectin and leptin

Adiponectin is a factor derived from adipocytes and is sensitive to insulin. Leptin is a protein product encoded by the obesity gene and a circulating hormone secreted by adipose tissue. Nicholson *et al.* [34] studied 11464 women at 11–



13 weeks of pregnancy, including 297 patients with GDM. It was found that the levels of adiponectin and sex hormone binding globulin in GDM patients were lower than those in normal controls. The detection rate for screening GDM according to mother's age, BMI, race, GDM and macrosomia history was 61.6%, while the detection rate using adiponectin and sex hormone binding globulin was increased to 74.1%. It is suggested that adiponectin can be used as one of the early predictors of GDM. Other studies showed that the level of serum leptin in GDM pregnant women was significantly higher than that in normal pregnant women in early pregnancy, and the level of serum leptin was still significantly higher than that in non-GDM pregnant women after considering the influence of BMI, suggesting that leptin may be involved in the occurrence and development of GDM and could be used as one of the predictive factors for early screening of GDM [35]. The sensitivity of these two indicators is high, but they are not routine detection items, and the value of their clinical application is limited.

### 7.2 Triglycerides (TG)

The blood lipid levels of women during pregnancy are elevated but the specific mechanism is unknown. Most scholars believe that GDM patients not only have abnormal glucose metabolism, but also have abnormal blood lipid metabolism. Khosrowbeygi *et al.* found that low density lipoprotein cholesterol (LDL-C)/high density lipoprotein cholesterol (HDL-C), TG/HDL-C and total cholesterol/HDL-C ratio in patients with GDM were higher than those in normal pregnant women. There was a significant positive correlation between TG/HDL-C and the IR index [36]. The increase of TG was most significant in patients with GDM. The blood lipid levels of well-controlled GDM patients were positively correlated with neonatal birth weight, indicating that abnormal blood lipid levels in patients with GDM could increase the transfer of maternal blood lipids to the fetus, resulting in an increase in fetal fat quality and macrosomia [37]. Li *et al.* [38] studied the blood lipid levels of 2488 pregnant women at 6–15 weeks of pregnancy (average 11 weeks), of which 379 pregnant women developed GDM. The results showed that there was a significant correlation between the increase of triglycerides and GDM. After adjusting for confounding factors, compared with those with triglyceride concentration  $\geq 1.58$  mmol/L, the risk of GDM in pregnant women with pre-pregnancy BMI  $< 24$  kg/m<sup>2</sup> increased by 1.8 times, while that in women with pre-pregnancy BMI  $\geq 24$  kg/m<sup>2</sup> increased by 2.7 times. It is considered that HDL-C is a protective factor for GDM.

## 8. The relationship between liver enzyme levels and GDM

As the main site and target of glucose and insulin metabolism, the liver plays an important role in the pathogenesis of diabetes. At present, liver enzymes are the main index to reflect liver function. Common liver enzymes include alanine aminotransferase (ALT), aspartate transami-

nase (AST) and  $\gamma$ -glutamyltransferase (GGT). Erdoğan *et al.* [39] used liver enzymes to predict the occurrence of GDM and found that levels of ALT and GGT in the GDM group were significantly higher than those in the healthy control group, which may be important for the early prediction of GDM. Another prospective study of the relationship between liver enzymes and GDM diagnosis in the second trimester of pregnancy examined 2610 pregnant women, assessed for GDM by OGTT test at 28 weeks of gestation, and blood samples were drawn to determine the levels of GGT, ALT and AST. It was found that there was a correlation between maternal blood GGT levels and the occurrence of GDM, but there was no significant difference in ALT and AST levels between the two groups [40]. The study of Wang YY *et al.* [41] showed that the levels of GGT, aspartate aminotransferase, alkaline phosphatase, total bilirubin and fibrinogen in early pregnancy were closely related to the occurrence of GDM. Wang FL *et al.* [42] indicated that the levels of WBC, ALT and AST in patients with GDM were significantly increased in early pregnancy, and the combined monitoring of WBC, AST and ALT in early pregnancy could predict the occurrence of GDM.

## 9. The relationship between other factors and GDM

Impaired liver function often affects normal glucose metabolism and may even lead to impaired glucose tolerance or diabetes. Ryckman *et al.* [43] conducted a retrospective cohort study of 26350 pregnant women. The results showed that the risk of GDM in HBeAg positive pregnant women was higher than that in HBsAg positive pregnant women. Serum uric acid (UA) is a purine metabolite in the body. Studies have found that pregnant women with elevated maternal serum UA levels before 15 weeks of pregnancy have a higher incidence of GDM [44].

## 10. Summary

To sum up, China is a country with a large population. With the change in China's fertility policy, a variety of risk factors of pregnancy are significantly increased, which may well increase the incidence of GDM. The growing epidemiological trend and disease burden of GDM may lead to serious public health problems. So far there is no clear standard for early screening of GDM, which could have a significant impact on early detection and early intervention of GDM. Most scholars believe that early diagnosis and treatment of GDM can reduce the short-term complications of mother and fetus. Some of the hematological indicators mentioned above are items that must be screened during pregnancy, and these indicators are directly or indirectly related to the occurrence of GDM. Therefore, best practice would integrate the above simple and easy screening indicators with other significant risk factors, use health statistics to establish an appropriate prediction model, identify the potential risk factors of pregnant women in the early stage of pregnancy, and formulate

a practical and individualized pregnancy management plan, so as to achieve the purpose of early screening, early diagnosis, early intervention and early treatment for GDM, and improve the maternal and infant outcome.

## Author contributions

GLL was responsible for writing the article, while NZZ was responsible for guiding, revising and reviewing the article. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Fu Yang people's hospital.

## Acknowledgment

Thanks to the two reviewers for their help.

## Funding

This research received no external funding.

## Conflict of interest

The authors declare no conflict of interest.

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