International Journal of General Medicine

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REVIEW

A Review on Research Progress in the Application of Glycosylated Hemoglobin and Glycated Albumin in the Screening and Monitoring of Gestational Diabetes

This article was published in the following Dove Press journal:
International Journal of General Medicine

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Abstract: Glycosylated hemoglobin (HbA1C) and glycated albumin (GA) can be used for blood glucose management of a person with diabetes as a result of their convenience and stability. However, there is no corresponding standard for the application of glycosylated hemoglobin and glycosylated albumin in gestational diabetes mellitus (GDM). In this review, we summarize the published research and discuss three aspects of the significance of HBA1C and GA in GDM patients: screening of gestational diabetes mellitus, blood glucose monitoring and the relationship with pregnancy outcome. At present, studies suggest that HBA1C can be used as a screening indicator for pregnant women, but it cannot completely replace OGTT. HbA1C and GA can be used for blood glucose management in patients with GDM to reduce the incidence of GDM complications. However, the application of HBA1C and GA in GDM still needs more research and clinical practice support.

Keywords: blood glucose, diabetes mellitus, fasting blood glucose

Background

Gestational diabetes mellitus (GDM) is defined as hyperglycemia with onset or recognition at first pregnancy, which is not overt diabetes.[3] GDM is a common disease during pregnancy, and its incidence is increasing in line with improvements in standards of living and testing levels. According to an International Diabetes Federation survey conducted in 2017, the global prevalence of GDM has reached 16.2%.[4] GDM can lead to a variety of adverse pregnancy outcomes that early diagnosis and proper control of blood glucose levels during pregnancy can reduce.[5,6] Glycosylated hemoglobin is a non-enzymatic glycation product formed by the combination of hemoglobin and blood glucose. Its production is slow, continuous and irreversible and affects blood glucose levels within 2–3 months. Meanwhile, glycated albumin is the product of a non-enzymatic reaction between serum protein and glucose that is not affected by external factors such as red blood cell life but can affect blood glucose control within 2–3 weeks or even shorter periods.[1,2] Glycosylated hemoglobin and glycated albumin can be used for blood glucose management of diabetic patients as a result of their convenience and stability. This review will discuss the significance, advantages and limitations of HbA1C and GA in patients with GDM.

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http://doi.org/10.2147/IJGM.S296316

Application of Glycosylated Hemoglobin and Glycated Albumin in Screening of Gestational Diabetes

According to ADA and FIGO standards, screening and diagnosis of GDM are currently based on an oral glucose tolerance test (OGTT) at 24–28 weeks' gestation.[7,8] Some scholars are studying the application of HbA1C and GA in the screening of GDM. Some studies have shown that early screening of pregnant women can lead to early screening of GDM patients.[9] The treatment of early GDM can improve impaired glucose tolerance in the second trimester, and reduce the incidence of GDM complications.[6] At present, relevant studies believe that HbA1c in early pregnancy has a positive impact on the screening and diagnosis of GDM patients.[10–19] For example, some studies suggest that patients with elevated HbA1c in the first trimester of pregnancy have an increased risk of GDM.[10] Some studies have also shown that an increase of HbA1c can predict GDM.[11–14] Fong et al suggest that patients with early HbA1c elevation need to be more closely monitored and possibly screened for GDM.[12] Some studies have also found that early measurement of HbA1c can be used to diagnose GDM.[15–19] At present, however, research institutes choose different periods for measuring HbA1c in early pregnancy (from 8 weeks to 20 weeks), and research cut-off points also vary, which limitsa application of their findings.

For patients in the second trimester, some research considered that HbA1C was statistically significantly different between persons with GDM and normal pregnant women, and the ROC curve suggested good sensitivity as well as specificity. But the cut-off point for HbA1C in diagnosing GDM is not uniform at present, ranging from 5.45–6, and limits its application in screening.[20–23] Renz et al considered the different cut-off points of HbA1C for the diagnosis of GDM to be 5.7, 5.8 or 6.0; however, regardless of the cut-off value used, negative results require further sensitive tests to confirm the diagnosis.[24] It has also been suggested that HbA1C can be used as a screen for GDM, which would enable some pregnant women to avoid unnecessary OGTT.[24,25] Ye et al concluded that OGTT should be performed for women with HbA1C values between 4.8 and 5.5.[24] Rajput et al suggested that an OGTT should be performed for women with HbA1C values between 5.45 and 5.95, and women with an HbA1C value of 61.8 could avoid OGTT.[25] However, some scholars found that HbA1C is not meaningful for the screening of GDM.[26–30]

The current study found that the application of GA for the screening of gestational diabetes is still controversial.[31–33] Recent studies have shown that HbA1C as well as GA combined with indicators such as FBG and BMI can be predictive of GDM.[34–40]

For GDM patients, OGTT at 24–28 weeks' gestation is still an important basis for the diagnosis of GDM. Combined with the current research, HbA1c and GA cannot replace OGTT. This may be because OGTT can accurately reflect the blood glucose level of patients, and there is a unified standard. HbA1c and GA have their limitations in application. For example, HbA1c may be affected by anemia and kidney disease.[41] Anemia is very common in pregnant women, especially in late pregnancy. Some studies suggest that weight and other factors may affect GA value during pregnancy, leading to the limitation of GA application.[32] Moreover, different races and different monitoring methods may lead to different levels of HbA1c.[42] However, it is not convenient for pregnant women to have to take a certain amount of glucose on an empty stomach and measure their blood glucose three times within two hours. However, HbA1c and GA are not limited by time and only need to be measured once, which is a relatively convenient process. The current research reveals that HbA1c and GA can also be significant in the diagnosis of GDM (see Table 1). Phase studies suggest that HbA1c in early pregnancy can help early screening and diagnosis of GDM. At present, the diagnosis results of HbA1c and GA in the second trimester are not consistent. Some researchers think that HbA1c can aid diagnosis; others think that HbA1c cannot be diagnosed but can help to screen out patients who need further OGTT. HbA1c and GA combined with other indicators also provide new ideas for the diagnosis of patients experiencing difficulty in improving OGTT.

Application of Glycosylated Hemoglobin and Glycated Albumin in Blood Glucose Monitoring of Patients with Gestational Diabetes

GDM can lead to various pregnancy complications including eclampsia, pregnancy-induced hypertension, miscarriage, premature birth, macrosomia, neonatal hypoglycemia, neonatal jaundice, neonatal respiratory distress, etc. In the Hyperglycemia and Adverse Pregnancy

Table 1 Application of HbA1C and GA in Screening of Gestational Diabetes

Author	Year	Country	Indicator	Time	Cut-Off
a. Application of early glycosylated hemoglobin in screening of gestational diabetes					
Pezeshki[14]	2014	Iran	HbA1C	20 to 24 weeks	5.75
Hughes[18]	2014	New Zealand	HbA1C	47 days	5.9
Nissim[17]	2019	Israel	HbA1C	<12 weeks	5.45
Fong[12]	2014	America	HbA1C	<20 weeks	5.7 to 6.4
Kattini[11]	2019	Canada	HbA1C	<20 weeks	5.7 to 6.4
Rowan[13]	2016	New Zealand	HbA1C	<24 weeks	5.9 to 6.7
Amylidi[15]	2016	Switzerland	HbA1C	First trimester	6
Benaiges[16]	2017	Spain	HbA1C	First trimester	5.6
Zhao[21]	2016	China	HbA1C		5.65
Kwon[19]	2015	Korea	HbA1C	24 to 28 weeks	5.05
Whitney[20]	2020	America	HbA1C		5.4
Amaefule[22]	2020	Spain	HbA1C		5.7
Balaji[23]	2007	India	HbA1C	24 to 26 weeks	6
b. Need for further OGTT					
Rajput[25]	2012	India	HbA1C	24 to 28 weeks	5.45 to 5.95
Ye[24]	2020	China	HbA1C	24 to 28 weeks	4.8 to 5.55
c. Application of glycosylated albumin in screening of gestational diabetes					
Ji[33]	2019	China	GA		12.40
Zhu[32]	2018	China	GA	24 to 28 weeks	No role in the diagnosis
Zhang[31]	2014	China	GA		No role in the diagnosis
d. Combined with other indicators					
Hua[40]	2016	China	HbA1C and hypersensitive C		
Wu[34]	2018	China	HbA1C combined with haematocrit.	12 to 16weeks	HbA1C≥5.25 haematocrit >38.8
Liu[39]	2017	China	Combined GA with HbA1C		
Jin[38]	2018	China	Combined GA with HbA1C		
Pi[35]	2015	China	Combined with HbA1C and GSP		

(*Continued*)

Table 1 (Continued).

Author	Year	Country	Indicator	Time	Cut-Off
Liu[36]	2015	China	Combined with BMI and HbA1C		HbA1C≥5.5%, BMI≥24
Cen[37]			Combined with two of BMI,FBG and HbA1C		BMI>23.25, FPG>4.25mmol/L, HbA1C≥4.95%

Notes: <: less than >: more than ≥: no less than.
Abbreviations: HbA1C, glycosylated hemoglobin; GA, glycated albumin.

Outcomes (HAPO) study, increased blood glucose levels were associated with adverse pregnancy outcomes.[5] Some studies consider the elevation of HbA1C to be associated with neonatal complications[17,30,43–55] (see Table 2). The American Diabetes Association (ADA) considers that the incidence of adverse fetal outcomes is lowest when HbA1C<6 in early pregnancy.[45] Elizabeth et al consider that HbA1C≥ 6.5 in the third trimester increases the probability of neonatal hypoglycemia.[46] Some studies suggest that a higher HbA1c is associated with an increased probability of neonatal macrosomia.[30,47] Sweeting et al consider that HbA1C≥5.9 at first trimester is associated with an increased probability of macrosomia.[47] Ho et al consider that an increased probability of macrosomia is associated with HbA1C≥ 5 in the second trimester.[30] The ADA study, however, suggests that HbA1C may not accurately reflect postprandial hyperglycemia, which is associated with greater macrosomia, and thus is not related to macrosomia.[45]

Some studies find that higher HbA1C is associated with an increased probability of LGA (large for gestational-age infants).[30,43,45,47,48,50] The ADA considers that HbA1C< 6 at mid and late pregnancy is associated with a minimization of LGA risk.[45] Sweeting et al suggest that HbA1C>5.9 at first trimester is associated with an increased probability of LGA.[47] Morris et al suggest that HbA1C>6 at first trimester is associate with increased probability of LGA.[48] Ho et al consider that an increased probability of LGA is associated with HbA1C≥5 in the second trimester.[30] Antoniou et al suggest that HbA1C>5.5 in third pregnancy is associated with an increased probability of LGA.[49] Barquiel et al suggest that HbA1C>5.5 at late pregnancy is associated with an increased probability of LGA.[43] Morris et al find that HbA1C≥6 at first trimester is associated with an increased probability of hyperbilirubinemia.[48]

Some studies suggest that high HbA1C increases the probability of congenital malformations. Inkster et al found it possible to calculate a relative risk reduction of congenital malformation for each 1-percent decrease in HbA1C, which varied from 0.39 to 0.59.[51] Hughes et al find that an increased probability of congenital malformation is associated with HbA1C>5.9 at first trimester.[18] Ho et al suggest that HbA1C>5 at second trimester is associated with a higher probability of NICU admission and perinatal mortality.[30] In addition to increased HbA1C being associated with increased probability of infant complications, Bi et al suggest that a normal HbA1C range is an independent risk factor for preterm delivery, macrosomia and LGA and that a lower HbA1C helps prevent adverse birth outcomes.[52] Some other researchers argue that GA is more relevant in terms of infant complications. Li et al[53] consider that the risk of macrosomia is significantly increased if GA≥13.00 at 24–28 weeks' gestation and GA ≥12.00 at 36–38 weeks' gestation. Sugawara et al[54] consider that when HbA1C is not statistically different, the risk of infant complications increases if GA≥15.80. Mendes et al[55] consider that GA is correlated with the neonatal complications of GDM patients while there is no significant correlation between HbA1C and the neonatal complications of GDM patients.

Some scholars suggest that the elevation of HbA1C is associated with other maternal complications[18,30,45,47,56–58] (see Table 3). The ADA suggests that HbA1C<6 at mid-pregnancy is associated with the lowest risk of maternal complications.[45] Some research suggests that premature abortion and the probability of cesarean section are associated with higher HbA1C.[30,47,57] Some studies consider that the elevation of HbA1C is related to gestational hypertension and preeclampsia.[17,30,47,56] Other studies suggest that elevated first- trimester HbA1C is associated with severe maternal morbidity (SMM) or risk of death.[17,58] Hughes et al[18] suggest that HbA1C≥5.9 at first trimester is associated with an increased risk of SMM or death, and

Table 2 Relationship Between HbA1C, GA and Infant Complications

Author	Year	Country	Indicator	Time	Cut-Off	With Relation	Odds Ratio (95%CI)
a. Hypoglycemia in newborns							
Elizabeth[46]	2020	Nigeria	HbA1C	At 36 weeks	≥6.5	Yes	
Zhang[57]	2017	China	HbA1C			Yes	
Sugawara[54]	2016	Japan	GA		≥15.8	Yes	3.7 (1.6–8.5)
b. Neonatal macrosomia							
Sweeting[47]	2017		HbA1C	First trimester	≥5.9	Yes	3.5 (1.4–8.6)
ADA[45]	2019		HbA1C	First trimester	≥6	No	
Mañé[59]	2019	Latin-American	HbA1C	First trimester	≥5.8	Yes	
		Asian	HbA1C	First trimester	≥5.9	Yes	
		Caucasian	HbA1C	First trimester		No	
Ho[30]	2017	China	HbA1C	Mid-pregnancy	≥5	Yes	
Li[53]	2017	China	GA	24–28 weeks	≥13.00	Yes	1.485–4.599
			GA	36–38 weeks	≥12.00	Yes	10.941
C. Large for gestational age							
Morris[48]	1985	America	HbA1C	In early gestation	>6	Yes	
Sweeting[47]	2017		HbA1C	First trimester	≥5.9	Yes	2.7 (1.5–4.9)
Mañé[59]	2019	Latin-American	HbA1C	First trimester	≥5.9	Yes	
		Asian	HbA1C	First trimester	≥5.4	Yes	
		Caucasian	HbA1C	First trimester		No	
ADA[45]	2019		HbA1C	Mid-trimeste	≥6	Yes	
Ho[30]	2017	China	HbA1C	Mid-pregnancy	≥5	Yes	2.22–27.86
Barquiel[42]	2015	Spain	HbA1C	Third trimester	>5.0	Yes	
Antoniou[49]	2019	Switzerland	HbA1C	Third trimester	>5.5	Yes	
Kurishita[50]	1994	Japan	HbA1C			Yes	
Sugawara[54]	2016	Japan	GA		≥15.8	Yes	5.1 (2–12.5)
d. Perinatal mortality							
Hughes[18]	2016	China	HbA1C	Early gestation	≥5.9	Yes	3.96 (1.54–10.16).
Elizabeth[46]	2020	Nigeria	HbA1C	At 36 weeks	≥6.5	Yes	
e. Neonatal hyperbilirubinemia							
Morris[48]	1985	America	HbA1C	In early gestation	>6	Yes	
f. Congenital malformation							
Hughes[18]	2016	China	HbA1C	Early gestation	≥5.9	Yes	2.67 (1.28–5.53)
Inkster[51]	2006	IRAN	HbA1C				

(*Continued*)

Table 2 (Continued).

Author	Year	Country	Indicator	Time	Cut-Off	With Relation	Odds Ratio (95%CI)
g. Admission to the neonatal intensive care unit							
Ho[30]	2017	China	HbA1C	Mid-pregnancy	≥5	Yes	0.88–3.15

Notes: <: less than >: more than ≥: no less than -: to.
Abbreviations: HbA1C, glycosylated hemoglobin; GA, glycated albumin.

Ray et al suggest that HbA1C≥6.5 at first trimester is associated with an increased risk of SMM or death.[58]

The above studies consider that poor control of HbA1C and GA are associated with pregnancy outcomes. They suggest that we can reduce the occurrence of complications by controlling HbA1C as well as GA. But there are still some problems that need to be solved. First, the cut-offs and conclusions are different for different ethnicities and experimental methods. For example, Mañé et al[59] suggest that HbA1C is not associated with pregnancy outcomes in Caucasians and the cut-offs varied among other ethnicities. Second, current studies also consider that blood glucose in different gestational periods is associated with different complications. For example, some studies found that macrosomia and LGA are associated with blood glucose in the second and third trimesters, and other studies found that neonatal malformations are associated with an increased risk of maternal glycemia in the first trimester.[60,61] Thus the different targets of HbA1C at different periods with different ethnicities and experimental methods need to be confirmed. Current studies suggest that GA is more associated with infant complications related to gestational diabetes. However the research is not large enough and there is a need for further studies.

Besides maternal and fetal complications during pregnancy, GDM patients are associated with an increased risk of developing postpartum glucose intolerance compared with normal pregnant women.[62,63] GDM patients should thus be screened postpartum. GDM patients are associated with postpartum glycemia, insulin resistance and beta-cell dysfunction.[64] Some studies suggest that HbA1C is associated with abnormal postprandial glucose tolerance,[65–68] and can be used for postpartum blood glucose monitoring. Katreddy et al[67] conclude that HbA1C can be used for screening of diabetes in GDM in the early postpartum period. Kim et al[68] consider that HbA1C has a lower association with single measures of glucose in the

Table 3 Relationship Between HbA1c, GA and and Maternal Complications

Author	Year	Country	Indicator	Time	Cut-Off	With Relation	Odds Ratio (95%CI)
a. Increase in premature abortion and probability of cesarean section							
Sweeting[47]	2012		HbA1C	First trimester	≥5.9	Yes	3.6 (2.1–6.2)
Ho[30]	2017	China	HbA1C	Mid-pregnancy	≥5	Yes	1.31–5.16
Zhang[57]	2017	China	HbA1C			Yes	
b. Severe maternal morbidity or death in pregnancy or postpartum							
Ray[58]	2020	Canada	HbA1C	Early gestation	≥6.5		
c. Gestational-hypertension and preeclampsia							
Sweeting[47]	2017		HbA1C	First trimester	≥5.9	Yes	2.6 (1.1–5.8)
Hughes[18]	2016	China	HbA1C	First trimester	≥5.9	Yes	2.42 (1.34–4.38)
Mañé[56]	2019	Asian	HbA1C	First trimester	≥ 5.4	Yes	
Ho[30]	2017	China	HbA1C	Mid-pregnancy	≥5	Yes	1.20–9.98

Notes: <: less than >: more than ≥: no less than -: to.
Abbreviations: HbA1C, glycosylated hemoglobin; GA, glycated albumin.

postpartum year but HbA1C>5.7 can still help screen for abnormal postpartum glucose tolerance. Some studies believe that the combination of HbA1c and FBG may be useful to identify women with glucose intolerance.[69–71]

Application of Glycosylated Hemoglobin and Glycated Albumin in Blood Glucose Monitoring of Patients with Gestational Diabetes

As mentioned above, adverse maternal and infant outcomes in patients with GDM are significantly associated with maternal blood glucose. Therefore, the blood glucose management of patients with GDM is very important. Relevant studies consider HbA1C and GA during pregnancy to be associated with glycemia in pregnant women.[72,73] What should be noted is that the values ofHbA1C and GA differ in pregnancy and non-pregnancy. Nielsen et al consider that the normal range for HbA1C decreases from 6.3 to 5.7 in the first trimester to 5.6 in the third trimester.[74] Hiramatsu et al illustrate that GA declines gradually during pregnancy, and the reference range for GA is 11.5–15.7.[75] The ADA suggests that HbA1C can be used for glucose monitoring of patients with gestational diabetes, ideally with a target of HbA1C 6–7 in the first trimester and HbA1C< 6 in the second to third trimesters.[45] Hashimoto et al suggest that HbA1C results may be affected by iron deficiency anemia in some pregnant women.[42] However, GA is not affected by external factors such as red blood cell lifespan and can respond to shorter periods of addressing blood glucose levels. GA can also better respond to situations of postprandial hyperglycemia and fluctuations in blood glucose.[76] Thus, it could reflect the glycemic status of GDM patients more precisely. Dong et al demonstrate that GA not only monitors blood glucose control but also emphasizes the severity of the condition because the value of GA may increase as the condition worsens.[77] The basic treatment for GDM is lifestyle management and insulin therapy.[78] Some studies suggest that glycemic management of GDM patients should be enhanced when HbA1C and GA are poorly controlled.[79,80] Others consider that HbA1c is a reference for insulin therapy but the cut-offs are different.[81–86] Tang et al consider that patients with HbA1C≥5.3 require treatment with insulin.[81] González-Quintero et al consider that patients with HbA1C≥6 require treatment with insulin.[82] Ducarme et al consider that patients with HbA1C≥5.4 and Bakiner et al consider that patients with HbA1C>5.485 should be treated with insulin.[83,84] Vintzileos and Thompson suggest that glycated hemoglobin can be used as an indicator of long-term glycemic control and helps to evaluate the efficacy of treatment.[86] Pan et al suggest that, compared with HbA1C, GA is more closely related to fasting and postprandial blood glucose levels, can accurately reflect the change of blood glucose, and might be a better monitoring indicator for GDM patients treated with insulin or diet.[87]

Some studies found that pregnant women with a negative OGTT may have impaired glucose tolerance in the third trimester due to weight gain.[88] Ensenauer et al believe that HbA1C≥5.7 at delivery can help screen obese women with negative OGTT for advanced glucose intolerance, which can indicate further health management for the mother as well as the infant to reduce negative pregnancy outcomes.[89]

Discussion

Glycosylated hemoglobin and glycated albumin can be used for the blood glucose management of diabetic patients. We discussed published reports from different periods and countries. Most researchers found that HbA1c and GA can be used for screening and management of GDM. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) suggests that HbA1c can be used to screen for gestational diabetes; however, a single test alone is not feasible and cannot yet replace an OGTT for diagnosis.[90] Current studies consider that HbA1c is a feasible indicator for screening pregnant women and selecting those who need further OGTT, while HbA1c in combination with other indicators such as GA can be applied for diagnosis. Current studies consider that both HbA1c and GA are associated with blood glucose during pregnancy and poor control of HbA1c as well as GA during pregnancy is associated with adverse pregnancy outcomes. Thus, HbA1c and GA can be applied to manage GDM and reduce complications of GDM. However, there are still some questions which require more research and clinical practice to answer. First, the standard of HbA1c and GA in different gestational periods, different ethnic groups and different detection methods needs further research. The values of HbA1c and GA for diagnosing GDM still require further research. Second, the relationship of different pregnancy outcomes with different gestational periods as well as cut-off points needs to be refined again.

Finally, the target of glycemic control needs to be further researched.

Conclusion

HbA1c and GA may be good indicators for screening and management of GDM. However, the application of HBAIC and GA in GDM still needs more research and clinical practice support.

Funding

This research was supported by the National Natural Science Foundation of China (No.81700706), the 345 Talent Project of Shengjing Hospital, the Clinical Research Project of Liaoning Diabetes Medical Nutrition Prevention Society (No.LNSTNBYXYYFZXH-RS01B) and the Science Foundation of Liaoning Education Department (No. LK201603).

Disclosure

The authors report no conflicts of interest in this work.

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