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*Original Research*

# Glycated Hemoglobin and Hypertensive Disorders of Pregnancy

**Qi Chen[1,2]*, Zhaoxia Liang [1]***

[1]Obstetrical Department, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China.

[2]Hangzhou Fuyang Women and Children Hospital, Hangzhou, Zhejiang, China.

## Abstract

Hypertensive disorder of pregnancy (HDP) is a disease that occurs during pregnancy with varying degrees of elevated blood pressure. It is a common complication of obstetrics and one of the three main causes of maternal death. The main clinical manifestations are elevated blood pressure, proteinuria and edema, which seriously affect the function of various organs in pregnant women. Glycated hemoglobin (HbA1c) is a stable measure of the average blood glucose level over the past 2-3 months. In recent years, many domestic and foreign literatures have confirmed that there is a close relationship between HbA1c and the occurrence of HDP, which may be closely related to endothelial dysfunction caused by hyperglycemia and insulin resistance, sympathetic nerve stimulation, and inflammatory factor release behind high HbA1c. HbA1c level not only affects the occurrence and development of HDP, but also affects the maternal and infant complications of pregnant women with HDP. This article reviews the correlation between glycated hemoglobin and hypertensive disorders complicating pregnancy.dose constraints.

**Keywords**: Glycated hemoglobin; Hypertensive disorder of pregnancy; Mechanism; Pregnancy outcome.

## Introduction

Hypertensive disorder of pregnancy (HDP) is a condition characterized by varying degrees of elevated blood pressure during pregnancy, and is broadly categorized into gestational hypertension, preeclampsia-eclampsia, chronic hypertension in pregnancy, and chronic hypertension with preeclampsia(1). It is one of the three leading causes of maternal mortality, second only to postpartum hemorrhage in incidence (2), especially in developing countries, where its prevalence reaches 4-25%(3, 4). It is important to differentiate between pre-existing chronic hypertension and hypertensive disorders occurring during pregnancy, which typically develop after 20 weeks of gestation and usually subside within 6 weeks postpartum. Over the past 50 years, the incidence of HDP has increased with the rising number of older, overweight, and obese pregnant women (5) . Studies have shown that HDP are closely associated with serious maternal complications such as eclampsia, stroke, heart failure, pulmonary edema, placental abruption, etc. It may also lead to the development of adverse fetal outcomes such as preterm delivery, fetal growth failure, and intrauterine fetal death (6, 7). Therefore, there is an urgent need to identify the risk factors for HDP and intervene early to minimize the occurrence of adverse pregnancy outcomes.

Studies have shown that women with gestational diabetes mellitus (GDM) are more likely to develop HDP than women without GDM (8) , and that glycemic control during pregnancy closely influences the development and progression of HDP. Previous studies have found that hyperglycemia is an independent risk factor for HDP (9) . Glycated hemoglobin (HbA1c) is a common indicator for evaluating glycemic control in patients with diabetes mellitus, which reflects the level of glycemic control over the past 2-3 months, and has the advantages of no need for fasting, simple detection, high stability, repeatability, and so on (10) , which is closely related to the occurrence and development of HDP. HbA1c in mid-gestation has been found to be strongly associated with adverse pregnancy outcomes, including the risk of pre-eclampsia (11) . It has also been found that pregnant women with HDP generally have higher blood glucose levels and HbA1c levels than patients without HDP (12) . Therefore, we summarized and reviewed the relevant domestic and international literature on the correlation between HbA1c and HDP and the research progress.

## HbA1c

### What is HbA1c?

HbA1c is the end product of molecular rearrangement and cross-linking between glucose in the blood and the N-terminal valine on the β-chain of hemoglobin (13). The main factors affecting HbA1c are the concentration and duration of blood glucose in the blood, as well as the life span of hemoglobin. The normal human hemoglobin life span is about 120 days, so it accurately reflects the average blood glucose level over the past 2-3 months, and it is structurally stable with less fluctuation (14). In addition, it has the advantages of not requiring an empty stomach, being simple to test, and being highly reproducible. It is often used in the diagnosis of diabetes and monitoring of blood glucose control and is receiving increasing attention. Many studies have focused on its predictive role in hypertensive disease.

### Testing of HbA1c and influencing factors

There are two mainstream methods for laboratory testing of HbA1c: one is based on the separation and analysis of hemoglobin (Hb), and

***Corresponding Author:** *Qi Chen. Obstetrical Department, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China. 310006.

E-mail: y217180720@zju.edu.cn, Tel: +86 18758190963

*Zhaoxia Liang. Obstetrical Department, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China. 310006.

E-mail: xiaozaizai@zju.edu.cn, Tel: +86 0571-87061501

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the other is based on the chemical reaction of the N-terminal valine on the β-chain of Hb(15) . The method of separating Hb is mainly used because HbA1c and non-glycated Hb have different chemical properties, so HbA1c can be separated and quantified. This principle is mainly achieved by ion exchange chromatography (IEC), capillary electrophoresis (CE) or affinity chromatography (AC)(15-17) . Chemical methods, on the other hand, measure the glycosylation of the specific valine residue at the N-terminus of the β-chain. These methods are mainly based on immunochemical or enzymatic assays (18, 19) . HbA1c involves the monitoring of a patient's blood sugar over a period of ten years or even decades. It is important to find a reliable test that is highly reproducible and reliable, while also being efficient, stable and low-cost. Based on the basic detection principle, hundreds of improved detection methods have been derived. Although these methods measure different analytes, laboratories can standardize their analyses according to the reference measurement procedure (RMP) provided by the International Federation of Clinical Chemistry (IFCC)(20, 21). While considerable improvements have been made to current testing methods, the use of different methods in different laboratories remains a potential source of inaccuracy in HbA1c (13, 22) . Laboratory uncertainty is often underestimated by clinicians.

Nevertheless, the primary factor influencing HbA1c remains hemoglobin within red blood cells. Consequently, any condition that diminishes the lifespan of red blood cells also impacts the detection of HbA1c. For example, conditions such as renal anemia, acute blood loss, recent blood transfusion, and hemolytic anemia may result in a falsely low HbA1c value. Additionally, liver disease, dialysis, and chronic malaria may also result in a falsely low value of HbA1c. Conversely, iron deficiency anemia may result in falsely elevated HbA1c values due to alterations in the rate of glycation(23) . Furthermore, ethnicity is a factor that affects HbA1c. Studies have demonstrated that individuals belonging to ethnic groups such as Blacks, Hispanics, American Indians, and Asians exhibit higher HbA1c levels compared to their White counterparts. This phenomenon may be attributed to underlying differences in hemoglobin glycosylation or red blood cell survival rates among different ethnic groups (24) . Other studies have demonstrated that individuals of African American and Hispanic descent exhibit elevated HbA1c concentrations relative to those of Caucasian descent (23, 25) . The impact of age has also been the subject of discussion. Some studies have demonstrated that for each additional decade of age, there is an approximate 1 mmol/mol (0.1%) increase in HbA1c concentration (26) . Additionally, other factors such as pregnancy, advanced age, high triglycerides, hyperbilirubinemia, hemoglobinopathies, and so forth may also exert some influence on HbA1c levels. Specifically, during the initial stages of pregnancy, the production of fetal red blood cells and a further reduction in fasting blood glucose can result in a decline in HbA1c levels in the early stages of pregnancy (27) . Consequently, the identification of HbA1c necessitates the formulation of targeted reference values and clinical decision limits based on age, ethnicity, and specific patient groups, and the utilization of these tools to enhance individualized patient care (15).

**The clinical significance of HbA1c**

HbA1c is a globally recognized indicator of blood glucose status. Furthermore, HbA1c is utilized for the diagnosis of diabetes, the guidance of diabetes treatment, and the evaluation of the quality of diabetes care. Additionally, it serves as an effective predictor of diabetes complications(23, 28) . As a slow, continuous, irreversible non-enzymatic product of glucose and hemoglobin, HbA1c has become the gold standard for clinicians to assess patients' long-term blood glucose levels(29) . During pregnancy, HbA1c is frequently employed to evaluate glycemic control in pregnant women with diabetes or GDM and is also utilized to identify undiagnosed pre-existing diabetes in the early stages of pregnancy. Furthermore, it facilitates the identification of high-risk groups with an increased likelihood of adverse pregnancy outcomes (11, 30) . Nevertheless, the current research indicates that HbA1c is not yet recommended for GDM screening (31) . In accordance with the 2012 American Diabetes Association (ADA) diabetes guidelines, a diagnosis of diabetes can be made when the HbA1c level is ≥6.5%, pre-diabetes when the HbA1c level is between 5.7% and 6.4%, and normal when the HbA1c level is <5.7% (32) . A HbA1c level of 6.5% or higher during pregnancy is diagnostic of preexisting diabetes, while a level of 5.7% to 6.4% in early pregnancy is a risk factor for GDM (31) . Long-term prospective studies, including the Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study Group (UKPDS), and the Epidemiology of Diabetes Interventions and Complications (EDIC), have provided compelling evidence that diabetes complications are directly related to average blood glucose values. Furthermore, these studies have demonstrated the value of standardized HbA1c concentration measurement as a diagnostic tool for monitoring long-term blood glucose control, defining specific treatment goals, and making effective decisions (33-35) . In routine clinical practice, HbA1c levels are not always measured in subjects without diabetes, and levels below the diabetic range are not usually treated accordingly(36). However, it has been demonstrated that HbA1c levels below the diabetic range also have corresponding clinical significance. They can not only prevent the development of diabetes, but also estimate the risk of coronary heart disease and subsequent cardiovascular disease, which can be used for clinical monitoring and intervention to reduce the impact of this risk(36).

## HbA1c and HDP

**Mechanism by which HbA1c affects the occurrence and development of HDP**

The vascular endothelium is a multifunctional organ that is distributed throughout the body, and which plays a role in regulating vascular tone and maintaining vascular structure. The function of vascular endothelial cells is of great importance in maintaining homeostasis within the body. The system plays a pivotal role in maintaining equilibrium between vasoconstriction and vasodilation, and its dysregulation has been linked to the onset and progression of cardiovascular disorders such as hypertension. As previously stated, HbA1c represents the average blood glucose level over the past 2-3 months, with a higher HbA1c level indicating a state of insulin resistance in the body. In a healthy body, insulin primarily activates nitric oxide synthase (NOS) via the phosphatidylinositol 3-kinase (PI3K) pathway, stimulating endothelial cells to produce NO, thereby relaxing blood vessels. The production of excess insulin in a state of insulin resistance can result in damage to the phosphatidylinositol 3-kinase (PI3K) pathway, which in turn affects the activity of nitric oxide synthase. A reduction in enzyme activity results in a decline in NO production, which ultimately impairs vasodilation. Furthermore, insulin resistance can facilitate the release of inflammatory factors, which can result in vascular endothelial dysfunction, accelerate the reabsorption of sodium and water by the renal tubules, and ultimately contribute to the onset and progression of hypertension (37) . Furthermore, it has been demonstrated that elevated insulin levels can stimulate the mitogen-activated protein kinase pathway, which ultimately results in endothelial cell proliferation. This cell proliferation may contribute to vascular wall remodeling, increased stiffness, and a diminished capacity of the body to autonomously regulate blood pressure (38) . Ultimately, this may lead to vascular stenosis, augmented vascular resistance, and elevated blood pressure.

Impairment of vascular endothelial function has a significant impact on the occurrence and development of hypertensive disorders in pregnancy. In the context of typical pregnancy, proteins released by the

gestational trophoblast and natural killer cells have the capacity to stimulate vascular endothelial cell remodeling, which in turn leads to an increase in the diameter of the uterine spiral artery(39) . Hyperinsulinemia in a hyperglycemic state result in endothelial dysfunction, which subsequently impairs the remodeling of the placental spiral artery, reduces placental perfusion, and gives rise to a cascade of effects that influence fetal growth and intrauterine hypoxia (40, 41) . This endothelial dysfunction is not limited to the placental vasculature; it also occurs in the systemic vasculature of the mother. As a result, HDP can develop into a complex multisystem disease that affects various systems of the body. Studies have demonstrated a strong correlation between an increase in HbA1c and the onset of microvascular disease, which plays a pivotal role in the pathogenesis of HDP (42) . In general, an increase in HbA1c indicates a worsening of abnormal glucose metabolism in the body, which in turn has a detrimental impact on the small blood vessels throughout the body. This results in a narrowing of the blood vessel lumen, a lack of oxygen supply to the tissues, spasm of the small arteries throughout the body, and ultimately a progressive increase in blood pressure.

The findings of recent research indicate that another crucial mechanism through which hyperinsulinemia affects blood pressure control is the excitation of the sympathetic nervous system. This can lead to an enhancement in the response of systemic small blood vessels to sympathetic nervous system excitation, thereby increasing the likelihood of pregnancy-induced hypertension(43) . It has been demonstrated that in healthy volunteers, the administration of insulin is associated with a dose-dependent increase in the release of norepinephrine, particularly within skeletal muscle tissue, and an enhancement in the discharge of sympathetic neurons (44, 45) . Furthermore, elevated insulin levels have been shown to stimulate the release of endothelin-1 and type 1 plasminogen activator inhibitor, enhance the production of reactive oxygen species, inhibit nuclear factor B, and inhibit platelet aggregation, which can directly or indirectly influence blood pressure control (46, 47).

**The relationship between HbA1c and HDP**

A substantial body of research has demonstrated that approximately two-thirds of individuals diagnosed with diabetes also present with hypertension (48) . HbA1c levels within the normal range but at the high end are an independent risk factor for the development of atherosclerosis(49) Bower et al. discovered that elevated HbA1c levels were linked to an increased risk of hypertension in both diabetic and non-diabetic patients (50) . Furthermore, the researchers reported that HbA1c levels within the prediabetic range (5.7–6.4%) were independently associated with self-reported hypertension events when compared to patients with HbA1c levels below 5.7%. Other studies have demonstrated that HbA1c can predict the onset of hypertension and is linearly and positively correlated with the risk of hypertension (37, 51).

During the specific period of pregnancy, blood glucose exerts a comparable influence on the progression of hypertension. As HbA1c levels rise, the risk of developing preeclampsia also increases (52) . The trajectory of HbA1c during pregnancy is biphasic, initially declining and subsequently rising (53) . In the early, middle, and late stages of pregnancy, different HbA1c thresholds are associated with adverse pregnancy outcomes (53) . In a similar vein, Zhang Qiuhong and colleagues also observed that in individuals with GDM, elevated HbA1c levels during the second trimester were associated with an increased risk of gestational hypertension (54) . Additionally, Mary Parfet and colleagues discovered that among pregnant women with diabetes, those with an HbA1c exceeding 5.5% in the second trimester exhibited an elevated risk of preeclampsia. Strict monitoring of weight gain during pregnancy and lowering of HbA1c levels may prove an effective strategy for reducing the risk of PIH in Chinese women with GDM (11) . Studies based on early pregnancy have identified HbA1c levels prior to 16 weeks as a risk factor for increased risk of HDP (55). Similarly, studies based on late pregnancy have demonstrated that elevated HbA1c levels in the third trimester are associated with an increased risk of preeclampsia and gestational hypertension in women with GDM (56) . The current literature on HbA1c at different stages of pregnancy indicates that elevated levels are a significant risk factor for HDP.

**The effect of HbA1c on pregnancy outcomes in pregnant women with HDP**

Few articles have explored the effect of HbA1c on pregnancy outcomes in pregnant women with HDP. Most of the articles are based on the analysis of unilateral factors. For example, abnormal glucose metabolism can further increase the risk of pregnancy complications, such as macrosomia, polyhydramnios, gestational hypertension, and preeclampsia(30) . HbA1c in the second trimester is closely related to adverse pregnancy outcomes such as preterm birth, macrosomia, preeclampsia, and primary cesarean section (11) . HDP is closely related to severe complications in the mother, such as eclampsia, stroke, heart failure, pulmonary edema, and placental abruption, and it can also lead to adverse fetal outcomes, such as preterm birth, fetal growth retardation, and intrauterine fetal death. HDP is closely related to severe complications in the mother, such as eclampsia, stroke, heart failure, pulmonary edema, and placental abruption, and it can also lead to adverse fetal outcomes, such as preterm birth, fetal growth retardation, and intrauterine fetal death (6, 7). Both elevated HbA1c and HDP have a negative impact on pregnancy outcomes. Reasonable HbA1c monitoring during pregnancy can help clinicians identify high-risk groups and intervene in a timely manner to some extent. It is not yet known whether guidelines and recommendations for HbA1c control at different stages of pregnancy can improve pregnancy outcomes to some extent. This requires more research and evidence-based medical evidence to confirm.

## Conclusion

In summary, there is a strong correlation between HbA1c and HDP, which explains why pregnant women with GDM and high HbA1c levels are more likely to develop HDP. Pregnant women with both GDM and HDP are at serious risk for both mother and child. HbA1c has a stable structure with relatively little variation. It has the advantages of not requiring an empty stomach, being easy to test, and having high repeatability. It is a good indicator for assessing glycemic control during pregnancy in clinical settings and is also an independent risk factor for predicting HDP. Keeping HbA1c within an optimal range not only reduces the incidence of diabetes, but also effectively reduces the incidence of HDP, further reducing the socioeconomic and health burden on the public. The close relationship between HbA1c and hypertension risk reminds us that we must not only pay attention to traditional risk factors for hypertension, but also closely monitor blood glucose monitoring indicators that may affect the development of HDP.

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