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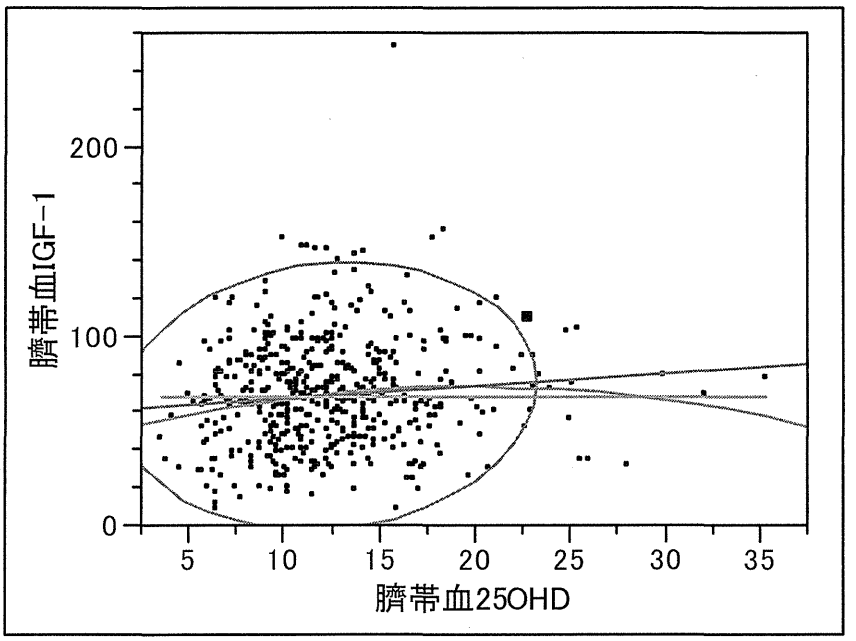
H．知的財産権の出願・登録状況

なし。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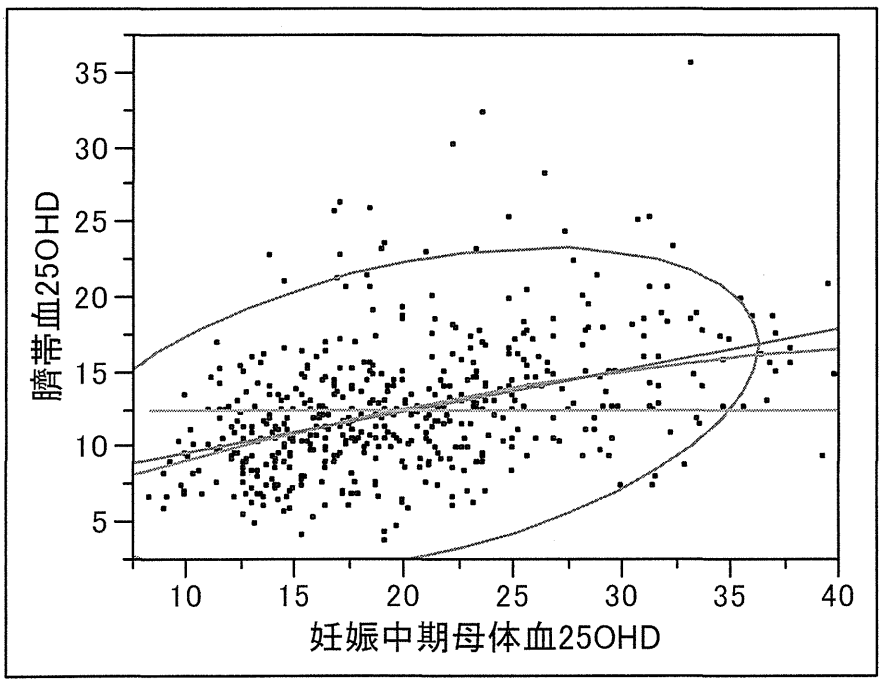
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妊娠中期母体血25OHD

Ⅲ．研究成果の刊行に関する一覧表

別紙4

研究成果の刊行に関する一覧表

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Ⅳ．研究成果の刊行物・別刷

Hypertension Research (2012) 35, 565–566

www.nature.com/hr

CORRESPONDENCE

Response to Metoki

Hypertension Research (2012) **35,** 565–566; doi:10.1038/hr.2012.34; published online 22 March 2012

We thank Dr Metoki for his thoughtful comments.[1] He raises the important points that mid-pregnancy fall may have an impact on the occurrence of pregnancy-induced hypertension (PIH) and that seasonal variations in blood pressure (BP) may affect the BP changes during pregnancy and contribute to the occurrence of PIH. We assessed clinic BP values at week 30 and at a time after week 34 in healthy pregnant women who participated in the previous study.[2] As shown in Figure 1, a decreasing BP in the second trimester was observed. Because pregnant women with low BP at week 20 had less risk of PIH,[2] even if these women had high BP at week 16, a mid-pregnancy fall in BP is thought to be inversely correlated with the occurrence of PIH. As suggested by Metoki *et al.*,[3] endothelial function may contribute to the relationship between the mid-pregnancy fall in BP and the occurrence of PIH. In addition, we assessed the seasonal trend in BP changes during pregnancy. As shown in Table 1, pregnant women who delivered in the hot season (May to October, average daily temperature $\geqslant 15\,^{\circ}C$ in Tokyo) had higher BPs before 16 weeks and at 20 weeks of gestation than those who delivered in the cold season (December to April, average daily temperature $< 15\,^{\circ}C$ in Tokyo). By contrast, pregnant women who delivered in the cold season tended to have a higher BP at 30 weeks and after 34 weeks than those who delivered in the hot season. These results suggest that seasonal changes in temperature may affect clinic BP values during pregnancy. However, the occurrence of PIH was unaffected by the seasonal trend in BP changes. The odds ratio of PIH in pregnant women who delivered in the cold season was 0.63 compared with that in pregnant women who delivered in the hot season; this is statistically insignificant.

Consistent with previous studies showing that home BP fell from the first trimester to the second trimester and then continued to increase until the time of delivery,[3] and that pregnant women who delivered in winter tended to have higher home BPs than those who delivered in summer,[4] we confirmed the mid-pregnancy fall in BP and the seasonal trend in BP changes during pregnancy even if BPs are measured at the clinic. We hope that our study will inspire researchers to further examine the effects of the mid-pregnancy fall in BP and the seasonal trend in BP changes during pregnancy on predicting the risk of PIH.

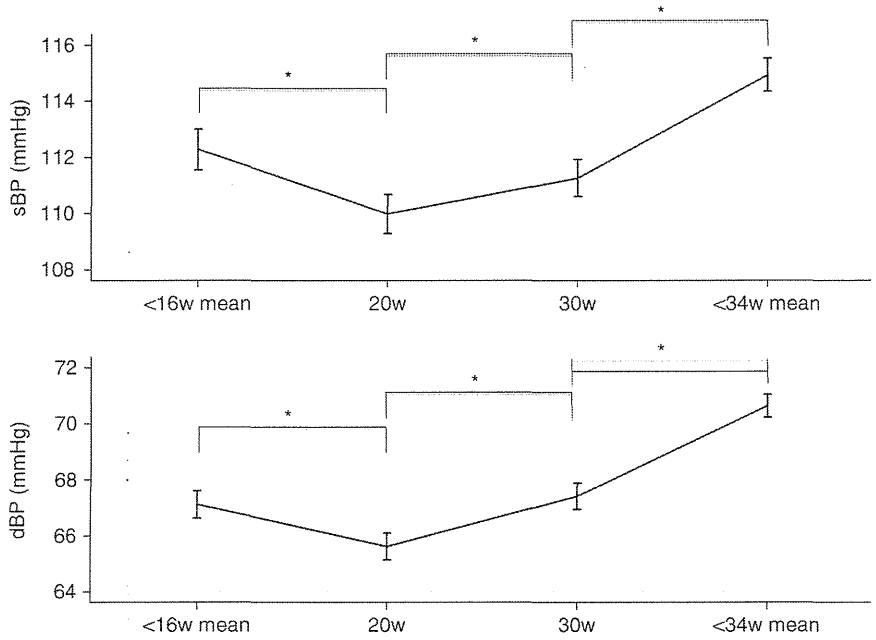

Figure 1 Systolic/diastolic blood pressure (sBP/dBP) in 976 pregnant women. *$P<0.0001$.

Table 1 BP values and OR (95% CI) of PIH stratified by season in 976 pregnant women

	EDC_Hot season (n = 503)		*EDC_Cold season (n = 473)*		P-value
Systolic BP					
Before 16 weeks of gestation	114.0	11.9	110.4	10.9	<0.0001
20 weeks of gestation	111.6	11.6	108.3	10.4	<0.0001
30 weeks of gestation	110.6	10.1	111.9	11.0	0.059
After 34 weeks of gestation	114.4	9.7	115.5	9.1	0.073
Diastolic BP					
Before 16 weeks of gestation	67.8	8.4	66.4	7.5	0.009
20 weeks of gestation	66.4	7.8	64.8	7.4	0.001
30 weeks of gestation	66.8	7.1	68.1	7.5	0.004
After 34 weeks of gestation	70.2	6.5	71.1	6.4	0.052
PIH	Reference		0.63	(0.30–1.3)	0.21

Abbreviations: BP, blood pressure; CI, confidence interval; EDC, estimated date of confinement; OR, odds ratio; PIH, pregnancy-induced hypertension.
BP values are given as mean (s.d.).
Occurrence of PIH is given as OR and 95% CI.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL

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Marked decline in beta cell function during pregnancy leads to the development of glucose intolerance in Japanese women

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Abstract. The aim of this study is to investigate glucose metabolism longitudinally during pregnancy to explore mechanisms underlying gestational diabetes mellitus (GDM). We reviewed a total of 62 pregnant Japanese women who underwent a 75g oral glucose tolerance test (OGTT) twice during pregnancy (median: early, 13; late, 28 weeks' gestation) because of positive GDM screening. All showed normal OGTT results in early pregnancy. Based on late OGTT, 15 had GDM (late-onset GDM) and 47 normal glucose tolerance (NGT). In early pregnancy, there were no significant differences in insulin sensitivity (insulin sensitivity index derived from OGTT [IS_{OGTT}] and homeostasis model assessment for insulin resistance [HOMA-IR]) and insulin secretion (a ratio of the total area-under-the-insulin-curve to the total area-under-the-glucose-curve [$AUC_{ins/glu}$] and insulinogenic index [IGI]) between the NGT and late-onset GDM groups. In each group, insulin sensitivity significantly decreased from early to late pregnancy, most in the late-onset GDM group (each $p < 0.05$). The insulin secretion showed no significant changes with advancing pregnancy in both of the groups, although late-onset GDM showed significantly lower IGI compared with NGT in late OGTT ($p < 0.05$). When assessed beta cell function by OGTT-derived disposition index (i.e. Insulin Secretion-Sensitivity Index-2 and IGI/fasting insulin), the indices significantly decreased from early to late pregnancy in the both groups (each $p < 0.05$). Women with late-onset GDM showed significantly lower indices compared with NGT (each $p < 0.05$). The failure of beta cell to compensate for decreased insulin sensitivity could contribute to the development of the late-onset GDM.

Key words: Insulin sensitivity, Insulin secretion, Disposition index, Glucose metabolism, Pregnancy

IT HAS BEEN widely recognized that insulin sensitivity decreases as pregnancy advances, reaching the nadir in the third trimester [1]. When insulin secretion fails to compensate for the escalated insulin needs during pregnancy, pregnant women are diagnosed to have gestational diabetes mellitus (GDM)[2]. To date, studies on glucose metabolism in pregnant women have shown impaired beta cell function in GDM [3, 4, 5]. As a consequence, beta cell dysfunction is thought to be a potential etiology of GDM [6].

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Several prospective studies in Caucasian population have demonstrated that beta cell function could deteriorate from early to late pregnancy in women with normal glucose tolerance as well as GDM [1, 7]. Especially, women diagnosed with GDM in late pregnancy (i.e. late-onset GDM) showed marked decline in beta cell function during pregnancy [3,5]. This observation might be one explanation that women with a history of GDM are at high risk for the future glucose intolerance (i.e. type 2 diabetes) on a background of chronic insulin resistance. However, data on longitudinal changes in glucose metabolism of pregnant Japanese women are unavailable because only cross-sectional studies have been reported [5].

In the current study, we retrospectively examined the glucose metabolism of pregnant Japanese women. Using a cohort of pregnant women undergoing oral

glucose tolerance test (OGTT) twice in early and late pregnancy, alterations in indices of insulin sensitivity, insulin secretion, and beta cell function were examined. Furthermore, the indices in early and late pregnancy were compared between those with and without late-onset GDM.

Methods

Subjects

We conducted a retrospective cohort study of 62 consecutive pregnant Japanese women who underwent the diagnostic OGTT between 2004 and 2010. Each woman met the following criteria: 1) normal OGTT results after the universal early testing based on high-risk characteristics (i.e. early OGTT), 2) positive GDM screening using glucose challenge test (GCT) between 24 and 27 weeks of gestation. All women were cared for at the perinatal unit of Keio University Hospital. The gestational age was confirmed in the first trimester by crown-rump length measurements. Excluded from this study were women with multiple pregnancies and women whose neonates exhibited congenital anomalies. The research was performed in accordance with the Declaration of Helsinki and informed consent was obtained from patients where appropriate. The institutional review board at Keio University School of Medicine approved the study.

GDM screening and glucose tolerance test

In our hospital, each woman underwent a two-step screening for GDM: universal testing and a standard 1 h, 50-g GCT in early and late pregnancy, respectively. The universal early testing included the clinical risk factors, as follows: 1) pregestational obesity (BMI ≥ 25), 2) past history of gestational diabetes, 3) past history of macrosomia (birth weight ≥ 4,000g), and 4) family history of diabetes. If woman has any of the clinical risk factors at early prenatal visit, the diagnostic 75-g OGTT (i.e. early OGTT) was performed as soon as feasible after confirming that the random plasma glucose level did not exceed 200 mg/dl. The OGTT was performed after a 12 h overnight fast. Venous blood samples for measurement of plasma glucose levels and insulin concentrations were drawn in the fasting state and at 30 min, 1 h and 2 h after ingestion of the glucose drink. Women with the negative early testing or normal OGTT results underwent a standard 1 h, 50-g GCT between 24 and 27 weeks of gestation as a universal screening. If the GCT result exceeded 140 mg/dl, the diagnostic 75-g OGTT (i.e. late OGTT) was then performed.

During the study period between 2004 and 2010, GDM was diagnosed according to the former criteria defined by the Japan Diabetes Society (JDS) if two or more values reached or exceeded the following thresholds: fasting, 100 mg/dl; 1 h, 180 mg/dl; 2 h, 150 mg/dl [8]. Plasma glucose and insulin levels were measured by a glucose oxidase method and enzyme immunoassay, respectively. The normal glucose tolerance (NGT) group comprised women with normal OGTT results in spite of positive GDM screen.

Assessment of insulin sensitivity, insulin secretion and beta cell function

Insulin sensitivity and insulin secretion were evaluated using measurements from the diagnostic OGTT. The insulin sensitivity was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) and the whole-body insulin sensitivity index derived from the OGTT (IS_{OGTT}). The HOMA-IR was calculated as fasting plasma glucose (mg/dl) x plasma insulin (mU/l) / 405, and the IS_{OGTT} was calculated by the following formula: 10,000 / square root $\{Glu_0 \times Ins_0 \times (Glu_0 + Glu_{60} \times 2 + Glu_{120}) / 2 \times (Ins_0 + Ins_{60} \times 2 + Ins_{120}) / 2\}$, where Glu_y and Ins_y represent plasma glucose (mg/dl) and insulin values (mU/l), respectively, at time y min during the OGTT[9]. Insulin secretion was assessed by the insulinogenic index (IGI: $\{Ins_{30} - Ins_0\} / \{Glu_{30} - Glu_0\}$) and the ratio of the total area under the insulin curve to the total area under the glucose curve ($AUC_{ins/glu}$) during the OGTT. To evaluate beta cell function, we calculated the OGTT-derived disposition index (DIo) using the following measures: Insulin Secretion-Sensitivity Index-2 (ISSI-2: the $AUC_{ins/glu}$ multiplied by IS_{OGTT}) and IGI/fasting insulin [5, 10-12].

Statistical analysis

Data were presented as mean ± SD in text and tables, and illustrated as mean ± SEM in figures. Continuous variables were tested for normality of distribution and were compared between the groups using the unpaired Student's *t* test. Changes in indices of insulin sensitivity, insulin secretion, and beta cell function between the early and late OGTT within each study group (i.e. the NGT and late-onset GDM) were assessed by the paired Student's *t* test. Categorical variables were presented as proportions and were assessed with the χ^2 test or

Fisher's exact test. Statistical analysis was performed using the SPSS (version 19.0, IBM, Chicago, IL, USA). $p < 0.05$ was considered as statistically significant.

Results

Maternal demographic characteristics and 75g-OGTT profiles

Of 62 women, 15 were diagnosed to have GDM with late OGTT (i.e. the late-onset GDM group) and 47 showed the normal OGTT results (i.e. the NGT group). There were no significant differences in maternal age, a history of GDM, family history of diabetes, and gestational weeks at OGTT between the NGT and late-onset GDM groups (Table 1). Maternal body weight gain was comparable between the two groups, although pregravid body weight and BMI in the late-onset GDM group were significantly lower than those in the NGT group ($p < 0.05$).

In early OGTT, plasma glucose levels at 60 and 120 min in the late-onset GDM group was significantly higher than those in the NGT group (Table 2). With regard to late OGTT, the late-onset GDM group showed significantly higher levels of plasma glucose at all time points, compared with the NGT group. When analyzed the insulin profiles, fasting insulin levels in late OGTT significantly increased compared with early OGTT in both of the NGT and late-onset GDM groups. In late OGTT, levels of plasma insulin concentration at 120 min were significantly higher in the late-onset GDM group than those in the NGT group.

Changes in insulin sensitivity, insulin secretion and beta cell function during pregnancy

In early OGTT, the IS_{OGTT} and HOMA-IR were comparable between the NGT and late-onset GDM groups. The IS_{OGTT} significantly decreased from early to late OGTT in the NGT as well as late-onset GDM

Table 1 Maternal demographic characteristics

	NGT (n = 47)	Late-onset GDM (n = 15)
Age (years)	37 ± 5	38 ± 4
Parous (%)	25.5	33.3
Prior GDM (%)	6.8	7.1
Family history of diabetes (%)	31.1	40.0
Pregravid body weight (kg)	63.5 ± 11.1	50.6 ± 11.3*
Pregravid BMI	25.2 ± 4.4	20.3 ± 4.6*
Gestational weeks at early OGTT (weeks)	14 ± 4	14 ± 4
Gestational weeks at late OGTT (weeks)	28 ± 3	29 ± 3
Body weight at late OGTT (kg)	68.5 ± 9.9	56.4 ± 9.9*
Body weight gain by late OGTT (kg)	5.2 ± 4.4	4.3 ± 1.9

NGT; normal glucose tolerance; GDM; gestational diabetes mellitus. * $p < 0.05$ vs. the NGT group.

Table 2 Plasma glucose and insulin profiles of early and late OGTT

	NGT (n = 47)		Late-onset GDM (n = 15)	
	early OGTT	late OGTT	early OGTT	late OGTT
Plasma glucose (mg/dl)				
0 min	84 ± 7	84 ± 7	85 ± 7	91 ± 9*#
30 min	141 ± 18	140 ± 17	150 ± 13	156 ± 12*
60 min	143 ± 25	155 ± 20§	159 ± 12*	189 ± 11*#
120 min	129 ± 21	130 ± 17	150 ± 23*	176 ± 26*#
Insulin (mU/l)				
0 min	8.0 ± 4.7	9.2 ± 3.8§	8.7 ± 8.1	11.7 ± 8.8#
30 min	64.8 ± 26.2	65.7 ± 27.2	60.7 ± 33.4	53.1 ± 23.8
60 min	72.9 ± 37.5	79.8 ± 34.5	69.2 ± 39.3	77.5 ± 42.4
120 min	69.3 ± 54.2	72.2 ± 42.0	75.3 ± 48.5	104.4 ± 64.9*#

NGT; normal glucose tolerance, GDM; gestational diabetes mellitus, * $p < 0.05$ vs. the NGT group, § $p < 0.05$ for late vs. early OGTT of the NGT group, # $p < 0.05$ for late vs. early OGTT of the GDM group.

groups ($p < 0.05$, Fig. 1A). Consistent with this observation, HOMA-IR significantly increased in late OGTT compared with early OGTT in both of the groups ($p < 0.05$), most in the late-onset GDM group (Fig. 1B). In the NGT group, pregravid obese women (n = 27) showed significantly lower levels of IS_{OGTT} and higher levels of HOMA-IR compared with non-obese subjects in early and late OGTT (each $p < 0.05$). With regard to early and late OGTT results of late-onset GDM, levels of IS_{OGTT} and HOMA-IR in pregravid obese women ($n = 5$) were significantly lower and higher than those in non-obese subjects, respectively (each $p < 0.05$).

There were no significant differences in $AUC_{ins/glu}$ and IGI between NGT and late-onset GDM in early OGTT. The $AUC_{ins/glu}$ was comparable between early and late OGTT in the NGT as well as late-onset GDM groups (Fig. 1C). The IGI showed no significant differences between early and late OGTT in both of the NGT and late-onset GDM groups, although the late-onset GDM group showed significantly lower IGI compared with the NGT group in late OGTT (Fig. 1D).

Beta cell function was assessed by validated DIo (i.e. ISSI-2 and IGI/fasting insulin, Fig. 1E and F). The ISSI-2 and IGI/fasting insulin of late OGTT sig-

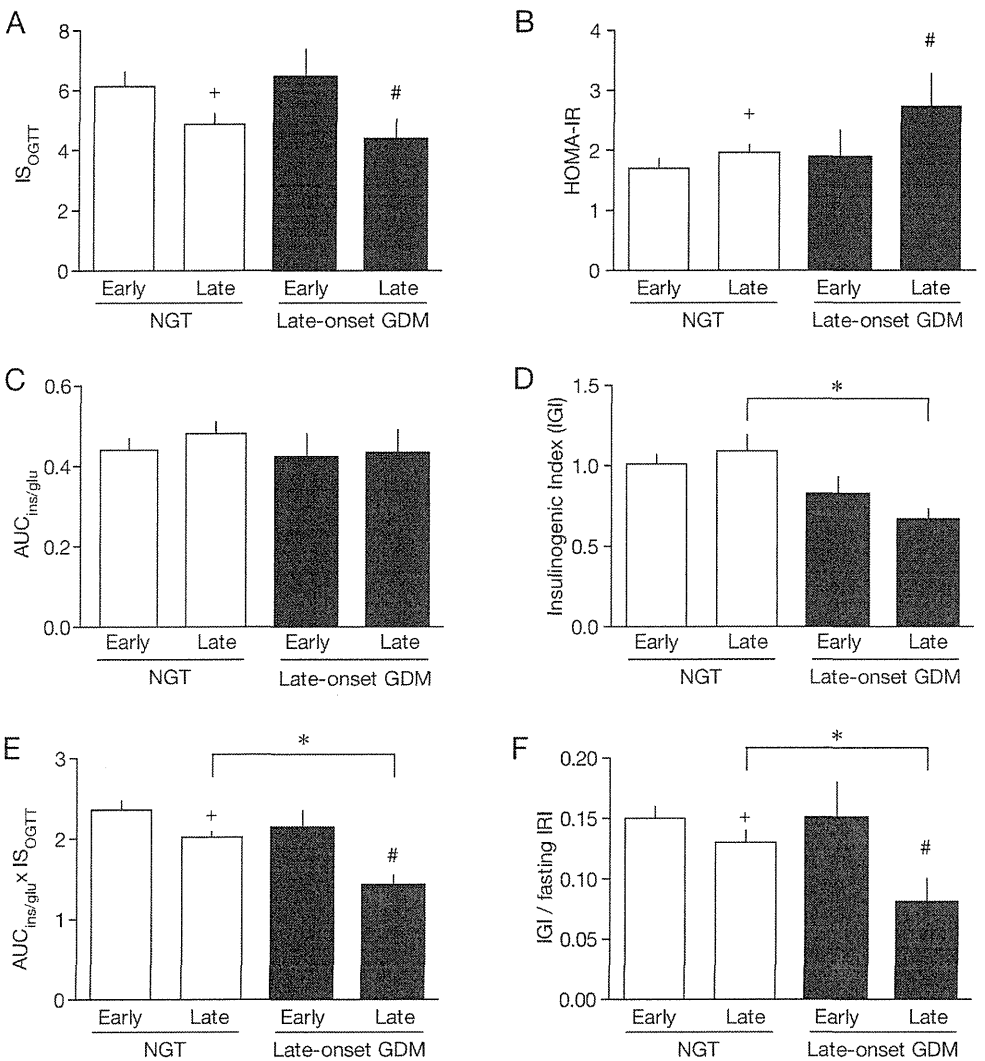

Fig. 1 Insulin sensitivity (A and B), insulin secretion (C and D) and beta cell function (E and F) of early and late OGTT in women with normal glucose tolerance (NGT) and those with late-onset gestational diabetes (late-onset GDM). * $p < 0.05$ vs. the NGT group, + $p < 0.05$ for late vs. early OGTT of the NGT group, # $p < 0.05$ for late vs. early OGTT of the late-onset GDM group.

nificantly decreased compared with those of early OGTT in the NGT as well as late-onset GDM groups ($p < 0.05$). Women with late-onset GDM showed significantly lower levels of ISSI-2 and IGI/fasting insulin compared with NGT ($p < 0.05$).

Discussion

The present study demonstrated that 1) beta cell function evaluated using DIo significantly decreased from early to late pregnancy, most in women with late-onset GDM, 2) the possible mechanism of decline in beta cell function during pregnancy could be ascribed to insufficient compensatory increase in insulin secretion against marked decrease in insulin sensitivity. To date, no studies on longitudinal assessment of glucose metabolism during pregnancy in Japanese women have been reported.

Insulin sensitivity decreases with advancing gestation, especially in late pregnancy [1]. It has also been reported that women with GDM have lower insulin sensitivity than those with body weight-matched normal glucose tolerance [2, 3, 5]. In this study, insulin sensitivity assessed by IS_{OGTT} and HOMA-IR significantly deteriorated in late OGTT compared with early OGTT in both of the late-onset GDM and NGT group. There were no significant differences in maternal baseline characteristics between the late-onset GDM and NGT groups, except that pregravid BMI in the late-onset GDM group were significantly lower than those in the NGT group. However, body weight gain from early to late OGTT was comparable between the two groups. Peripheral tissues, probably skeletal muscle, are primarily responsible for disposal of glucose [13, 14]. Therefore, the reduced skeletal muscle mass could be possible contributors to decreased insulin sensitivity. This might be associated with our findings that insulin sensitivity in early pregnancy was comparable between the NGT and late-onset GDM groups, although women with late-onset GDM were leaner than those with NGT. Further studies will be needed to clarify factors related to alterations in insulin sensitivity in late-onset GDM.

Albeit decreased insulin sensitivity in late pregnancy, insulin secretion assessed by $AUC_{ins/glu}$ and IGI did not change from early to late OGTT in the NGT as well as late-onset GDM groups. Consistent with our findings, several studies have shown the minimal increase in insulin secretion from early to late pregnancy[1, 2, 7]. Of interest, women with late-onset GDM showed lower levels of IGI compared with those with NGT in late OGTT. In the Caucasian population, studies on insulin secretion using the intravenous glucose tolerance test revealed that a decrease in early-phase insulin response contributes to the development of late-onset GDM [15]. The IGI is one of the OGTT-derived measures for the early-phase insulin secretion [10]. Similar to the Caucasian population, defective early phase of insulin response could be associated with late-onset GDM in Japanese women.

The beta cell function assessed by DIo significantly decreased from early to late OGTT in the NGT and late-onset GDM groups, with greater deterioration in the late-onset GDM group. In our previous investigation, beta cell dysfunction was demonstrated in Japanese women with late-onset GDM [5], which is similar to Caucasian population [6]. However, alterations in beta cell function during pregnancy in women with late-onset GDM were not investigated. Therefore, we examined the longitudinal changes in ISSI-2 and IGI/fasting insulin in the current study. In this investigation, both of two measures of beta cell function significantly deteriorated during pregnancy in late-onset GDM. As was found in the assessment of insulin secretion, women with late-onset GDM showed lower levels of IGI compared with NGT. Both of the defective initial insulin response and impaired beta cell function seemed associated with late-onset GDM, as are reported in type 2 diabetes [16]. Additionally, we found beta cell dysfunction in women with GDM detected early pregnancy using DIo (unpublished data). Taken all together, beta cell dysfunction seems characteristic of early- and late-onset GDM.

Similar to women with late-onset GDM, those with NGT showed decline in beta cell function from early to late OGTT. In this study, the NGT group comprised of women with normal OGTT results in early and late pregnancy. However, those have positive screen for GDM. It has been reported that a milder degree of glucose intolerance in pregnancy (i.e. abnormal GCT with normal OGTT) is related with the future risk of pre-diabetes or diabetes [17]. Our results suggest that those with positive GDM screen are at risk of beta cell dysfunction on a background of decreased insulin sensitivity.

The main limitation of this study is that the number of women examined was small. Since we reviewed clinical data of women who underwent the diagnostic OGTT twice during pregnancy because of positive GDM screening, the number of subjects was lim-

ited. To confirm our findings, studies using a larger cohort of pregnant Japanese women should be performed. The second limitation was that this study was conducted using a cohort of tertiary hospital patients in urban area of Japan. Therefore, most women examined were over the age of 35. Since beta cell function could decline with advancing age [18, 19], some may argue that advanced maternal age could have influence on the results. With regard to analysis performed in this study, maternal age was comparable between those with NGT and late-onset GDM. However, we should be cautious in interpreting absolute values of index examined. It might be of interest to investigate changes in metabolic phenotype of younger pregnant women. Finally, beta cell function (i.e. ISSI-2 and IGI/fasting insulin) at early OGTT was not associated with the development of GDM at late OGTT in our study population (data not shown). Because of the observational nature of this study, it is difficult to determine whether beta cell dysfunction is a cause or consequence of the development of late-onset GDM.

The DIo is valid when the relationship between insulin sensitivity and insulin secretion is expressed as a hyperbolic curve [12]. Using a model of log (secretion measures) = constant + $\beta \times$ log (sensitivity measures), a hyperbolic relationship can be established if β is approximately equal to -1, with 95% CI excluding 0. In our previous study cohort including a part of the present study population, mathematical measures have shown the hyperbolic relationship between insulin secretion ($AUC_{ins/glu}$) and sensitivity (IS_{OGTT}) in both of the NGT and late-onset GDM groups in pregnant Japanese women [5, 11], as was found in pregnant Caucasian women [20, 21]. Consistent with previous findings [10, 12], the relationship between IGI and fasting insulin was also hyperbolic in a study cohort of our previous report, although ISSI-2 showed more satisfactory results about the hyperbolic criteria (unpublished data). The hyperbolic relationship of ISSI-2 was reproducible in this study population (i.e. β: NGT, -0.8, 95% CI -0.6 to -0.9; GDM: -0.8, 95% CI -0.5 to -0.9). Nonetheless, because of the small sample size of this study, further investigation using a larger cohort is needed.

To our knowledge, this is the first report on longitudinal alterations in glucose metabolism during pregnancy in Japanese women. We have demonstrated a marked decline in beta cell function in women who developed the late-onset GDM, with the underlying mechanism of inadequate increase in insulin secretion against decreased insulin sensitivity. Additionally, adaptive increase in insulin secretion was minimal and beta cell function could deteriorate during pregnancy in women with positive screen for GDM. Our data imply that women with gestational glucose intolerance are likely to develop beta cell dysfunction on a background of chronic insulin resistance.

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