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ORIGINAL ARTICLE

Changes in insulin requirements during pregnancy in Japanese women with type 1 diabetes

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Abstract

Aims We investigated the changes in insulin requirements, and other relevant factors, in pregnant Japanese women with type 1 diabetes.

Methods This retrospective observational study was conducted on 77 singleton pregnant women with type 1 diabetes, treated with multiple daily injections of insulin. We examined changes in daily insulin dose during pregnancy and defined the increased insulin doses as the ratio of maximum dose to the pre-pregnancy dose. The relationship between the increased insulin doses and maternal features or pregnancy outcomes was investigated.

Results The insulin dose gradually increased during pregnancy, reaching a maximum dose that was 1.6 times of that prior to pregnancy, at 35 weeks of gestation. A negative significant correlation was observed between the insulin dose increases and duration of diabetes ($p = 0.008$). Greater increases in insulin doses were noted in women with multiparity, compared to nulliparity ($p = 0.047$). Multiple regression analyses revealed that shorter duration of diabetes was independently associated with the increases in insulin dose during pregnancy.

Conclusions Women with a longer duration of diabetes required smaller increases in insulin dose during pregnancy, suggesting that long diabetic duration may decrease placental function. Further investigations are needed to clarify the mechanisms that the duration of diabetes influences on insulin requirement during pregnancy.

Keywords Type 1 diabetes · Pregnancy · Insulin dose · Duration of diabetes · Multiparity

Introduction

Significant alternations in maternal metabolism during pregnancy ensure a continuous supply of nutrients to the fetus. Glucose is the primary energy source for the fetus. In early pregnancy, increases in maternal insulin sensitivity enable storage of energy and nutrients. In late pregnancy, maternal insulin resistance develops due to increases in pregnancy-related hormones, such as progesterone, human placenta lactogen and prolactin [1], as well as inflammatory cytokines, such as tumor necrosis factor-α [2]. These changes facilitate the supply of glucose toward the fetus.

Strict glycemic control is necessary to prevent maternal and fetal complications [3, 4] in pregnant women with type 1 and type 2 diabetes. To counteract insulin resistance and achieve adequate metabolic control in late pregnancy, the dose of insulin may need to be increased. Understanding insulin requirements in pregnant women with type 1 diabetes would help them to maintain tight glycemic control. Omori et al [5] reported more than two decades ago that the insulin requirements in Japanese women with type 1 diabetes peaked at 36–38 weeks of gestation, at a dose that was 1.5 times pre-pregnancy doses. However, the internal and external environments of pregnant women with diabetes may have been changed during the last two decades, possibly affecting insulin requirement during pregnancy. We, therefore, conducted this study to investigate changes in insulin requirements in contemporary pregnant Japanese women with type 1 diabetes, compared to the previous reports [5]. Furthermore, we evaluated the associations between the change in insulin dose during pregnancy, and maternal clinical factors or pregnancy outcomes.

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Research design and methods

Subjects

We conducted a retrospective observational study of 90 Japanese women with type 1 diabetes mellitus who were managed from before conception or the first trimester, to the postpartum period and delivered at Tokyo Women's Medical University Hospital between January 2006 and March 2016. Type 1 diabetes mellitus was diagnosed according to the Japan Diabetes Society (JDS) criteria [6]. Women were eligible if their pregnancy was singleton and their diabetes was treated with multiple daily injections of insulin during pregnancy. We excluded 13 patients for the following reasons: multiple pregnancy ($n = 1$); continuous subcutaneous insulin infusion ($n = 6$); delivery before 36 weeks of gestation ($n = 4$); intravenous ritodrine hydrochloride infusion for premature delivery ($n = 2$). Thus, 77 women were included in this study. For bolus insulin, 26 subjects used insulin lispro, 24 used insulin aspart, 10 used regular insulin and 17 used a combination. For basal insulin, 39 subjects used NPH insulin, 28 used insulin detemir, 3 used insulin glargine and other 7 used a combination. Thirty-three subjects injected basal insulin once a day and the remains twice a day.

Metabolic control during pregnancy

The patients were instructed to record their self-monitoring of blood glucose (SMBG) values in diabetic diaries, which were evaluated at each clinical visit. They were also instructed to adjust the insulin dose by themselves between clinical visits based on the SMBG profiles, targeting blood glucose of 70–100 mg/dL for pre-prandial levels and below 120 mg/dL at 2-h postprandial levels. Insulin doses were also adjusted further at each biweekly visit, using the SMBG profiles, glycated hemoglobin (HbA1c) and glycated albumin (GA) levels.

Study methods

To describe the insulin requirements, we recorded daily insulin dose [units day^{-1} and units kg^{-1} day^{-1} (current weight)] from prior to pregnancy to delivery and one month after delivery. Daily insulin dose was determined by the weekly average. We defined increased insulin doses as the ratio of maximum insulin dose to the pre-pregnancy dose. We also collected the following information, regarding maternal clinical features, from the medical record: maternal age, duration of diabetes, pre-pregnancy body weight, body mass index (BMI), HbA1c prior to pregnancy and in the first, second and third trimester, parity, the presence of retinopathy and nephropathy. We also noted pregnancy outcomes: gestational age at delivery, mode of delivery, weight gain during pregnancy, sex of the baby, infants' birth weight, Apgar scores at 1 and 5 min, placental weight and neonatal complications such as respiratory problems, hypoglycemia, hyperbilirubinemia, polycythemia, congenital malformations and hypocalcemia. We analyzed the association between the insulin dose prior to pregnancy or increases in insulin doses, and clinical factors such as maternal clinical features and pregnancy outcomes.

BMI was calculated by the following formula: weight (kg) divided by height (m) squared. For neonatal complications, respiratory problem included respiratory distress syndrome, transient tachypnea of the newborn, apnea, and other respiratory disorders requiring respiratory management and neonatal hypoglycemia was defined as a blood glucose level less than 50 mg/dL. Hyperbilirubinemia was a need for phototherapy and we defined polycythemia as the hematocrit more than 65%. Congenital malformations were defined as those that impede life or those that cause dysfunction requiring surgical intervention and hypocalcemia was defined as the Ca^{2+} level less than 0.75 mmol/L.

Plasma glucose levels were measured by the hexokinase UV method using the Qualigent GLU regent (Sekisui Medial, Tokyo, Japan) (ADAMS Glu GA1171 analyzer, Arkray Corp., Tokyo, Japan). HbA1c level was analyzed by high-performance liquid choromatography assay (ADAMS A1c HA8180 analyzer, Arkray Corp., Tokyo, Japan). If HbA1c levels were displayed according to JDS standardization, we converted the levels to National Glycohemoglobin Standardization Program (NGSP) equivalent values, using the following formula: 1.02 × HbA1c (JDS value, %) + 0.25% [7]. The serum GA level was determined by the enzymatic method using albumin-specific proteinase, ketoamine oxidase, and an albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Corp., Tokyo Japan).

Statistical analysis

Quantitative data are presented as mean values ± standard deviations (SDs). We used the Student's t test to compare variables between groups. We used univariate linear regression analysis to investigate potential relationships between the insulin dose prior to pregnancy or increases in insulin dose, and the clinical factors as maternal clinical features and pregnancy outcomes. Then, we performed multiple regression analysis to identify the variables that were independently associated with increases in insulin dose. Statistically significant differences were defined as p value < 0.05. Statistical analysis was conducted with SPSS version 21 for Windows (IBM Corp., Armonk, NY, USA).

Results

Characteristics of the subjects and pregnancy outcome

The mean age of the 77 subjects was 32.1 ± 4.2 years, mean duration of diabetes was 14.6 ± 8.2 years, mean pre-pregnancy body weight was 55.1 ± 7.5 kg and mean BMI was 21.6 ± 2.4 kg/m^2 (Table 1). Pre-gestational HbA1c level was 7.3 ± 1.2% and reduced to 6.9 ± 0.7% in the first trimester, 6.1 ± 0.6% in the second trimester and 6.3 ± 0.6% in the third trimester. During pregnancy, 20 patients had simple retinopathy, one had preproliferative retinopathy, and two had proliferative retinopathy which was treated by laser photocoagulation before pregnancy and kept stable during pregnancy. There was one patient with microalbuminuria before pregnancy, which did not deteriorate during pregnancy.

The rate of patients with nulliparity was 55.8%. The gestational age of delivery was 38.4 ± 0.7 weeks, and cesarean section was performed in 34 patients. The infants' average birth weight was 3036 ± 413 g (range 2269–4330 g) and 13 cases were heavy-for-dates infants. Of the babies, 33 had some of neonatal complications: 10 had respiratory problems, 17 had hypoglycemia, eight had hyperbilirubinemia and one had polycythemia.

Insulin requirements

The daily insulin dose (units day^{-1}) gradually increased and reached the maximum at 35 weeks of gestation and declined thereafter (Fig. 1a). The total insulin requirement at 35 weeks of gestation was 67 ± 19 units day^{-1}, corresponding to 1.6 ± 0.5 times the average pre-pregnancy dose. The basal insulin dose and the bolus insulin dose at 35 weeks of gestation were 22 ± 9 units day^{-1}, 1.4 times the pre-pregnancy average, and 45 ± 14 units day^{-1}, 1.7 times the pre-pregnancy dose. The insulin doses expressed as units per kg body weight per day showed an identical trend (Fig. 1b) to the daily insulin dose (unit day^{-1}). The substantial increase in insulin dose was observed starting at 20 weeks of gestation and a highest degree was found at 28–29 weeks of gestation.

Clinical factors associated with insulin dose prior to pregnancy

Insulin dose prior to pregnancy was associated with pre-pregnancy body weight, BMI and HbA1c levels before pregnancy and in the first trimester (Table 2). Insulin dose prior to pregnancy was higher in patients with male infant than patients with female infants.

Table 1 Clinical characteristics of subjects and pregnancy outcomes

Maternal characteristics		Pregnancy outcomes	
Maternal age (years)	32.1 ± 4.2	Gestational age at delivery (weeks)	38.4 ± 0.7
Duration of diabetes (years)	14.6 ± 8.2	Vaginal delivery/Cesarean section (*n*)	43/34
Pre-pregnancy body weight (kg)	55.1 ± 7.5	Weight gain during pregnancy (kg)	11.2 ± 3.3
Pre-pregnancy BMI (kg/m^2)	21.6 ± 2.4	Sex of the infant male/female (*n*)	37/40
HbA1c before pregnancy (%)	7.3 ± 1.2	Birth weight of infant (g)	3036 ± 413
HbA1c in first trimester (%)	6.9 ± 0.7	Macrosomia (*n*)	2
HbA1c in second trimester (%)	6.1 ± 0.6	Low birth weight (*n*)	7
HbA1c in third trimester (%)	6.3 ± 0.6	LFD/AFD/HFD (*n*)	3/61/13
GA in first trimester (%)	19.4 ± 2.6	Placental weight (g)	595 ± 113
GA in second trimester (%)	17.7 ± 2.3	Apgar score at 1 min < 7 points/≥ 7 points (*n*)	3/74
GA in third trimester (%)	15.7 ± 2.0	Apgar score at 5 min < 7 points/≥ 7 points (*n*)	1/76
Retinopathy NDR/SDR/pre PDR/PDR (*n*)	54/20/ 1/2	Neonatal complications absence/presence (*n*)	44/33
Nephropathy none/microalbuminuria (*n*)	76/1		
nulliparity/multiparity (*n*)	43/34		

Data are shown as the mean ± standard deviation or number. Microalbuminuria was defined as urine albumin excretions ≥ 30 mg/gCr. Macrosomia was defined as birth weight ≥ 4000 g. Low birth weight was defined as birth weight < 2500 g

HbA1c glycated hemoglobin, *GA* glycated albumin, *NDR* no diabetic retinopathy, *SDR* simple diabetic retinopathy, *pre PDR* preproliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy, *LFD* light-for-dates infant, *AFD* appropriate-for-dates infant, *HFD* heavy-for-dates infant

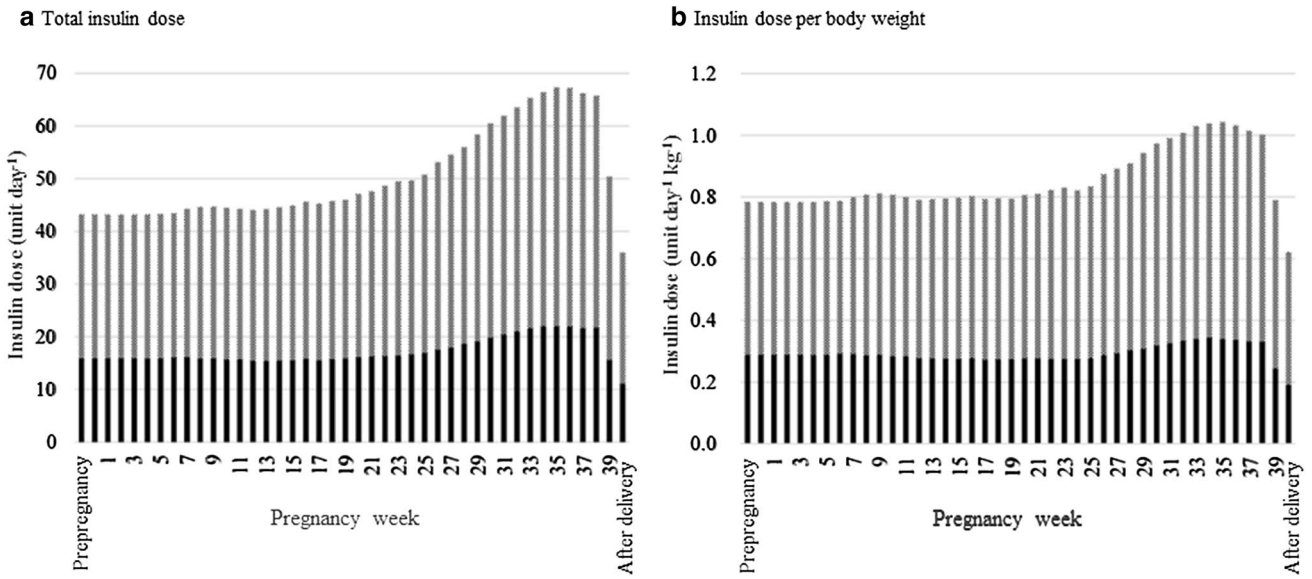

Fig. 1 Insulin requirements during pregnancy, expressed as units per day (left panel) and units per kg body weight per day (right panel). There were 77 subjects before 35 weeks of gestation; 75, 36 weeks of gestation; 72, 37 weeks of gestation; 61, 38 weeks of gestation; 14, 39 weeks of gestation. Black bar shows the basal insulin and gray bar shows the bolus insulin dose

Clinical factors associated with increased insulin doses

We observed greater increases in insulin doses in the subjects with multiparity, compared to those with nulliparity (Table 2; Fig. 2a). There was a significant negative correlation between increases in insulin doses and the duration of diabetes (Table 2; Fig. 2b). There were no significant associations between insulin dose increases and maternal age, HbA1c levels during pregnancy, pre-pregnancy BMI, weight gain during pregnancy, diabetic complications, mode of delivery, birth weight or sex of the infants, placental weight or neonatal complications. A multiple regression analysis showed that shorter duration of diabetes was an independently associated with the greater increases in insulin doses (Table 3).

Discussion

In this study, we found that the maximum insulin dose required during pregnancy in Japanese women with type 1 diabetes was 1.6 times that of the pre-pregnancy dose at 35 weeks of gestation. We also found that shorter duration of diabetes independently predicted greater increases in insulin dose.

In normal pregnancy, pancreatic insulin secretion increases 2- to 4-fold to compensate for peripheral insulin resistance, caused by placental hormones and cytokines [8, 9]. Insulin doses necessary to achieve optimal glycemic control in type 1 diabetic woman, increases as pregnancy advances, and reaches maximum dose of 1.5–2 times of that of pre-pregnancy doses [5, 10–12]. In this study, a substantial increase in insulin dose was observed beginning at 20 weeks of gestation, had the highest degree at 28–29 weeks of gestation, and reached peak dose at 35 weeks of gestation. That is warning that expeditious adjustment of insulin doses is necessary during this period.

An earlier study from our institution [5] showed maximum increases in insulin doses at 36–38 weeks of gestation that were 1.5 times the average pre-pregnancy dose in pregnant Japanese women with type 1 diabetes, consistent with our current study. In the meantime, internal and external environments and management of pregnant diabetic women have drastically changed. Lifestyle and eating habits of young Japanese people have changed. Insulin lispro [13, 14] and insulin aspart [15], rapid-acting human insulin analogs, reduced postprandial glucose excursions and provided better glycemic control than human insulin during pregnancy. Insulin detemir, a long-acting insulin analog, decreased fasting plasma glucose without increased hypoglycemia rates, compared with neutral protamine Hagedorn (NPH) insulin in pregnant women with type 1 diabetes [16]. Nonetheless, profiles of insulin requirements during pregnancy were almost identical over the last two decades. We did not investigate differences in insulin changes between human insulin and insulin analogs because of the small number of subjects, which is one of the limitations of this study.

The rate of insulin increases, in this study, was smaller than those observed in recent studies from Western

Table 2 Correlation of clinical factors and insulin dose, or change in required insulin using the single regression analysis

	Insulin dose before pregnancy		Increased insulin doses	
	r	*p*	*r*	*p*
Maternal characteristics				
Maternal age (years)	− 0.185	0.108	0.129	0.265
Duration of diabetes (years)	0.52	0.653	− 0.298	0.008
Pre-pregnancy body weight (kg)	0.326	0.004	0.019	0.872
Pre-pregnancy BMI (kg/m^2)	0.433	< 0.001	− 0.063	0.587
HbA1c before pregnancy (%)	0.3	0.02	− 0.168	0.2
HbA1c in the first trimester (%)	0.329	0.003	− 0.088	0.446
HbA1c in the second trimester (%)	0.219	0.056	− 0.073	0.528
HbA1c in the third trimester (%)	0.19	0.098	− 0.031	0.79
Diabetic retinopathy*		0.204		0.062
Diabetic nephropathy*		0.905		0.405
Parity*		0.791		0.047
Pregnancy outcomes				
Gestational age at delivery (weeks)	0.024	0.836	− 0.091	0.429
Mode of delivery*		0.222		0.573
Weight gain during pregnancy	− 0.058	0.618	− 0.079	0.495
Sex of the infant*		0.016		0.052
Birth weight of infant	− 0.045	0.701	− 0.11	0.342
Apgar score at 1 min	0.166	0.148	0.073	0.527
Apgar score at 5 min	0.013	0.91	0.118	0.306
Placental weight	− 0.033	0.773	− 0.105	0.364
Neonatal complications*		0.507		0.6

*Correlation of factors was analyzed using the Student's t test. Increased insulin doses were defined as the ratio of maximum insulin dose to the pre-pregnancy dose

countries [10, 12]. The maternal age was higher and the BMI was lower in this study. However, the weight gain during pregnancy was not shown in those studies, so that we could not compare the data. It is suggested that the change in insulin requirements may reflect insulin resistance during pregnancy because of regional and racial differences, such as later child-bearing, small physical constitution, eating habits, and weight gain during pregnancy.

Some studies [10, 17] showed decreased insulin requirements during the late first trimester, which was not observed in this study. Morning sickness, over-insulinization, and declining progesterone and thyroid hormone, during the first trimester, may explain observed decreases in insulin requirements. Higher BMI was associated with decreased insulin requirements during the late first trimester [17]. It is possible that the effects of hormonal changes, on insulin sensitivity, are smaller in Japanese patients, compared to patients from Western countries.

While insulin dose prior to pregnancy was associated with pre-pregnancy body weight, BMI and HbA1c levels, dose increases during pregnancy were associated with the duration of diabetes and parity, and the duration of diabetes was the only factor that predicted increased insulin dose rates during pregnancy. Steel et al. [18] reported that the insulin rise during pregnancy, in women with type 1 diabetes mellitus, had a positive relationship with weight gain during 20–29 weeks of gestation, maternal weight at booking and had a negative correlation between the duration of diabetes mellitus. While correlations were not found with maternal complications, fetal complications, fetal birth weight, or placental weight. Even after about 20 years, we proved reproducibility of the relationship between the duration of diabetes and change of insulin requirements during pregnancy. Interestingly, McManus et al. [19] demonstrated that insulin dosage declines after 36 weeks of gestation was only associated with the duration of diabetes, but not with maternal or fetal complications, or fetal birth weight. These results suggest that the patients who have a long duration of type 1 diabetes may have less increased placental hormone due to placental dysfunction, even if they do not have diabetic complications, or perinatal complications. In the present study, the levels of placental hormone and placental pathology were not investigated; however, fetal well-being was evaluated carefully by biophysical profile scoring and fetal Doppler ultrasound examination. In addition, we did not include subjects with preterm delivery before 36 weeks of gestation. The placenta in patients with diabetes has been characterized by villous immaturity, chorangiosis, increased weight, and vascular damage results in uteroplacental damage [20]. Although pathological placental changes may differ across different types of diabetes, it is not clear that maternal conditions such as race, metabolic control, duration of diabetes, and insulin use, contribute to abnormalities of placenta.

Of all variables analyzed in this study, the duration of diabetes was the only independent variable that was predicted the increased insulin doses and the R^2 was very low. This finding suggests that various factors related to insulin requirement during pregnancy, although the duration of diabetes may participate in the regulation of insulin requirement. Many other factors, such as glucagon, cytokine, and lipid metabolism, are involved in determining the requirement of insulin. Some adipokines play an important role of insulin secretion, insulin sensitivity, and appetite control. Maternal tumor necrosis factor-α and leptin concentrations were higher, and maternal adiponectin concentration was lower in patients with gestational diabetes compared to nondiabetic pregnant women [21]. It was reported that increase in circulating adiponectin concentrations in patients

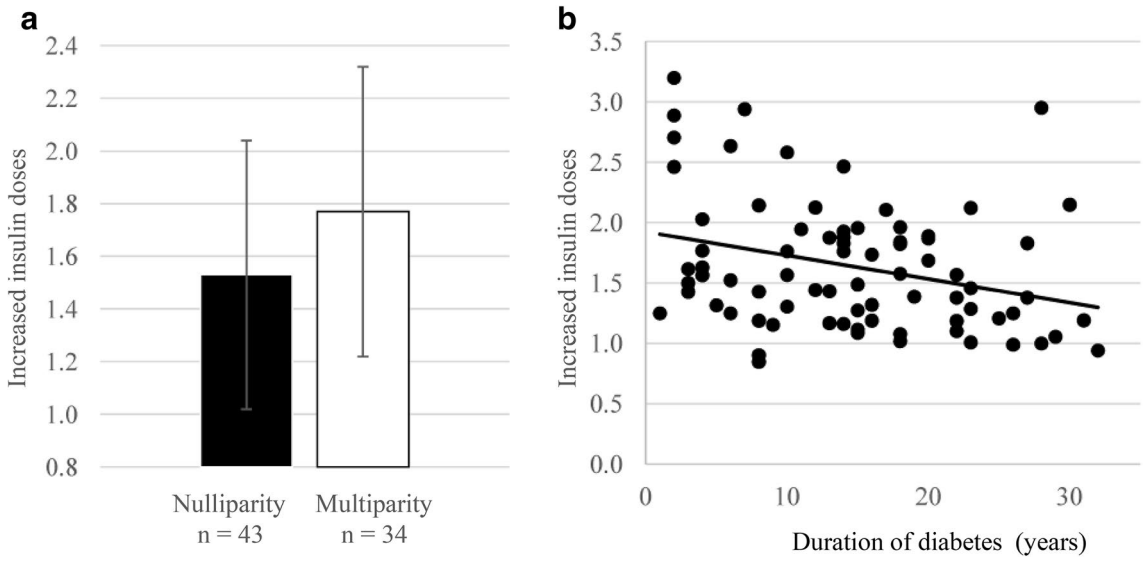

Fig. 2 **a** Comparison of changes in insulin doses during pregnancy in patients with nulliparity and multiparity ($p = 0.047$). **b** Correlation between increased insulin doses and duration of diabetes, using the single regression analysis ($y = -0.019x + 1.922$, $R^2 = 0.089$, $p = 0.008$)

Table 3 Correlation of clinical factors and increased insulin doses using the multiple regression analysis (stepwise method)

Dependent:	Increased insulin doses			
R^2	0.089			
	B	*β*	95% confidence interval	*p*
Duration of diabetes	− 0.019	− 0.298	− 0.034 to − 0.005	0.008

Excluded: parity

Increased insulin doses were defined as the ratio of maximum insulin dose to the pre-pregnancy dose

with type 1 diabetes appeared to be strongly associated with long diabetes duration [22]. Elevated free fatty acid levels also cause insulin resistance during pregnancy [23]. It was reported that the glucagon levels in type 1 diabetic patients in a hypoglycemic state did not increase and did not decrease in a hyperglycemic state [24]. Paradoxical glucagon release may appear in the course of type 1 diabetes progression [25]. These factors might contribute insulin sensitivity during pregnancy. We did not examine these factors in this retrospective study.

In this study, the insulin dose prior to pregnancy was associated with sex of the infants. Recent report suggested that women carrying a male infant had a higher postprandial glycemia and an increased risk of gestational diabetes [26]. There was no report showing the relationship between the sex of infant and insulin dose prior to pregnancy.

In conclusion, the maximum insulin dose during pregnancy was 1.6 times the pre-pregnancy dose at 35 weeks of gestation in pregnant Japanese women with type 1 diabetes. This change was much smaller than those observed in Western countries, and similar to the results of Japanese studies published over two decades ago. The patients with a long duration of diabetes required slight increases in insulin dose during pregnancy, suggesting that long disease duration may decrease placental function. Further investigations are needed to clarify the mechanisms that the duration of diabetes influences on insulin requirement during pregnancy.

Compliance with ethical standards

Conflict of interest Author Babazono received lecture fees from MSD K.K., Kyowa Hakko Kirin Co., Ltd., Novo Nordisk Phama Ltd., Takeda Pharma Ltd., Mitsubishi Tanabe Pharma Corp, Astellas Pharma Inc., Chugai Pharma Manufacturing Co., Ltd., Boehringer Ingerheim, Astra Zeneca K.K., Otsuka Pharmacuetical Co., Ltd., Kowa Shinyaku Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., and Daiichi Sankyo Co., Ltd., and research grants from Novartis Phama K.K., Astellas Pharma Inc., Pfizer Japan Inc., Chugai Pharma Manufacturing Co., Ltd., Boehringer Ingerheim, Astra Zeneca K.K., Kyowa Hakko Kirin Co., Ltd., Alcon, Otsuka Pharmacuetical Co., Ltd., Nipro; Eli Lilly Japan K.K., Kowa Shinyaku Co., Ltd., Eizai Co., Ltd., Takeda Pharma Ltd., Sanofi K.K., Mitsubishi Tanabe Pharma Corp., MSD K.K., Ono pharmaceutical Co., Novo Nordisk Phama Ltd., Terumo Corp., Sumitomo Dainippon Pharma Co., Ltd., and Daiichi Sankyo Co., Ltd. Other authors declare that they have no conflict of interest.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. This study was approved by the Ethical Committee of Tokyo Women's Medical University School of Medicine (Approval No. 3920R, approval date: 2 June 2017).

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