Sustained Decrease of Early-Phase Insulin Secretion in Japanese Women with Gestational Diabetes Mellitus Who Developed Impaired Glucose Tolerance and Impaired Fasting Glucose Postpartum

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ABSTRACT

OBJECTIVE: The aim of this study was to compare glucose intolerance in the antenatal and the postpartum periods using a 75-g oral glucose tolerance test (OGTT) in the Japanese women with gestational diabetes mellitus (GDM) using a retrospective design.

PATIENTS AND METHODS: Data were obtained from 85 Japanese women with GDM who delivered from April 2011 through April 2015 and who underwent an OGTT 6–14 weeks postpartum. The women were divided into two groups based on the results of the postpartum OGTT: one group with normal glucose tolerance (NGT) and the other with impaired glucose tolerance (IGT) as well as impaired fasting glucose (IFG). We analyzed the associations between postpartum IGT–IFG and various factors.

RESULTS: Antenatally, a significant difference was observed between the groups only in the 1-hour plasma glucose level of the 75-g OGTT. Postpartum results of plasma glucose level were significantly higher at 0.5, 1, and 2 hours in the IGT–IFG group than those in the NGT group. Moreover, a significant decrease in the levels of 0.5-hour immunoreactive insulin and insulinogenic index was observed in the IGT–IFG group compared to those in the NGT group. Homeostasis model assessment-insulin resistance and homeostasis model assessment β-cell function of both groups were found to significantly decrease in the postpartum period; however, there was no significant change in the insulinogenic index of either group.

CONCLUSIONS: Our study clearly showed that the postpartum IGT and IFG levels of Japanese women with GDM are affected by impaired early-phase insulin secretion; however, insulin resistance promptly improves.

KEYWORDS: gestational diabetes mellitus, insulinogenic index, homeostasis model assessment-insulin resistance

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Introduction

Diabetes mellitus (DM) is attracting increasing concern because of its high prevalence in the developed countries[1] and the pathologic consequences of diseases of the small arteries and the peripheral nervous system, which leads to retinopathy, nephropathy, and peripheral neuropathy, as well as metabolic abnormalities that lead to hyperlipidemia and hypertension. Lifestyle changes add to the increased risk of developing not only DM but also gestational diabetes mellitus (GDM).[2,3] Bellamy et al recently reported that habitual and behavioral effects prevent or delay the development of GDM to type 2 DM.[4]

In regard to the Japanese population, not only insulin resistance but also insulin secretion is thought to play an important role in the underlying mechanism of DM.[5–7] GDM is also reported to be related to impaired insulin secretion.[8] The aim of this study was to compare glucose intolerance in the antenatal and the postpartum periods using oral glucose tolerance test (OGTT) in the Japanese women with GDM using a retrospective design.

Patients and Methods

We conducted a retrospective study of 85 Japanese women with GDM who delivered a singleton pregnancy at Graduate School of Medicine, Osaka City University, from April 2011 through April 2015. The study protocol received the Institutional Review Board approval (no.2608) of Osaka City University Graduate School of Medicine. An informed consent was obtained from each subject for participation in the study. Our research complied with the principles of the Declaration of Helsinki.

If the Japanese women had any diabetes risk factors, such as casual hyperglycemia (>100 mg/dL [5.6 mmol/L]),

polyhydramnios, or a heavy-for-date infant, a 75-g OGTT was performed. For the measurement of plasma glucose levels and immunoreactive insulin (IRI) concentration, an OGTT was performed after a 12-hour overnight fast. Venous blood samples were drawn in the fasting state at 0.5, 1, and 2 hours after ingestion of the glucose solution. GDM was diagnosed in accordance with the International Association of Diabetes and Pregnancy Study Groups criteria.[9] To analyze the associations between postpartum glucose tolerance and risk factors, information regarding maternal characteristics and pregnancy outcomes was obtained.

The initial standard treatment for women with GDM is diet and self-monitoring of blood glucose. Based on the results of self-monitoring of blood glucose, insulin therapy was initiated if the patient exhibited fasting hyperglycemia (>95 mg/dL [5.3 mmol/L]) or 2-hour postprandial hyperglycemia (>120 mg/dL [6.7 mmol/L]).

Patients underwent a 75-g OGTT 6–14 weeks postpartum. We used the World Health Organization criteria[10] to assess glucose tolerance and classified them into the following two groups: (1) normal glucose tolerance (NGT) group (fasting glucose level <110 mg/dL [6.1 mmol/L] and 2-hour glucose level <140 mg/dL [7.8 mmol/L]) and (2) impaired glucose tolerance–impaired fasting glucose (IGT–IFG) group (fasting glucose level ≥110 mg/dL [6.1 mmol/L] and <126 mg/dL [7.0 mmol/L] or 2-hour glucose level ≥140 mg/dL [7.8 mmol/L] and <200 mg/dL [11.1 mmol/L]). To eliminate the possibility of pregestational DM, we excluded women who had overt diabetes during pregnancy and women who were included in the DM group postpartum (fasting glucose level ≥126 mg/dL [7.0 mmol/L] or 2-hour glucose level ≥200 mg/dL [11.1 mmol/L]).

Insulin resistance and insulin secretion were evaluated using measurements from the results of the OGTT as follows. Homeostasis model assessment-insulin resistance (HOMA-IR) is an indicator of insulin resistance, and this was calculated using the following equation: HOMA-IR = (fasting plasma glucose level) × (fasting insulin)/405.[11] Homeostasis model assessment β-cell function (HOMA-B) is an indicator of insulin secretion, and this was calculated using the following equation: HOMA-B = (fasting insulin) × 360/(fasting plasma glucose level – 63).[11] The insulinogenic index is a surrogate for early-phase insulin secretion from the pancreas, and it was calculated using the following equation: insulinogenic index = (0.5-hour insulin – fasting insulin)/(0.5-hour plasma glucose level – fasting plasma glucose level).[12] Incidentally, some patients who were transferred to our facility after GDM was diagnosed did not undergo an OGTT at our hospital during pregnancy; therefore, their data did not contain a 0.5-hour glucose level or insulin concentration.

Statistical analysis was performed with SPSS (version 20.0; IBM). Continuous variables were presented as the median

Table 1. Maternal characteristics and pregnancy outcomes.

	NGT (n = 69)	IGT-IFG (n = 16)	*P*
Maternal age (years)	34 (19–45)	37 (25–45)	0.237
Primipara (%)	61	44	0.266
Pregestational BMI	23.2 (16.4–51.7)	22 (16.2–32.5)	0.525
Maternal weight change during pregnancy (kg)	6.9 (–24–+26)	7.3 (1.3–18)	0.657
Postpartum BMI	23.1 (16.9–39.1)	22.4 (17.8–30.0)	0.537
Gestational age at OGTT (week)	28 (9–38)	26.5 (7–36)	0.636
Gestational weeks at delivery	39 (32–41)	39 (37–41)	0.237
Birth weight (g)	3070 (1900–4205)	3245 (2415–3980)	0.080
Proportion of C/S (%)	29	19	0.311
Total daily insulin dosage	0 (0–32)	8 (0–70)	0.185
Proportion of insulin usage (%)	45	62	0.161
Weight of placenta (g)	570 (325–980)	570 (490–895)	0.645
Proportion of breast feeding (%)	93	75	0.050
Ap.(1)	8 (4–9)	8 (6–10)	0.093
Ap.(5)	9 (7–10)	9 (8–10)	0.431
2-h PG of neonate (mg/dL)	71 (33–132)	68 (56–106)	0.697
Proportion of HFD (%)	13	18	0.401
Proportion of TTN (%)	16	12	0.539
Proportion of low PG	11%	0%	0.230

Abbreviations: NGT, normal glucose tolerance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; BMI, body mass index (calculated as weight in kilograms divided by the square of the height in meters); OGTT, oral glucose tolerance test; C/S, cesarean section; Ap., Apgar score; h, hour; PG, plasma glucose level; HFD, heavy-for-date; TTN, transient tachypnea of the newborn.

(range). The Mann–Whitney *U* test and the Wilcoxon signed-rank test were used to analyze the results. Categorical variables were presented as proportions and were assessed using the Fisher's exact test. $P < 0.05$ was considered to be statistically significant.

Results

Patient characteristics are shown in Table 1. There were no significant differences between the NGT and IGT–IFG groups. Table 2 shows the results of 75-g OGTT during pregnancy and postpartum. There were 69 women in the NGT group and 16 women in the IGT–IFG group. In all, 40 of the 69 women in the NGT group and 9 of the 16 women in the IGT–IFG group had all data regarding the plasma glucose level and IRI. Antenatally, a significant difference was observed between the groups only in the 1-hour plasma glucose level of the 75-g OGTT. Postpartum results of plasma glucose levels were significantly higher at 0.5, 1, and 2 hours in the IGT–IFG group than those in the NGT group. Moreover, a significant decrease was observed in the 0.5-hour IRI and insulinogenic index of the IGT–IFG group in comparison to those levels of the NGT group.

The changes in the indices of insulin resistance and insulin secretion are shown in Figures 1–3. HOMA-IR and HOMA-B of both groups were found to significantly decrease in the postpartum period. Conversely, there was no significant change in the insulinogenic index of either group.

Discussion

Our study demonstrated that antenatal 1-hour plasma glucose level might be related to postpartum IGT–IFG. In addition, the postpartum insulinogenic index of the IGT–IFG group was significantly lower than that of the NGT group, although the antenatal insulinogenic index showed no difference probably due to the relatively small study population. HOMA-IR and HOMA-B of both groups showed a significant decrease in

Table 2. 75-g OGTT results of the NGT and IGT–IFG groups classified by OGTT in the postpartum period.

	NGT	n	IGT-IFG	n	*P*
OGTT results in the antenatal period (n = 85 or 49)					
Fasting PG (mg/dL)	86.5 (51–117)	69	83.5 (75–106)	16	0.828
0.5-h PG	146 (112–193)	40	172 (127–196)	9	0.052
1-h PG	178 (119–258)	69	191 (102–226)	16	0.037
2-h PG	158 (88–216)	69	162 (101–200)	16	0.365
Fasting IRI (μU/mL)	9.95 (1.9–34)	40	9.5 (6.8–17.4)	9	0.909
0.5-h IRI	47.7 (20.5–196)	40	42.8 (20.8–131)	9	0.549
1-h IRI	72.3 (28.3–158)	40	72.9 (20.2–169)	9	0.602
2-h IRI	77.7 (21.7–275.8)	40	75.4 (39.1–189.3)	9	0.815
HOMA-IR	2.25 (0.36–8.81)	40	1.93 (1.41–4.55)	9	0.929
HOMA-B	149.1 (48.8–698.4)	40	145.7 (100.8–257.1)	9	1.000
Insulinogenic index	0.723 (0.177–2.643)	40	0.449 (0.180–1.349)	9	0.086
HbA1c at diagnosis (%)	5.4 (4.9–6.3)	69	5.9 (5.0–6.2)	16	0.600
OGTT results in the postpartum period (n = 85)					
Fasting PG (mg/dL)	90 (73–109)	69	91 (75–117)	16	0.589
0.5-h PG	144 (89–171)	69	156 (115–193)	16	0.013
1-h PG	140 (70–191)	69	176 (82–233)	16	<0.001
2-h PG	116 (72–139)	69	152 (83–184)	16	<0.001
Fasting IRI (μU/mL)	5.7 (1.1–25.5)	69	5.2 (2.1–10)	16	0.378
0.5-h IRI	40.6 (9.1–149)	69	29.8 (13.8–94.2)	16	0.048
1-h IRI	42.2 (9.3–175.2)	69	31.8 (15.8–100.6)	16	0.245
2-h IRI	33.1 (13.1–167.7)	69	34.8 (14.2–122.4)	16	0.723
HOMA-IR	1.28 (0.20–5.73)	69	1.12 (0.42–2.42)	16	0.527
HOMA-B	78.8 (34.3–327.8)	69	56 (26.1–163.4)	16	0.091
Insulinogenic index	0.68 (0.18–2.9)	69	0.38 (0.13–1.15)	16	0.006
HbA1c (%)	5.6 (4.9–6.3)	69	5.7 (5.3–6.0)	16	0.332

Abbreviations: OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; h, hour; PG, plasma glucose level; IRI, immunoreactive insulin; HOMA-IR, homeostasis model assessment-insulin resistance; HOMA-B, homeostasis model assessment β-cell function.

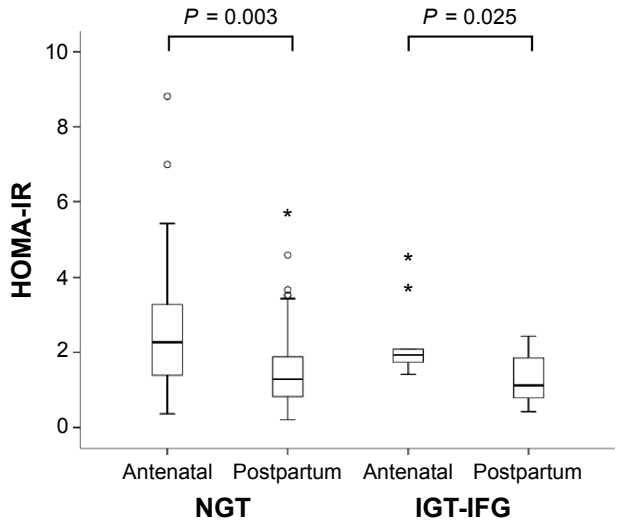

Figure 1. HOMA-IR levels of the two groups. The median is represented by black bars, the interquartile range (IQR) by boxes, values within 1.5 IQR by whiskers, and values exceeding 1.5 IQR by circles and those exceeding 3.0 IQR by asterisks.

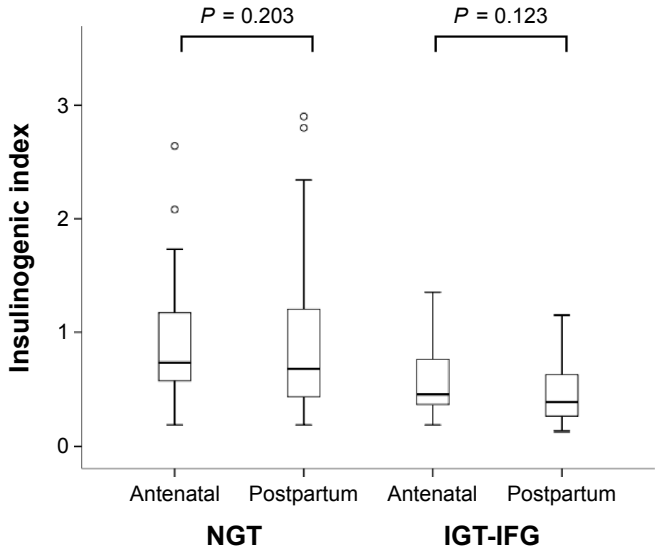

Figure 3. Insulinogenic index of the two groups. The median is represented by black bars, IQR by boxes, values within 1.5 IQR by whiskers, and values exceeding 1.5 IQR by circles.

the postpartum period, while the insulinogenic index did not change in regard to the measured periods in either group.

Elevated 1-hour plasma glucose level after a 75-g OGTT, even with a normal glucose level at fasting and/or at 2 hours, was recently reported to be a high risk for subsequent DM,[13,14] and this phenomenon is thought to be caused by impaired early-phase insulin secretion.[15] As shown in our study, antenatal 1-hour plasma glucose level was significantly higher in the IGT–IFG group and the insulinogenic index was decreased in the postpartum period. A significant increase in the 0.5- and 1-hour glucose levels may suggest impaired early-phase insulin secretion of the IGT–IFG group.

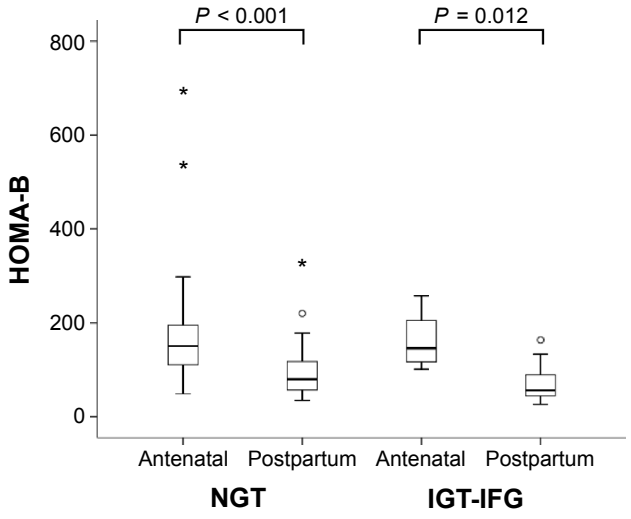

Figure 2. HOMA-B levels of the two groups. The median is represented by black bars, the IQR by boxes, values within 1.5 IQR by whiskers, and values exceeding 1.5 IQR by circles and those exceeding 3.0 IQR by asterisks.

O'Reilly et al reported that breast-feeding might reduce the prevalence of abnormal postpartum glucose tolerance in women with prior GDM,[16] and the authors concluded that breast-feeding may confer beneficial metabolic effects after GDM and should be encouraged. Interestingly, also in our study, the percentage of breast-feeding was higher in the NGT group, although it did not reach statistical significance. The mechanisms are not fully understood, but lactation is thought to enhance pancreatic β-cell proliferation and function and reduce insulin resistance.[17]

In our study, both the HOMA-IR and HOMA-B levels in the postpartum period showed a significant decrease in comparison to those levels during pregnancy, suggesting a rapid improvement of insulin resistance postpartum. Sustained elevation of HOMA-IR through pregnancy and postpartum is a high risk factor for the development of type 2 DM.[18] Conversely, Kugishima et al reported that among Japanese women with GDM, a lower insulinogenic index and use of insulin therapy during pregnancy are associated with early postpartum IGT–IFG.[19] In our study, use of insulin was not associated with postpartum IGT–IFG; this might be due to the small sample size. In some GDM patients, impaired early-phase insulin secretion would be involved in the future pathogenesis of DM. This explanation is supported by our observation that an antenatal decrease in the insulinogenic index was sustained even in the postpartum period.

A limitation of the present study is that it involves a relatively small number of cases. The antenatal data of plasma glucose level at 0.5 hours and IRI were limited because the 75-g OGTT was performed without these measurements in some

cases (previous care at another facility). However, we considered that conducting an additional 75-g OGTT to obtain the plasma glucose level at 0.5 hours and an IRI during pregnancy is not always necessary.

In conclusion, our study suggested that the postpartum IGT and IFG levels of Japanese women with GDM affected by impaired early-phase insulin secretion; however, insulin resistance promptly improves. Our findings might add essential information for the management of GDM.

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Author Contributions

Conceived and designed the experiments: HK. Analyzed the data: HK, DT. Wrote the first draft of the manuscript: HK, DT. Contributed to the writing of the manuscript: HK, DT. Agree with manuscript results and conclusions: AH, TM, KM, TM, SF, MI. Jointly developed the structure and arguments for the paper: ME. Made clinical revisions and approved final version: HK, MK. All authors reviewed and approved of the final manuscript.

REFERENCES

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care*. 1998;21(9):1414–1431.
2. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature*. 2001;414(6865):782–787.
3. Momeni Javid F, Simbar M, Dolatian M, Alavi Majd H. Comparison of lifestyles of women with gestational diabetes and healthy pregnant women. *Glob J Health Sci*. 2014;7(2):162–169.
4. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet*. 2009; 373(9677):1773–1779.
5. Morimoto A, Tatsumi Y, Deura K, et al. Impact of impaired insulin secretion and insulin resistance on the incidence of type 2 diabetes mellitus in a Japanese population: the Saku study. *Diabetologia*. 2013;56(8):1671–1679.
6. Tanaka Y, Atsumi Y, Asahina T, et al. Usefulness of revised fasting plasma glucose criterion and characteristics of the insulin response to an oral glucose load in newly diagnosed Japanese diabetic subjects. *Diabetes Care*. 1998;21(7): 1133–1137.
7. Matsumoto K, Miyake S, Yano M, et al. Glucose tolerance, insulin secretion, and insulin sensitivity in nonobese and obese Japanese subjects. *Diabetes Care*. 1997;20(10):1562–1568.
8. Buchanan TA. Pancreatic B-cell defects in gestational diabetes: implications for the pathogenesis and prevention of type 2 diabetes. *J Clin Endocrinol Metab*. 2001;86(3):989–993.
9. International Association of Diabetes and Pregnancy Study Groups Consensus Panel; Metzger BE, Gabbe SG, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010;33(3):676–682.
10. World Health Organization, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation; 2006. Available from: http://www.who.int/iris/handle/10665/43588
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412–419.
12. Seltzer HS, Allen EW, Herron AL Jr, Brennan MT. Insulin secretion in response to glycemic stimulus: relation of delayed initial release to carbohydrate intolerance in mild diabetes mellitus. *J Clin Invest*. 1967;46(3):323–335.
13. Kuzuya T, Nakagawa S, Satoh J, et al; Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *Diabetes Res Clin Pract*. 2002;55(1):65–85.
14. Göbl CS, Bozkurt L, Prikoszovich T, Tura A, Pacini G, Kautzky-Willer A. Estimating the risk after gestational diabetes mellitus: can we improve the information from the postpartum OGTT? *Am J Physiol Endocrinol Metab*. 2013; 304(5):E524–E530.
15. Abdul-Ghani MA, DeFronzo RA. Plasma glucose concentration and prediction of future risk of type 2 diabetes. *Diabetes Care*. 2009;32(suppl 2):S194–S198.
16. O'Reilly MW, Avalos G, Dennedy MC, O'Sullivan EP, Dunne F. Atlantic DIP: high prevalence of abnormal glucose tolerance post partum is reduced by breastfeeding in women with prior gestational diabetes mellitus. *Eur J Endocrinol*. 2011;165(6):953–959.
17. Gunderson EP. Impact of breastfeeding on maternal metabolism: implications for women with gestational diabetes. *Curr Diab Rep*. 2014;14(2):460.
18. Ignell C, Shaat N, Ekelund M, Berntorp K. The impact of ethnicity on glucose homeostasis after gestational diabetes mellitus. *Acta Diabetol*. 2013;50(6): 927–934.
19. Kugishima Y, Yasuhi I, Yamashita H, et al. Risk factors associated with abnormal glucose tolerance in the early postpartum period among Japanese women with gestational diabetes. *Int J Gynaecol Obstet*. 2015;129(1):42–45.