

Risk Factors for Pregnancy Complications and Postpartum Glucose Intolerance in Women With Gestational Diabetes Mellitus

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Abstract

This prospective cohort study aimed to evaluate the risk factors for pregnancy complications and postpartum glucose intolerance (GI) in women with gestational diabetes mellitus (GDM). A total of 140 women with GDM were enrolled. Of these, 115 underwent a 75-g oral glucose tolerance test (OGTT) at 12 weeks after delivery. Clinical factors and parameters in the antepartum 75-g OGTT associated with pregnancy complications and postpartum GI were evaluated. Women with GDM experienced pregnancy complications, including hypertensive disorders of pregnancy (HDP, n=19), preterm delivery (PD, n=17), heavy-for-date (HFD, n=19), and light-for-date (LFD, n=12), and 22 of the 115 women with GDM developed postpartum GI. The univariate and multivariable logistic regression analyses revealed the following risk factors: histories of hypertension (odds ratio [OR], 23.8; 95% confidence interval [CI], 4.2–134.7; $p<0.01$) for HDP; histories of hypertension (OR, 9.8; 95% CI, 2.5–38.9; $p<0.01$) for PD; HbA1c levels (OR, 7.6; 95% CI, 1.5–37.9; $p<0.05$) for HFD; and oral deposition index (DI) (OR, 0.1; 95% CI, 0.02–0.7; $p<0.01$) for postpartum GI. Higher HbA1c levels and lower oral DI on the antepartum 75-g OGTT may be useful markers for identifying GDM women who are at high risk for HFD and postpartum GI, respectively.

Introduction

Pregnant women with gestational diabetes mellitus (GDM) have an increased risk of pregnancy and neonatal complications, including hypertensive disorders of pregnancy (HDP), preterm delivery (PD), polyhydramnios, shoulder dystocia, macrosomia, heavy-for-date (HFD) newborn, light-for-date (LFD) newborn, and neonatal hypoglycemia^{1–6}.

Previous studies have evaluated associations between maternal clinical or laboratory findings of antepartum 75-g oral glucose tolerance test (OGTT) and pregnancy complications in women with GDM. PD and HDP are associated with normal fasting and elevated post-load blood glucose (BG) levels⁶. HFD is associated with elevated fasting and normal post-load BG levels^{6,7} and post-load hyperglycemia⁸. Moreover, macrosomia is associated with post-load hyperglycemia⁸, fasting hyperglycemia, and excessive gestational weight gain^{7,9}.

A systematic review and meta-analysis has demonstrated that women with GDM have a 7.4-fold increased risk of developing type 2 diabetes mellitus after delivery compared with those without GDM¹⁰. We have reported that, in women with GDM, the low insulinogenic index (II) levels on the antepartum 75-g OGTT is a risk factor for developing glucose intolerance (GI) during the early postpartum period¹¹.

This prospective cohort study aimed to assess predictive clinical factors and laboratory parameters in the antepartum 75-g OGTT for pregnancy complications and GI during the early postpartum period among women with GDM.

Results

Of 3,494 pregnant women who had singleton deliveries at the Kobe University Hospital, 140 (4.0%) were diagnosed with GDM from January 2011 to December 2018. The indications for the antepartum 75-g OGTT in the 140 pregnant women with GDM were as follows: a 1-hr BG level on a 50-g glucose challenge tests \geq 140 mg/dL (n=99); casual BG level \geq 100 mg/dL (n=13); suspicion of HFD and/or polyhydramnios on ultrasound examinations during pregnancy (n=10); and presence of other risk factors of GDM, including a history of GDM, obesity, and persistent glycosuria (n=18). Twenty-five of the 140 women with GDM refused to receive a 75-g OGTT at 12 weeks after delivery. Therefore, 115 of the 140 (82.1%) women with GDM were included in the analyses of risks for GI during the early postpartum period.

Clinical factors and parameters in the antepartum 75-g OGTT associated with the occurrence of HDP in women with GDM

Nineteen of the 140 (13.6%) pregnant women with GDM had HDP. **Table 1** shows the clinical characteristics of participants and result of logistic regression analyses of factors associated with HDP. The group of GDM women with HDP (HDP group) had a significantly higher body mass index (BMI) prior to pregnancy ($p<0.05$) and the frequency of a history of hypertension ($p<0.01$) than the group without HDP (non-HDP group). Furthermore, the HDP group had a significantly less weight gain during pregnancy ($p<0.01$) than the non-HDP group. No significant differences were observed in any parameter in the antepartum 75-g OGTT between the two groups.

Univariate logistic regression analyses demonstrated that the BMI prior to pregnancy (odds ratio [OR], 1.1; 95% confidence interval [CI], 1.0–1.2; $p<0.05$), weight gain during pregnancy (OR, 0.8; 95% CI, 0.8–0.9; $p<0.01$), frequency of the presence of a history of hypertension (OR, 43.3; 95% CI, 8.2–229.4; $p<0.01$), and 1-hr BG levels (OR, 1.0; 95% CI, 0.96–1.0; $p<0.05$) were associated with the occurrence of HDP in women with GDM. Multivariable logistic regression analyses of the three factors revealed that the presence of a history of hypertension (OR, 23.8; 95% CI, 4.2–134.7; $p<0.01$) was a single independent factor associated with HDP.

Clinical factors and parameters in the antepartum 75-g OGTT associated with the occurrence of preterm delivery at 36 or less gestational weeks (GW) in women with GDM

Seventeen of the 140 (12.1%) pregnant women with GDM had PD at 36 or less GW. Eleven of the 17 (64.7%) pregnancies resulted in preterm births following a threatened premature labor, and the remaining 6 (35.3%) resulted in medically indicated preterm births (5 for HDP; 1 for exacerbations of underlying diseases).

Table 2 shows the clinical characteristics of participants and result of logistic regression analyses of factors associated with PD. The group of GDM women with PD (PD group) had a significantly higher parity ($p<0.05$) and frequency of the presence of a history of hypertension ($p<0.01$) than the group without PD (non-PD group).

Univariate logistic regression analyses demonstrated that the presence of a history of hypertension (OR, 9.8; 95% CI, 2.5–38.9; $p<0.01$) was a single independent factor associated with PD in pregnant women with GDM.

Clinical factors and parameters in the antepartum 75-g OGTT associated with the occurrence of HFD infants in women with GDM

Nineteen of the 140 (13.6%) women with GDM had HFD newborns. **Table 3** reveals the clinical characteristics of participants and results of logistic regression analyses of factors associated with HFD. The group of GDM women with HFD (HFD group) had a significantly higher weight gain during pregnancy ($p<0.05$) and HbA1c levels ($p<0.05$) than the group without HFD (non-HFD group).

Univariate logistic regression analyses demonstrated that HbA1c levels (OR, 7.6; 95% CI, 1.5–37.9; $p<0.05$) was an independent factor associated with HFD.

Clinical factors and parameters in the antepartum 75-g OGTT associated with the occurrence of LFD infants in women with GDM

Twelve of the 140 (8.6%) pregnant women with GDM had LFD newborns. **Table 4** exhibits the clinical characteristics of participants and result of logistic regression analyses of factors associated with LFD. The group of GDM women with LFD (LFD group) had a significantly lower HbA1c levels ($p<0.05$) than the group without LFD (non-LFD group).

No clinical factors and parameters in the antepartum 75-g OGTT were selected as factors associated with LFD in pregnant women with GDM by univariate logistic regression analyses.

Clinical factors and parameters in the antepartum 75-g OGTT associated with the occurrence of postpartum GI in women with GDM

Twenty-two of the 115 (19.1%) pregnant women with GDM had GI at 12 weeks after delivery, including one, two, and 19 women with diabetes mellitus (DM), impaired fasting glucose (IFG), and impaired glucose tolerance (IGT), respectively.

Table 5 shows the clinical characteristics of participants and results of logistic regression analyses of factors associated with GI during the early postpartum period. The group of GDM women with postpartum GI (GI group) had a significantly lower oral DI ($p<0.01$) than the group without postpartum GI (non-GI group).

Univariate logistic regression analyses demonstrated that fasting BG (FBG) (OR, 1.0; 95% CI, 1.0–1.1; $p<0.05$) and oral disposition index (DI) (OR, 0.1; 95% CI, 0.03–0.5; $p<0.01$) were associated with the occurrence of GI during the early postpartum period in women with GDM. Multivariable logistic regression analyses of the two factors revealed that oral DI (OR, 0.1; 95% CI, 0.02–0.7; $p<0.01$) was an independent factor associated with GI during the early postpartum period.

Discussion

This study used the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria for diagnosing GDM¹², and 140 of the 3,494 (4.0%) pregnant women who had singleton deliveries were diagnosed with GDM. Because medians of the prevalence of GDM in Japan were reported to be 2.8%–13.0%¹³, the prevalence of GDM in this study was thought to be valid. The incidences of HDP, PD, HFD newborns, and LFD newborns among women with GDM were 13.6%, 12.1%, 13.6%, and 8.6%, respectively. The incidences of pregnancy complications in women with GDM that were diagnosed based on the IADPSG criteria have been reported as follows: HDP, 8.2%¹⁴; PD, 6.5%–8.4%^{15,16}; large-for-gestational-age (LGA) newborns, 9.1%–21.4%^{15,16}; and small-for-gestational-age (SGA) newborns, 7.6%–8.0%^{16,17}. Although the present study had higher incidences of HDP and PD than the previous studies, the incidence (19.1%) of GI during the early postpartum period in women with GDM was comparable to those (16.7%–36.6%) in previous studies^{11,18,19}. Our study had higher incidences of HDP and PD than the previous studies because Kobe University Hospital has a maternal-fetal center where pregnant women with HDP and threatened premature labor are often referred from other hospitals and clinics.

For the first time, this prospective cohort study of pregnant women with GDM simultaneously assessed both the clinical factors and parameters in the antepartum 75-g OGTT for pregnancy complications and GI at 12 weeks after delivery by logistic regression analyses using a stepwise approach, and revealed the following risk factors: the presence of histories of hypertension both for HDP and PD at 36 or less GW; higher HbA1c levels for HFD infants; and lower oral DI for postpartum GI.

Obesity, chronic hypertension, and a history of HDP have been reported as major risk factors for HDP^{20,21}. Our result is comparable with those in previous studies.

Previous prospective cohort studies, including a general population of pregnant women, revealed that older maternal age, lower BMI, and GDM were risk factors for PD^{22,23}. When subjects were limited to women with GDM as in our study, not maternal age and BMI prior to pregnancy, but a history of hypertension was selected as a risk factor for PD. In addition, we found that a history of hypertension was an independent risk factor for HDP in women with GDM. It is likely that pregnancies of GDM women with histories of hypertension result in preterm births due to recurrent HDP.

Several retrospective studies demonstrated that elevated fasting BG levels were associated with HFD^{6,7}, and others suggested that post-load hyperglycemia was associated with HFD⁸. In this prospective cohort study, the univariate and multivariable logistic regression analyses demonstrated that the higher HbA1c level was a risk factor for HFD in pregnant women with GDM. This result indicated that HFD in women with GDM was more closely associated with continuous hyperglycemia, which higher HbA1c levels reflect, rather than higher levels of fasting or post-load BG on the antepartum 75-g OGTT.

The present study also found neither differences in clinical factors and parameters in the antepartum 75-g OGTT between the LFD and non-LFD groups nor any factors associated with the occurrence of LFD in

pregnant women with GDM. SGA/LFD newborns are likely to be associated with severe DM^{7,24} rather than GDM.

Univariate and multivariable logistic regression analyses revealed for the first time that oral DI was an independent risk factor for postpartum GI in pregnant women with GDM. Previous retrospective studies demonstrated that low II and II/fasting IRI were associated with postpartum GI in patients with GDM^{18,25}. A previous prospective cohort study of 72 pregnant women with GDM revealed that a low II in the antepartum 75-g OGTT is an independent risk factor for developing GI during the early postpartum period¹¹. It was reported that among the Japanese-American adults, including males and non-pregnant women, the low oral DI was predictive of developing DM in the future²⁶. DI represents a hyperbolic relationship between insulin secretion and insulin sensitivity^{27,28}. Therefore, this parameter represents the insulin secretory capacity of pancreatic β cells adjusted for insulin sensitivity²⁶. An adequate insulin secretory response of pancreatic β cells adapting to changes in insulin sensitivity might be significant for the maintenance of normal glucose tolerance during the postpartum period. Pregnant women with low oral DI on the antepartum 75-g OGTT are at high risk not only for GI during the early postpartum period, but also for DM in the future.

This prospective cohort study demonstrated that a history of hypertension was a risk factor for HDP and PD in pregnant women with GDM, and higher HbA1c levels was a risk factor for HFD newborns. A low oral DI on the antepartum 75-g OGTT was an independent risk factor for GI during the early postpartum period in women with GDM. These findings may enable clinicians to effectively identify and manage women with GDM who are at high risks for pregnancy complications and DM in the future.

Methods

Study design and participants

This prospective cohort study enrolled women with singleton pregnancies who were diagnosed with GDM by the 75-g OGTT during pregnancy and delivered at the Kobe University Hospital from January 2011 to December 2018. The study was approved by the Institutional Review Board of the Kobe University Hospital (reference number 200228), and informed consent was obtained from all participants. All research was performed in accordance with the relevant guidelines and regulations.

Procedures

All pregnant women who visited or were referred to the Kobe University Hospital underwent screening for GDM both at 10–14 and 24–28 GW. Pregnant women who had casual BG levels of ≥ 100 mg/dL (5.5 mmol/L) at 10–14 GW, or those who had 1-hr BG levels of ≥ 140 mg/dL (7.8 mmol/L) on 50-g glucose challenge tests (GCT) at 24–28 GW, or those with risk factors for GDM, including obesity, family history of DM, past history of macrosomia, presence of persistent glycosuria, polyhydramnios, and suspected HFD, underwent the 75-g OGTT. According to the IADPSG criteria¹², the diagnosis of GDM is

made when any of the following are met: FBG \geq 92 mg/dL (5.1 mmol/L), 1-hr BG \geq 180 mg/dL (10.0 mmol/L), or 2-hr BG \geq 153 mg/dL (8.5 mmol/L). BG and immunoreactive insulin (IRI) levels at 0, 0.5, 1, 1.5, and 2 hr after the oral ingestion of 75-g glucose were also measured, and the total area under the curve (AUC) of glucose and insulin were calculated by the trapezoid method.

As an insulin resistance parameter, the homeostasis model assessment-insulin resistance (HOMA-IR) ($=\text{FBG} (\text{mg/dL}) \times \text{fasting IRI (FIRI)} (\mu\text{U/mL}) / 405$) was used. HOMA- β ($=360 \times \text{FIRI} (\mu\text{U/mL}) / [\text{FBG} (\text{mg/dL}) - 63]$) and insulinogenic index (II) ($= [\text{0.5-hr IRI} (\mu\text{U/mL}) - \text{FIRI} (\mu\text{U/mL})] / [\text{0.5-hr BG} (\text{mg/dL}) - \text{FBG} (\text{mg/dL})]$) were calculated for evaluating the insulin secretory capacity of pancreatic β cells. The oral DI, which represents the compensation of pancreatic β cells for insulin resistance, was calculated as the product of the Matsuda index of insulin sensitivity and the ratio of the AUC of insulin to the AUC of glucose during the OGTT²⁷. The Matsuda index was calculated using the following formula: $10^4 / \sqrt{(\text{FGB} \times \text{FIRI} \times \text{mean BG during 75-g OGTT} \times \text{mean IRI during 75-g OGTT})^{29}}$.

All pregnant women diagnosed with GDM were referred to diabetologists in the Kobe University Hospital and underwent self-monitoring of blood glucose (SMBG) and diet therapy. If FBG levels exceeded 100 mg/dL, or 2-hr BG levels exceeded 120 mg/dL in SMBG regardless of diet therapy, an insulin therapy was started. Insulin doses were adjusted to achieve both FBG levels of <100 mg/dL and 2-hr BG levels of <120 mg/dL.

All pregnant women with GDM were instructed to undergo a 75-g OGTT at 12 weeks after delivery. Using the WHO's 1999 criteria³⁰, DM was diagnosed by either FBG levels of \geq 126 mg/dL (7.0 mmol/L) or 2-hr BG levels of \geq 200 mg/dL (11.1 mmol/L). IFG was diagnosed by FBG levels of \geq 110 mg/dL (6.1 mmol/L), and IGT was diagnosed by 2-hr BG levels of \geq 140 mg/dL (7.8 mmol/L). GI was defined by the presence of DM, IFG, or IGT. FBG levels of <110 mg/dL (6.1 mmol/L) and 2-hr BG levels of <140 mg/dL (7.8 mmol/L) were identified as normal.

This study assessed pregnancy complications, including HDP, PD at 36 or less GW, and HFD or LFD newborns. HFD and LFD were defined as newborns with a birth weight >90th and <10th percentile for gestational age, respectively.

Statistical analysis

Clinical characteristics were compared between pregnancies with each pregnancy complication or with GI during the early postpartum period and pregnancies without them. Differences between the two groups were analyzed using the Mann-Whitney *U* test, Fisher exact test, and χ^2 test. *P* values <0.05 were considered statistically significant. The stepwise approach was used to evaluate clinical factors and parameters in the antepartum 75-g OGTT associated with each pregnancy complication and GI during the early postpartum period. Variables with *P* values <0.05 in univariate logistic regression analyses were subjected to multivariable logistic regression analyses, and variables with *P* values <0.05 in multivariable logistic regression analyses were determined as clinical factors and parameters in the antepartum 75-g OGTT associated with each pregnancy complication or GI during the early postpartum period in women

with GDM. All statistical analyses were performed using the SPSS software, version 19 (SPSS Inc., Chicago, Illinois).

Declarations

Data availability

The datasets analyzed during the current study are available from the corresponding authors upon a reasonable request.

Author contributions statement

N.M. performed statistical analysis and made a draft of the manuscript. K.T. helped to analyze the data and write the manuscript. N.K., H.I., M.D., K.F., Y.O., Y.H., and W.O. collected the data and supervised the study. H.Y. designed the study and revised critically the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interest.

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Tables

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