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Review Article

Application of glycated hemoglobin in the perinatal period

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Abstract: Glycated hemoglobin (HbA1c) is a special fragment formed by the binding of glucose to the C chain or D chain of hemoglobin A and as a result of non-enzymatic catalysis of mature hemoglobin and glucose, which is an indicator used to evaluate the blood glucose control in diabetes mellitus (DM) patients. Recent researches indicated that HbA1c could be applied in gestational diabetes mellitus (GDM) and pregnancy combined DM, and increasing of HbA1c was close associated with adverse outcomes of women with pregnancy combined DM and GDM. HbA1c was reported to have a significant importance in monitoring congenital malformation, abortion, perinatal mortality, preeclampsia, postpartum abnormal glucose metabolism, vascular complications and so on, which could be a test item during the second trimester. Sensitivity of HbA1c in diagnoses of DM is lower than oral glucose tolerance test (OGTT), thus OGTT is still the golden standard of GDM. Emphasis should be put on standardization of detection and threshold of HbA1c and establishment of HbA1c normal ranges of different trimesters, when HbA1c is used to diagnose pregnancy combined DM and GDM, and evaluate effects of treatments.

Keywords: Glycated haemoglobin, pregnancy, diabetes mellitus

Introduction

Glycated hemoglobin (HbA1c) has been widely accepted as an indicator used to evaluate the blood glucose control in diabetes mellitus (DM) patients. However, evidence on the application of HbA1c in the diagnosis and follow up of gestational diabetes mellitus (GDM) and pregnancy combined DM is very poor. Herein, we summarize the available studies on this issue.

Concept of HbA1c

HbA1c is a special fragment formed by the binding of glucose to the C chain or D chain of hemoglobin A (HbA) and as a result of non-enzymatic catalysis of mature hemoglobin (Hb) and glucose. The synthesis of HbA1c is very slow and relatively irreversible. HbA1c can maintain in the whole lifespan (120 days) of red blood cells. The synthesis rate of HbA1c is positively rated to the glucose concentration of red blood cells and HbA1c can reflect the mean blood glucose level within past 8 to 10 weeks. The HbA1c is independent of accurate glucose detection, the acute change in blood glucose and the interval between prior meal and HbA1c detection. In addition, HbA1c detection has good repeatability, and is stable and not influenced by the time of blood collection, fasting status and use of insulin. In addition to self-measurement of capillary blood glucose, HbA1c detection is an established tool in the assessment of glycemic control [1]. In the 59th Annual Meeting of Diabetes Association of USA, HbA1c detection is recommended as a golden standard for evaluating the glucose control.

HbA1c and normal pregnancy

In non-pregnant women, the HbA1c is 4.7-6.3% [2]. However, in pregnant women, the HbA1c might be lower than that in healthy controls because 1) pregnant women are younger and the fasting blood glucose increases over age. Thus, relatively older, healthy non-pregnant women may have high HbA1c; 2) the lifespan of red blood cells reduces in pregnant women (including those with diabetes mellitus [DM]), resulting in reduction in HbA1c.

Although the HbA1c reference intervals for the general population are well established, reference intervals for healthy pregnant women are not clearly defined.

There is no consensus on the reference range of HbA1c in pregnant women, and even there is controversy on the HbA1c in women at different gestational ages. O'Kane et al proposed that the reference range of HbA1c was 4.1-5.9% in pregnant women without DM, and in the first, second and third trimesters, the HbA1c was 5.1%, 4.9% and 5.0%, respectively [3]. Nielsen et al found that HbA1c reduced in the first trimester and further decreases at the third trimester. On the basis of their findings, they proposed that the reference range of HbA1c was 4.5-5.7% in the first trimester and 4.4-5.6% in the third trimester [2]. However, Radder et al reported that HbA1c values reduced in the first trimester, while upper reference was 5%, but increased in the third trimester to no higher than 5.9%. They speculated that the low HbA1c in the first trimester was ascribed to the low blood glucose before and after a meal and the increased HbA1c in the third trimester was attributed to the increase in postprandial glucose [4]. O'Connor et al showed the normal reference range of HbA1c was 4.8-5.5% in white pregnant women, 4.3-5.4% in the first trimester, 4.4-5.4% in the second trimester and 4.7-5.7% in the third trimester. HbA1c in the first and second trimesters was significantly lower than that in non-pregnant women. They speculated that the reference range of HbA1c was different in the different stages of pregnancy [5]. Mosca et al found the HbA1c reference intervals were 4.0%-5.5% for pregnant nondiabetic women and 4.8%-6.2% for nonpregnant controls. The HbA1c results for nondiabetic pregnant women at different gestational periods were 3.8-5.5% at 15-24 weeks, 4.0-5.5% at 25-27 weeks, and a small but significant increase in HbA1c values at 28-36 weeks, 4.4-5.5% [6]. Versantvoort et al also determined HbA1c in healthy pregnant women at three trimesters. The calculated upper reference HbA1c values for the three trimesters were 5.4, 5.5 and 5.8% (35.5, 36.6 and 39.9 mmol/mol), respectively. Compared with 6.5% (47.5 mmol/mol) in non-pregnant women, HbA1c is lower in all three trimesters of normal pregnancy [7]. Although no consensus on the reference range of HbA1c in pregnant women, published results indicate that healthy pregnant women have lower HbA1c concentrations than nonpregnant women and the internationally accepted levels of good control for diabetic pregnant women (< 7% (53.0 mmol/mol)) may be too high.

HbA1c and perinatal outcome

For type I and type II DM patients, favorable blood glucose control is one of important factors determining a good perinatal outcome. A poor glucose control may cause miscarriage, congenital malformation, high perinatal mortality and morbidity. The increased HbA1c is close associated with complications of pregnant women with DM and detection of HbA1c is important for the monitoring of acute and chronic complications (such as macrosomia, birth defects, stillbirth and preeclampsia, etc). In women with pre-existing diabetes before conception are attempted, HbA1c target below 6.1% is recommended by National Institute for Health and Clinical Excellence (NICE) [8], < 7% by American Diabetes Association (ADA) [9]. Women with diabetes whose HbA1c is above 10% should be strongly advised to avoid pregnancy [8]. Pre-existing diabetes (both type 1 and type 2) is associated with an increased risk of stillbirth. How about the relation between HbA1c and stillbirth? Tennant et al found increasing periconception HbA1c concentration above values of 49 mmol/mol (6.6%) was significantly associated with either fetal death (aOR 1.02 [95% CI 1.01, 1.04], $P = 0.01$) or infant death (OR 1.03 [95% CI 1.00, 1.06], $P = 0.01$), with each 1 mmol/mol increase (above 49 mmol/mol) conferring a 2% and 3% relative increase, respectively. Increasing third-trimester HbA1c concentration above values of 43 mmol/mol (6.1%) was significantly associated with the odds of a late stillbirth or infant death (aOR 1.06 [95% CI 1.03, 1.09], $P < 0.001$) [10].

Inkster et al evaluated the association between HbA1c and outcomes (congenital malformation, miscarriage and perinatal mortality) in pregnant women with type I or type II DM in the first trimester, while patients were classified as good control group and poor control group according to HbA1c. Results showed the poor HbA1c control had the pooled odds ratio of 3.23 for miscarriage, 3.03 for perinatal mortality and 3.44 for congenital malformation (especially the cardiovascular malformation). In addition, the relative risk for congenital malformation reduced by 0.39-0.59 when the HbA1c reduced

by 1%; the relative risk for congenital malformation increased by 1.63-2.34 when the HbA1c increased by 1% [11].

Nielsen et al conducted a study on perinatal outcome in pregnant women with type I DM, outcome classified as good (neonates surviving for at least 1 month and having no severe congenital abnormalities) or poor (spontaneous abortion, therapeutic abortion, stillbirth, neonatal death, or severe congenital abnormalities identified within 1 month after birth). They found the poor outcome was 12% with HbA1c < 7.2%, 79% with HbA1c > 10.3%. The poor outcome had a nearly linear relationship with HbA1c > 7%. An increment of HbA1c of 1% increased the risk for poor outcome by 5.5%. Moreover, there was no linear association between HbA1c < 7% and outcome [12].

Women with pregestational diabetes are at significant risk for fetal anomalies due to the effects of hyperglycemia on the developing embryo. Fetal anomalies involve cardiac, musculoskeletal, urogenital, and central nervous systems. Studies show that poor glycemic control in early pregnancy is associated with an increased risk of CHD in offspring. In type 1 or type 2 diabetes patients with the worst control (HbA1c > 8.5%), the risk of CHD increases dramatically, more than 10 times higher than the background. The incidence of CHD in patients with HbA1c level ≥ 8.5% was 8.3% compared with 3.9% in patients with an HbA1c level < 8.5% ($P = 0.03$). The adjusted OR with CHD was 2.55 (95% CI, 1.18-5.50) in patients with an HbA1c level ≥ 8.5% after adjusted for confounders such as age, body mass index (BMI), gestational age at the time the HbA1c drawn, and diabetes type. The rate of major CHD (requiring referral for surgery immediately or early in childhood) in the patients with an HbA1c level ≥ 8.5% was almost three times higher than that in those with HbA1c level < 8.5% (6.4 vs. 2.4%; $P = 0.02$) [13]. Meanwhile, Miller JL et al reported the HbA1c was the primary determinant of anomalies (r^2, 0.15; $P < 0.001$) and > 8.35% was the optimal cutoff for prediction of anomalies with an area under the curve of 0.72 (95% confidence interval,0.57-0.88). Therefore, first-trimester prediction of anomalies was best in women with increased NT or HbA1c > 8.3% (sensitivity 70.6%, specificity 77.4%, positive predictive value 16.2%, negative predictive value 97.7%, $P < 0.001$) [14].

Hyperglycaemia and elevated HbA1c in type 1 diabetes pregnancy are associated with preterm delivery or large for gestational age (LGA) babies. A 1%-point increase in HbA1c doubled the odds of preterm delivery (OR 1.75). The percentage of patients experiencing LGA/macrosomia increased with increasing third-trimester HbA1c: HbA1c 55.5%, 19% of patients experiencing LGA/macrosomia; HbA1c 5.5-5.9%, 26%; HbA1c 6-6.4%, 35%; HbA1c 46.4%, 52% [15].

Versantvoort et al found a significant correlation between the differences of the first and second trimester HbA1c values and the birth weight percentiles ($r = -0.251$; $P = 0.032$). All women with a decrease in the HbA1c value from the first to the second trimester had a birth weight percentile ≤ 90. In women with no change or an increase in the HbA1c value from the first to the second trimester there was no relation between HbA1c values and birth weight percentiles, but 23.3% had a birth weight percentile of > 90. The change in HbA1c from the first to the second trimester predicts the percentile of birth weight [7].

HbA1c and GDM

GDM is one of common complications of pregnancy in women and the incidence is about 7%. The poor blood glucose control may increase the risk for spontaneous abortion, hypertensive disorders in pregnancy, infection, macrosomia and dystocia and cause ketoacidosis. GDM usually has no typical symptoms and GDM women sometimes have normal fasting blood glucose (FPG). In addition, FPG only reflects the transient blood glucose and cannot be used to evaluate the blood glucose control in an interval, which may cause misdiagnosis of GDM. Thus, to performed oral glucose tolerance test (OGTT) at 24-48 weeks before pregnancy is necessary. However, OGTT has difficult procedures and is time consuming. Furthermore, blood collection should be repeated performed. These significantly compromise the compliance of patients to this test.

To improve the adverse pregnancy outcomes in pregnant women with DM, to strictly control the blood glucose is necessary. Measurement of blood glucose may not actually reflect the mean blood glucose. Thus, HbA1c as an important parameter in the detection of blood glucose is

appropriate to serve as an adjunctive parameter reflecting the blood glucose in pregnancy.

O'Shea et al performed a study in 622 patients with GDM diagnosed by OGTT. Their results showed that when the threshold of HbA1c in the second trimester was 5.4%, 46% of pregnant women with GDM could be diagnosed with GDM by HbA1c detection. Thus, they proposed that it is necessary to include HbA1c as a parameter in the clinical examinations in the second trimester [16].

There is controversy opinion. Raiput R et al showed that by using different ranges of HbA1c for the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria and the old ADA criteria, an OGTT could be avoided in approximately 40% (IADPSG) and 60% (ADA) of women [17]. The HAPO study showed that associations with adverse outcomes were significantly stronger with glucose measures than with HbA1c and the findings suggest that Hba1c measurement is not a useful alternative to an OGTT in pregnant women [18]. According to diagnostic criteria for GDM by IADPSG [19], the definition of GDM has 2 categories of "overt" and "gestational" diabetes in pregnancy. The overt diabetes in pregnancy is defined as fasting plasma glucose ≥ 126 mg/dl or random glucose ≥ 200 mg/dl or glycated hemoglobin A1c (HbA1c) ≥ 6.5%, during the first antenatal visit; the gestational diabetes as fasting plasma glucose (FPG) ≥ 92 but < 126 mg/dl at any gestational age or as at least one abnormal value (≥ 92, ≥ 180 and ≥ 153 mg/dl for fasting, 1 h and 2 h plasma glucose concentration, respectively), after a 75 g oral glucose tolerance test (OGTT), performed between the 24th and 28th week of pregnancy [20]. However, Rowan JA et al found most women with GDM screened by OGTT had an HbA1c ≤ 40 mmol/mol. In the 22.1% of women with an HbA1c > 40 mmol/mol, the OGTT was normal in 61.8%. So, a subgroup of pregnant women have a normal OGTT but elevated HbA1c and often require pharmacotherapy, suggesting an HbA1c > 40 mmol/mol during pregnancy is a clinically relevant finding [21].

In a study on the role of HbA1c in pre-pregnancy examinations, Hiramatsu et al detected the HbA1c, random blood glucose, urine protein and body mass index (BMI) at non-pregnancy state. Their results showed HbA1c reduced significantly in the second trimester but increased in the third trimester. However, the random blood glucose reduced in both first and second trimesters. In healthy pregnant women, the reference range of HbA1c is 4.5-5.7%, and HbA1c increases significantly in pregnant women positive for proteinuria. Moreover, obese pregnant women (BMI > 25 kg/m^2) have significantly increased HbA1c when compared with healthy controls [22].

HbA1c and postpartum glucose intolerance

The Atlantic Diabetes in Pregnancy (Atlantic DIP) detected HbA1c in 316 women. Their results showed the proportion of subjects with compromised glucose intolerance after delivery was 11.4%, 48.0% and 70.0% in women with HbA1c of < 6%, 6.0-6.4% and > 6.4%, respectively, during the delivery. Women with HbA1c of as high as 6.5% have a high odd ratio (OR) for high blood glucose within 12 weeks after delivery and the adjusted OR was 18.156 [23].

To evaluate the role of HbA1c in the re-classification of postpartum GDM, Megia, Naf et al performed OGTT and HbA1c measurement after delivery in 364 women with GDM. Their results showed 3.3%, 1.9% and 0.6% women were diagnosed with DM by OGTT, FPG and HbA1c. When compared with FPG and OGTT, the sensitivity and specificity of HbA1c were 16.7% and 100%, respectively, in the diagnosis of DM. The cutoff point (threshold) of HbA1c of 5.5%, together with detection of FPG, can be used to diagnose glucose intolerance in 95.1% subjects. Thus, they speculated that HbA1c of > 6.5% alone after delivery may reduce the sensitivity in the diagnosis of DM when compared with OGTT. However, when HbA1c is combined with FPG, HbA1c at a low threshold can be used to diagnose glucose intolerance [24].

In another study, Picón et al performed OGTT and detection of FPG and HbA1c in 231 GDM women within 1 year after delivery. Results showed the detection rate of abnormal carbohydrate metabolism was 45.89%, 19.05%, 38.10% and 46.75% with OGTT, HbA1c, FPG and HbA1c combined with FPG (HbA1c-FPG), respectively. In the diagnosis of abnormal carbohydrate metabolism, when OGTT is used as a golden standard in the diagnosis of DM, the sensitivity and positive predictive value of

HbA1c were 22.64% and 54.55%, respectively; those of FPG were 83.02% and 100%, respectively; those of HbA1c-FPG were 83.02% and 81.48%, respectively. Of note, 18 women with normal carbohydrate metabolism were diagnosed with abnormal carbohydrate metabolism by HbA1c-FPG. Thus, It was postulated that HbA1c alone or combined with FPG has poor sensitivity and specificity in the diagnosis of abnormal carbohydrate metabolism in GDM women [25].

Katon et al systemically reviewed the relationship of HbA1c in pregnancy with the outcomes of women and their offspring. Results showed HbA1c was positively related to the postpartum abnormal glucose metabolism in GDM patients. In women with postpartum type II DM or glucose intolerance, the mean HbA1c is higher than that in women with postpartum normal blood glucose. In GDM women, an increment of HbA1c by 1% may increase the risk for abnormal glucose metabolism by 2.63 folds within 6 weeks after delivery. However, the results are conflicting on the association between HbA1c and neonatal birth weight, and the correlation coefficient ranges from 0.11 to 0.51. Thus, they speculated that, when compared with OGTT which has complex detection procedures and is costly, HbA1c seems an attractive indicator used to predict the poor outcome of GDM women [26].

HbA1c and complications of DM

HbA1c has a high affinity to oxygen and the increased HbA1c may cause hypoxia. Thus, long term increase in HbA1c may lead to hypoxia in tissues, resulting in vascular complications. HbA1c has been used as an indicator to evaluate the vascular complications of DM and blood glucose control in DM patients. Results have revealed that HbA1c of 8-10% suggests moderate lesions and HbA1c of > 10% implies severe lesions, rendering patients to be susceptible to vascular complications of DM such as diabetic retinopathy and diabetic nephropathy.

American Diabetes Association recommends the blood glucose is < 6.67 mmol/L and HbA1c is < 7% in the therapy of DM. It also recommends that HbA1c should be routinely detected twice yearly in DM patients. For DM patients with good blood glucose control, HbA1c may be measured once every 2-3 months; for patients with poor blood glucose control, HbA1c should be measured once every 1-2 months. However, for pregnant women with DM (especially type I DM), HbA1c should be measured once monthly, aiming to adjust the dose of anti-diabetic drugs timely to better control the blood glucose. When HbA1c is > 10%, the dose of anti-diabetic drugs should be adjusted as soon as possible.

HbA1c and blood glucose

The correlation coefficient between HbA1c and blood glucose is 0.80. Generally, HbA1c of 6% is equivalent to blood glucose of 135 mg/dl (7.5 mmol/l). An increment of HbA1c by 1% may cause the increase in blood glucose by 35 mg/dl (1.95 mmol/l) [27].

HbA1c is determined by FPG and postprandial blood glucose. When HbA1c is < 7.3%, postprandial blood glucose contributes more influence on HbA1c; when HbA1c is 7.3-8.4%, FPG and postprandial blood glucose have comparable influence on HbA1c; when HbA1c is > 8.5%, FPG contributes more influence on HbA1c. Thus, for patients with high HbA1c, it is necessary to more strictly control the blood glucose. For patients with HbA1c of 7-8%, it is better to control the postprandial blood glucose, aiming to maintain HbA1c in an acceptable range and avoid hypoglycemia.

Monnier et al found that, for type II DM patients with good blood glucose control, postprandial blood glucose contributes more influence on HbA1c, and the influence of FPG on HbA1c increases with the deterioration of DM [28]. Balaji et al detected HbA1c and performed OGTT at the same time. They found that the mean HbA1c was 5.36 ± 0.36% in women with normal glucose tolerance and 5.96 ± 0.63% in GDM women at the first trimester [29].

Factors influencing HbA1c

Some factors may affect HbA1c. For example, the threshold of HbA1c is different among races. DM patients with increased renewal rate of red blood cells, red blood cell diseases, anemia, chronic blood loss or uremia have a reduced HbA1c; DM patients with increased hemoglobin have an elevated HbA1c. In pregnant women with above diseases, the threshold of HbA1c might be different from that in healthy controls.

Current issues

Currently, few studies have been conducted to investigate the normal reference range of HbA1c in pregnant women, and the normal reference range of HbA1c is obtained from non-pregnant subjects. The majority of studies focus on HbA1c in the third trimester has a small sample size and is retrospective.

When compared with non-pregnant women, HbA1c in pregnant women changes over time. Thus, it is better to define the reference range of HbA1c in healthy pregnant women and pregnant women with glucose intolerance, GDM, and type I or II DM, which is helpful for the improvement of pregnancy outcome.

There are no detection and diagnostic criteria for HbA1c, and thus different reference ranges of HbA1c have been proposed by distinct institutes, leading to difference in the prevalence of DM diagnosed with HbA1c. Thus, to define the standard procedures for the detection of HbA1c and to determine the threshold of HbA1c are important for the wide use of HbA1c in the diagnosis of DM in pregnancy and in the evaluation of therapeutic efficacy.

HbA1c may reflect the long term mean blood glucose. Some investigators propose that HbA1c may be used as a sensitive indicator in the screening of GDM, which, however, is not confirmed in prospective studies with large sample size. The sensitivity of HbA1c in the diagnosis of DM is relatively low when compared with OGTT, and thus normal HbA1c may not be used to exclude DM or pre-DM. Thus, OGTT is still a golden standard in the diagnosis of GDM.

Some problems with OGTT are reproducibility of glucose measurements, relating to preanalytical and analytical variables, the different population characteristics and different OGTT and HbA1c thresholds in different country. Therefore, normal OGTT result does not always exclude GDM and false-negative rate of the OGTT cannot be accurately calculated. At the same time, published data raise questions about a possible role for HbA1c in high risk women with a nondiagnostic OGTT.

Disclosure of conflict of interest

None.

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