Original Contribution

Kurume Medical Journal, 62, 47-51, 2015

Predictors of Abnormal Glucose Tolerance in the Early Postpartum Period in Patients with Gestational Diabetes

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Received 13 March 2015, accepted 31 October 2015
J-STAGE advance publication 25 May 2016

Edited by YUJI HIROMATSU

Summary: This study was designed to investigate the clinical predictors of abnormal glucose tolerance 5-7 weeks after delivery. Subjects were 155 women diagnosed with gestational diabetes mellitus (GDM) between October 2005 and September 2013 whose pregnancy and delivery were managed at our center. Subjects were divided into a normal glucose tolerance group (NGT; n = 113), or abnormal glucose tolerance group (AGT; n = 42) with borderline or overt diabetes mellitus, based on 75-g oral glucose tolerance test (75 gOGTT) results 5-7 weeks after delivery. We extracted profiles by which abnormal glucose tolerance levels 5-7 weeks after delivery were predicted using a classification and regression tree (CART) from parameters measured at the time of GDM diagnosis. Logistic regression analysis was used to determine prediction accuracy. Subjects with fasting plasma glucose (FPG) $\geq$ 92 mg/dL and immuno-reactive insulin level <100 μU/mL 60 min after load (IRI60min) at time of diagnosis showed a significantly higher risk of developing abnormal glucose tolerance 5-7 weeks after delivery than subjects with FPG <92 mg/dL ($p < 0.0001$). Subjects with FPG $\geq$92 mg/dL and IRI60min $\geq$100 μU/mL had the same risk as those with FPG of <92 mg/dL. Patients with gestational diabetes who met the criteria specified above at diagnosis were at a higher risk of developing diabetes mellitus in the future. By explaining this issue to patients, we expect to improve the rate of postpartum follow-up. This should facilitate early detection of diabetes, and help prevent associated complications.

Key words classification tree, gestational diabetes mellitus, insulin secretion, postpartum period, glucose tolerance test

INTRODUCTION

O'Sullivan et al. [1] reported that approximately 40% of women who had gestational diabetes mellitus (GDM) developed diabetes mellitus 20 years later. Bellamy et al. [2] reported that meta-analysis using data from 10,859 incidents of Type 2 diabetes mellitus onset, from 20 different reports on 67,5445 women in 14 countries between 1960 and 2009, showed that the relative risk of Type 2 diabetes mellitus occurring in women who had had gestational diabetes, during a follow-up period ranging from 6 months to 28 years, was 7.43-fold higher (95% confidence interval, 4.49-11.51) than in non-pregnant women. These reports demonstrate that women with a history of gestational diabetes mellitus are at a higher risk of developing diabetes mellitus in the future, and that early detection and intervention are

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Abbreviations: AGT, abnormal glucose tolerance group; BMI, body mass index; CART, classification and regression tree; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HOMA-IR, homeostasis model assessment-insulin resistance; HOMA-beta, homeostasis model assessment beta cell function; IADPSG, International Association of the Diabetes and Pregnancy Study Groups; IRI, immuno-reactive insulin level; I.I., insulinogenic idex; NGT, normal glucose tolerance group; 75gOGTT, 75-g oral glucose tolerance.

important to prevent the occurrence of diabetes.

Insulin resistance associated with pregnancy is genetic, and there are also environmental factors in GDM women. After delivery, impaired glucose tolerance usually returns to normal, because insulin resistance associated with pregnancy improves rapidly. However, in some patients, this impaired glucose tolerance persists even after delivery, and as this may progress to diabetes mellitus in some cases, postpartum follow-up is important. By informing GDM women during their pregnancy of the risk of developing diabetes mellitus, it is expected there will be an increase in the rate of postpartum follow-ups. Early detection of diabetes mellitus and early intervention are important in preventing complications. If it were possible to predict during pregnancy, which women might later develop abnormal glucose tolerance suitable explanations could be provided to these patients during antenatal examinations or during admission for delivery. Here we conducted a study on the predictors of abnormal glucose tolerance in the early postpartum period, in patients with GDM.

MATERIALS AND METHODS

This study was approved by the local ethics board (Kurume University School of Medicine, number #12021) and performed in accordance with the Declaration of Helsinki. All participants gave written informed consent to participate in the study.

Patients who had been diagnosed with GDM between October 2005 and September 2013, and whose pregnancy and delivery had been managed at our center, were recruited for the present study. GDM was diagnosed using the IADPSG (International Association of the Diabetes and Pregnancy Study Groups) diagnostic criteria. Explanatory variables used were a family history of diabetes mellitus, body mass index (BMI) prior to pregnancy, insulin therapy during pregnancy, plasma glucose value after 75-g oral glucose tolerance (75gOGTT) in second trimester diagnosis of gestational diabetes (fasting and 30, 60, and 120 min after load), immunoreactive insulin (IRI) value (fasting and 30, 60, and 120 min after load), HbA1c level, the insulinogenic index (I.I., an index of early insulin secretion ability), homeostasis model assessment-insulin resistance (HOMA-IR, an index of insulin resistance), and homeostasis model assessment beta cell function (HOMA-beta, an index of pancreatic islet beta cell function). The objective variable was the presence of abnormal glucose tolerance by 75g OGTT performed 5-7 weeks postpartum. Subjects were divided into two groups: the normal glucose tolerance group (NGT), comprised 113 subjects whose 75gOGTT results were normal 5-7 weeks after delivery, and the abnormal glucose tolerance group (AGT) comprised 42 subjects whose results during the same period indicated borderline or overt diabetes mellitus.

Statistical Analysis

In order to compare patient backgrounds between the two groups, continuous variables were analyzed using the Mann–Whitney *U* test, and categorical variables were analyzed using Fisher's exact test. Subsequently, the above-mentioned explanatory variables were added to the model simultaneously, and a classification and regression tree (CART) was constructed to extract profiles to predict abnormal glucose tolerance at 5-7 weeks postpartum. CART analysis can be used either to produce an accurate classifier or to uncover the predictive structure of a problem. The computer program CART incorporates this standardized set of splits. CART analysis is a tree-building technique in which several "predictor" variables are tested to determine how they impact the outcomes of traditional methods, as in multivariate regression [3]. CART analysis has been used in a variety of applications in collaboration with non-statistically oriented chemists, doctors, meteorologists, and physicists [4]. Logistic regression was used to analyze whether there was a significant difference in the percentage of patients who developed abnormal glucose tolerance and the total number of extracted profiles. A p value of <0.05 was considered to be significant. JMP Ver.10 (SAS Institute Inc., Cary, NC, USA) and SAS Ver.13 (SAS Institute Inc., Cary, NC, USA) were used for analysis.

RESULTS

In total, 155 women were enrolled in this study. The characteristics of the NGT and AGT groups are summarized in Table 1. No significant differences were observed between the two groups in terms of maternal age, gestational age at diagnosis of GDM, or pre-pregnancy BMI. The median gestational age at delivery was significantly lower in the AGT group (38.2 weeks) than the NGT group (38.5 weeks) ($p = 0.007$). The AGT group had a higher incidence of family history of diabetes mellitus (48.8%) than the NGT group (22.5%) ($p = 0.003$). Furthermore, the AGT group required insulin therapy during pregnancy more frequently (42.5%) than the NGT group (19.5%) ($p = 0.006$).

A prognosis prediction model was created using CART (Fig. 1). FPG values were used at the first bifurcation and divided into values <92 mg/dL and val-

TABLE 1.
The characteristics of the NGT and AGT groups

	NGT group (n = 113)	AGT group (n = 42)	p value
Maternal age (years)	34 (32-37)	34 (31-37)	0.978
Gestational age at diagnosis of GDM (weeks)	26.0 (16.3-28.6)	25.2 (16.5-27.6)	0.448
Gestational age at time of delivery (weeks)	38.5 (38.1-39.4)	38.2 (38.0-38.5)	0.006*
Neonatal body weight (g)	3078 (2390-3361)	2880 (2390-3207)	0.053
Pre-pregnancy BMI	23.9 (20.1-27.3)	26.6 (21.2-31.6)	0.179
Family history of diabetes mellitus†	25/111 (22.5%)	20/41 (48.8%)	0.003*
Insulin therapy during pregnancy	22/113 (19.5%)	17/40 (42.5%)	0.006*

GDM, gestational diabetes mellitus; BMI, body mass index; NGT group, normal glucose tolerance group; AGT, abnormal glucose tolerance group.
†: Family history of diabetes mellitus was considered to be the presence of diabetes mellitus in a 2nd degree relative or closer
*: $p < 0.05$
Data are expressed as median (range) or number of patients (percentage). Statistical analysis was performed using the Mann-Whitney U test or Fisher's exact test.

TABLE 2.
The results of logistic regression analysis

Profiles	Odds ratio	Confidence interval		p value
		Below 95%	Above 95%	
FPG <92 mg/dL	1	reference		
FPG ≥ 92 mg/dL and IRI60min ≥ 100 μU/mL	1.03	0.27	3.25	0.96
FPG ≥ 92 mg/dL and IRI60min < 100 μU/mL	8.14	3.55	19.6	<0.0001

FPG, fasting plasma glucose; IRI60min, immunoreactive insulin value 60 min after glucose load

ues ≥ 92 mg/dL in the CART. Only 14 out of 90 subjects (15.6%) had abnormal glucose tolerance in the group with FPG <92 mg/dL. The group with FPG ≥ 92 mg/dL was further subdivided into two groups using the IRI value 60 min after glucose load IRI <100 μU/mL and IRI ≥ 100 μU/mL. In the IRI <100 μU/mL group, 24 out of 40 subjects (60.0%) had abnormal glucose tolerance. In the IRI ≥ 100 μU/mL group, 4 out of 25 subjects (16.0%) had abnormal glucose tolerance.

We analyzed whether the ratio of abnormal glucose tolerance significantly varied using logistic regression analysis (Table 2). Subjects with FPG ≥ 92 mg/dL and IRI <100 μU/mL after 60 min of glucose load at diagnosis were at significantly greater risk of having abnormal glucose tolerance in the early postpartum period compared with subjects having FPG <92 mg/dL (odds ratio, 8.14-fold, $p < 0.0001$: 95% confidence interval, 3.54 to 19.62). Subjects with FPG ≥ 92 mg/dL and IRI >100 μU/mL after 60 min of glucose load at diagnosis

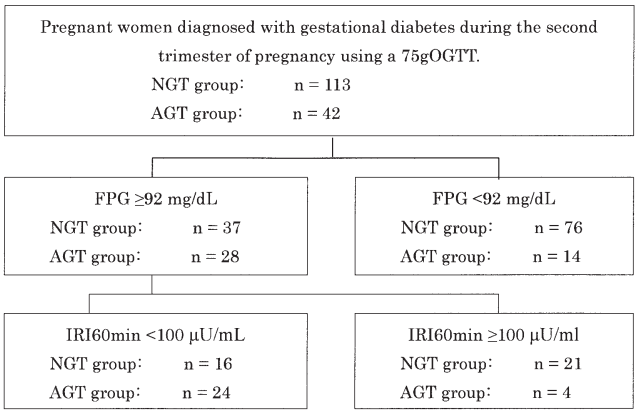

Fig. 1. A prediction model from CART for abnormal glucose tolerance after delivery prognosis

CART, classification regression tree; 75gOGTT, 75-g oral glucose tolerance test; NGT group, normal glucose tolerance group; AGT, abnormal glucose tolerance group; FPG, fasting plasma glucose; IRI60min, immunoreactive insulin value 60 min after glucose load.

had the same risk of developing abnormal glucose tolerance as subjects with FPG <92 mg/dL (odds ratio, 1.03-fold, p = 0.96: 95% confidence interval, 0.27 to 3.25).

DISCUSSION

In this study, the factors extracted using CART were FPG values and IRI 60 min after glucose load by 75gOGTT. Subjects with FPG ≥ 2 mg/dL and IRI <100 μU/mL after 60 min of glucose load at diagnosis with gestational diabetes had an 8.14-fold higher risk of developing abnormal glucose tolerance in the early postpartum period than subjects with FPG <92 mg/dL.

Risk factors for developing diabetes mellitus from gestational diabetes mellitus included obesity (central obesity/visceral fat) [3,5-7], a higher value of fasting plasma glucose [5, 8, 9], and decreased total insulin secretion [6,9]. Schaefer-Graf et al. [10] reported that women with ≥ 2 risk factors have a high risk for abnormal glucose tolerance in the postpartum period. Christian et al. [11] reported that 2hr 75g-OGTT ≥ 140 mg/dL, HDL cholesterol less than 50 mg/dL, and age older than 35 years were identified as the best predictors for developing diabetes after GDM.

Various FPG values have been reported as a risk factor for diabetes mellitus after delivery. Damm et al. [9] reported 3-fold higher relative risk at FPG of 101 mg/dL compared with FPG of 85 mg/dL, and Steinhart et al. [12] reported 11-fold higher relative risk at FPG values greater than 106 mg/dL, compared with values lower than 106 mg/dL. In this study, we divided subjects into those with FPG values <92 mg/dL and those with FPG values ≥ 92 mg/dL.

In addition, the next bifurcation subdivided subjects into those with IRI <100 μU/mL and those with IRI ≥ 100 μU/mL after 60 min of glucose load. Logistic regression showed that even among subjects with FPG ≥ 92 mg/dL, IRI ≥ 100 μU/mL negated the risk of developing abnormal glucose tolerance during the early postpartum period (p = 0.96). Fukushima et al. [13] reported that the peak normal IRI value was reached after 60 min, and the borderline and diabetic peak IRI values were reached after 90 min in Japanese subjects. These results reflect the fact that insulin secretion is delayed in Japanese subjects with abnormal glucose tolerance . In our study, the risk of developing abnormal glucose tolerance during the early postpartum period was greater when the IRI was <100 μU/mL after 60 min of glucose load because of delayed insulin secretion.

In conclusion, pregnant women diagnosed with GDM who have FPG ≥ 92 mg/dL and IRI <100 μU/mL at 60 min after glucose load 75gOGTT, had a significantly greater risk of having abnormal glucose tolerance in the early postpartum period. By explaining this risk factor to patients, we expect to improve the rate of postpartum follow-up. This should lead to the early detection of diabetes, and help prevent the complications of this disease.

ACKNOWLEDGMENTS: This study was supported by the Alumni Association of the Department of Obstetrics and Gynecology, Kurume University School of Medicine.

DISCLOSURE: The authors have no relationships with companies that may have a financial interest in the information contained in the manuscript.

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