ORIGINAL ARTICLE

Prevalence of Glucose Intolerance in Early Postpartum and Its Associated Factors Among Women With History of Gestational Diabetes Mellitus

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ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) is a known risk of developing type 2 diabetes mellitus in the future. The prevalence of glucose intolerance in the early postpartum period among women with GDM ranges between 13.5% to 50%, depending on the population. This study aims to estimate the prevalence of glucose intolerance 6 to 12 weeks postpartum and its associated factors among women with GDM in Putrajaya, a federal government administrative centre of Malaysia. **Methods:** All women with history of GDM who had oral glucose tolerance test (OGTT) done 6 to 12 weeks postpartum at Putrajaya clinic from June 2013 to December 2016 were included. Sociodemographic data, details of GDM diagnosis and management, and postpartum OGTT results were collected. **Results:** There were 443 women with a mean age of 31.7 years. Postpartum OGTT showed 58 (13.2%) had prediabetes and 10 (2.1%) had diabetes. The independent risk factors associated with early postpartum glucose intolerance were 2-hour plasma glucose of diagnostic OGTT, gestational age of GDM diagnosis and HbA1c level in pregnancy. **Conclusion:** A diagnosis of postpartum glucose intolerance can occur early in women with history of GDM. Factors such as 2-hour plasma glucose of diagnostic OGTT, gestational age of GDM diagnosis and HbA1c level increase the risk of postpartum glucose intolerance.

Keywords: Early postpartum, Glucose intolerance, Gestational diabetes mellitus

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INTRODUCTION

"Gestational diabetes mellitus (GDM) is any point of glucose intolerance first detected during pregnancy, regardless of whether the condition persisted after delivery"(1). Glucose intolerance is classified into pre-diabetes (impaired fasting glucose [IFG], impaired glucose tolerance [IGT], or combined IFG/IGT) and type 2 diabetes mellitus (T2DM)(2). Women with GDM are at risk of progressing to glucose intolerance in the year after their index pregnancy(3), but some develop glucose intolerance even in the early postpartum period. A systematic review looking at early postpartum glucose intolerance included studies that had an oral glucose tolerance test (OGTT) done as early as 6 weeks to a year postpartum. The prevalence of early postpartum glucose intolerance ranges between 12.3% to 60% depending on population(4–7). In Malaysia, a study reported 12.3% women had glucose intolerance at 6 weeks postpartum (7).

Diagnosing pre-diabetes early in these women would allow the introduction of interventions to delay the progression to overt T2DM and complications. Most international organizations such as the World Health Organization (WHO), American Diabetes Association (ADA), and National Diabetes Data Group (NDDG) recommend that a 75-g OGTT to be done at 6 to 12 weeks postpartum (8). In line with this, The Malaysian Clinical Practice Guideline of Diabetes (CPG T2DM) recommends an OGTT at 6 weeks postpartum and then the annual screening for diabetes (9).

Several studies have attempted to determine factors associated with early postpartum glucose intolerance. A systematic review that included 13 studies found that age, body weight before pregnancy, early diagnosis of GDM, receiving insulin treatment during pregnancy, and FPG and 2hPG level at diagnosis in pregnancy were risk factors for glucose intolerance in early postpartum(4). There was 6.6 times increased risk of having abnormal postpartum OGTT at a maternal age of more than 40 years(10). Some studies demonstrated that the risk of women with GDM developing T2DM are Asian ethnicity(11) and overweight(6). In another study, "women with FPG ≥ 5.4 mmol/L and 2hPG ≥ 9.3 mmol/L

during OGTT in pregnancy have 2.5-fold increased risk of developing postpartum glucose intolerance" (12).

Since diabetes is a disease with many complications, early detection in high-risk groups such as those with history of GDM will help in early treatment of pre-diabetes and prevent the progression to diabetes. A paucity of glucose intolerance in early postpartum data especially pre-diabetes data will lead to unrecognized of the high-risk patients, thus no proper follow up will be given. Therefore, the aim of this study was to determine the prevalence of pre-diabetes and diabetes in women with a history of GDM at 6 to 12 weeks postpartum period, and to identify the factors predicting postpartum glucose intolerance.

MATERIALS AND METHODS

Study design

This was a cross sectional study using secondary data from 3 health clinics in Putrajaya i.e Klinik Kesihatan Presint 9, Klinik Kesihatan Presint 11 and Klinik Kesihatan Presint 18. The study population was women with gestational diabetes mellitus (GDM) who underwent OGTT between 6 and 12 weeks postpartum from 1st June 2013 till 31st December 2016. Exclusion criteria were: (i) pre-existing type 1 or type 2 diabetes; (ii) use of diabetes medication at time of postpartum OGTT; and (iii) any disease or condition that can affect the glucose level such as thyrotoxicosis, acromegaly, Cushing etc. According to Malaysian T2DM 2015, all pregnant women with high risk factors such as body mass index (BMI) >27 kg/m2, previous big baby weighing ≥ 4 kg, previous GDM, 1st degree relative with diabetes, history of unexplained intrauterine death, history of congenital anomalies, glucose detection in the urine at the 1st or any prenatal visit and current obstetric problem such as hypertension were screened for GDM with a 75-g modified OGTT as early as possible after the booking visit and again at 24 to 28 weeks if the initial test was normal . Diagnosis of GDM was made when FPG ≥ 5.6 mmol/L or 2hPG ≥ 7.8 mmol/L or both.

Sample size estimation was calculated using the population proportion formula suggested by Charan & Biswas in 2013(13). Prior data by Fatin et al. indicate the proportion of the prevalence of postpartum intolerance in women with history of GDM is 0.12(7). If the Type 1 error probability and precision are 0.05 and 0.05 respectively with an additional 20% of drop out, the sample size needed was 204 samples.

Data collection

According to Malaysia CPG T2DM 2015, OGTT should be done 6 weeks postpartum with the blood glucose interpretation as: 1) normal glucose level (NGT), defined by a FPG level <6.1mmol/L and 2hPG level <7.8 mmol/L; 2) impaired fasting glucose (IFG), defined by a FPG level from 6.1 to 6.9 mmol/L with a 2hPG level <7.8 mmol/L; 3) impaired glucose tolerance (IGT), defined a FPG level <6.1 mmol/L and a 2hPG from 7.8 to 11.0 mmol/L, 4) combined IFG/IGT, defined by a FPG from 6.1 to 6.9 mmol/L and a 2hPG from 7.8 to 11.0 mmol/L, and 5) diabetes defined by a FPG level ≥7.0 mmol/L or a 2hPG level ≥11.1 mmol/L(9). The outcome measures were abnormal glucose tolerance which consists of pre-diabetes (IGT, IFG and combined IFG/IGT) and T2DM at 6-12 weeks postpartum. The variables such as age, race, parity, family history of diabetes, previous history of GDM, FPG and 2hPG of diagnostic OGTT, gestational age of GDM diagnosis, insulin treatment needed during pregnancy, gestational age of insulin initiation, maximum insulin dosage per day during pregnancy and glycosylated haemoglobin (HbA1c) during pregnancy were retrieved from electronic medical record and patients' files. The data were recorded into data collection form. Data was extracted and entered into an excel file for subsequent data analysis.

Statistical analysis

The primary outcome which is the prevalence of glucose intolerance (pre-diabetes and T2DM) were presented as numbers and percentages. Continuous variables (age, weight at first antenatal visit, BMI, FPG and 2hPG of diagnostic OGTT and HbA1c) were expressed as mean and standard deviation, and categorical variables (race, parity, family history of diabetes, past history of GDM, gestational age of GDM diagnosis, need for insulin therapy during pregnancy, and gestational age of insulin initiation) as numbers and percentages unless otherwise stated. The differences of normally distributed variables between women with normal and abnormal postpartum OGTT result were analysed by Independent t-test and One-way ANOVA. Chi-square and Fisher's exact test were used to analyse categorical variables. Univariate and multivariate logistic regression were used to test for relationship between the probability of occurrence of glucose intolerance at 6-12 weeks after delivery and risk factors such as age, pre-pregnancy BMI, and previous history of GDM, gestational age of GDM diagnosis, FPG and 2hPG of diagnostic OGTT, HbA1c level and insulin treatment needed during pregnancy. The analysis findings were demonstrated as odds ratios (OR) and 95% confidence interval (95%CI). The significance level was set at $p<0.05$. IBM SPSS Statistics Version 21 was used for all data analysis.

Ethical clearance

The approval of this study was obtained from Medical Research and Ethics Committee, Ministry of Health, Malaysia, NMRR-17-201-34480. There was no ethical issue encountered in this study.

RESULTS

There was a total of 452 women who underwent postpartum OGTT in Klinik Kesihatan Putrajaya from 2013 to 2016 and 443 women fulfilled the

inclusion criteria. Nine women were excluded due to pre-existing Type 2 DM and already on antidiabetic medication postpartum. Sixty-eight women (15.3%) had early postpartum glucose intolerance, in which 60 (13.5%) had pre-diabetes and 8 (1.8%) had diabetes. Demographic and clinical characteristics of women who had normal and abnormal postpartum OGTT are summarized in Table I.

In general, women with abnormal OGTT were significantly older and had higher BMI, as compared to women who had normal OGTT. In comparison with women with normal postpartum OGTT, women with abnormal OGTT had significantly higher frequency of previous history of GDM and required insulin treatment during pregnancy. They were also diagnosed GDM earlier in the pregnancy with higher mean FPG and 2hPG of diagnostic OGTT, and higher HbA1c level. No significant difference in family history of diabetes.

A univariate logistic regression analysis showed age, BMI, history of previous GDM, FPG and 2hPG of diagnostic OGTT, gestational age of GDM diagnosis, insulin treatment needed during pregnancy and HbA1c level in pregnancy had higher risk for postpartum glucose intolerance (Table II). Multivariate logistic regression analysis was carried out to identify demographic and antepartum variables that are significantly and independently associated with abnormal postpartum OGTT (Table III). We included those variables that were tested statistically significantly by univariate analysis and noted only 2hPG of diagnostic OGTT, gestational age of GDM diagnosis and HBA1c during pregnancy were the independent risk factors of early postpartum glucose intolerance in these women.

Table II: Univariate logistic regression for factors associated with early postpartum glucose intolerance

Factors	Crude OR	95% CI	p-value
Age (year)	1.073	1.01, 1.14	0.031
Weight at 1st antenatal visit (kg)	1.02	1.00, 1.04	0.052
BMI (kg/m²)	1.03	0.98, 1.07	0.269
Previous GDM			
Yes	1.86	1.10, 3.17	0.022
No	1.00(ref)		
Family History of DM			
Yes	1.260	0.75, 2.12	0.384
No	1.00(ref)	1.00(ref)	
Diagnostic OGTT result			
FPG of OGTT	2.33	1.70, 3.19	<0.001
2hPG of OGTT	1.61	1.34, 1.91	<0.001
Gestational age at GDM diagnosis	0.94	0.89, 0.98	0.004
Insulin treatment			
Yes	4.67	2.16, 10.60	<0.001
No	1.00(ref)		
HbA1c	4.47	2.56, 7.84	<0.001

OR=odd ratio, 95%CI= 95% Confident Interval

DISCUSSION

The results of our study demonstrated that 15.3% of

Table I: Demographic and clinical characteristics of women who had postpartum OGTT

Variables	Total (n=443)	Postpartum OGTT		p-value	Missing, n(%)
		Normal (n=375)	Abnormal (n=68)		
Age, (years)	31.6 (4.05)	31.6 (3.89)	32.7 (4.76)	0.030[a]	0 (0)
Race, n (%)				0.642[b]	0 (0)
Malay	433(97.7)	366 (97.6)	67 (98.5)		
Chinese	3 (0.7)	2 (0.5)	1 (1.5)		
Indian	2 (0.5)	3 (0.6)	0		
Others	5 (1.1)	5 (1.3)	0		
Parity, n (%)				0.331[c]	0 (0)
1	91 (20.5)	79 (21.1)	12 (17.6)		
2– 5	338 (76.3)	286 (76.0)	52 (76.5)		
>5	14 (3.2)	10 (2.7)	4 (5.9)		
Weight at 1st antenatal visit, (kg)	64.8 (13.37)	64.3(13.37)	67.7 (13.09)	0.051[a]	0 (0)
BMI (kg/m²), median (IQR)	26.6 (5.65)	25.9 (6.75)	27.3 (7.66)	0.086[d]	0 (0)
Previous GDM, n(%)				0.020[c]	0 (0)
Yes	136 (30.7)	107 (28.5)	29 (42.6)		
No	307 (69.3)	268 (71.5)	39 (57.4)		
Family History of DM, n(%)				0.383[c]	0 (0)
Yes	226 (51.0)	188 (50.1)	38 (55.9)		
No	217 (49.0)	187 (49.9)	30 (44.1)		
Gestational age at GDM diagnosis (week), median (IQR)	24.3 (5.84)	28 (9.0)	20 (10.0)	0.004[b]	0 (0)
Insulin treatment, n(%)				<0.001[c]	0 (0)
Yes	31 (7.0)	18 (4.8)	13 (19.1)		
No	412 (93.0)	357 (95.2)	55 (80.9)		
Diagnostic OGTT result					
FBS (mmol/l), median(IQR)	4.9 (0.76)	4.9 (0.74)	5.2 (1.21)	<0.001[a]	0 (0)
2hPG (mmol/l), median(IQR)	8.6 (1.24)	8.5 (1.17)	9.0 (2.87)	<0.001[a]	0 (0)
HbA1c (%)	5.17 (0.56)	5.1 (0.52)	5.6 (0.6)	<0.001[a]	53 (12.0)

Data are mean ± S.D., unless otherwise stated.
IQR = Interquartile range
[a] Independent t-test [b] Mann-Whitney test [c] Chi-square test [d] Fisher exact test

Table III: Multivariate logistic regression for factors significantly associated with early postpartum glucose intolerance

Factors	Adj. OR	95% CI	p-value*
2hPG of diagnostic OGTT	1.39	1.14, 1.69	0.001
Gestational age at GDM diagnosis	0.92	0.87, 0.97	0.003
HbA1c during pregnancy	3.39	1.84, 6.27	<0.001

Adj. OR= Adjusted odd ratio, 95%CI= 95% Confident Interval
*Adjusted for age, weight at first antenatal booking, BMI, previous history of GDM, fasting plasma glucose and 2-hour plasma glucose of diagnostic OGTT, insulin treatment needed in pregnancy and HbA1c level.

the GDM women had glucose intolerance at 6-12 weeks postpartum. This prevalence is slightly higher compared to a local study done in 72 public health clinics in Selangor (14) .The study looked mainly at the prevalence of GDM and associated factors where only 53.8% women came for OGTT 6 weeks after delivery in which 12.1% had abnormal OGTT. The definition of abnormal OGTT was not defined in the study. The prevalence would be expected to be higher if all the GDM women came for OGTT 6 weeks postpartum. The women who had GDM in this study were also older compared to our study where 30.4% women were more than 35 years old whereas the mean age in our study was 31.6 years. Our study did not look at the percentage of women who had GDM and returned for OGTT but only focused on the GDM women that came for OGTT 6 weeks post-delivery.

In comparison to another study done in Johor Bahru, the prevalence of postpartum glucose intolerance was 12.3% (7) . This study was done at primary health clinics in Johor Bahru who had OGTT at 6 weeks postpartum from January to June 2016. Only 122/341 (35.7%) women came back for OGTT 6 weeks postpartum and 15/122 (12%) had postpartum glucose intolerance. The median age of women was 31.69 ± 4.79. years.

Another local study done by Chew et al. among GDM women who did OGTT between 3 months to 15 years postpartum reported the prevalence of postpartum glucose intolerance of 30% (14). The prevalence is expected to be higher as there is increased risk of progression to glucose intolerance in the years after the index pregnancy (15). In addition, different diagnostic criteria were used in the study, namely WHO 2002 criteria. The difference from the criteria that we used was the value of FPG which was ≥ 5.6 mmol/l instead of ≥ 6.1 mmol/l which was used in our study.

There was a study done in Korea using the same diagnostic criteria for postpartum glucose intolerance with our study showed a prevalence of pre-diabetes of 44.8% and diabetes of 5.2% (6). Women were older with mean age of 34.2 ± 3.7 years. Despite the lower BMI, which was 23.5 ± 3.8, the prevalence of pre-diabetes and diabetes were still higher compared to our study. Another study in Japan showed 45/123 (36.6%) had glucose intolerance 8-12 weeks after delivery (5). This study showed similar result as the study done in Korea where women were older with lower BMI (19.2-23.1). There is a possibility of the influence of certain ethnicity in a study by Sinha et al. which showed Asian ethnicity has higher risk of glucose intolerance 6 to 12 weeks postpartum (11) .

Our study also examined the risk factors associated with early postpartum glucose intolerance. In univariate logistic regression analysis, we revealed that age, history of previous GDM, FPG and 2hPG of diagnostic OGTT, gestational age of GDM diagnosis, insulin treatment needed during pregnancy and HbA1c level in pregnancy associated with higher risk for postpartum glucose intolerance. Similar finding was also seen in the local study done in primary health clinics in Johor Bahru which showed that the HBA1c, insulin usage, NICU admission and hospital follow up were associated with glucose intolerance 6 weeks postpartum. In the study, the mean HbA1c done was 5.4% where as in our study was 5.5% (7). Another local study by Logakodie et al. reported insulin usage and working mother as the risk factors for postpartum glucose intolerance. In these studies, no multivariate analyses were done as the number of women with glucose intolerance was small.

In multivariate analysis, we reported that 2hPG of diagnostic OGTT was associated with 1.3-fold increased risk of glucose intolerance at 6-12 weeks postpartum. This finding is similar to a study done by Ogonowski et al. on 318 GDM women who had OGTT 6 weeks postpartum where 2hPG of diagnostic OGTT was associated with early postpartum glucose intolerance (15). The mean 2hPG was slightly higher in Oganowski et al. (9.5 ± 0.2mmol/L) compared to our finding (9.2 ± 3.16 mmol/L). Chew et al. has reported the same finding where the 2hPG at diagnosis was significantly higher only in women with Type 2 diabetes when compared to women with normal glucose tolerance. However, this study involved women where the duration from the index pregnancy with GDM ranged from 3 months to 15 years postpartum (16). The association of 2hPG with the risk of early postpartum glucose intolerance explains the possibility of insulin resistance in these women. A possible reason for this finding is due to insulin resistance which has association with 2hPG compared to fasting blood glucose.

Another significant finding in our multivariate analysis was HbA1c level during pregnancy. Oganowski et al. reported that HbA1c taken at the time of GDM diagnosis was associated with 2.36 times risk of developing postpartum glucose intolerance. The timing of the OGTT was at 24-28 weeks which was the same as in our study. The mean HbA1c was similar with our study which was 5.5 %. Another study done among GDM women at 6-12 weeks postpartum showed HbA1c levels of ≥ 6.2% had 5.1-fold increased risk of postpartum diabetes(17). In our study, there were only 88% of the women who had HbA1c done. The available studies

on HbA1c had shown a level of more than 5.5% to be the risk factor for development of postpartum glucose intolerance or diabetes. According to our guideline HbA1c is not used to diagnose GDM but it is important parameter to monitor glycemic control. Although it is not recommended as a routine test in Malaysia, these results probably showed that HbA1c has a role in predicting the risk of post-partum glucose intolerance.

Another independent significant risk factor in our study was gestational age of GDM diagnosis where the earlier diagnosis of GDM had higher risk of early postpartum glucose intolerance. In our study, the patients who had postpartum glucose intolerance were diagnosed to have GDM at the median gestational age of 20 weeks. Sinha et al. has also reported a significant finding of diagnosis of GDM before 20 weeks of pregnancy with postpartum glucose intolerance amongst Indo-Asians(11).The same findings were also seen in another study done by Ogonowski among Caucasian women. This shows the importance of screening for diabetes postpartum in women with earlier diagnosis of GDM.

Previous studies had shown a significant association in other factors with glucose intolerance at 6-12 weeks postpartum. Kim et al. reported higher BMI, insulin dosage during late pregnancy and family history of diabetes were independently associated with postpartum diabetes(5). A study on Italian women who had 6-8 weeks postpartum OGTT had shown age, pre-pregnancy BMI and FPG at diagnostic OGTT were associated with increased risk of postpartum glucose intolerance. Another study in Australia done among GDM women who returned for OGTT at 6-12 weeks revealed FPG of diagnostic OGTT ≥5.4 mmol/L predicted postpartum glucose intolerance(12). However, we did not find any significant association between these factors and early postpartum glucose intolerance. This is probably due to the small sample size of women with postpartum glucose intolerance.

The limitation of this study is that we were unable to include the data of women who did not return for postpartum OGTT to the same clinic. This may affect the true prevalence of glucose intolerance in Putrajaya. Another limitation of the study is that majority of the women were Malays. Further studies are needed for multi-ethnic inclusion with a bigger sample which may represent the population of Malaysia.

CONCLUSION

In conclusion, the prevalence of early postpartum glucose intolerance among women with history of GDM is 15.3% where 2-hour plasma glucose of diagnostic OGTT, gestational age of GDM diagnosis and HbA1c level during pregnancy are associated risk factors. It is important to detect early postpartum glucose intolerance to prevent progression to Type 2 DM.

ACKNOWLEDGEMENTS

We would like to express our gratitude to the Director General of Health for the permission to publish this article. We also thank the district health officer of Putrajaya, doctors, and nurses from Klinik Kesihatan Putrajaya for their assistance during the study.

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