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The Relationship between Glycosylated Hemoglobin, Gestational Weight and Pregnancy Outcome in Patients with Gestational Diabetes

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Abstract **Purpose**: To observe the relationship between the level of glycosylated hemoglobin (HbA1c) during pregnancy and the incidence of gestational diabetes mellitus (GDM) and the outcome of pregnancy in GDM patients. **Methods**: There were 334 pregnant women with GDM and 366 pregnant women with normal blood glucose selected into our research who had undergone regular check-ups and deliveries in our hospital from October 2018 to October 2019. **Results**: (1) Pregnant women with overweight and obesity before pregnancy have higher HbA1c in the first and third trimesters than those with normal and low weight before pregnancy (P<0.05). And the pregnancy of excessive weight gain during the second and third trimester and the total weight excessive gain pregnancy were statistically significant in HbA1c of third trimesters (P<0.05). (2) HbA1c in early pregnancy is a risk factor for the onset of GDM (OR=4.591, 95%CI 2.504-8.418). And the prediction critical point of GDM prediction of HbA1c in early pregnancy is 5.25%. (3) Logistic multivariate regression analysis found that HbA1c in the third trimester of pregnancy was the risk factor of adverse outcome of pregnancy including hypertensive disorders of pregnancy (OR=3.997, 95%CI 1.697-9.411), cesarean section (OR=2.024, 95%CI 1.179-3.474), and macrosomia (OR=2.261, 95%CI 1.198-4.267). **Conclusion**: The detection of HbA1c in early pregnancy helps to screen high-risk pregnancy of GDM and intervene them earlily. And HbA1c in the third trimester can help predict adverse pregnancy outcomes.

Keywords: *glycosylated hemoglobin, gestational diabetes mellitus, adverse pregnancy outcome*

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1. Introduction

GDM (Gestational diabetes mellitus, GDM) refers to varying degrees of impaired glucose tolerance during pregnancy, which is closely related to adverse outcomes of pregnancy and newborn, such as preeclampsia, abnormal amniotic fluid, macrosomia and fetal growth restriction, which seriously affects maternal and infant health [1]. The pre-pregnancy and during pregnancy have gradually increased the incidence of overweight/obesity with the adjustment of lifestyle and Chinese policies, and the number of elderly mothers has gradually increased, and the prevalence of GDM has increased year by year. In order to reduce the incidence of GDM and alleviate a series of adverse effects of GDM on mothers and infants, the Department of Obstetrics and Gynecology and Nutrition of our hospital carried out a series of weight and nutrition management for pregnant women.

Current research generally believes that excessive weight gain during pregnancy is a high risk factor for GDM [1-2]. HbA1c (Glycosylated hemoglobin) is a great significant test of HbA1c for the diagnosis and detection of glycemic control of GDM.

Therefore, this study intends to observe the weight gain and HbA1c level in GDM and non-GDM pregnant women in our hospital from 2018 to 2019 to analyze their relationship with the occurrence of adverse pregnancy outcomes, so as to provide scientific basis for nutrition guidance and maternal health care during pregnancy.

2. Methods

2.1. Research Objects

This retrospective study was collected 334 GDM pregnant women and 366 pregnant women with normal blood glucose who had regular prenatal examination and gave birth in our hospital from October 2018 to October 2019. The exclusion criteria were as follows: had hypertension, diabetes and malignant tumor before pregnancy; had abnormal pregnancy and childbirth history; had heart, liver, lung, kidney and other important organ diseases and severe gastrointestinal diseases during

pregnancy; had multiple pregnancy during present pregnancy. This study has been approved by the Medical Ethics Committee.

2.2. Research Methodology

The required information was obtained from the medical records, and the demographic characteristic of pregnant women was analyzed retrospectively, which including previous childbirth, body mass index (BMI), the weight at the time of filing (9-12 weeks of pregnancy), 24 weeks and the delivery as well as the information of maternal and neonatal outcome.

2.3. Diagnostic Criteria of GDM

75g OGTT (oral glucose tolerance test, OGTT) was used at 24-28 weeks. All pregnant women were fasting for 8 hours, and 75g glucose liquid 300 ml was taken orally 5min during the examination. Venous blood was taken on an empty stomach and 1 and 2 hours after oral glucose liquid, and the blood glucose concentration was detected. Three blood glucose levels < 5.1 mmol/L, < 10.0 mmol/L and < 8.5 mmol/L are normal, and one of them is unqualified, which is diagnosed as GDM [2].

2.4. HbA1c Detection Method

The HbA1c level was detected by Dongcao G8 glycosylated hemoglobin meter. HbA1c was detected in the first trimester of pregnancy (6-8 weeks of pregnancy) and in the third trimester of pregnancy at 35-36 weeks of pregnancy.

2.5. Evaluation Weight Gain during Pregnancy

According to the Chinese standard [3], pregnant women are classified based on BMI before pregnancy as thin (BMI < 18.5), normal weight (18.5≤BMI<24), overweight (24≤BM1<28), and obesity (BMI≥28). Due to the small number of obesity group, it merged with overweight group.

According to the weight gain standard during pregnancy recommended of IOM (Institute of Medicine, IOM) [4], 700 pregnant women were divided into insufficient weight gain group, suitable weight gain group and excessive weight gain group in early pregnancy, 12-24 weeks of pregnancy, after 24 weeks of pregnancy and the whole pregnancy.

2.6. Statistical Analysis

SPSS 18.0 software was used for data analysis. The measurement data were expressed as mean±standard deviation, and the comparison between the two groups was carried out by T test. T-test (homogeneous population variance) or *t* '-test (heterogeneous population variance), analysis of variance (homogeneous population variance, further multiple comparisons by LSD test), or Kruskal-Wallis H test (heterogeneous population variance, further multiple comparisons by Bonferroni method). The counting data were expressed by frequency sum rate (%), and the comparison between groups was carried out by χ^2 test. F test was used to compare the groups (Bonferroni method was used for multiple comparisons). Multivariate Logistic regression was used to analyze the risk factors of GDM, hypertensive disorders of pregnancy, cesarean delivery and the factors affecting neonatal weight. $P<0.05$ means that the difference is statistically significant.

3. Result

3.1. Demographic Characteristic of Pregnant Women

The age of 700 pregnant women in this survey was between 18 and 45 years, and with an average age of (31.5±3.6) years. Among them, 334 patients with GDM were with an average age of (32.3±3.6) years, and 366 patients without GDM were with an average age of (30.8±3.4) years. The age of pregnant women, pre-pregnancy BMI, family history of diabetes, weight gain during pregnancy and total weight gain were significantly different between the two groups ($P< 0.05$). There was no significant difference in the number of deliveries and the weight of newborns between the two groups ($P> 0.05$) (Table 1).

Table 1. Demographic characteristic of pregnant women in GDM and non-GDM groups

	GDM group (n=334)	Non-GDM group (n=366)	*P*
Production age ≤ 30	118 (35.3)	178 (48.6)	< 0.001
31-34	132 (39.5)	141 (38.5)	
≥35	84 (25.2)	47 (12.9)	
Pre-pregnancy BMI < 18.5	14 (4.2)	44 (12.0)	< 0.001
18.5-23.9	197 (59.0)	272 (74.3)	
≥24	123 (36.8)	50 (13.7)	
Family history of diabetes	34 (10.2)	18 (4.9)	0.008
None of history of diabetes	300 (89.8)	348 (95.1)	
Production times Primipara	224 (67.1)	249 (68.0)	0.785
Non-Primipara	110 (32.9)	117 (32.0)	
HbA1c in early pregnancy (%)	5.31±0.54	5.07±0.26	< 0.001
HbA1c in third trimester of pregnancy (%)	5.26±0.42	5.09±0.29	< 0.001
Total weight gain during pregnancy (kg)	9.7±4.3	13.2±3.6	< 0.001
Weight gain in early pregnancy (kg)	0.8±2.3	0.2±1.8	< 0.001
Weight gain at 12-24 weeks of gestation (kg)	5.0±2.6	6.1±2.3	0.001
Weight gain after 24 weeks of gestation (kg)	3.9±2.9	6.6±2.3	< 0.001
Neonatal weight (g)	3335.1±504.0	3376.9±429.4	0.241

3.2. Comparison of Weight Gain during Pregnancy between GDM and Non-GDM Patients

According to the pre-pregnancy BMI group to compare the weight gain of GDM and non-GDM patients during each period of pregnancy, it was found that the total weight gain and the weight gain after 24 weeks of gestation for pregnant women with different pre-pregnancy BMI in the GDM group were less than those in the non-GDM group, and the differences were statistically significant (P<0.05). Only GDM pregnant women with normal weight before pregnancy had statistically significant differences in weight gain during early pregnancy and 12-24 weeks of gestation compared with the non-GDM group (P<0.05) (Table 2).

3.3. Relationship between HbA1c and Pre-pregnancy BMI and Weight Change

According to Chinese BMI standard grouping, it was found that there was no significant difference in HbA1c in the first and third trimester of pregnancy between the thin before pregnancy group and the normal weight before pregnancy group (P>0.05), and the other groups had significant differences in HbA1c in the first and third trimester of pregnancy (P<0.001). With the increase of BMI before pregnancy, HbA1c in early pregnancy and late pregnancy showed an increasing linear correlation trend (P<0.001) (Table 3).

700 pregnant women were divided according to the weight gain standard during pregnancy recommended of IOM [4]. The results showed that according to the weight gain in the first trimester of pregnancy, there was no significant difference in HbA1c between the first trimester of pregnancy and the third trimester of pregnancy (P>0.05). According to the weight gain from 12 to 24 weeks of gestation, it was found that there was difference in HbA1c in the third trimester between the groups with excessive weight gain and suitable weight gain (P=0.018). According to the weight gain after 24 weeks of pregnancy, it was found that there was difference in HbA1c in the third trimester of pregnancy between the groups with insufficient weight gain and too fast weight gain (P=0. 014). According to the total weight gain, it was found that there was significant difference in HbA1c in the third trimester of pregnancy among the excessive weight gain group, the insufficient weight gain group and the normal weight gain group(P<0.001). There was no significant difference in HbA1c among other groups in the second and third trimester of pregnancy (P>0.05) (Table 4).

Table 2. The relationship between GDM and weight gain during pregnancy

		Weight gain throughout pregnancy (kg)	Weight gain during early pregnancy (kg)	Weight gain during 12-24 weeks of gestation (kg)	Weight gain after 24 weeks of gestation (kg)
Thin before pregnancy	GDM (n=14)	11.4±3.1	0.9±1.5	5.8±1.9	4.7±1.9
	Non-GDM (n=44)	14.4±2.9	0.5±2.1	6.8±2.0	7.2±2.3
	P	0.002	0.527	0.102	0.000
Normal weight before pregnancy	GDM (n=198)	10.3±4.0	1.0±2.2	5.2±2.6	4.1±2.7
	Non-GDM (n=272)	13.4±3.6	0.1±1.6	6.3±2.2	6.6±2.3
	P	<0.001	<0.001	<0.001	<0.001
Overweight/obesity before pregnancy	GDM (n=122)	8.5±4.7	0.4±2.5	4.5±2.7	3.6±3.2
	Non-GDM (n=50)	11.1±3.9	0.1±2.2	4.7±2.8	5.9±2.6
	P	<0.001	0.451	0.618	<0.001

Table 3. HbA1c in early and third pregnancy with different pre-pregnancy BMI pregnant women

	Thin before pregnancy	Normal weight before pregnancy	Overweight/obesity before pregnancy	R (pre-pregnancy BMI and HbA1c)
HbA1c in early pregnancy (%)	5.05±0.25	5.11±0.31	5.4±0.64	0.340
HbA1c in the third trimester of pregnancy (%)	5.06±0.31	5.12±0.33	5.34±0.42	0.286

Table 4. HbA1c in early and third pregnancy with different weight gain in different trimester of pregnancy

	insufficient weight gain group		suitable weight gain group		excessive weight gain group		*P* (HbA1c in early pregnancy)	*P* (HbA1c in the third trimester of pregnancy)
	HbA1c in early pregnancy (%)	HbA1c in the third trimester of pregnancy (%)	HbA1c in early pregnancy (%)	HbA1c in the third trimester of pregnancy (%)	HbA1c in early pregnancy (%)	HbA1c in the third trimester of pregnancy (%)		
Weight gain throughout pregnancy compare to IOM	5.21±0.44	5.14±0.39	5.15±0.38	5.15±0.33	5.20±0.55	5.30±0.39	0.237	<0.001
Weight gain during early pregnancy compare to IOM	5.17±0.38	5.16±0.35	5.18±0.52	5.18±0.39	5.21±0.38	5.23±0.37	0.744	0.296
Weight gain during 12-24 weeks of gestation compare to IOM	5.24±0.51	5.16±0.38	5.14±0.35	5.14±0.37	5.17±0.43	5.22±0.35	0.058	0.047
Weight gain after 24 weeks of gestation compare to IOM	5.18±0.31	5.13±0.32	5.19±0.51	5.18±0.41	5.18±0.49	5.22±0.38	0.967	0.043

3.4. The Relationship between HbA1c and Gestational Weight and Pregnancy Outcome in Patients of GDM

Logistic multivariate regression analysis was used to select the factors with differences in univariate analysis (P<0.05). It was found that the age of production, BMI before pregnancy, weight gain in the first trimester, weight gain in 12-24 weeks of pregnancy, and HbA1c in the first trimester were all related to the onset of GDM by Logistic regression analysis (Table 5).

Table 5. Analysis of influencing factors of GDM

	OR	95%CI	*P*
family history of diabetes	1.178	0.591-2.347	0.642
Production age	1.102	1.048-1.158	< 0.001
Pre-pregnancy BMI	1.148	1.083-1.218	< 0.001
Weight gain in early pregnancy	1.177	1.075-1.290	< 0.001
12-24 weeks of pregnancy	0.882	0.821-0.948	0.001
HbA1c in early pregnancy	4.591	2.504-8.418	< 0.001

The ROC curve of HbA1c in the first trimester showed that AUC was 0.659, P < 0.001, 95% CI was 0.618-0.700, the predictive critical value was 5.25%, and Youden index was 0.245 (47.4% sensitivity and 77.1% specificity).

3.5. The Relationship between HbA1c and Pregnancy Outcomes in Patients

Chi-square analysis was used to analyze the occurrence of pregnancy outcomes. It was found that the occurrence of hypertensive disorders of pregnancy, cesarean section and premature delivery in GDM higher than in non-GDM (P<0.05), and the occurrence of higher than recommended weight gain throughout pregnancy and after 24 weeks of gestation lower in GDM (P<0.05). There was no significant difference in the number of low birth weight infant and macrosomia between the two groups (P>0.05).

Logistic multivariate analysis was used to analyze the influence of pregnancy outcomes. It was found that HbA1c in the third trimester of pregnancy had an impact on the incidence of hypertensive disorders of pregnancy, cesarean section and macrosomia(P<0.05) (Table 6).

Table 6. The influence of GDM pregnancy and HbA1c in the third trimester to pregnancy outcome

	Outcomes					HbA1c in the third trimester of pregnancy		
	GDM (n=334)		Non-GDM (n=366)		*P*	OR	Multivariate adjusted relative risk (95% CI)	*P*
	n	%	n	%				
hypertensive disorders of pregnancy	39	11.7	18	4.9	0.001	3.997	1.697-9.411	0.002
cesarean section	129	38.6	103	28.2	0.003	2.024	1.179-3.474	0.011
low birth weight infant	16	4.8	12	3.3	0.304	0.656	0.111-3.890	0.643
macrosomia	34	10.2	24	6.5	0.082	2.261	1.198-4.267	0.012
premature delivery	24	7.2	13	3.6	0.032	0.590	0.138-2.518	0.476
Higher than recommended weight gain throughout pregnancy	39	11.7	69	18.9	0.012	2.549	0.899-7.221	0.078
Higher than recommended weight gain after 24 weeks of gestation	54	16.2	149	40.7	<0.001	1.676	0.954-2.943	0.072

4. Discussion

At present, it is generally believed that persistent hyperglycemia in GDM patients during pregnancy is related to a series of adverse pregnancy outcomes, which seriously affect maternal and infant health. In this study compared with non-GDM pregnant women, GDM pregnant women had higher cesarean section rate, premature birth rate and pregnancy-induced hypertension prevalence rate, but there was no significant difference in newborn weight.

Some studies have shown that elevated blood glucose in the first trimester of pregnancy can increase the spontaneous abortion rate to 5 ~ 20% [5]. At present, GDM is generally diagnosed by OGTT at 24-28 weeks of pregnancy. The screening process in early pregnancy is not clear. It is often observed through fasting blood glucose. Pregnant women with abnormal glucose metabolism in early pregnancy are often missed, which may make GDM high-risk pregnant women miss the best intervention opportunity. At this time, the surviving fetus will also be adversely affected by factors such as pregnancy-induced hypertension, polyhydramnios and pelvic infection subsequent to the mother. Early detection of high-risk pregnant women with GDM and control of blood glucose level are of great significance to the prognosis of mother and infant.

Therefore, we used Logistic multivariate regression analysis to observe the influence of HbA1c in early pregnancy on the incidence of GDM. It was found that after controlling the maternal age, BMI before pregnancy, family history of diabetes and weight gain of pregnancy (P < 0.05), every 1% increase in HbA1c in the first trimester of pregnancy increased the incidence of GDM by 3.591 times (OR=4. 591, 95% CI 2.504-8.418). The ROC curve of HbA1c predicting GDM in early pregnancy found that the prediction critical point (5.25%) can better screen GDM patients, which is close to the related literature report (5.08%) [5]. But some studies found that HbA1c test in early pregnancy test should not be used alone to screen or diagnose GDM, because of its poor sensitivity and less optimal specificity [6-8]. We consider test HbA1c in early pregnancy is beneficial to screen pregnant women who actually have elevated blood glucose at ordinary times due to their poor living and diet habits. Only test fasting blood glucose can't screen these pregnant women in time so as to intervene as early as possible. But there is not sufficient evidence of HbA1c

insteading OGTT [6-8]. In addition, it has begun to perform OGTT in early pregnancy for pregnant women with risk factors, such as history of GDM, history of macrosomia, hypertension, anomaly HbA1c and so on in our hospital.

Regarding weight gain during pregnancy, compared with the weight gain of non-GDM pregnant women, which basically conforms to the recommended range of IOM [4], GDM pregnant women gained more weight in the first trimester of pregnancy ($P< 0.05$), and the weight gain after diagnosis of GDM at 24 weeks of pregnancy was significantly lower than that of non-GDM patients ($P< 0.05$). And in this study, whether overweight and obese in pre-pregnancy or excessive weight gain in middle and third trimester of pregnancy, the HbA1c of pregnant women was higher than that of normal and light weight pregnant women ($P < 0.05$). The changes of body weight and HbA1c before and during pregnancy were relatively consistent. This means that it helped pregnant women control blood glucose level of controlling weight gain before and during pregnancy, whether they were GDM pregnancy or not. Overweight and obesity before pregnancy and excessive weight gain during pregnancy could lead to increased insulin resistance and higher blood glucose level which due to excessive fat accumulation in pregnant women, all of which increase the risk of adverse pregnancy outcomes [9-12].

Other studies have also found infant birth weight is related with pre-gestational BMI in GDM pregnancy who had pre-gestational BMI≥25 [13], and the infant birth weight of excessive weight gain pregnant women was almost 0.5 kg higher than non-excessive weight gain women in with Type 2 diabetes[14]. Therefore, Logistic multivariate regression analysis was further used to study pregnancy outcomes, and it was found that HbA1c level in the third trimester of pregnancy was closely related to pregnancy-induced hypertension, cesarean section and macrosomia. For every 1% increase in HbA1c in the third trimester of pregnancy, the incidence of pregnancy-induced hypertension increased by 2.997 times (OR=3.997, 95% CI 1.697-9.411), the rate of cesarean section increased by 1.024 times (OR=2. 024, 95% CI 1.179-3.474), and the incidence of macrosomia increased by 1.261 times (OR=2. 261, 95% CI 1.198-4.267). Previous studies have also found that gestational higher HbA1c level is an independent risk factor for preterm birth, macrosomia, and large for gestational age. Intervention for reducing HbAc1 may help to prevent adverse birth outcomes [15-22]. But most of studies use the HbAc1 of the first trimester of pregnancy to observed outcomes. Only Beatriz et. al found third-trimester HbA1c level≥5% is factor for neonatal complications in GDM mothers [21]. In this study, we found the HbAc1 of the third trimester of pregnancy could help predict adverse pregnancy outcomes, not the HbAc1 of the first trimester of pregnancy. We thought after controlled diet and exercise during pregnancy, only pregnant women who are in a state of high blood glucose load for a long time will lead to fetal hyperinsulinemia, increase protein synthesis in the body of the fetus. Excessive deposition of nutrients will form macrosomia, which is difficult to give birth naturally, resulting in an increase in cesarean section rate. The influence of GDM on pregnancy outcome depends on the long-term blood glucose load during pregnancy. Therefore, it is important of controlling blood glucose level and test HbAc1 during every trimester of pregnancy.

Some researchers found that HbA1c levels ≥5.9%, pre-pregnancy overweight or obesity and excess gestational weight gain are all independent risk factors of pregnancy-related hypertensive disorders [22]. In this study, pre-pregnancy BMI and the HbAc1 of the third trimester are also independent risk factors, and GDM pregnant women have a higher incidence of gestational hypertension, which is consistent with the results of many studies [23,24]. But excess gestational weight gain was not related with hypertensive disorders of pregnancy in this study, which may be related to insufficient sample size. Higher pre-pregnancy weight and hyperglycemia during pregnancy will increase the metabolic burden of the body, increase the risk of vascular diseases and increase the incidence of hypertensive disorder complicating pregnancy [25]. Therefore, the author believes that the management of weight and blood glucose during pregnancy should be strengthened, which will help reduce the occurrence of adverse pregnancy outcomes such as pregnancy-induced hypertension, cesarean section and macrosomia [26-28].

This study also found that some non-GDM pregnant women relaxed the management of diet and weight after passing the glucose tolerance test for 24 weeks, and the weight increased too fast in the third trimester of pregnancy. At this time, the blood glucose level gradually increased, which also led to the increase of complications. It is suggested that the detection of HbA1c in the second trimester of pregnancy should be increased in the prenatal examination process, and intervention should be given to pregnant women as soon as possible to improve the pregnancy outcome.

5. Conclusions

In a word, it is key to control the blood glucose level of pregnant women and improve the adverse outcomes of mothers and infants that early detection of HbA1c to screen high-risk pregnancy and early management of pregnant women through diet, exercise and blood glucose monitoring. On the other time, the detection of HbA1c in the third trimester of pregnancy can predict the pregnancy outcome to some extent, and intervene them as early as possible. Both periods can more stably and accurately reflect the blood glucose status of pregnant women, providing reference for clinical intervention strategies.

To our knowledge, this study earily observed the influence of HbA1c in the first trimester and the third trimester of pregnancy at the same time in GDM and non-GDM pregnant women. And the relationship between HbA1c and weight gain during pregnancy was also discussed in this study.

But the study had several limitations. First, due to workload, the study has not investigated all non-GDM pregnant women who deliveried in this year (October 2018-October 2019), only selected some of pregnant women who deliveried from February 2019 to April 2019, which resulted in insufficient number of subjects. Second, only pregnant women with GDM were tested for HbA1c

at 24 weeks of gestation, and non-GDM pregnant women were not tested, therefore HbA1c in second trimester were not observed. Third, since it is a retrospective study, we could not investigate confounding factors, such as food intake, physical activity, socioeconomic factors and so on.

In the future, we will further analysis body composition analysis of different stages of pregnancy, and explore appropriate weight gain and blood glucose control levels for GDM.

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