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## OBSTETRICS

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# Postpartum Glucose Intolerance in Gestational Diabetes Mellitus Women

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### ABSTRACT

**Objective:** To study the prevalence of and determine antepartum factors for postpartum glucose intolerance in women with gestational diabetes mellitus (GDM).

**Materials and Methods:** Medical records of women who had been diagnosed with GDM and underwent 75-gram oral glucose tolerance test (OGTT) at six weeks postpartum in our institution between January 2004 and June 2008 were included. The clinical features of those who had postpartum normoglycemia, and glucose intolerance were compared. Multivariable analysis was used to determine risk factors for postpartum glucose intolerance.

**Results:** Of 330 women, 190 (57.6%) had postpartum normoglycemia and 140 (42.4%) had glucose intolerance (28.8% and 13.6% developed impaired glucose tolerance and permanent diabetes respectively). In comparison to women who remained normoglycemic, those who developed postpartum glucose intolerance had significantly higher degree of hyperglycemia (glucose challenge test [GCT] value and plasma glucose levels of OGTT) and GDM classification, and higher rate of insulin use. In a multivariable analysis, higher GCT level ( $\geq 200$  mg/dl), 1-hour ( $\geq 190$  mg/dl) and 3-hour plasma glucose of OGTT ( $\geq 145$  mg/dl) were identified as the antepartum risk factors for postpartum glucose intolerance (3.6-fold;  $p < 0.001$ , 5.7-fold;  $p < 0.001$  and 19.4-fold;  $p < 0.001$  respectively).

**Conclusion:** The prevalence of postpartum glucose intolerance in the present GDM population was 42.4%. Women with higher GCT level, 1-hour and 3-hour plasma glucose of OGTT are at increased risk of postpartum glucose intolerance.

**Keywords:** antepartum characteristics; gestational diabetes mellitus; postpartum glucose intolerance

### Introduction

Gestational diabetes mellitus (GDM) is a state of glucose intolerance with first onset during

pregnancy, and is a common medical disorder facing the obstetricians in their daily practice.<sup>(1)</sup> Evidences from several studies suggest that the GDM-affected

women are at increased risk of both adverse perinatal effects and future type 2 diabetes.<sup>(2-4)</sup> Regarding the latter complication, the prevalence rates of permanent diabetes following GDM were varied, ranging from 3-41%.<sup>(2,5-7)</sup> This depends on the criteria used for GDM diagnosis, population background, and timing of permanent diabetes diagnosis post delivery.

Considering that the global prevalence of GDM has increased over the past decades, this would in turn lead to an increase in the prevalence of future type 2 diabetes. Thus, identifying the GDM individuals who are at high risk for this metabolic disease might be useful because the screening and preventive program could be targeted to the selected population. Some characteristic features of the GDM women were identified as the independent risk factors for overt diabetes later in life. These included high parity,<sup>(1)</sup> obesity,<sup>(4)</sup> early-onset GDM,<sup>(2,3,5)</sup> higher degree of hyperglycemia,<sup>(4,8)</sup> and insulin requirement.<sup>(6,9)</sup>

Although several authors reported the prevalence rates of and risk factors for postpartum glucose intolerance in women with GDM, the data are still limited in the Southeast Asians particularly in Thai people. As it is known that such population group is at high risk to develop diabetes, the preventive program, especially primary prevention for this metabolic disorder, would accordingly be beneficial. The aim of the present study was to determine the prevalence of postpartum glucose intolerance in Thai women who were affected by GDM. Further aim was to explore antepartum risk factors for the development of this metabolic derangement.

## Materials and Methods

The study was conducted after an approval of the Bangkok Metropolitan Administration (BMA) Ethics Committee for Researches Involving Human Subjects. Eligibility criteria were pregnant women who presented for antenatal booking within the first trimester ( $\leq 14$  weeks), were diagnosed with GDM based on the National Diabetes Data Group criteria,

and consecutively underwent a 75-gram oral glucose tolerance test (OGTT) at six weeks postpartum at Department of Obstetrics and Gynecology, BMA Medical College and Vajira Hospital between January 2004 and June 2008. Individuals who had known overt diabetes, had elsewhere delivery, and those whose obstetric charts had incomplete clinical data were excluded from the study.

According to the departmental policy of universal screening for GDM, all pregnant women in the study underwent glucose challenge test (GCT) for GDM screening. Women without any risk factors were screened at 24-28 weeks of gestation. The women with the following characteristics were screened at an initial visit or as soon as possible: age  $\geq 35$  years, body mass index (BMI)  $\geq 27$  kg/m<sup>2</sup>, any first-degree relatives with type 2 diabetes, history of GDM in previous pregnancy, prior delivery of a newborn weighing  $\geq 4000$  grams, history of any adverse obstetric events ( $\geq$  two miscarriages, congenital malformation, or stillbirth), or glucosuria. If the first GCT was normal, the test would be repeated at 28-32 weeks. Individuals with abnormal GCT (glucose value  $\geq 140$  mg/dl) would be scheduled for a diagnostic 100-gram OGTT. For a diagnosis of GDM, the National Diabetes Data Group (NDDG) criteria were used.<sup>(10)</sup> All women who were diagnosed with GDM were managed with diet modification and insulin therapy if needed, under close surveillance of the endocrinologists. After delivery, these GDM women would be scheduled for a 75-gram OGTT at 6-week postpartum. The results were interpreted according to the criteria of the American Diabetes Association (ADA): normal glucose tolerance (NGT) referred to fasting plasma glucose  $< 110$  mg/dl and 2-h plasma glucose  $< 140$  mg/dl, impaired glucose tolerance (IGT) meant fasting plasma glucose between 110-125 mg/dl or 2-h plasma glucose between 140-199 mg/dl, and diabetes mellitus referred to fasting plasma glucose  $\geq 126$  mg/dl or 2-h plasma glucose  $\geq 200$  mg/dl.<sup>(11)</sup> Postpartum glucose intolerance included both IGT and diabetes.

Obstetric records of the eligible women

were reviewed. Data collected were: maternal demographics, risk factors for GDM, gestational ages (GA) at which screening and diagnostic tests were performed, 50-gram GCT and all four OGTT values, treatment modality of GDM, and postpartum 75-gram OGTT result. BMI was determined as the first-visit BMI.

Statistical analysis was performed with the SPSS software package version 11.5 (SPSS Inc., Chicago, IL, USA) The Stata 7.0 (Stata Corp., College station, TX, USA) was additionally used for analyzing the  $\chi^2$  for trend. Continuous variables among the three groups (NGT, IGT, and diabetes) were compared using one-way analysis of variance (ANOVA); when overall analyses revealed statistically significant, the intergroup comparisons were then made by the Scheffe method. Categorical variables between two- and three groups were compared with the  $\chi^2$  test and  $\chi^2$  for trend respectively. Stepwise logistic regression analysis adjusted for the significant variables in Table 1 was used to determine the predictors of the development of glucose intolerance at 6-week postpartum. P-value of < 0.05 was considered statistically significant.

## Results

During the study period, total of 645 women who had been diagnosed with GDM received an appointment for 75-gram OGTT at 6-week postpartum. Of these, 330 (51.2%) actually attended the postpartum clinic and underwent the test. Mean age and mean BMI of the 330 women were  $31.9 \pm 5.3$  years and  $24.9 \pm 4.8$  kg/m<sup>2</sup> respectively. One hundred and ninety (57.6%) had postpartum NGT while 140 (42.4%) developed glucose intolerance; 28.8% and 13.6% developed IGT and permanent diabetes respectively. Antepartum characteristics of women with postpartum normal glucose tolerance, impaired glucose tolerance and diabetes are shown in Table 1. Among these three groups of women, there were no statistically significant differences in overall mean age, mean GA at GCT, rates of multipara, family history of GDM, and abnormal 2-h value ( $\geq 165$  mg/dl) of OGTT. The variables which

were significantly different among these three groups were mean BMI, mean GA at GDM diagnosis, rates of GCT  $\geq 200$  mg/dl, abnormal fasting value ( $\geq 105$  mg/dl) of OGTT, abnormal 1-h value ( $\geq 190$  mg/dl) of OGTT, abnormal 3-h value ( $\geq 145$  mg/dl) of OGTT, GDM class A2, and insulin use.

The significant variables in Table 1 were entered into a multivariable analysis to determine the independent risk factors for glucose intolerance at 6-week postpartum (Table 2). From an analysis, GCT  $\geq 200$  mg/dl, 1-h value of OGTT  $\geq 190$  mg/dl, and 3-h value of OGTT  $\geq 145$  mg/dl were identified as the three significant factors which were respectively associated with 3.6-fold, 5.8-fold, and 19.4-fold risks of glucose intolerance. These three variables were also found to be the independent factors contributing to permanent diabetes at 6-week postpartum.

The study women were further categorized into four subgroups according to their number of significant predictive factors (i.e. 0–3) for postpartum glucose intolerance. In subgroup of women whose number of risk factors was zero, the incidence of glucose intolerance at six weeks was only 33.3% (all women had IGT) whereas subgroup of women whose number of risk factors was three would have a high probability of 78.5% to develop glucose intolerance (27.7% for IGT and 50.8% for diabetes). Details of the incidence of postpartum glucose intolerance in each subgroup are shown in Table 3.

**Table 1.** Clinical and metabolic characteristics of women with gestational diabetes according to glucose tolerance status postpartum

	Postpartum glucose tolerance status			p value
	NGT N=190	IGT N=95	Diabetes N=45	
Age(years), mean (SD)	31.6 (5.2)	32.1(5.0)	31.6(6.1)	0.25
Parity, n (%)				0.88
Primipara	88(46.3%)	41(43.2%)	20(44.4%)	
Multipara	102(53.7%)	54(56.8%)	25(55.6%)	
BMI(kg/m <sup>2</sup> ), mean (SD)	24.2(4.5)	25.3(5.0)	27.4(4.8)†	<0.001
GA at GCT (weeks), mean (SD)	23.1(8.2)	23.3(8.5)	20.8(8.3)	0.21
GA at GDM diagnosis (weeks), mean (SD)	27.2(6.5)*	26.0(7.3)‡	22.4(8.3)†	<0.001
Family history of DM, n (%)				0.38
Yes	46(24.2%)	28(29.5%)	15(33.3%)	
No	144(75.8%)	67(70.5%)	30(66.7%)	
Antepartum GCT >200 mg/dl, n (%)	30(15.8%)*	35(36.8%)‡	38(84.4%)†	<0.001
Antepartum OGTT(mg/dl), n (%)				
Fasting ≥105 mg/dl	28 (14.7%)*	30(31.6%)‡	36(80.0%)†	<0.001
1-h >190 mg/dl	138 (72.6%)*	80(84.2%)‡	43(95.6%)†	0.001
2-h >165 mg/dl	167(87.9%)	85(89.5%)	45(100%)	0.05
3-h >145 mg/dl	81(42.6%)*	83(87.3%)‡	42(93.3%)†	<0.001
Class of GDM, n (%)				<0.001
GDM A1	162(68.6%)*	65(27.5%)‡	9(3.8%)†	
GDM A2	28(29.8%)*	30(31.9%)‡	36(38.3%)†	
Insulin use, n (%)				<0.001
Yes	12(6.3%)*	15(15.8%)‡	31(68.9%)†	
No	178(93.7%)*	80(84.2%)‡	14(31.1%)†	

BMI = Body Mass Index; GA = Gestational age; GCT = Glucose Challenge Test; GDM = Gestational Diabetes Mellitus;

IGT = Impaired Glucose Tolerance; NGT = Normal Glucose Tolerance; OGTT= Oral glucose tolerance test

\* p value < 0.05 when compared normal glucose tolerance and impaired glucose tolerance.

† p value < 0.05 when compared normal glucose tolerance and diabetes.

‡ p value < 0.05 when compared impaired glucose tolerance and diabetes.

**Table 2.** Multivariable analysis for predictors of the development of glucose intolerance at 6 weeks postpartum

Factor	Odds ratio*	95%CI	p value
BMI( $\geq 27$ kg/m <sup>2</sup> )	1.76	0.91-3.44	0.91
GA at diagnosis GDM( $\geq 24$ weeks)	0.83	0.40-1.72	0.40
GCT > 200 mg/ml	3.57	1.77-7.20	<0.001
OGTT			
Fasting > 105 mg/ml	1.96	0.20-19.27	0.56
1-h $\geq 190$ mg/ml	5.75	2.80-11.81	<0.001
3-h $\geq 145$ mg/ml	19.37	9.40-39.92	<0.001
insulin use	2.21	0.66-7.45	0.20
GDMA2	0.79	0.08-7.29	0.83

BMI = Body Mass Index; GA = Gestational age; GCT = Glucose Challenge Test;

GDM = Gestational Diabetes Mellitus; GDM A2 = Gestational Diabetes Mellitus class A2;

OGTT= Oral glucose tolerance test

\*Adjusted for the other variables in the Table.

**Table 3.** Incidence of postpartum glucose intolerance in each subgroup of women categorized by their number of independent risk factors for glucose intolerance

Number of predictor	Number of women	Number (%) of IGT	Number (%) of diabetes
0	6	2 (33.3)	0
1	136	36 (26.5)	1 (0.7)
2	123	39 (31.7)	11 (8.9)
3	65	18 (27.7)	33 (50.8)

GCT = glucose challenge test; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test.

Predictor : 1) GCT > 200 mg/ml, 2) 1-h OGTT  $\geq 190$  mg/ml, 3) 3-h OGTT >145 mg/ml

## Discussion

The prevalence of glucose intolerance including type 2 diabetes is increasing rapidly worldwide. This metabolic disorder becomes a significant public health problem due to its certain risk to micro- and macrovascular diseases,<sup>(11)</sup> such as, blindness, stroke, or end-stage renal disease. From a health economic point of view, preventing the occurrence of this metabolic dysfunction is better than treating the patients with diabetes-related complications. Thus, it is important for healthcare providers to identify at-risk individuals, so that screening and preventive program could be targeted

to the selected population.

A number of conditions are recognized as factors contributing to glucose intolerance or type 2 diabetes; one of which is GDM. Regarding the GDM-affected women in the present study, the overall rate of glucose intolerance development at 6-week postpartum was as high as 42.4%. This prevalence rate was comparable to that (41.2%) in the study of Jang et al in Korean women<sup>(8)</sup> but was higher than those (15-22%) in previous studies conducted in Caucasian, African-American, or Hispanic populations.<sup>(2,3,5,6)</sup> Aside from the influence of ethnicity, the criteria used to diagnose GDM (NDDG,

ADA, or world health organization [WHO]) and postpartum glucose intolerance (ADA or WHO), timing of blood glucose testing at postpartum period, and years of study in previous reports and in the present study were dissimilar. These may be the potential factors for the differences in the prevalence rates of postpartum glucose intolerance. Nevertheless, the high prevalence rates of postpartum glucose intolerance which were found in the study of Jang et al and the present study supported previous proposition<sup>(11)</sup> that peoples with South or East Asian origins are at high-risk of type 2 diabetes. These data should alert the physicians to be aware of future IGT or diabetes in the Asian women with a history of GDM, although without any other risk factors.

Several clinical features during pregnancy of the GDM women were reported to be associated with the development of glucose intolerance in postpartum period. These included obesity, earlier GA at diagnosis of GDM, degree of hyperglycemia during pregnancy, and insulin use.<sup>(2-5,8,9)</sup> In a univariate analysis, such characteristics were also related to postpartum glucose intolerance in the present study (Table 1). However, when a multivariate analysis was performed, there were only three independent factors left; all of which were GCT  $\geq 200$  mg/dl, abnormal 1-h ( $\geq 190$  mg/dl), and 3-h ( $\geq 145$  mg/dl) values of OGTT. These findings were in agreement with the results from previous studies<sup>(3-5,8)</sup> which demonstrated that higher degree of hyperglycemia during pregnancy or severity of GDM were independently associated with future glucose intolerance. Few studies<sup>(4,8,12,13)</sup> reported that the association between postpartum diabetes or IGT and the metabolic severity during pregnancy (as represented by higher levels of GCT or OGTT values) might be related to pancreatic  $\beta$ -cell dysfunction. This was corroborated by the findings of a poor insulin response to an OGTT.<sup>(8,13)</sup> In the present study, the authors did not measure insulin level under OGTT tested in the GDM women during pregnancy. Further prospective studies are needed to explore the association between insulin response

to an OGTT or other markers of impaired  $\beta$ -cell function and the development of postpartum glucose intolerance in Thai women.

There are some limitations of the present study. Due to a retrospective nature in design, data of some cases might be unnoticeably missed. In addition, although the authors attempted to identify antepartum predictive factors for postpartum glucose intolerance, there might be other variables which were not included in the analysis. Lacking of data on women who did not return for postpartum blood glucose testing is another possible issue; given that only 51.2% of the study population underwent postpartum blood glucose testing, therefore reliability of the results might be lessened if the clinical features of women who did and did not return were markedly different. To be noted, according to the high rate (48.8%) of women who did not visit the postpartum clinic for glucose testing in the present study which were similar to the prevalence rates (52.2-63%) in previous studies,<sup>(6,8,13)</sup> further studies are required to identify factors related to this condition. This may help in improving the quality of preventive program for future IGT or type 2 diabetes in the GDM-affected women.

Based on the results of the present study, the authors agree with previous authors that the screening and preventive protocols for future glucose intolerance are crucial for women with a history of GDM. In view of the 78.5% prevalence of glucose intolerance in individuals whose numbers of the predictive factors are three, the authors suggest that this group of women should undergo blood glucose screening every year, although their OGTT results at 6-week postpartum are normal. Long-term investigations for the prevalence rates of IGT and permanent diabetes in the GDM group are necessary and might be useful in initiating an appropriate interval period to monitor blood glucose testing. Aside from the screening program, the potential action of the practitioners to reduce the prevalence of postpartum glucose intolerance is to encourage the GDM women to control their weight, to change their lifestyle and dietary habits, and to aware of diabetes-



related complications. With this stringent preventive policy, the authors believe that long-term outcomes of the GDM-affected women would be improved.

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## ความผิดปกติของความทนน้ำตาลกลูโคสในระยะหลังคลอดในสตรีที่มีภาวะเบาหวานขณะตั้งครรภ์

พริณ ปิตะหงษ์นันท์, ชาดากานต์ ผลไธการ, สุนนมาลย์ มนัสศิริวิทยา, บุษบา วิริยะศิริเวช\*

**วัตถุประสงค์ :** เพื่อศึกษาหาความชุกและปัจจัยในระยะก่อนคลอดที่สัมพันธ์กับการเกิดความผิดปกติของการทดสอบความทนน้ำตาลกลูโคส 75 กรัม ที่ระยะ 6 สัปดาห์หลังคลอดในหญิงตั้งครรภ์ที่มีภาวะเบาหวานขณะตั้งครรภ์ที่มาฝากครรภ์และคลอด

**รูปแบบวิจัย :** การวิจัยเชิงพรรณนาแบบย้อนหลัง

**วัสดุและวิธีการ :** หญิงตั้งครรภ์ที่มารับการฝากครรภ์ และได้รับการวินิจฉัยว่ามีภาวะเบาหวานขณะตั้งครรภ์และมารับการตรวจติดตามภาวะเบาหวานหลังคลอดที่วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล โดยเก็บข้อมูลตั้งแต่ปี 2547 จนกว่าจะครบจำนวนที่ต้องการ จะถูกค้นหาระเบียบผู้ป่วยใน รวบรวมประวัติส่วนตัว ผลตรวจทางห้องปฏิบัติการ นำมากรอกข้อมูลในแบบบันทึกการวิจัย

**ตัววัดที่สำคัญ :** ความชุกและปัจจัยในระยะก่อนคลอดที่สัมพันธ์กับการเกิดความผิดปกติของการทดสอบความทนน้ำตาลกลูโคส 75 กรัม ที่ระยะ 6 สัปดาห์หลังคลอด

**ผลการวิจัย :** จากจำนวนตัวอย่างหญิงตั้งครรภ์ 330 คนพบว่า 190 คน(57.6%) มีค่าการทดสอบความทนน้ำตาลกลูโคส 75 กรัมปกติ และ 140 คน(42.4%) มีค่าการทดสอบความทนน้ำตาลกลูโคส 75 กรัมผิดปกติ และจากการศึกษาปัจจัยในระยะก่อนคลอดที่สัมพันธ์กับการเกิดความผิดปกติของการทดสอบความทนน้ำตาลกลูโคส 75 กรัม ที่ระยะ 6 สัปดาห์หลังคลอดในหญิงตั้งครรภ์ โดยพบว่าอายุ, จำนวนการตั้งครรภ์และจำนวนการคลอดบุตรไม่มีความแตกต่างกันอย่างมีนัยสำคัญ ในขณะที่เมื่อเปรียบเทียบระหว่างกลุ่มที่ผลการทดสอบน้ำตาลปกติและผิดปกติพบว่าระดับของน้ำตาลในการตรวจคัดกรองภาวะเบาหวานขณะตั้งครรภ์ที่สูงและระดับน้ำตาลที่ใช้ในการวินิจฉัยเบาหวานขณะตั้งครรภ์ที่สูง, ความรุนแรงของภาวะเบาหวานขณะตั้งครรภ์และความต้องการอินซูลินที่สูงขึ้นมีความแตกต่างกันอย่างมีนัยสำคัญ

**สรุป :** จากการศึกษาพบความชุกในการเกิดความผิดปกติของการทดสอบความทนน้ำตาลกลูโคส 75 กรัม ที่ระยะ 6 สัปดาห์หลังคลอดเท่ากับร้อยละ 42.4 และพบว่าปัจจัยในระยะก่อนคลอดที่สัมพันธ์กับการเกิดความผิดปกติของการทดสอบความทนน้ำตาลกลูโคส 75 กรัม ที่ระยะ 6 สัปดาห์หลังคลอดในหญิงตั้งครรภ์ได้แก่ ระดับของน้ำตาลในการตรวจคัดกรองภาวะเบาหวานขณะตั้งครรภ์ที่สูงเกิน 200 มิลลิกรัมต่อเดซิลิตร, ค่าระดับน้ำตาลที่ 1 ชั่วโมงหลังรับประทานน้ำตาล 100 กรัมที่สูงเกิน 190 มิลลิกรัมต่อเดซิลิตรและค่าระดับน้ำตาลที่ 3 ชั่วโมงหลังรับประทานน้ำตาล 100 กรัมที่สูงเกิน 145 มิลลิกรัมต่อเดซิลิตร

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