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ORIGINAL

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 $\geq$ 25), 2) past history of gestational diabetes, 3) past history of macrosomia (birth weight $\geq$ 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 $\{Glu_0 \times Ins_0 \times (Glu_0 + Glu_{60} \times 2 + Glu_{120}) \times 0.5 \times (Ins_0 + Ins_{60} \times 2 + Ins_{120}) \times 0.5\}$, 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 at late OGTT signif-

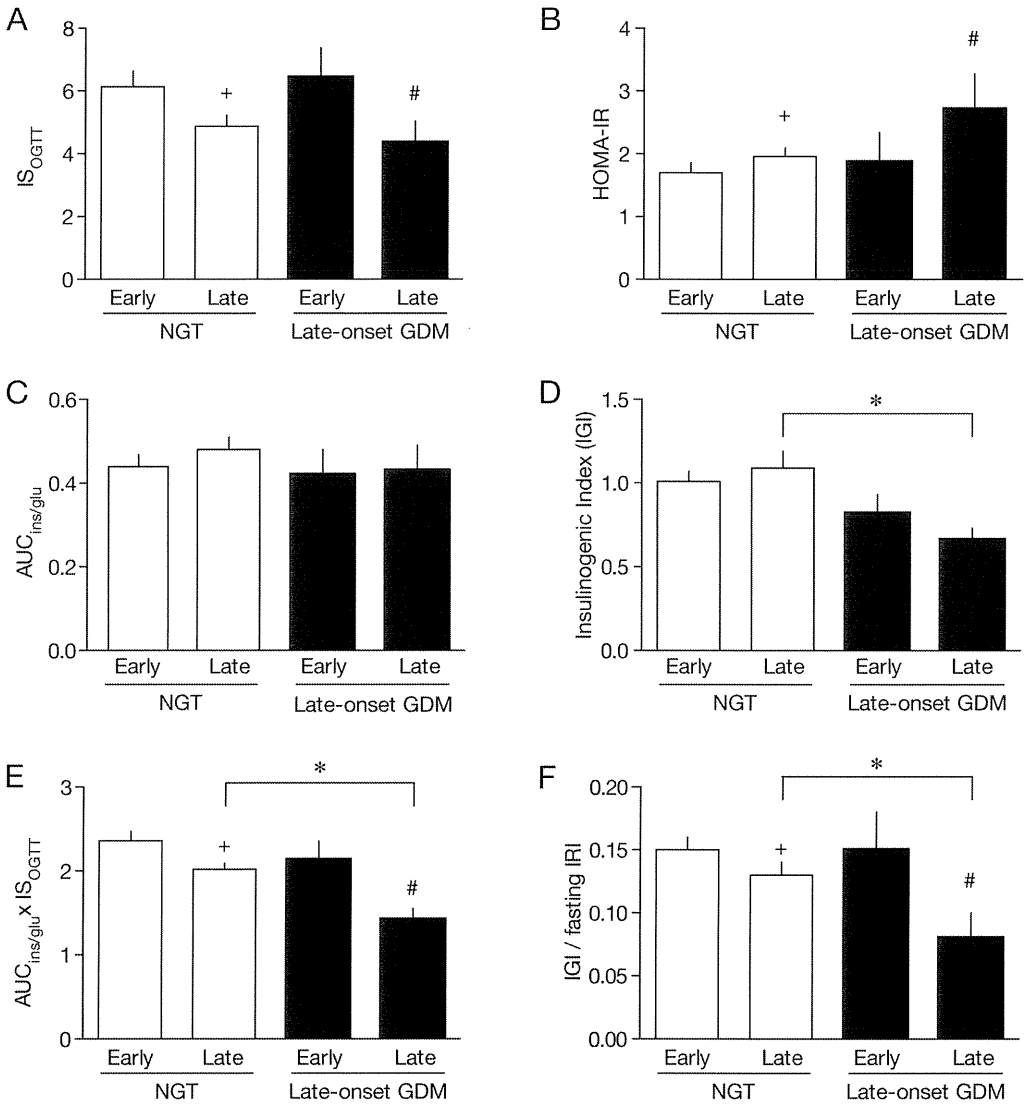

Fig. 1 Insulin sensitivity (A and B), insulin secretion (C and D) and beta cell function (E and F) of early and late OGTT in women with normal glucose tolerance (NGT) and those with late-onset gestational diabetes (late-onset GDM). * $p < 0.05$ *vs.* the NGT group, + $p < 0.05$ for late *vs.* early OGTT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

icantly decreased compared with those at 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 at 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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Clinical impact of women with gestational diabetes mellitus by the new consensus criteria: two year experience in a single institution in Japan

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Abstract. There is a paucity of information on perinatal data regarding gestational diabetes mellitus (GDM) by the new criteria from a real experience because the number of health care associations implementing the new criteria is still limited. The aim of this study is to investigate perinatal features of the new criteria-defined GDM. We reviewed a total of 995 women with singleton pregnancy that underwent GDM screening followed by a diagnostic oral glucose tolerance test (OGTT). All women found to have GDM underwent self-monitoring of blood glucose measurements as well as dietary management. Insulin treatment was initiated when dietary treatment did not achieve the glycemic goal. Of the 995 women, 141 had GDM (14.2%): 104 with one, 27 with two, and 10 with three abnormal OGTT values. Women with two or three abnormal OGTT values needed insulin treatment more frequently than those with one abnormal OGTT value (1-AV) (70.3% vs 23.1%, $P < 0.0001$). After adjustment for age, pregravid overweight, gestational weeks at diagnosis, a first-degree family history of diabetes was correlated with the implementation of insulin treatment in women with 1-AV (adjusted odds ratio 3.9; 95% Confidence Interval 1.7-9.2; $P = 0.001$). When compared perinatal outcomes between women with normal glucose tolerance and GDM, fetal growth and the occurrence of pregnancy-induced hypertension were comparable between the two groups. Our data suggest that the IADPSG-defined GDM with 1-AV show less severe glucose intolerance, but might be at risk of insulin requirement when a first-degree family history of diabetes exists.

Key words: The new consensus criteria, Gestational diabetes mellitus, Large-for gestational age, Gestational hypertension

IN 2010, International Association of Diabetes and Pregnancy Study Group (IADPSG) proposed new criteria for diagnosing and classifying gestational diabetes mellitus (GDM), based on data of the observational hyperglycemia and adverse pregnancy outcomes (HAPO) study [1]. Since the new diagnostic criteria would increase the frequency of GDM diagnosis without a detailed cost-effectiveness analysis, the number of health care associations implementing the new criteria is still limited [2]. Thus, there is a paucity of information on the IADPSG-defined GDM from a real experience. Especially, clinical significance of GDM by one abnormal value under the IADPSG criteria remains unknown [3].

In Japan, the IADPSG recommendation was adopted in July 2010 [4], and is commonly used in the obstetric practice, although the screening strategy varies in hospitals. With this background, we have investigated perinatal outcomes of the IADPSG-defined GDM in our hospital. First, maternal clinical and metabolic features were compared between women with a single and two or three abnormal oral glucose tolerance test (1- and 2/3-AV) values. Second, factors associated with insulin treatment in women with 1-AV were investigated. Third, perinatal outcomes were compared between women with normal glucose tolerance and IADPSG-defined GDM.

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Materials and Methods

Subjects

We conducted a retrospective cohort study of 995 consecutive pregnant Japanese women who were cared for at the perinatal unit of Keio University Hospital from 2011 to 2012. Gestational age was confirmed in the first trimester by crown-rump length measurements. Excluded from this study were women with multi-fetal pregnancies and women whose neonates exhibited congenital anomalies. Women with a medical history indicating either impaired glucose tolerance or diabetes mellitus (DM), or the use of medications known to affect glucose metabolism were also excluded. The research was performed in accordance with the Declaration of Helsinki and informed consent was obtained from patients where appropriate. This study was approved by the institutional review board at Keio University School of Medicine.

GDM screening and glycemic control

Each woman underwent a two-step screening for GDM: universal early testing and a standard 1-h 50g oral glucose challenge test (GCT) in early and late pregnancy, respectively, based on the clinical recommendation by Japan Society of Obstetrics and Gynecology (JSOG) [4]. The universal early testing included the clinical risk factors, as follows: (1) pregravid overweight (BMI $\geq$ 25), (2) prior GDM, (3) past history of macrosomia (birth weight $\geq$ 4000g), (4) a family history of DM in the first-degree relatives, (5) random plasma glucose $\geq$ 95 mg/dl. Levels of HbA1c and glycoalbumin (GA) were also examined as early testing in our institution (cut-off values: HbA1c $\geq$ 5.9%, GA $\geq$ 15.8%). Women with positive early testing underwent a diagnostic 75-g OGTT with the measurement of plasma glucose (mg/dl) and insulin concentration (mU/l) in the fasting state and at 30 min, 1 h, and 2 h after the glucose load. Plasma glucose and insulin levels were measured by a glucose oxidase method and enzyme immunoassay, respectively. Women with negative early testing or normal OGTT results underwent a standard GCT between 24 and 27 weeks of gestation. If the GCT result exceeded 140 mg/dl, the diagnostic 75-g OGTT was then performed. Based on the IADPSG criteria, GDM was diagnosed if one or more values reached or exceeded the following thresholds: fasting, 92 mg/dl; 1 h, 180 mg/dl; 2 h, 153 mg/dl [1]. Overt diabetes in pregnancy was defined as HbA1c $\geq$ 6.5% or fasting plasma glucose $\geq$ 126 mg/dl or random plasma glucose exceeded 200 mg/dl, the latter needing to be confirmed by one of the former [1]. The normal glucose tolerance (NGT) group comprised women with normal GCT or normal OGTT results.

All women found to have IADPSG-defined GDM underwent self-monitoring of blood glucose (SMBG) measurements as well as dietary management (daily calorie intake: early, 30 kcal/kg + 150 kcal; late, 30 kcal/kg + 350 kcal; if obese, 30 kcal/kg throughout pregnancy). Dietary management includes three meals and three snacks. Daily capillary glucose profiles were obtained seven times a day under dietary management: fasting, 2 h-post-breakfast, before lunch, 2 h-post-lunch, before dinner, 2 h-post-dinner, and bedtime. Capillary glucose levels were measured with a Medisafe Fit Pro blood glucose meter (Terumo Corporation, Tokyo, Japan). Insulin treatment was initiated when dietary treatment did not consistently maintain fasting and pre-meal capillary glucose $\leq$ 100 mg/dl and 2 h postprandial capillary glucose $\leq$ 120 mg/dl, respectively. Regular, or rapid acting, and NPH insulin were used to achieve the glycemic target and insulin dose was adjusted according to insulin algorithm based on SMBG values.

Assessment of insulin sensitivity, insulin secretion and beta cell function

Insulin sensitivity and insulin secretion were evaluated using measurements from the diagnostic OGTT [5, 6]. The insulin sensitivity was estimated by the whole-body insulin sensitivity index derived from the OGTT (IS_{OGTT}). 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. Insulin secretion was assessed by 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 using the following measures: Insulin Secretion-Sensitivity Index-2 (ISSI-2: the $AUC_{ins/glu}$ multiplied by IS_{OGTT}) [7].

Perinatal outcomes

Maternal characteristics and perinatal outcomes were collected from the patients' hospital records. Gestational hypertension was defined as a blood pres-

sure of at least 140/90 mmHg occurring for the first time after mid-pregnancy, without proteinuria or pre-existing hypertension. Proteinuria was defined as urinary excretion of at least 0.3 g in a 24-hour period. A diagnosis of preeclampsia was made in women who developed gestational hypertension and proteinuria. Using the Japanese standard sex- and parity-specific birthweight percentile curves, birthweight ≥ 90th percentile was defined as large-for-gestational age (LGA), and birthweight < 10th percentile was designated small-for-gestational age (SGA). Macrosomia was defined as birthweight above 4000 g.

Statistical analysis

Data were presented as mean ± SD or percentage in text and tables, where appropriate. Continuous data were compared between groups by Student's *t* test. Categorical variables were analyzed with the chi-square test or Fisher's exact test. Statistical analysis was performed using the JMP (SAS Institute, Cary, NC, USA). A value of $P < 0.05$ was considered statistically significant.

Results

Among 995 pregnant women, 141 (14.2%) were diagnosed to have GDM: 104 with a single abnormal value, 27 with two abnormal values, and 10 with three abnormal values. Of women with GDM, 68 were diagnosed by universal early testing in the first trimester. Two women (2/995 cases, 0.02%) had overt diabetes in pregnancy.

When compared the clinical features between women with 1- and 2/3-AV, there were no significant differences in maternal age, pregravid overweight (BMI ≥ 25), prior GDM, a family history of DM, and gestational weeks at diagnosis (Table 1). Compared with 1-AV, women with 2/3-AV showed significantly lower levels of IS_{OGTT} ($P < 0.01$), although insulin secretion assessed by $AUC_{ins/glu}$ was comparable between the two groups. As a result, levels of ISSI-2 in women with 2/3-AV were significantly lower than those with 1-AV ($P < 0.0001$). To achieve glycemic goal, women with 2/3-AV needed insulin treatment more frequently than those with 1-AV (70.3% vs 23.1%, $P < 0.0001$, Table 1).

With respect to clinical features in the 1-AV group, there were no significant differences in metabolic phenotypes (insulin sensitivity, insulin secretion, and beta cell function) as well as maternal age, pregravid overweight (BMI ≥ 25), prior GDM, gestational weeks at diagnosis between women with and without insulin treatment (Table 2). Of interest, a family history of DM was more prevalent in women requiring insulin treatment (41.7% vs. 15.0%, $P < 0.01$, Table 2). The time point showing abnormal values as well as levels of plasma glucose and insulin at the diagnostic OGTT were not associated with the implementation of insulin treatment (Table 3). After adjustment for age, pregravid overweight, gestational weeks at diagnosis, a family history of DM was significantly correlated with insulin treatment in women with 1-AV (adjusted odds ratio 3.9; 95% Confidence Interval 1.7-9.2; $P = 0.001$).

Table 1 Maternal clinical features in women with a single and two/three abnormal oral glucose tolerance test results

		A single abnormal OGTT result (n=104)	Two/three abnormal OGTT results (n=37)
Maternal age	, years	35.7 ± 4.4	35.8 ± 4.8
Pregravid BMI	, kg/m^2	20.7 ± 3.4	22.3 ± 5.1*
Pregravid overweight		10 (9.6%)	8 (21.6%)
Prior GDM		1 (1.0%)	2 (5.4%)
A family history of diabetes		22 (21.2%)	11 (29.7%)
Gestational age at diagnosis	, weeks	21 ± 8	22 ± 7
Diagnosed before 20 weeks' pregnancy		51 (49.0%)	17 (46.0%)
HbA1c at diagnosis	, %	5.4 ± 0.3	5.4 ± 0.3
IS_{OGTT}		6.4 ± 3.0	4.8 ± 2.7 #
$AUC_{ins/glu}$		0.34 ± 0.21	0.41 ± 0.22
ISSI-2		2.1 ± 0.62	1.6 ± 0.49 ##
Insulin treatment		24 (23.1%)	26 (70.3%) ##

OGTT, oral glucose tolerance test; BMI, body mass index; overweight, BMI ≥ 25; GDM, gestational diabetes mellitus; IS_{OGTT}, insulin sensitivity index derived from the oral glucose tolerance test; $AUC_{ins/glu}$, the ratio of the total area under the insulin curve to the total area under the glucose curve during the oral glucose tolerance test; ISSI-2, Insulin Secretion-Sensitivity Index-2 (i.e. the $AUC_{ins/glu}$ multiplied by IS_{OGTT}); *, $P < 0.05$; #, $P < 0.01$; ##, $P < 0.0001$

Table 2 Maternal characteristics in women with a single abnormal oral glucose tolerance test result

		Insulin Treatment (n=24)	Dietary management only (n=80)
Maternal age	, years	36.1 ± 5.0	35.9 ± 4.3
Pregravid BMI	, kg/m^2	21.1 ± 2.6	20.5 ± 3.6
Pregravid overweight		3 (12.5%)	7 (8.8%)
Prior GDM		0 (0.0%)	1 (1.25%)
A family history of diabetes		10 (41.7%)	12 (15.0%) #
Gestational age at diagnosis	, weeks	20 ± 8	22 ± 8
Diagnosed before 20 weeks' pregnancy		13 (54.2%)	38 (47.5%)
HbA1c at diagnosis	, %	5.4 ± 0.3	5.4 ± 0.3
IS_{OGTT}		6.6 ± 3.4	6.3 ± 2.9
$AUC_{ins/glu}$		0.37 ± 0.18	0.40 ± 0.22
ISSI-2		2.1 ± 0.74	2.1 ± 0.58

OGTT, oral glucose tolerance test; BMI, body mass index; overweight, BMI ≥ 25; GDM, gestational diabetes mellitus; IS_{OGTT}, insulin sensitivity index derived from the oral glucose tolerance test; $AUC_{ins/glu}$, the ratio of the total area under the insulin curve to the total area under the glucose curve during the oral glucose tolerance test; ISSI-2, Insulin Secretion-Sensitivity Index-2 (i.e. the $AUC_{ins/glu}$ multiplied by IS_{OGTT}); #, $P < 0.01$

Table 3 Profiles of the diagnostic oral glucose tolerance test in women with a single abnormal result

		Insulin Tratment (n=24)	Dietary management only (n=80)
Plasma glucose (mg/dl)			
	0 min	89.3 ± 7.1	88.9 ± 7.4
	30 min	145.2 ± 17.8	141.7 ± 22.4
	60 min	152.8 ± 29.0	153.7 ± 27.3
	120 min	146.6 ± 29.6	135.8 ± 26.2
Plasma insulin (mU/l)			
	0 min	6.4 ± 3.2	6.6 ± 4.3
	30 min	58.9 ± 30.6	60.5 ± 38.9
	60 min	62.0 ± 34.7	71.4 ± 47.3
	120 min	69.2 ± 37.9	64.3 ± 41.5
Abnormal value of plasma glucose#			
	0 min	9 (37.5%)	40 (50%)
	60 min	3 (12.5%)	14 (17.5%)
	120 min	12 (50%)	26 (32.5%)

#, Cases showing abnormal plasma glucose values at each time point in the diagnostic oral glucose tolerance test

The overall perinatal features of this study cohort were as follows: the mean maternal age was 34.9 ± 4.8 years, pregravid BMI 19.8 ± 4.6, gestational age at delivery 38.0 ± 2.4 weeks, mean birthweight 2841 ± 551 g, and 680 (68.0%) were primiparas. Twenty-five women (2.5%) developed gestational hypertension, and 19 (2.9%) preeclampsia. The occurrence of SGA and LGA was 6.9% (69/995 cases) and 6.0% (60/995 cases), respectively.

The baseline characteristics and pregnancy outcomes of women with NGT or GDM are shown in Table 4. There were significant differences in maternal age, pregravid overweight, and a family history of DM among subjects with NGT and GDM. With regard to fetal growth, the prevalence of LGA and SGA were comparable between the NGT and GDM groups. Additionally, no significant differences in the occurrence of pregnancy-induced hypertension (i.e. gestational hypertension and preeclampsia) were found between the two groups.

Discussion

Currently, prospective data on the potential frequency of GDM with the IADPSG criteria has been slow. To the best of our knowledge, this is the first report on perinatal features of women with GDM in the clinical situations that adopted the IADPSG consen-

Table 4 Baseline characteristics and perinatal outcomes in women with normal glucose tolerance or gestational diabetes mellitus

		NGT (n=852)	GDM (n=141)
Maternal age	, years	34.7 ± 4.8	36.1 ± 4.6 *
Nulliparous		591 (69.4%)	89 (63.1%)
Pregravid BMI	, kg/m^2	19.6 ± 4.7	21.1 ± 4.0 #
Pregravid overweight		36 (4.2%)	18 (12.8%) ##
Prior GDM		5 (0.6%)	3 (2.1%)
A family history of diabetes		57 (6.7%)	33 (23.4%) ##
Gestational age at delivery	, weeks	38.1 ± 2.4	37.8 ± 2.8
Birth weight	, g	2845 ± 548	28121 ± 573
LGA		59 (6.9%)	10 (7.1%)
Macrosomia		9 (1.1%)	1 (0.7%)
SGA		53 (6.2%)	7 (5.0%)
Gestational hypertension		21 (2.5%)	4 (2.8%)
Preeclampsia		17 (2.0%)	2 (1.4%)

NGT, normal glucose tolerance, defined as negative screen for gestational diabetes mellitus or normal oral glucose tolerance results. GDM, gestational diabetes mellitus; BMI, body mass index, overweight, BMI ≥ 25; LGA, large-for-gestational age, defined as birth weight ≥ 90th percentile for gestational age; SGA, small-for-gestational age, defined as birth weight < 10th percentile for gestational age; Macrosomia, birth weight ≥ 4000g. *, $P < 0.05$; #, $P < 0.001$; ##, $P < 0.0001$.

sus criteria. In our institution, the prevalence of GDM by the former JSOG criteria was 2.3%, as previously reported [8]. Compared with the former situations, the IADPSG criteria lead to an increase in the frequency of GDM diagnosis in our hospital. Additionally, the majority (104/141 cases, 74%) of women with GDM showed 1-AV, which was consistent with data in the complete HAPO cohort [1]. Our results demonstrated that the frequency of GDM would increase significantly with the IADPSG criteria, mainly by those with 1-AV.

The implementation of insulin treatment was based on daily glucose profile during dietary management in our hospital. In this retrospective analysis, more women with 2/3-AV needed the addition of insulin treatment to achieve the glycemic control, compared with 1-AV. With respect to beta cell function, levels of ISSI-2 in women with 2/3-AV were significantly lower than those with 1-AV. The level of beta cell function is associated with the severity of glucose intolerance in GDM [9]. Additionally, our previous investigation demonstrated that beta cell dysfuntion in women with 2/3-AV appeared more severe than those with 1-AV [10]. Taken altogether, our data indicated women with 2/3-AV had more severe levels of glucose intolerance, compared with 1-AV.

Approximately one-quarter of women with 1-AV needed the insulin treatment. Most women with the IADPSG-defined GDM have 1-AV and factors associated with insulin treatment are needed in the clinical practice. The insulin treatment did not depend on which glucose result met or exceeded single IADPSG-defined OGTT threshold. When analyzed maternal characteristics, a family history of DM was correlated with the induction of insulin treatment. Of women with the IADPSG-defined GDM, therefore, those with 1-AV appear less severe glucose intolerant, but might be at risk of insulin requirement when a family history of DM exists.

There were significant differences in pregravid overweight, prior GDM, and a family history of DM among subjects with NGT and GDM, as were noted in the former situations [11]. Of note, no significant differences were found in the occurrence of perinatal outcome including LGA and pregnancy-induced hypertension between the NGT and GDM groups in this study cohort. Previous analysis based on reevaluated data before the adoption of the IADPSG criteria has shown increased risk of the development of LGA and gestational hypertension in the IADPSG-defined GDM [12]. Additionally, Black *et al.* have shown that IADPSG-defined GDM could be at risk of adverse outcomes including LGA, gestational hypertension and shoulder dystocia/birth injury [13]. To date, two trials have demonstrated the advantages of treatment for women with mild degree glucose intolerance, although inclusion criteria for the trial were different from the

IADPSG recommendation [14, 15, 16]. Our results suggest that intervention for women with IADPSG-defined GDM could contribute to the improvement of pregnancy outcomes, although further studies on the clinical and cost-effective management are needed.

Benefit of treatment of IADPSG-defined GDM remains unknown because no randomized control trial has been conducted using the IADPSG criteria and additional well-designed trial and other clinical studies will be needed to determine the optimal treatment targets [1]. In the clinical settings, therefore, appropriate management of IADPSG-defined GDM remains unclear. Our data is only a local experience but could be useful for other healthcare professionals considering the IADPSG criteria.

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Disclosure

Authors declare no conflict of interest with regard to this manuscript.

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BMI mediates the association between low educational level and higher blood pressure during pregnancy in Japan

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Abstract

Background

Research investigating the association between socioeconomic status (SES) and blood pressure (BP) during pregnancy is limited and its underlying pathway is unknown. The aim

of this study was to investigate the mediators of the association between educational level as an indicator of the SES and BP in early and mid-pregnancy among Japanese women.

Methods

Nine hundred and twenty-three pregnant women in whom BP was measured before 16 weeks and at 20 weeks of gestation were enrolled in this study. Maternal educational levels were categorized into three groups: high (university or higher), mid (junior college), and low (junior high school, high school, or vocational training school).

Results

The low educational group had higher systolic (low vs. high, difference = 2.39 mmHg, 95% confidence interval [CI]: 0.59 to 4.19) and diastolic BP levels (low vs. high, difference = 0.74 mmHg, 95% CI: –0.52 to 1.99) in early pregnancy. However, the same associations were not found after adjustment for pre-pregnancy body mass index (BMI). BP reduction was observed in mid-pregnancy in all three educational groups and there was no association between educational level and pregnancy-induced hypertension.

Conclusion

In Japanese women, the low educational group showed higher BP during pregnancy than the mid or high educational groups. Pre-pregnancy BMI mediates the association between educational level and BP.

Keywords

Socioeconomic status, Pregnancy, Blood pressure, Educational level, Pregnancy-induced hypertension

Background

Blood pressure (BP) control during pregnancy is crucial for the safety of both mothers and neonates. In previous reports, BP values during pregnancy have been shown to be associated with a continuous inverse effect in fetal growth. Systematic sampling with 24-h ambulatory BP monitoring during pregnancy indicated that a 5-mmHg increase in the mean diastolic BP was inversely associated with a 68-g decrease in birth weight in normotensive [1], and a 68.5-g decrease in hypertensive pregnancies [2]. In addition, subsequent BP elevation results in occurrence of maternal pregnancy-induced hypertension (PIH). High BP in early and mid-pregnancy is strongly associated with the later occurrence of PIH [3,4], which affects 3–10% of all pregnancies and is associated with high levels of maternal, fetal, and neonatal morbidity and mortality [5]. The long-term prognosis of women with a history of PIH also includes increased risk of future cerebrovascular disease, cardiovascular disease, and renal disease [6,7].

A low socioeconomic status (SES) is reported as a risk factor for high BP in adult people [8-10]. This inverse gradient is stronger and more consistent in women than in men. Although it is well known that pregnancy is regarded as a stress test for future hypertension [11,12], few

studies have investigated the association between SES and BP during pregnancy [13]. Furthermore, mediators of the association between SES and BP are not well known. Silva et al. reported that the association between educational levels and BP was mediated by pre-pregnancy BMI; however, weight gain, smoking, alcohol intake, or salt intake might be other mediators for this link as these factors were identified in other non-pregnant adult studies [14-17]. In addition, previous literature on SES and BP during pregnancy is limited to Western societies. Japanese diet, lifestyle, or health system might affect on the association between SES and BP in a different manner [18,19]. Thus, the purpose of this study is to investigate the association between educational levels as an indicator of SES and BP in early and mid-pregnancy, PIH, and to elucidate the mediating factors of these associations among Japanese pregnant women.

Methods

Study population

This study was a part of the Tokyo-Children's Health, Illness, and Development study (T-CHILD Study), a single-center, prospective, birth cohort study conducted at the National Center for Child Health and Development (Tokyo, Japan). Study participants were enrolled before 16 weeks of gestation at the obstetrical department from October 2003 to December 2005. The institutional review board at the National Center for Child Health and Development approved this study. Written informed consent was obtained from all participants. This study was a secondary analysis of the data.

The inclusion criteria of the current study were access to educational information, BP measurement before 16 weeks of gestation (early pregnancy) and at 20 weeks of gestation (mid-pregnancy), and delivery at the National Center for Child Health and Development after 22 weeks of gestation. We excluded women with multiple pregnancies. In total, 923 participants were enrolled in this study.

Educational level

Information on the educational level was obtained from a questionnaire at the time of enrollment. Participants were divided into 3 educational groups: high (university or higher), mid (junior college), and low (less than high school, high school or vocational training school). We categorized the participants with vocational school education into the low educational group because vocational schools usually do not require an entrance examination.

Measurement of blood pressure

BP was measured in the sitting position after 5 min of rest with the right arm held at heart level and by using an automated sphygmomanometer (Omron BP-203RVIII oscillometer; Nippon Colin, Tokyo, Japan). BP measurement was performed at 2 points: before 16 weeks and 20 weeks of gestation. If BP was measured several times before 16 weeks of gestation, the average systolic and diastolic value was calculated.

Pregnancy-induced hypertension

PIH was defined according to the 2009 guideline for care and treatment of hypertension in pregnancy proposed by the Japanese Society of the Study of Hypertension in Pregnancy as "hypertension with or without proteinuria occurring after 20 weeks of gestation but resolving by 12 weeks postpartum" [20].

Mediators and confounders

We considered the following potential mediators: pre-pregnancy BMI, smoking, family income, alcohol and salt consumption during pregnancy, and body weight gain until 20 weeks of gestation. The pre-pregnancy BMI was calculated as weight [kg]/height^2 [m], which was obtained from the questionnaire at the time of enrollment. Data on maternal smoking and family income were also obtained through the questionnaire. Maternal salt and alcohol consumption during pregnancy was based on data obtained during pregnancy from a brief-type self-administered diet history questionnaire which had been used in a previous study [21].

Maternal age, parity, gestational age at BP measurement, pre-pregnancy complications (diabetes mellitus [DM], hypertension, and renal disease), previous pregnancy history of PIH, and family history of hypertension were used as potential confounders in this study. Information on maternal age and family history of hypertension was collected from the questionnaire. Data on parity, maternal pre-pregnancy complications, and previous history of PIH were obtained from medical charts and delivery records.

Statistical analysis

Associations between the participants' baseline information and educational levels were assessed by using ANOVA for continuous variables and χ^2 or Fisher's exact test for discrete variables. The association between educational levels and BP was assessed by multiple regression analysis applying the following models. First, we examined the association between BP and educational level in an unadjusted model. Second, confounders (i.e., gestational age at BP measurement, maternal age, parity, maternal pre-pregnancy complication of hypertension, DM, renal disease, previous pregnancy history of PIH, and family history of hypertension) were adjusted as basic model. Then, potential mediators (i.e., pre-pregnancy BMI, smoking, salt intake, alcohol intake, income, and body weight gain until mid-pregnancy) were added to the basic model one by one as covariates. Finally, we used a full model adjusted for all possible mediators and confounders. Similar to BP difference, the association between educational levels and PIH was assessed by multiple logistic regression analysis. A P value <0.05 was considered as statistically significant. All analyses were performed with the STATA software (Version 11.1 for Windows, USA).

Results

Maternal characteristics of the study population stratified by educational level are shown in Table 1. Among the 923 participants, the number of participants in the high educational group was highest (n = 467, 50.6%), followed by the mid (n = 228, 24.7%) and low (n = 228, 24.7%) educational groups, which was skewed to higher educational attainment compared with mothers in the general population who delivered babies in Japan [22]. The mean age of

participants was 33.7 years (standard deviation [SD] = 7.1). The participants in the low educational group were more likely to be overweight, parous, smokers, and to gain body weight until mid-pregnancy. Participants in the high educational group were more likely to have a larger annual household income. History of hypertension was most often seen in the mid educational group, probably by chance.

Table 1 Characteristics of sample stratified by educational level

Characteristics	**All (n= 923)**	**Low (n=228)***	**Mid (n=228)***	**High (n=467)***	***P* value**
Maternal age (yrs)	33.7 (4.1)	33.4 (4.7)	34.1 (4.1)	33.6 (3.8)	NS
Prepregnancy BMI (kg/m^2)	20.2 (2.3)	21.0 (2.9)	20.1 (2.2)	19.8 (2.0)	<0.0001
BMI>25, n(%)	41 (4.4)	19 (8.3)	10 (4.4)	12 (2.6)	<0.05
BMI>30, n(%)	3 (0.3)	2 (0.9)	1 (0.4)	0 (0)	NS
Parity					
0, n(%)	452 (49.0)	97 (42.5)	104 (45.6)	251 (53.8)	<0.0001
≧1, n(%)	471 (51.0)	131 (57.5)	124 (54.4)	216 (46.2)	
Mean gestational age before 16 weeks blood pressure	14.3 (0.98)	14.3 (0.98)	14.3 (0.98)	14.3 (1.0)	NS
Mean gestational age at 20 weeks blood pressure	20 (1.2)	19.9 (1.2)	20.1 (1.2)	20.0 (1.1)	NS
Maternal prepregnancy complications					
Diabetes mellitus, n(%)	5 (0.5)	3 (1.3)	1 (0.44)	1 (0.21)	NS
Hypertension, n(%)	5 (0.5)	0 (0.0)	4 (1.8)	1 (0.21)	<0.05
Renal disease, n(%)	4 (0.4)	1 (0.4)	1 (0.44)	2 (0.43)	NS
Prepregnancy complications					
PIH, n(%)	11 (1.2)	4 (1.8)	1 (0.44)	6 (1.3)	NS
Family History					
Diabetes mellitus, n(%)	72 (7.8)	14 (6.1)	19 (8.3)	39 (8.4)	NS
Hypertension, n(%)	69 (7.5)	13 (5.7)	14 (6.1)	42 (9.0)	NS
Smoking					
Never or former, n(%)	891 (96.9)	209 (92.5)	224 (98.7)	458 (98.1)	<0.001
Current, n(%)	29 (3.2)	17 (7.5)	3 (1.3)	9 (1.9)	
Income (per year), n(%)					
<4 million yen	49 (5.7)	23 (10.6)	10 (4.8)	16 (3.7)	<0.001
<6 million yen	199 (23.2)	78 (35.9)	50 (24.2)	71 (16.4)	
<8 million yen	189 (22.1)	56 (25.8)	47 (22.7)	86 (19.9)	
<10 million yen	185 (21.6)	34 (15.7)	44 (21.3)	107 (24.7)	
over 10 million yen	235 (27.4)	26 (12.0)	56 (27.1)	153 (35.3)	
Salt Intake					

low, n(%)	302 (34.1)	81 (37.7)	66 (30.0)	155 (34.3)	NS
moderate, n(%)	295 (33.3)	65 (30.2)	72 (32.7)	158 (35.0)	
high, n(%)	290 (32.7)	69 (32.1)	82 (37.3)	139 (30.8)	
Alcohol Intake					
None or former, n(%)	749 (84.4)	183 (85.1)	192 (87.3)	374 (82.7)	NS
Current, n(%)	138 (15.6)	32 (14.9)	28 (12.7)	78 (17.3)	
Body weight gain until midpregnancy (kg)	3.4 (2.5)	3.9 (2.9)	2.9 (2.6)	3.4 (2.2)	<0.001

Values are given as mean ± standarad deviation for continuous variables.
PIH, pregnancy-induced hypertension; BMI, body mass index; NS, not significant; SD, standard deviation.
*"Low" denotes vocational training school, high school, or less; "Mid" denotes junior college; "High" denotes college or more than college.

The systolic BP patterns from early to mid-pregnancy in each educational group are shown in Figure 1. Overall, the low educational group showed higher systolic values both in early and mid-pregnancy compared to the high and mid educational groups. For the systolic BP at early pregnancy, the BP value of the low educational group was significantly higher than that of the high (difference = 2.39 mmHg, 95% confidence interval [CI]: 0.59 to 4.19) and mid (difference = 2.43 mmHg, 95% CI: 0.34 to 4.52) educational groups. Similarly, the systolic BP at mid-pregnancy was higher in the low educational group than in the high (difference = 1.52 mmHg, 95% CI: –0.27 to 3.30) or mid educational groups (difference = 1.23 mmHg, 95% CI: –0.84 to 3.30). However, these differences were not significant.

Figure 1 Mean systolic blood pressure in early, mid-pregnancy stratified by educational level. Mean blood pressure significantly different from that in subgroup of women with low (*) and mid (**) educational level (P<0.05).

The diastolic BP patterns from early to mid-pregnancy in each educational group are shown in Figure 2. The mean diastolic BP in early pregnancy was higher in the group of low educational level than of high level (low vs. high, difference = 0.74 mmHg, 95% CI: –0.52 to 1.99; low vs. mid, difference = 0.58 mmHg, 95% CI: –0.88 to 2.03). However, these differences were not significant. Similarly, no statistical differences between the educational groups were observed in mid-pregnancy. Decreases in both systolic and diastolic BP from early to mid-pregnancy were observed in all educational groups.

Figure 2 Mean diastolic blood pressure in early, mid-pregnancy stratified by educational level. Mean blood pressure did not significantly different from that in subgroup of women with low and mid educational level (P<0.05).

The associations between systolic and diastolic BP at early pregnancy and educational levels are shown in Table 2. In the basic model adjusted for maternal age, parity, gestational age at BP measurement, pre-pregnancy maternal complications, including DM, hypertension, and renal disease, previous pregnancy history of PIH, and family history of hypertension, the

mean systolic BP difference between low and high educational groups remained significant (difference = 2.42 mmHg, 95% CI: 0.61 to 4.23). Furthermore, after adding pre-pregnancy BMI to the basic model, the difference in systolic BP between low and high educational groups became no longer statistically significant (difference = 1.19 mmHg, 95% CI: –0.62 to 3.00). Adding other possible mediators (i.e., smoking, salt and alcohol intake, weight gain until mid-pregnancy) did not further attenuate the difference in BP between the low vs. high educational groups, with the exception of income. When the pre-pregnancy BMI was added in the full model, BP was not statistically different between the educational groups. With regard to the diastolic BP, the BP differences between the educational groups were not statistically significant. However, similar to systolic BP, diastolic BP differences were attenuated after adding pre-pregnancy BMI to the basic model.