Glycemic changes in women after gestational diabetes *mellitus*

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Abstract

Gestational diabetes *mellitus* (GDM) is a glucose intolerance initially diagnosed throughout the 2nd and 3rd trimester of pregnancy. The purpose of this study was to estimate postpartum diabetes reassessment rates in women with GDM by identifying the persistence of glycemic changes and associated factors. The research is characterized as a retrospective cohort, investigating the postpartum follow-up data from 2010 to 2018. The mothers were divided into two groups: one with normal oral glucose tolerance tests (OGTT) and another group with abnormal tests. Subsequently, a comparison of variables between the two groups was performed considering: the average time for the development of GDM, maternal age, body mass index, gestational age at diagnosis, type of treatment used and postpartum return. Multinomial logistic regression calculations were performed. Data from 578 pregnant women were used and from these, 263 (45.50%) who returned after delivery were evaluated, 197 (74.90%) represented the normoglycemic group and 66 (25.09%) the group with glycemic changes. 41 (15.59%) had carbohydrate intolerance and 25 (9.5%) developed type 2 diabetes *mellitus*. There was no increased chance of altered OGTT postpartum with maternal ages >35 years, obesity and type of treatment used during prenatal care. Consecutively, the statistical data showed an increased chance of altered OGTT in the second trimester diagnosis of GDM (3.493% CI95% 1.570-7.770), and, concomitantly, glycosylated hemoglobin A1C fraction was >5.8 during prenatal care (3.014 CI95% 1.084-8.380). Moreover, the diagnosis in the third trimester was demonstrated as having a protective effect (0.484 95% CI 0.271-0.865). Less than 50% of the patients returned, and of these, 25% had altered OGTT. This study points to an increased risk of altered OGTT when GDM is diagnosed in the second trimester of pregnancy. Thus, a diagnosis in the second gestational trimester and a glycosylated hemoglobin fraction >5.8 increased the chances of altered OGTT, meanwhile, a diagnosis in the third trimester decreased the chances of OGTT alterations postpartum.

Keywords: Pregnancy. Glycemic index. Gestational diabetes.

INTRODUCTION

Diabetes *mellitus* is a metabolic disease that affects carbohydrate, protein and lipid metabolism. This syndrome may manifest itself as a lack of insulin either when the body stops producing it, or when its production is inefficient and/or existing insulin fails to be use. The first leads to the onset of type 1 diabetes mellitus (DM1), while the second leads to the onset of type 2 diabetes mellitus (DM2)[1].

Gestational diabetes mellitus (GDM) is described as glucose intolerance of various levels with onset or first diagnosis during the second or third trimester of pregnancy. It has an incidence of 3% to 8% in pregnant women[2] and may or may not persist after delivery[3]. The importance of diagnosing GDM in clinical practice stems from the risk to the mother of having diabetes in the future, as studies indicate GDM as an early marker of postpartum DM2, even with the disappearance of the condition

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after birth[4,5].

Postpartum women with a history of GDM are indicated for reevaluation of whether or not abnormal glucose tolerance changes within 6 to 12 weeks after labor. If the tests show a normal a result, the reassessment could be done every 3 years. Patients with fasting glucose and/or glucose tolerance altered should be reevaluated every year[3].

Some studies have already shown that the establishment of T2DM can be delayed or avoided in high-risk groups through lifestyle changes or medication use[6,7]. Therefore, the identification of possible characteristics associated with the development of T2DM in women with GDM could contribute to risk stratification, aiming at prevention. The aim of the study was to reassess the postpartum glycemic index of women with a history of GDM and to identify associations between pregnancy characteristics and progression to different glycemic outcomes.

METHODOLOGY

This is a retrospective observational cohort study. Data from 578 pregnant women attended at the maternity service of the Unimed Hospital Center in Joinville-SC, Brazil, who had a diagnosis of GDM between January 2010 and May 2018 were used. Clinical data were collected for the development of postpartum diabetes in electronic medical records and physical medical records.

These mothers underwent the 75g oral glucose tolerance test (OGTT) between 45 and 60 days postpartum, and were divided into 2 groups, one with normal OGTT and one with altered OGTT. The variables were compared between the two groups. The study protocol followed the norms of Resolution No. 466 from December 12, 2012 of the National Health Council, of the Ministry of Health considering the respect for human dignity and the special protection due to participants in scientific research involving human beings. This study received approval under opinion number 2.335.419 of the Research Ethics Committee (CEP) of the Hans Dieter Schmidt Regional Hospital, SC, Brazil.

Diagnostic values for GDM were determined as follows in OGTT with 75g glucose load: fasting glucose 92 to 125 mg/dL, after 1 hour ≥180 mg/dL or after 2 hours from 153 to 199 mg/dL. A single atypical value is sufficient to diagnose GDM. According to criteria published by the World Health Organization, the classification for carbohydrate intolerance is when fasting glucose between >110 and <126 mg/dL and two hours after between ≥140 and <200 mg/dL. The diagnosis of diabetes *mellitus* (DM) occurs when fasting blood glucose is ≥126mg/dL, or ≥200 mg/dL two hours later.

The pregnant women chosen were those who developed GDM and returned postpartum for glycemic evaluation from 2010 to 2018, aged over 18 years, regardless of the gestational age of diagnosis, and whose surveillance, delivery and postpartum reclassification occurred in this maternity ward. Pregnant women with incomplete medical records and patients who did not return for glycemic reevaluation were excluded.

Postpartum follow-up data for these women concerning clinical profile, mean time to develop GDM, and other clinical details such as maternal age, BMI, gestational age at diagnosis, type of treatment used, and postpartum follow-up were evaluated. Characteristics of newborns such as weight, type of delivery, gestational age at delivery and a classification comparing weight and gestational age as small for gestational age (SGA), appropriate for gestational age (AGA) or large for gestational age (GIG) were also evaluated.

All the information obtained was released in the Microsoft Excel version 2016 software and later analyzed using the Statistical Package for the Social Science (SPSS) version 21.0 software. Quantitative variables were presented as means and standard deviations, and qualitative variables were as absolute and relative frequencies. Once the normality of distribution of the characteristics studied by the Kolmogorov-Smirnov test was confirmed, the T-test for normally distributed quantitative variables was applied. When the assumption of normality was rejected, the non-parametric Mann Whitney test was used. For qualitative variables, the chi-squared test (or Fisher's exact

test for frequencies below 5) was applied. In all analytical models, p values less than 0.05 were considered significant. Multinomial logistic regression models were constructed to calculate odds ratios for examining factors related to the altered OGTT outcome, considering confounding variables.

RESULTS

Of the patients treated, 263 (45.50%) returned after delivery for reassessment of glycemic status were analyzed, and of these, 197 (74.90%) represented the group without glycemic alterations and 66 (25.09%) represented the group with glycemic alterations. In the group with glycemic alterations, 41 (15.59%) were carbohydrate intolerant and 25 (9.5%) developed T2DM. There were no pregnant women excluded. The diagnosis made in the second trimester was approximately three times more likely to change in OGTT, and the third trimester demonstrated a protective effect; both were significant. HbA1C>5.8 during prenatal care was almost three times more likely to develop postpartum glucose intolerance or T2DM.

The characteristics of pregnant women, shown in Table 1, show the group profile: age and body mass index (BMI). In the studied population no difference was found between the groups.

Table 2 shows data related to GDM, such as glycemic control, type of treatment (diet, metformin or insulin), gestational age at diagnosis and glycosylated hemoglobin A1C fraction (HbA1C). There was a difference in gestational age at diagnosis (p=0.041). It was found that in both groups the diagnosis in the second and third trimester was different (p 0.014 and p=0.007). There was no difference regarding the type of treatment, however, the option to perform the treatment with a diet had a p-value close to significance (p=0.057). No difference in HbA1C values between groups was demonstrated.

Regarding the characteristics of the newborns (NB), shown in Table 3, there was a higher prevalence of cesarean delivery when compared to the number of vaginal deliveries in both groups. However, the type of delivery did not differ in this population. There was also no difference regarding gestational age of delivery, the size of the newborn and referral to the intensive care unit (ICU). Regarding hypoglycemia in newborns due to GDM, this study found a p-value close to significance.

Amidst the findings, we found no increased chance of altered OGTT postpartum at maternal ages >35 years or with obesity. The diagnosis of GDM made in the first trimester was not significant. However, being diagnosed in the second trimester was approximately three times more likely to develop postpartum glycemic changes. On the other hand, the diagnosis made in the third trimester proved to be a protective factor. The type of GDM treatment was not statistically relevant. As for those with HbA1C >5.8, they were almost three times more likely to develop postpartum glucose intolerance or DM2, according to Table 4.

Table 1 – General characteristics of pregnant women according to normal and altered glycemic index, between January 2010 and May 2018 in the maternity ward of the Unimed Hospital Center in Joinville, SC, Brazil.

Characteristics	Normal N=197	N (%)	OGTT (altered) N=66	N (%)	P-value
Age	31.51 ± 4.99		32.39 ±4.60		*0.680
BMI	26.84 ± 4.96		27.68 ±5.43		†0.536
Low weight	4	2.03	2	3.03	‡0.643
Normal	76	38.57	24	36.36	§0.748
Obese	117	59.39	40	60.60	§0.862

*Student's T Test; † Mann-Whitney test; ‡ Fisher test; § Chi-squared test; BMI-body mass index, OGTT-oral glucose tolerance test.

Table 2 – Characteristics of glycemic control, type of treatment, age of diagnosis and glycosylated hemoglobin, between January 2010 and May 2018 at the maternity hospital of Unimed Hospital in Joinville, SC, Brazil.

Characteristics	Normal N=197	N (%)	OGTT (altered) N=66	N (%)	P-value
GA	27.81 ±5.94		25.85 ±5.96		*0.041
1st Trimester	10	5.07	5	7.57	†0.541
2nd Trimester	46	23.35	26	39.39	‡0.014
3rd Trimester	141	71.57	35	53.03	‡0.007
TTO					
Diet	72	36.54	16	24.24	‡0.057
MTF	76	38.57	30	45.45	‡0.338
Insulin	49	24.87	20	30.30	‡0.423
HBA1C 3T	5.22 ±0.49		5.34 ±0.54		*0.422

*Mann-Whitney test; † Fisher test; ‡ Chi-squared test; BMI- body mass index; GA-Gestational age; TTO-treatment; MTF-metformin; HBA1C 3T-glycosylated hemoglobin, OGTT-oral glucose tolerance test.

Table 3 – Characteristics of newborns according to the normal and altered glycemic index of pregnant women, between January 2010 and May 2018 at the maternity hospital of Unimed Hospital in Joinville, SC, Brazil

Characteristics	Normal N=197	N (%)	TOTG (alterado) N=66	N (%)	Teste P
ND	31	15.73	14	21.21	*0.282
CS	166	84.26	52	78.78	*0.332
NB weight	3187.59 ± 444.74		3250.49 ±386.65		†0.663
GA at brith	38.16 ±1.35		38.09 ±1.32		†0.478
SGA	0	0	0	0	
AGA	134	68.02	46	69.69	*0.746
LGA	63	31.97	20	30.30	*0.746
Hypoglicemia	14	7.10	10	15.15	*0.054
ICU	10	5.07	5	7.57	‡0.466

*Chi-squared test; †Mann-Whitney test; ‡Fisher test; ND- normal delivery; CS-cesarean section; NB- newborn; GA-Gestational age; SGA-small for gestational age; AGA-appropriate for gestational age; LGA-large for gestational age; ICU intensive care unit; OGTT-oral glucose tolerance test.

Table 4 – Odds ratio of developing postpartum glycemic changes between January 2010 and May 2018 in the maternity ward of the Unimed Hospital Center in Joinville, SC, Brazil.

Characteristics	Normal/ altered	P	RC	CI95%
Age> 35a	81/55	0.849	1.080	0.490-2.378
Obesity	40/117	0.403	0.719	0.331-1.558
1st trimester	5/10	0.119	3.401	0.729-15.871
2nd trimester	26/46	0.002	3.493	1.570-7.770
3rd trimester	35/141	0.014	0.484	0.271-0.865
Diet	16/72	0.060	0.545	0.289-1.025
MTF	30/76	0.338	1,314	0.751-2.297
Insulin	20/49	0.424	1.285	0.695-2.377
HBA1C ≥5.8	21/169	0.034	3.014	1.084-8.380

MTF-metformin; HBA1C-glycosylated hemoglobin A1C fraction; OR- odds ratio

DISCUSSION

In Brazil, according to the Unified Health System (SUS) using the diagnostic criteria currently proposed in the literature8-10, it is estimated that the prevalence of GDM is approximately 18%. Pregnant women diagnosed with GDM have a risk of developing glucose intolerance or postpartum T2DM, which indicates the need for greater vigilance as well as proper screening of this population[7,11-15].

In the midst of this context, the American College of Gynecology and Obstetrics is mandatorily predicting postpartum follow-ups for screening for glucose intolerance or T2DM[16]. Although screening has increased over the past decade, it is still inefficient in Brazil. In the present study, women with GDM who returned to the glycemic control screening represented 45.5% of the research sample. These results are lower than those found by the American College and other developed countries, such as Australia, that have major concerns for screenings, indicating postpartum segment levels of 74 and 73%, respectively[16,17].

However, a recent report from a similar patient population in Boston (USA)[18] and a study by Thomas Jerfferson University of Philadelphia

(USA)[1,9] have reported that, respectively, only 23.4% and 20% of patients were referred by obstetrician-gynecologists for screening tests after delivery. This study showed a more satisfactory return percentage. Given this, there seems to be a difficulty in catching patients after delivery. Hypotheses suggested by different researchers are that the first retest coincides with the period of adaptation of women to the NB and the lack of indication by the medical team[2,7].

The prevalence of postpartum T2DM was 9.5%, a percentage similar to data described in the international literature, which reports 3-14%[20,21]. This variation in relation to the prevalence rates of GDM in the various studies evaluated must have occurred due to a dependence on the characteristics of the population and the methods used for screening and diagnosis of the disease. Some authors, for example, identified maternal weight gain and BMI as significant; however, the present study did not identify their relevance[2,14,22].

The data from the current study show that 60.6% of patients who developed glycemic alterations were classified as obese. Obesity has been identified as one of the main risk factors for T2DM, as it is responsible for the glucose-insulin homeostasis disorder. This results in several pathophysiological changes such as reduced insulin extraction from the liver, with increased hepatic glucose production and decreased glucose uptake by muscle tissue. Although there are references indicating a BMI greater than 25 kg/m^2 as a higher chance[7,23], the follow-up of the study did not show clinical relevance in its statistical significance.

Regarding the associations between mother's age and OGTT alterations, the present study identified that a maternal age >35 years does not demonstrate a significantly increased chance of altering OGTT. Other studies have also stated that age does not imply a higher chance for the diagnosis of T2DM[21,24,25]. These findings may be explained by the fact that fertility declines gradually until the age of 35, and then rapidly declines after this age. As the age of the pregnant woman increases, the increased likelihood of structural defects in the eggs and the frequency of chronic pathologies, which makes the reproductive history progressively more complicated.

It is noteworthy that the population of women with GDM is of reproductive age, and postpartum screening and subsequent diagnoses of diabetes affect not only mothers but also future pregnancies. Therefore, the risk of complications, especially stillbirths and congenital anomalies, may be reduced with optimal glycemic control before subsequent pregnancy[26].

Although there are studies that considered GDM diagnosed in the first trimester as having a greater chance of alterations[2,7], this analysis diverged with the present research, which indicated a greater chance in the second trimester. In addition, it was found that diagnoses in the third trimester have clinical and statistical relevance as a protective factor for the development of glycemic alterations. One possibility, which does not corroborate the literature regarding diagnosis in the first trimester, would be the small population found in this study of only 15 pregnant women.

The variable between carbohydrate intolerant patients and patients with T2DM, regarding the type of treatment, was considered to be a potential factor to revert maternal and neonatal adversities[2,22]. In this study, there was no difference regarding the type of treatment, however, the option of dieting was nearly to significance. According to the comparative publication of the drugs, there are no changes in perinatal outcomes in patients with GDM[12]. This information differs from research that has shown insulin as being a higher risk factor for postpartum T2DM evolution[2,7,27]; perhaps because they did not use metformin in the treatment of GDM or carried out the diet incorrectly. Considering this aspect, Polish findings identified in recent works have assessed that the use of insulin during pregnancy would be one of the reasons for adherence to postpartum screening[27].

Patients in the current study with HbA1c rates greater than 5.8 were three times more likely to develop postpartum glucose intolerance or T2DM. In contrast, the literature described a six-fold increased chance[7,28]. Results indicate that HbA1c may be a useful measure for identifying patients with GDM who are at a higher risk for abnormal postpartum glucose.

Regarding the results of the newborns, the mean gestational age at delivery was similar between the two groups, corroborating other studies described in the literature[14,22,29].

There was a higher prevalence of cesarean delivery in both groups when compared to the number of vaginal deliveries; unlike a study conducted in Portugal that reported a reduction in the number of caesarean sections in diabetic patients[22].

It is necessary to highlight some limitations of the present study because it is based on the information recorded in an electronic medical record. However, we consider that the issue highlighted in the article is relevant to clinical practice, given the increase in cases of GDM and its consequences for women, as well as for children. Thus, it is extremely important to have data on postpartum GDM assessment and analyses for a better understanding of the topic, as well as providing information for risk stratification and contributing to the prevention of T2DM with early treatment.

Thus, strategies to increase the rate of return to assess postpartum glycemic status and eventually prevent T2DM include orienting the patients on the importance of this reevaluation during pregnancy and the immediate postpartum period, and even contacting the patients via telephone calls if they do not attend the appointment. Therefore, postpartum interventions are necessary, as well as health policies that make women aware of and ensure their return after childbirth; especially, since lifestyle changes through diet, physical activity, and medication, when well-indicated, have benefitted this population[7,26.27,31,32].

CONCLUSION

This research showed changes in OGTT in 25% of patients who returned postpartum. There is an increased risk of altered OGTT when the diagnosis of GDM occurs in the second trimester. Thus, a diagnosis in the second trimester and a glycosylated hemoglobin fraction >5.8 was associated with an increased chance, and diagnosis in the third trimester was associated with a decreased chance of postpartum OGTT changes.

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