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A Single-center Study of the Predictors of Postpartum Prediabetes in Pregnant Women with Gestational Diabetes

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ABSTRACT

Objective: We aimed to investigate the association between prediabetes risk factors, such as hemoglobin A1c (HbA1c) levels, age, body mass index, treatment regimen, and history of gestational diabetes mellitus (GDM) in women with GDM and impaired glucose tolerance postpartum. Methodology: We retrospectively reviewed the medical records of the women with GDM who were followed up at King Abdulaziz University Hospital, Jeddah, Saudi Arabia, between January 2014 and January 2018. A data collection form was designed to collect demographic and clinical data. The likelihood of postpartum pre-diabetes was predicted using binomial logistic regression. Results: Medical charts of 267 women (240 with normal and 27 with abnormal oral glucose tolerance test results) were reviewed. We found that age ≥ 45 years (p=0.001), obesity (p=0.041), oral hypoglycemic agent use (p=0.006), and insulin use (p=0.016) were significantly associated with a higher risk for postpartum glucose intolerance. Conclusion: The predictors of prediabetes among women visiting our clinics were age ≥45 years, obesity, oral hypoglycemic agent use, and insulin use. Identifying these factors antepartum is necessary to prevent the occurrence of prediabetes in GDM cases.

Key words: *Gestational diabetes mellitus; HbA1c; postpartum prediabetes; predictive factors; pregnancy.*

INTRODUCTION

Gestational diabetes mellitus (GDM) is diabetes that is initially diagnosed in women in their second or third trimester of gestation with no evidence of preexisting type 1 or type 2 diabetes. [1] This is a common condition affecting many pregnancies, as 3.4 million cases of hyperglycemia during pregnancy were reported from the Gulf and North Aftriac in 2013, with a crude prevalence rate of 22.3% of live births. Age-adjusted prevalence rates of gestational diabetes mellitus (GDM) from other areas of the world are also high (9.5% in Africa and 26.6% in Southeast Asia) [2, 3].

Publihsed literature demonstrates that GDM is a precursor to type 2 diabetes mellitus (T2DM) in predisposed women who also experienced metabolic challenges during pregnancy, [4] highlighting the importance of postpartum follow-up for women with GDM. Furthermore, evidence suggests that lifestyle changes and antihyperglycemic agents may avert or delay the development of T2DM in women with GDM. [5-10] However, there is a low uptake of postpartum screening in mothers with GDM, and most women with GDM fail to attend postpartum visits. [11, 12] Identification of predictors of developing diabetes after delivery may allow health care professionals closely monitor those at risk and propose interventions during pregnancy, which is the period when these patients are more likely to follow them.

Hemoglobin A1c (HbA1c) analysis has previously been validated as a screening tool for undetected diabetes in early pregnancy; [13-15] however, it has not yet been established as a diagnostic test for GDM. Although HbA1c has a lower sensitivity than an oral glucose tolerance test (OGTT), [11, 16-20] it offers some benefits as it can be

performed in non-fasting patients and is more reproducible and convenient for physicians and patients than an OGTT. [21] Although women with GDM have normal glucose regulation shortly after birth, they have an increased risk of developing T2DM, metabolic syndrome, and cardiovascular diseases several months to years after delivery. [22-24] A meta-analysis that included 20 studies conducted across 14 countries reported that that women with history of GDM were 7 times more likely to develop T2DM when compared with those without such history. [22] In another report, it was stated that the rates of conversion from GDM to T2DM vary from 2.6% to 70% six to 28 years after delivery. [23] The discrepancy in the interval during which a woman with GDM might develop T2DM across studies is possibly due to genetic differences among the populations under investigation, the criteria used for GDM and T2DM diagnoses, the study inclusion criteria, and the duration of follow-up.

The aim of this study was to determine the association between risk factors of prediabetes HbA1c levels, age, body mass index (BMI), treatment regimen, and a history of GDM in women with GDM and impaired glucose tolerance postpartum. Few studies in the literature have reported on this.

METHODOLOGY

Study Design

This study was a retrospective chart review of all women with GDM refered to King Abdulaziz University Hospital, Jeddah, Saudi Arabia, between January 2014 and January 2018. Ethical approval was obtained prior to conducting the study [approval no. 106-18]. Informed consent was not required. The inclusion criterion was cases with GDM. However, women with confirmed diagnosis of pregestational diabetes were excluded from the study.

Data Collection

A data collection form was used to collect data from the electronic medical records of patients. The following parameters were collected: age, nationality, height, weight, BMI, co-morbidities, HbA1c, OGTT, and medications.

Definitions

According to the American Diabetes Association, [1] the diagnosis of GDM can be achieved with either a one-step 75 OGTT or a two-step approach (first a 50-g screen is performed, then a 100-g OGTT is conducted for those with positive results on the first test). At our institution, the 100-g and 75-g OGTT are usually performed at 24–28 weeks of pregnancy. About 6 weeks to 6 months postpartum, a 75-g OGTT is performed to rule out prediabetes or T2DM. Women were considered to have GDM on the one-step 75 OGTT when they had a fasting glucose level ≥92 mg/dL, one-hour glucose level ≥180 mg/dL, or two-hour glucose level ≥153 mg/dL. According to the two-step strategy, a diagnosis of GDM was reached if at least two of the following criteria are met or exceeded fasting plasma glucose of 95 mg/dL; one-hour plasma glucose level on an OGTT of 180 mg/dL; two-hour plasma glucose level on an OGTT of 155 mg/dL; and three-hour plasma glucose level on an OGTT of 140 mg/dL. Impaired glucose intolerance, which falls under the broader term “prediabetes”, was defined as a two-hour plasma glucose level between 140 and 199 mg/dL during a 75-g OGTT. [1]

Statistical Analysis

The analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS statistics), version 20.0. The data are expressed as frequency and percentages. Descriptive statistics were used to calculate the means, standard deviations, medians, and quartiles. Chi-square and Fisher’s exact tests were used to determine the relation between the two categorized variables. An independent samples t-test (two-tailed) was used to determine whether there was statistical evidence that the mean difference in the outcome between the two groups (normal result and pre-diabetes) was significant. Binomial logistic regression (univariate and multivariate) was used to predict whether an observation would fall into one of two categories: normal result and pre-diabetes of a dependent variable based on one or more independent (risk factors) variables. A $p<0.05$ was used as the cut-off value for significance.

RESULTS

We retrospectively reviewed the medical charts of 267 women, including 240 with normal and 27 with abnormal OGTT results. The average age was 35.36±6.21 years (35.01±5.70 years for women with normal results vs 36.96±6.80 years for pre-diabetic mothers; p=0.100). The mean BMI of the sample was in the obesity range

(32.92±7.38 kg/m^2), with the mean value being higher in women with normal OGTT results (32.84±7.64 kg/m^2 vs 31.02±7.05 kg/m^2 for pre-diabetic women, p=0.379). The mean HbA1c of the sample was 5.72%±1.26%, with the mean value being higher in prediabetic women (5.77%±1.77% vs 5.68%±1.27% for women with normal OGTT results; p=0.782). A summary of the women's demographic and medical characteristics is presented in Table 1.

An independent samples t-test showed that women with normal OGTT results and pre-diabetic women did not differ significantly in mean age (p=0.100), BMI (p=0.379), and HbA1c (p=0.782). Chi-square test showed that the outcome was significantly dependent on age, with the highest frequency of pre-diabetes being documented in women ≥45 years (p=0.005; Table 2). Likewise, the outcome was dependent on FBS (p=0.002), FBS plus two-point glucose (p<0.0005), random blood glucose (p<0.0005), diet control only (p=0.002), and oral hypoglycemic medication use (p=0.038). Conversely, the outcome was not dependent on nationality (p=0.397), medical history (p=0.818), history of thyroid disease (p=0.999), history of GDM (p=0.795), two-point blood glucose (p=0.081), insulin use (p=0.076), or thyroxine use (p=0.456).

We identified the predictive factors for postpartum persistence of glucose intolerance using univariate logistic regression analysis, which revealed a significant association between age ≥ 45 years (odds ratio [OR] 5.94, 95% confidence interval [CI] 1.67–21.19, p=0.006), diet control only (OR 0.28, 95% CI 0.12–0.64, p=0.002), and oral hypoglycemic use (OR 3.41, 95% CI 1.13–10.27, p=0.029) and a higher risk of developing postpartum glucose intolerance after controlling for other factors. No association was found between medical history of GDM, BMI, HbA1c level, and insulin use and a higher risk of postpartum glucose intolerance (Table 3).

The multivariate logistic regression analysis showed that age ≥ 45 years (OR 58.78, 95% CI 5.12–675.07, p=0.001), obesity (OR 0.15, 95% CI 0.02–0.93, p=0.041), oral hypoglycemic agent use (OR 11.05, 95% CI 2.00–61.12, p=0.006), and insulin use (OR 6.49, 95% CI 1.42–29.70, p=0.016) were significantly associated with an increased risk of postpartum glucose intolerance. No association was found between medical history of GDM and a higher risk of developing postpartum glucose intolerance (Table 4).

Table 1. Demographic and clinical characteristics of the sample

Variables	Frequency*	Percent
Age (years)		
<35	158	42.1
35–44	197	52.5
>44	20	5.3
Nationality		
Saudi	130	34.7
Non-Saudi	73	19.5
Body mass index		
Normal	23	6.1
Overweight	53	14.1
Obese	127	33.9
Medical history		
None	294	78.4
Thyroid disease	26	6.9
Gestational diabetes mellitus	49	13.1
Thyroid disease and gestational diabetes mellitus	4	1.1
HbA1c (%)		
<6.0	120	32.0
6.0–6.5	31	8.3
6.6–7.0	11	2.9
>7.0	16	4.3
Two-point blood glucose		
Yes	5	1.3
Fasting blood glucose		
Yes	21	5.6
Fasting blood glucose plus two-point blood glucose		
Yes	21	5.6
Random blood glucose		

Yes	220	58.7
Medication		
Insulin	56	14.9
No medication or diet only	265	70.7
Oral hypoglycemic agent	24	6.4
Thyroxine	30	8.0

Abbreviation: HbA1c, hemoglobin A1c

Table 2. Association between demographic and clinical variables and the outcome

Variables	Outcome		Total	p-value
	Normal result	Prediabetes		
Age				
<35	107 (91.5%)	10 (8.5%)	117 (100.0%)	0.005
35–44	124 (91.2%)	12 (8.8%)	136 (100.0%)	
>44	9 (64.3%)	5 (35.7%)	14 (100.0%)	
Nationality				
Saudi	84 (88.4%)	11 (11.6%)	95 (100.0%)	0.397
Non-Saudi	51 (92.7%)	4 (7.3%)	55 (100.0%)	
Body mass index				
Normal	14 (82.4%)	3 (17.6%)	17 (100.0%)	- *
Overweight	39 (90.7%)	4 (9.3%)	43 (100.0%)	
Obese	82 (91.1%)	8 (8.9%)	90 (100.0%)	
Medical history				
None	179 (89.5%)	21 (10.5%)	200 (100.0%)	-*
Thyroid disease	16 (88.9%)	2 (11.1%)	18 (100.0%)	
GDM	41 (91.1%)	4 (8.9%)	45 (100.0%)	
Thyroid disease & GDM	4 (100.0%)	0 (0.0%)	4 (100.0%)	
HbA1c index				
<6.0	87 (87.0%)	13 (13.0%)	100 (100.0%)	-*
6.0–6.5	22 (88.0%)	3 (12.0%)	25 (100.0%)	
6.6–7.0	8 (88.9%)	1 (11.1%)	9 (100.0%)	
>7.0	12 (85.7%)	2 (14.3%)	14 (100.0%)	
Two-point blood glucose				
No	237 (90.5%)	25 (9.5%)	262 (100.0%)	0.081
Yes	3 (60.0%)	2 (40.0%)	5 (100.0%)	
Fasting blood glucose				
No	227 (91.9%)	20 (8.1%)	247 (100.0%)	0.002
Yes	13 (65.0%)	7 (35.0%)	20 (100.0%)	
Fasting blood glucose + two-point glucose				
No	229 (93.1%)	17 (6.9%)	246 (100.0%)	0.001
Yes	11 (52.4%)	10 (47.6%)	21 (100.0%)	
Random blood glucose				
No	28 (59.6%)	19 (40.4%)	47 (100.0%)	0.001
Yes	212 (96.4%)	8 (3.6%)	220 (100.0%)	
No medication or diet only				
No	77 81.9%)	17 (18.1%)	94 (100.0%)	0.002
Yes	163 (94.2%)	10 (5.8%)	173 (100.0%)	
Oral hypoglycemic agent				
No	225 (91.1%)	22 (8.9%)	247 (100.0%)	0.038
Yes	15 (75.0%)	5 (25.0%)	20 (100.0%)	
Insulin therapy				
No	196 (91.6%)	18 (8.4%)	214 (100.0%)	0.076
Yes	44 (83.0%)	9 (17.0%)	53 (100.0%)	
Thyroxine therapy				
No	222 (90.2%)	24 (9.8%)	246 (100.0%)	0.456

Yes	18 (85.7%)	3 (14.3%)	21 (100.0%)	

Abbreviation: GDM, gestational diabetes mellitus; HbA1c, hemoglobin A1c
*No association could be computed as >20% of cells had counts <5.

Table 3. Logistic regression analysis for the predictors of postpartum prediabetes

Variables	Odds ratio	95% CI		p-value
		Lower	Upper	
Age (years)				
<35	-	-	-	0.013
35–441.04		0.43	2.49	0.938
≥455.94		1.67	21.19	0.006
Body mass index				
Normal	-	-	-	0.548
Overweight	0.48	0.10	2.41	0.372
Obese	0.46	0.11	1.93	0.285
History of gestational diabetes mellitus				
Yes	0.75	0.25	2.29	0.618
HbA1c (%)				
<6	-	-	-	0.995
6.0–6.5	0.91	0.24	3.48	0.894
6.6–7	0.84	0.10	7.25	0.871
>7	1.12	0.22	5.56	0.894
No medication or diet only				
Yes	0.28	0.12	0.64	0.002
Oral hypoglycemic agent				
Yes	3.41	1.13	10.27	0.029
Insulin therapy				
Yes	2.23	0.94	5.29	0.069

Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c

Table 4. Multivariate logistic regression analysis of variables associated with the risk of postpartum diabetes

Variables	Odds ratio	95% Confidence interval		p-value
		Lower	Upper	
Age (years)				
<35	-	-	-	0.004
35–441.59		.38	6.66	0.522
≥4558.78		5.12	675.07	0.001
Body mass index				
Normal	-	-	-	0.118
Overweight	.21	.03	1.43	0.110
Obese	.15	.02	.93	0.041
History of gestational diabetes mellitus				
Yes	.37	.06	2.22	0.275
Oral hypoglycemic agent				
Yes	11.05	2.00	61.12	0.006
Insulin therapy				
Yes	6.49	1.42	29.70	0.016

Abbreviation: CI, confidence interval

DISCUSSION

Our analyses confirm the observations of previous studies that the risk of postpartum persistence of glucose intolerance was increased in women with a history of GDM. [25, 26] In this retrospective cohort study, 27 of the 267 women with GDM (10.1%) developed glucose intolerance postpartum. This percentage is lower than that reported by other investigators who found that 32.1% of women with GDM who had postpartum OGTT met the criteria for prediabetes. [25] Other researchers found that a very high proportion of women with GDM developed

DM or impaired glucose tolerance within two years postpartum. The disparities between our findings and those of other investigators may be due to the differences in the sample and the diagnostic criteria used to establish the diagnosis of postpartum impaired glucose tolerance.

Apart from advanced maternal age, the predictors of postpartum glucose intolerance identified in our univariate analysis are different from those reported in previous reports. [25, 27] After controlling for confounding factors in the multivariate model, we found that age ≥45 years, obesity, oral hypoglycemic agent use, and insulin use were independently associated with a higher risk of developing postpartum impaired glucose tolerance. Similar to our findings, Capula et al. [25] reported that advanced maternal age and a high BMI before pregnancy were predictors of postpartum glucose intolerance. Although age has been recognized as a risk factor for T2DM, [27, 28] some investigators did not find an association between a woman's age at GDM diagnosis and a higher risk of postpartum glucose intolerance. [29] Other investigators have reported conflicting results regarding the association between higher pre-pregnancy BMI and the risk for postpartum glucose intolerance [30, 31] and insulin therapy during pregnancy. [26] However, more consistent results have been reported in studies investigating the association between glucose levels during pregnancy and glucose intolerance after delivery. In previous studies, FBS during an OGTT was a predictor of postpartum glucose intolerance. [29, 30, 32] Although some investigators have reported an association between abnormal one-hour OGTT results during pregnancy and postpartum T2DM, [29, 33] others found that abnormal two-hour OGTT results were associated with postpartum prediabetes. [29, 34] Given that some predictors of postpartum glucose intolerance, such as obesity, are modifiable through lifestyle interventions, our results suggest that it is necessary to develop strategies aimed at educating women of child-bearing age about the need to maintain a healthy weight.

Other factors that are associated with a higher risk of postpartum glucose intolerance include a family history of T2DM, personal history of GDM, higher FBS at GDM diagnosis, and previous diagnosis of polycystic ovarian syndrome. [25] In our study, we did not explore the effect of family history of T2DM or previous diagnosis of polycystic ovarian syndrome on women with GDM after delivery.

This study should be interpreted in light of its limitations. First, this study has all the limitations inherent of retrospective chart reviews. Second, this was a single-center study that included a limited number of subjects. Third, follow-up data could only be obtained for women one year postpartum, and the data were unavailable for some cases. It would have been worth obtaining data for women two years after delivery, as a previous report suggested an association between the HbA1c level at GDM diagnosis. [35] Additionally, evidence suggests that the state of glucose metabolism two years after delivery is a reflection of glucose metabolism during gestation.

CONCLUSION

Overall, age ≥45 years, obesity, oral hypoglycemic agent use, and insulin use are independently associated with a higher risk of developing postpartum impaired glucose tolerance in patients with GDM, confirming the findings of previous reports. These findings need to be confirmed in larger prospective studies. This would allow prediction of risk factors in the antepartum period to prevent the occurrence of prediabetes in GDM cases.

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