JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Trends in maternal characteristics and perinatal outcomes among Japanese pregnant women with type 1 and type 2 diabetes from 1982 to 2020

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Keywords
Perinatal outcome, Type 1 diabetes mellitus, Type 2 diabetes mellitus

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J Diabetes Investig 2022; 13: 1761–1770

doi: 10.1111/jdi.13841

ABSTRACT

Aims/Introduction: This study investigated the time trends of the maternal characteristics and perinatal outcomes of Japanese pregnant women with diabetes.
Materials and Methods: This retrospective study included 621 deliveries in 429 Japanese women with diabetes between 1982 and 2020. The association of the delivery date with clinical features was analyzed using the generalized estimating equations to adjust for the within-person correlation.
Results: The mean age of delivery and the mean diabetes duration increased over time (both $P < 0.001$), while the prevalence of diabetic retinopathy decreased ($P = 0.006$). The mean HbA1c values during pregnancy decreased significantly over time (all $P < 0.001$). The decreasing trends were associated with preterm delivery ($P = 0.021$) but not with other perinatal outcomes. The time trends were significantly different between patients with type 1 diabetes mellitus and with type 2 diabetes mellitus in large for gestational age (LGA) and stillbirth (both P for interaction <0.05). The rate of LGA decreased among patients with type 2 diabetes ($P = 0.003$) but not those with type 1 diabetes ($P = 0.413$). In contrast, the prevalence of stillbirth was decreased among those with type 1 diabetes ($P < 0.001$) but not those with type 2 diabetes ($P = 0.768$). The proportion of major congenital anomalies did not change in the overall population ($P = 0.259$) and among patients with type 2 diabetes ($P = 0.229$), but it increased among those with type 1 diabetes ($P = 0.044$), although the difference between those with type 1 diabetes and type 2 diabetes was not statistically significant (P for interaction = 0.166).
Conclusions: Maternal glycemic control has improved over the decades, whereas the improvement of perinatal outcomes has been limited. Perinatal outcomes still need to be improved in Japanese women with diabetes.

INTRODUCTION

The prevalence of diabetes in pregnancy has been rising globally[1–3]. Preconceptionally diagnosed diabetes, namely pre-existing diabetes, substantially increases the risks of various perinatal adverse outcomes, including perinatal mortality, congenital anomaly, large for gestational age (LGA), preterm delivery, and preeclampsia[4]. These risks are also high in women with diabetes first detected during pregnancy, namely overt diabetes in pregnancy (ODP), which includes type 2 diabetes mellitus (type 2 diabetes) developed but was overlooked before pregnancy and type 1 diabetes mellitus developed during pregnancy[5,6]. Overt diabetes in pregnancy requires as careful perinatal management as pre-existing diabetes[5,6].

Several surveys in Europe and North America have reported recent time trends of perinatal outcomes in women with diabetes[2,3,7–11]. However, little is known about the trends in Japan,

Received 24 December 2021; revised 27 March 2022; accepted 18 May 2022

where maternal characteristics including obesity, smoking, and age, which can considerably affect perinatal outcomes are different from those in Europe and North America. Obesity and smoking are less frequent in Japan than in Europe and North America[12–15], while women in Japan give birth relatively late[16].

Another international difference lies in healthcare service provision. Japan recommends and supports approximately 14 checkups per pregnancy[17], whereas in the United Kingdom (UK), pregnant women usually have access to 7–10 antenatal checkups[18]. In the United States (US), although as frequent checkups as in Japan are recommended[19], more than 20% of pregnant women do not attend checkups during the first trimester[20]; in Japan, the corresponding proportion is <10%[21].

Furthermore, regimens of insulin therapy vary across countries. Insulin pumps are used by 50–60% of patients with type 1 diabetes in the US[22], whereas the proportion in Japan is <10% [23]. On the other hand, 30% and 20% of patients with type 1 diabetes and type 2 diabetes use insulin syringes in the US[22], respectively, whereas almost all patients use insulin pens in Japan.

These international differences may affect the perinatal features of pregnancies with diabetes. This study aimed to reveal the time trends of maternal characteristics and delivery outcomes in Japanese pregnant women with diabetes.

MATERIALS AND METHODS

Study population

We identified all pregnant women with diabetes, both pre-existing diabetes and ODP, who delivered in Osaka Women's and Children's Hospital, Izumi City, Osaka Prefecture, Japan, between 1982 and 2020. The hospital is a key facility for perinatal care in the prefecture. Women from abroad or those with diabetes due to other specific mechanisms or diseases[5] were excluded from our study. There were 633 deliveries during the study period. After excluding 12 multiple pregnancies, 621 single pregnancies were finally included for the current analysis. Clinical features of the 12 multiple pregnancies are summarized in Table S1.

Clinical data were extracted from the medical records of the hospital. The study protocol was in accordance with the Helsinki Declaration and approved by the institutional review boards of Osaka Women's and Children's Hospital and Osaka University Hospital. We applied the opt-out method, offering opportunities for refusal via the website of Osaka Women's and Children's Hospital instead of obtaining informed consent.

Definitions

Overt diabetes in pregnancy was diagnosed in women without pre-existing diabetes if their fasting blood glucose value was ≥126 mg/dL (7.0 mmol/L) or the HbA1c value was ≥6.5% (47 mmol/mol) during pregnancy[5]. The type of diabetes in women diagnosed with ODP was reconfirmed after delivery[5]. The information on the presence of pre-existing diabetes, defined as diabetes diagnosed before pregnancy, and the type of diabetes was extracted from existing medical records. The information was, therefore, based on the diagnostic criteria and the definitions used in the clinical settings at the time, rather than on unified criteria or definitions throughout the study period. The terms 'insulin-dependent diabetes mellitus' and 'non-insulin-dependent diabetes mellitus' without a clear specific mechanism or disease in the medical records were translated to type 1 diabetes and type 2 diabetes, respectively, in the current study. Diabetic retinopathy was defined as having pre-proliferative to proliferative retinopathy, a history of photocoagulation for retinopathy, or a history of vitreous surgery for vitreous hemorrhage. Maternal pre-pregnancy body mass index (BMI) was calculated as the pre-pregnancy weight in kilograms divided by the height in meters squared. A BMI of ≥25 kg/m^2 was defined as obesity[24]. Smokers included both current and former smokers.

Spontaneous miscarriage and stillbirth were defined as fetal loss before and after 22 weeks of gestation, respectively[17]. Preterm delivery was defined as delivery before 37 completed weeks of gestation[17]. Preeclampsia was defined as the onset of elevated blood pressure (≥140/90 mmHg [19/12 kPa]) and proteinuria (>300 mg/24 h or ≥2+ on two random urine samples collected at least 4 h apart)[25]. Cesarean section was defined as the primary cesarean section performed for the first time in the index woman. Large for gestational age was defined as sex- and parity-specific birth weight for gestational age above the 90th percentile of Japanese fetal growth curves[26]. Major congenital anomalies were determined as structural or functional anomalies diagnosed during pregnancy or within 7 days after delivery that required surgery or repeated medical checkups. Neonatal death denoted death of a liveborn infant within the first 28 days of life.

Maternal glycemic control was evaluated using HbA1c values. In Japan, the method of HbA1c measurement was not standardized by the Japan Diabetes Society (JDS) until 1995; therefore, we excluded the data measured before 1995. HbA1c (JDS) was converted to HbA1c (National Glycohemoglobin Standardization Program) units[27]. Maternal HbA1c was routinely measured every month in clinical settings at the hospital. We calculated the mean HbA1c values for each trimester by averaging all HbA1c values available during the trimester.

Statistical analysis

Dichotomous variables are presented as frequencies and percentages. Continuous variables are presented as mean and standard deviation. Descriptive statistics were demonstrated after the study population was divided into quartiles of the delivery date; April 14, 1982–October 9, 1997 (Period 1, $n = 155$); November 10, 1997–February 5, 2008 (Period 2, $n = 155$); February 24, 2008–July 12, 2014 (Period 3, $n = 155$); and August 6, 2014–December 27, 2020 (Period 4, $n = 156$). We also presented descriptive statistics by decades (1982–1991 [Period I], 1992–2001 [Period II], 2002–2011 [Period III], and 2012–2020 [Period IV]). The association of the delivery date with clinical features and the difference in clinical features between type 1 diabetes and type 2 diabetes were analyzed using generalized estimated equations to adjust for the within-person correlation. The interaction analysis was performed to check the difference between type 1 diabetes and type 2 diabetes related to the association of the date of delivery with clinical features using generalized estimated equations.

The missing data for the HbA1c values were addressed by the multiple imputation using the chained equations method. We generated 10 imputed datasets and combined the results based on Rubin's rule. The time trends of the HbA1c values were investigated with (1) all missing data of HbA1c values throughout the study period being imputed and (2) only missing data after 1995 (after the measurement standardization) being imputed. We also showed Supporting Information without imputation.

Two-sided *P*-values of <0.05 were considered significant. All statistical analyses were performed using R version 4.0.3 (R Development Core Team, Vienna, Austria).

RESULTS

This study included 621 deliveries in 429 women: 214 (34%) had type 1 diabetes and 407 (66%) had type 2 diabetes. Table 1 and Table S3 show the overall time trends of maternal characteristics and perinatal outcomes. The prevalence of type 1 diabetes, the mean age of delivery, and the mean duration of diabetes increased over time (all $P < 0.001$). The prevalence of ODP and diabetic retinopathy decreased significantly ($P < 0.001$ and $P = 0.006$). BMI and the prevalence of obesity, smokers, and nulliparity did not change significantly over time (all $P > 0.05$). The incidence of preterm delivery decreased significantly ($P = 0.021$), whereas those of other perinatal outcomes did not change significantly (all $P > 0.05$).

Table 2 shows the maternal characteristics and perinatal outcomes of patients with type 1 diabetes and with type 2 diabetes. Patients with type 2 diabetes were older ($P < 0.001$) and had a shorter duration of diabetes ($P < 0.001$) than those with type 1 diabetes. ODP, obesity, and smokers were more prevalent among patients with type 2 diabetes (all $P < 0.001$), whereas patients with type 2 diabetes less frequently had diabetic retinopathy ($P < 0.001$). The prevalence of most perinatal outcomes were similar among type 1 diabetes and type 2 diabetes patients; exceptions were primary cesarean section, preeclampsia, and major congenital anomaly, the prevalence of which were significantly higher in patients with type 2 diabetes ($P = 0.039$, 0.025, and 0.014, respectively).

Table 3 and Table S4 demonstrate the time trends in maternal characteristics and perinatal outcomes stratified by the type of diabetes. The type of diabetes had a significant effect on the time trends of the incidence of LGA and stillbirth (both *P* for interaction <0.05). The incidence of LGA decreased significantly among the patients with type 2 diabetes ($P = 0.003$) but not among those with type 1 diabetes ($P = 0.413$) (Figure S1a,b). In contrast, the incidence of stillbirth decreased significantly over time among patients with type 1 diabetes ($P < 0.001$) but not among those with type 2 diabetes ($P = 0.768$). The time

Table 1 | Overall trends of maternal characteristics and perinatal outcomes

	All	Period 1 (Apr 14, 1982–Oct 9, 1997)	Period 2 (Nov 10, 1997–Feb 5, 2008)	Period 3 (Feb 24, 2008–Jul 12, 2014)	Period 4 (Aug 6, 2014–Dec 27, 2020)	*P* for trend
Number of deliveries	*n* = 621	*n* = 155	*n* = 155	*n* = 155	*n* = 156	
Type 1 diabetes mellitus	34%	17%	36%	46%	39%	<0.001
Age (years)	32.7 (5.1)	31.2 (5.0)	31.7 (5.0)	33.4 (4.8)	34.6 (4.9)	<0.001
Duration of diabetes (years)	7.7 (7.9)	4.2 (5.4)	7.5 (7.5)	9.4 (8.6)	9.6 (8.5)	<0.001
ODP	19%	34%	17%	14%	12%	<0.001
Diabetic retinopathy	4.3%	6.5%	7.1%	2.6%	1.3%	0.006
BMI (kg/m^2)	26.4 (5.8)	26.3 (5.4)	26.5 (6.2)	25.9 (6.0)	27.1 (5.7)	0.250
Obesity	55%	57%	52%	51%	60%	0.681
Smokers	32%	35%	36%	31%	26%	0.071
Nulliparity	43%	33%	48%	53%	39%	0.113
Spontaneous miscarriage	9.0%	9.0%	9.0%	9.0%	9.0%	0.568
Preterm delivery	13%	17%	15%	8.4%	11%	0.021
Preeclampsia	9.8%	15%	7.7%	8.4%	8.3%	0.088
Primary cesarean section	22%	19%	23%	27%	19%	0.905
Large for gestational age	33%	41%	31%	31%	30%	0.090
Stillbirth	0.8%	1.9%	0.0%	1.3%	0.0%	0.238
Major congenital anomaly	7.4%	4.5%	7.7%	9.0%	8.3%	0.259
Neonatal death	0.6%	0.6%	0.6%	0.6%	0.7%	0.881

Data are shown as % or mean (standard deviation). Data were missing on the duration of diabetes at delivery in two women, on maternal BMI before pregnancy in six women, and on birthweight percentiles in three infants, respectively. *P* values for trend were derived from generalized estimating equations. BMI, body mass index; ODP, overt diabetes in pregnancy.

Table 2 | Comparisons of maternal characteristics and perinatal outcomes between type 1 diabetes mellitus and type 2 diabetes mellitus

	Type 1 diabetes mellitus	Type 2 diabetes mellitus	*P* value
Number of deliveries	214	407	
Age (years)	31.7 (4.8)	33.3 (5.2)	<0.001
Duration of diabetes (years)	13.4 (8.8)	4.7 (5.3)	<0.001
ODP	5.1%	27%	<0.001
Diabetic retinopathy	8.4%	2.2%	<0.001
BMI (kg/m^2)	22.2 (3.0)	28.6 (5.8)	<0.001
Obesity	16%	75%	<0.001
Smokers	18%	40%	<0.001
Nulliparity	46%	42%	0.266
Spontaneous miscarriage	11%	8.1%	0.277
Preterm delivery	12%	13%	0.682
Primary cesarean section	17%	25%	0.039
Preeclampsia	6.1%	12%	0.025
Large for gestational age	38%	31%	0.065
Stillbirth	0.9%	0.7%	0.794
Major congenital anomaly	3.7%	9.3%	0.014
Neonatal death	0.0%	1.0%	N.A.

Data are shown as % or mean (standard deviation). *P* values were by generalized estimating equations. BMI, body mass index; N.A., not applicable because no case was observed in type 1 diabetes mellitus; ODP, overt diabetes in pregnancy.

trends of the other maternal characteristics and perinatal outcomes of the type 1 diabetes and type 2 diabetes subgroups were not significantly different (all *P* for interaction >0.05), and their time trends were almost the same as those observed in the overall population (Table 1). An exception was BMI, which increased significantly over time among the type 1 diabetes and type 2 diabetes subgroups (Table 3), although the time trends did not reach statistical significance in the overall population (Table 1), suggesting Simpson's statistical paradox. Furthermore, the prevalence of major congenital anomaly increased significantly among patients with type 1 diabetes ($P = 0.044$) but not among the overall population ($P = 0.259$) or those with type 2 diabetes ($P = 0.229$), although the difference in trends among the patients with type 1 diabetes and type 2 diabetes did not reach statistical significance (*P* for interaction =0.166) (Figure S1c,d).

The mean maternal HbA1c values (95% confidence intervals) were estimated to be 7.5 (7.2–7.8)% (59 [55–62] mmol/mol) during the first trimester, 6.3 (6.2–6.4)% (45 [44–46] mmol/mol) during the second trimester, and 6.5 (6.2–6.8)% (48 [44–51] mmol/mol) during the third trimester. Women with type 1 diabetes had significantly lower mean HbA1c values than those with type 2 diabetes during the first trimester (7.0 [6.7–7.3]% vs 7.8 [7.4–8.2]%: 53 [50–56] mmol/mol vs 62 [57–66] mmol/mol, $P < 0.001$), but not during the second trimester (6.2 [6.0–6.4]% vs 6.3 [6.2–6.5]%: 44 [42–46] mmol/mol vs 45 [44–48] mmol/mol, $P = 0.248$) or the third trimester (6.5 [6.2–6.7]% vs 6.4 [6.1–6.8]%: 48 [44–50] mmol/mol vs 46 [43–51] mmol/mol, $P = 0.672$). As demonstrated in Table 4 and Table S5, the mean HbA1c values during all trimesters decreased significantly over time (all $P < 0.001$), with no significant effect of the type of diabetes (all *P* for interaction >0.05). In the subgroup with type 1 diabetes, the decreasing trends of HbA1c values did not consistently reach statistical significance ($P > 0.05$ in the third trimester during the overall study period and the second and third trimesters after 1995 in Table 4, and in the first to third trimesters without imputation in Tables S6 and S7). The proportion of cases with HbA1c < 6.5% (47 mmol/mol) followed similar time trends (Tables S8–S11); it generally increased over time, although the proportion was still 43.3 (38.2–48.3)%, 84.2 (80.0–88.3)%, and 76.8 (71.5–82.2)% during the first, second, and third trimesters, respectively, in Period 4.

DISCUSSION

The current study demonstrated the time trends of maternal characteristics and perinatal outcomes of Japanese pregnant women with diabetes from 1982 to 2020. HbA1c in all trimesters generally decreased over time, whereas the mean maternal age at delivery, the duration of diabetes, and BMI increased. During the study period, which spanned four decades, not all perinatal outcomes showed an improvement over time.

Several countries have reported recent time trends of perinatal outcomes of women with diabetes[2,3,7–11]. However, the time trends vary among countries. For example, the incidence of LGA among women with type 1 diabetes increased in the UK[7], while it was stable in the US and Spain[3,8]. The prevalence of congenital anomalies also followed different time trends across countries[2,9–11]. Perinatal outcomes can be affected by maternal characteristics and national healthcare systems. This is the first study reporting recent time trends of perinatal features of Japanese pregnant women with diabetes.

The current study confirmed that HbA1c values generally decreased over time, although the trends were not always significant for type 1 diabetes, despite no significant interaction between type 1 diabetes and type 2 diabetes. The non-significant decrease in patients with type 1 diabetes may be attributed to the small sample size. The overall improvement of glycemic control would reflect recent marked advances in antidiabetic treatment; in Japan, human insulin became clinically available in 1985, self-measurement of blood glucose was covered by medical insurance in 1986, insulin pens became available in 1988, insulin analogs became available in 2001, continuous subcutaneous insulin infusion for type 1 diabetes was covered by medical insurance in 2000, and the use of a sensor-augmented pump was started in 2015. Table S2 shows the time trends of antidiabetic treatment in the study population. These advances would contribute to the improvement of glycemic control over the past decades, although there is room for improvement (Tables S8–S11). During individual

Table 3 | Trends of maternal characteristics and perinatal outcomes stratified by the type of diabetes mellitus

	Period 1 (Apr 14, 1982–Oct 9, 1997)	Period 2 (Nov 10, 1997–Feb 5, 2008)	Period 3 (Feb 24, 2008–Jul 12, 2014)	Period 4 (Aug 6, 2014–Dec 27, 2020)	*P* for trend	*P* for interaction
Number of deliveries						
Type 1 diabetes mellitus	*n* = 27	*n* = 55	*n* = 71	*n* = 61		
Type 2 diabetes mellitus	*n* = 128	*n* = 100	*n* = 84	*n* = 95		
Age (years)						
Type 1 diabetes mellitus	30.0 (5.1)	29.8 (4.9)	32.2 (4.0)	33.4 (4.8)	<0.001	0.964
Type 2 diabetes mellitus	31.5 (5.0)	32.7 (4.8)	34.4 (5.2)	35.5 (4.8)	<0.001	
Duration of diabetes (years)						
Type 1 diabetes mellitus	8.8 (8.3)	13.2 (7.7)	14.7 (9.0)	14.1 (9.2)	0.004	0.287
Type 2 diabetes mellitus	3.3 (4.0)	4.4 (5.2)	4.9 (5.0)	6.7 (6.5)	<0.001	
ODP						
Type 1 diabetes mellitus	19%	3.6%	4.2%	1.6%	0.007	0.161
Type 2 diabetes mellitus	37%	25%	21%	19%	<0.001	
Diabetic retinopathy						
Type 1 diabetes mellitus	15%	18%	2.8%	3.3%	0.002	0.824
Type 2 diabetes mellitus	4.7%	1.0%	2.4%	0.0%	0.042	
BMI (kg/m^2)						
Type 1 diabetes mellitus	21.3 (3.1)	21.9 (2.8)	21.8 (2.8)	23.4 (3.1)	0.010	0.514
Type 2 diabetes mellitus	27.2 (5.2)	29.0 (6.1)	29.4 (5.8)	29.4 (5.8)	<0.001	
Obesity						
Type 1 diabetes mellitus	8.0%	13%	14%	25%	0.070	0.594
Type 2 diabetes mellitus	66%	74%	82%	82%	0.001	
Smokers						
Type 1 diabetes mellitus	33%	18%	13%	16%	0.056	0.076
Type 2 diabetes mellitus	35%	46%	46%	32%	0.918	
Nulliparity						
Type 1 diabetes mellitus	26%	58%	52%	38%	0.791	0.590
Type 2 diabetes mellitus	34%	43%	54%	40%	0.144	
Spontaneous miscarriage						
Type 1 diabetes mellitus	22%	9.1%	8.5%	9.8%	0.465	0.248
Type 2 diabetes mellitus	6.2%	9.0%	9.5%	8.4%	0.334	
Preterm delivery						
Type 1 diabetes mellitus	22%	15%	8.5%	9.8%	0.058	0.456
Type 2 diabetes mellitus	16%	15%	8.4%	12%	0.126	
Preeclampsia						
Type 1 diabetes mellitus	11%	3.6%	5.6%	6.6%	0.666	0.912
Type 2 diabetes mellitus	16%	10%	11%	9.5%	0.222	
Primary cesarean section						
Type 1 diabetes mellitus	15%	15%	24%	13%	0.700	0.886
Type 2 diabetes mellitus	20%	28%	29%	23%	0.687	
Large for gestational age						
Type 1 diabetes mellitus	48%	28%	40%	42%	0.413	0.026
Type 2 diabetes mellitus	40%	32%	23%	23%	0.003	
Stillbirth						
Type 1 diabetes mellitus	7.4%	0.0%	0.0%	0.0%	<0.001	0.003
Type 2 diabetes mellitus	0.8%	0.0%	2.4%	0.0%	0.768	
Major congenital anomaly						
Type 1 diabetes mellitus	0.0%	1.8%	4.2%	6.6%	0.044	0.166
Type 2 diabetes mellitus	5.5%	11%	13.1%	9.5%	0.229	
Neonatal death						
Type 1 diabetes mellitus	0.0%	0.0%	0.0%	0.0%	N.A.	N.A.
Type 2 diabetes mellitus	0.8%	1.0%	1.2%	1.1%	0.948	

Data are shown as % or mean (standard deviation). *P* values were derived from generalized estimating equations. BMI, body mass index; N.A., not applicable because no case was observed in type 1 diabetes mellitus; ODP, overt diabetes in pregnancy.

Table 4 | Trends in HbA1c values

	Period 1 (Apr 14, 1982–Oct 9, 1997)	Period 2 (Nov 10, 1997–Feb 5, 008)	Period 3 (Feb 24, 2008–Jul 12, 2014)	Period 4 (Aug 6, 2014–Dec 27, 2020)	Overall study period		After 1995	
					P for trend	*P* for interaction	*P* for trend	*P* for interaction
Trends in the overall population								
HbA1c in the first trimester (%)	8.3 (7.7–9.0)	7.7 (7.3–8.0)	7.1 (6.8–7.3)	7.0 (6.7–7.3)	<0.001		0.001	
(mmol/mol)	67 (61–75)	61 (56–64)	54 (51–56)	53 (50–56)				
HbA1c in the second trimester (%)	6.8 (6.6–7.0)	6.4 (6.3–6.5)	6.0 (5.9–6.2)	5.9 (5.8–6.0)	<0.001		<0.001	
(mmol/mol)	51 (49–53)	46 (45–48)	42 (41–44)	41 (40–42)				
HbA1c in the third trimester (%)	7.0 (6.4–7.5)	6.5 (6.2–6.8)	6.2 (6.0–6.4)	6.1 (6.0–6.3)	<0.001		0.002	
(mmol/mol)	53 (45–59)	48 (44–51)	44 (42–45)	43 (42–45)				
Trends by type of diabetes mellitus								
HbA1c in the first trimester								
Type 1 diabetes mellitus (%)	8.2 (7.4–9.0)	7.2 (6.9–7.5)	6.6 (6.4–6.8)	6.8 (6.5–7.0)	0.007	0.815	0.013	0.993
(mmol/mol)	66 (57–75)	55 (52–59)	49 (46–51)	51 (48–53)				
Type 2 diabetes mellitus (%)	8.3 (7.7–9.0)	7.9 (7.5–8.4)	7.5 (7.2–7.7)	7.2 (6.9–7.5)	0.003		0.013	
(mmol/mol)	67 (61–75)	63 (59–68)	59 (55–61)	55 (52–59)				
HbA1c in the second trimester								
Type 1 diabetes mellitus (%)	7.0 (6.6–7.4)	6.3 (6.1–6.5)	6.0 (5.9–6.1)	6.0 (5.9–6.2)	<0.001	0.686	0.069	0.452
(mmol/mol)	53 (49–57)	45 (43–48)	42 (41–43)	42 (41–44)				
Type 2 diabetes mellitus (%)	6.8 (6.5–7.0)	6.4 (6.3–6.5)	6.1 (5.9–6.2)	5.9 (5.8–6.0)	<0.001		<0.001	
(mmol/mol)	51 (48–53)	46 (45–48)	4 (41–44)	41 (40–42)				
HbA1c in the third trimester								
Type 1 diabetes mellitus (%)	7.3 (6.6–8.0)	6.5 (6.2–6.8)	6.3 (6.1–6.5)	6.3 (6.1–6.5)	0.053	0.502	0.230	0.514
(mmol/mol)	56 (49–64)	45 (44–51)	45 (43–48)	45 (43–48)				
Type 2 diabetes mellitus (%)	6.9 (6.3–7.4)	6.5 (6.2–6.8)	6.1 (5.9–6.4)	6.0 (5.8–6.2)	<0.001		0.002	
(mmol/mol)	52 (45–57)	45 (44–51)	43 (41–46)	42 (40–44)				

Data are shown as estimated means (95% confidence intervals). Data on HbA1c values in the first, second, and third trimesters were missing in 264, 233, and 204 deliveries, respectively. *P* values were derived from generalized estimating equations.

pregnancies, HbA1c values decreased from the first to the second trimesters, suggesting that glycemic control would be improved by intensified antihyperglycemic therapy after the confirmation of pregnancy. The mother's enhanced motivation for treatment would also contribute to the improvement. On the other hand, HbA1c values slightly increased from the second to the third trimesters. This apparent increase may be a false HbA1c elevation due to maternal iron deficiency[28] rather than a deterioration of glycemic control.

The prevalence of type 1 diabetes has increased (Table 1), as reported previously[29]. The increase may reflect the recent increasing feasibility of pregnancy in type 1 diabetes women. The recent advances in antidiabetic treatments reduce the risk of undesirable hyperglycemia, a key risk factor for low fertility[30]. Patients with type 1 diabetes, whose glycemic control is generally more challenging than that of patients with type 2 diabetes, would have more benefit from these advances. Appropriate glycemic control also reduces the risk of diabetic nephropathy, often considered as a contraindication to pregnancy. The prevalence of nephropathy has decreased in Japanese patients with type 1 diabetes[31], suggesting that fewer women with type 1 diabetes may be deprived of a chance of pregnancy by nephropathy than before.

The decreasing proportion of ODP may reflect a potential domestic increase of opportunities for medical checkups of women at college and in the workplace. In Japan, medical checkups are mandatory for first-year students in junior college and university, according to the Enforcement Regulations of the School Health and Safety Law. Furthermore, the Industrial Safety and Health Law obliges employers to make provisions for medical examinations of workers conducted by a physician, as provided by the Ordinance of the Ministry of Health, Labour, and Welfare. The employment ratio, as well as the enrolment ratio in tertiary education, has increased for women[32,33]. This suggests that young women will have more chances for medical checkups, and diabetes will less likely be left undiagnosed before pregnancy. The prevalence of ODP was higher among patients with type 2 diabetes than type 1 diabetes, which may be because type 2 diabetes is accompanied by milder signs and symptoms at the onset than type 1 diabetes. Type 2 diabetes would be more likely left undiagnosed in women who miss the opportunity for such health checkups. The prevalence of ODP may also be influenced by the screening system during pregnancy. In 1995, the Japan Society of Obstetrics and Gynecology first recommended screening all pregnant women for gestational diabetes mellitus by measuring

2–4 h postprandial glucose levels[34]. In 2008, the society revised their recommended screening method to random blood glucose during the early stage of pregnancy and a 50 g glucose challenge test between 24 and 28 gestational weeks[35]. Those changes in the screening opportunity during pregnancy may also affect the prevalence of ODP.

The increase in the delivery age over the decades was consistent with the nationwide time trend; in Japan, the average age of first-time mothers increased from 26.4 years in 1980 to 30.7 years in 2019[36]. Type 2 diabetes generally develops at a later age than type 1 diabetes, often after reaching reproductive age, and this may be attributed to the older delivery age of the patients with type 2 diabetes. Pregnancy before the diagnosis of type 2 diabetes was not included in this survey (i.e., statistically truncated), which would inevitably increase their mean age at delivery.

BMI and the proportion of obesity show different time trends between the overall population (Table 1) and the subgroups (Table 3). This phenomenon is statistically known as Simpson's paradox[37]. The prevalence of type 1 diabetes increased over time (Table 1), and the mean BMI of the overall population got closer to that of the patients with type 1 diabetes. Although the mean BMI increased over time in patients with type 1 diabetes as in those with type 2 diabetes (Table 3), the absolute value for the type 1 diabetes patients was lower than that for the type 2 diabetes patients (21.3–23.4 vs 27.2–29.4 kg/m^2). Consequently, the increasing trend of BMI was canceled by the increasing prevalence of type 1 diabetes when analyzed in the overall population. BMI and the prevalence of obesity increased, rather than was unchanged, over decades in pregnant women with diabetes, either type 1 diabetes or type 2 diabetes.

This increasing prevalence of obesity was inconsistent with the nationwide trend, where its prevalence in young female citizens was steadily approximately 10%[12], and their mean BMI value kept at approximately 21–22 kg/m^2 over the decades (Figure S2)[38]. However, recent domestic surveys of patients with diabetes in Japan showed that BMI and the prevalence of obesity increased gradually[39,40]. Pregnant women with diabetes would be no exception, although their values were much higher. The higher BMI of our cohort would be partially explained by their younger age; younger patients with diabetes are reported to have a higher prevalence of obesity[40]. Another reason for the higher BMI would be the requirement of strict glycemic control for pregnancy[4,5]. In women planning pregnancy, insulin is the only preferred medication for treating hyperglycemia[5]. However, the medication can cause weight gain[41]. Women with diabetes aiming at tight glycemic control would be subject to the risk of undesirable weight gain.

In Japan, the proportion of smokers in female citizens aged 20–39 years decreased from 34.8% in 2003 to 11.5% in 2019[12]. Our study revealed that the proportion of smokers was unchanged in both patients with type 1 diabetes and type 2 diabetes (Table 3). Moreover, the proportion of smokers in type 2 diabetes was higher than that in Japanese women in general. A higher proportion of smokers among young women with type 2 diabetes was also reported by the Japan Diabetes Clinical Data Management Study Group[42], indicating a considerable burden of smoking in young women with type 2 diabetes, irrespective of pregnancy.

The incidence of LGA among patients with type 1 diabetes remained as high as approximately 40% over the decades. In contrast, the prevalence of LGA among patients with type 2 diabetes decreased from 40% during Period 1 to 23% during Period 4. However, it should be noted that the proportion was still higher than that of the general Japanese population. Large for gestational age is defined as the 90th or higher percentile of birthweight[26], meaning that LGA should account for only 10% of the general population.

A higher incidence of major congenital anomalies among patients with type 2 diabetes than patients with type 1 diabetes would be attributable to patients with type 2 diabetes having higher HbA1c values during the first trimester, older age, and a higher prevalence of smoking and obesity, all of which are well-known risk factors for congenital anomalies[4,43]. The prevalence of major congenital anomalies in patients with type 1 diabetes significantly increased over time (P = 0.044). However, the increase marginally lost significance after adjusting for increased age (35 years or older) and BMI (30 kg/m^2 or higher) (P = 0.061), indicating that the increase would be, at least partially, explained by increased maternal age and BMI in recent decades. The advances in image inspections such as fetal ultrasonographic examination, enabling the easy detection of mild abnormalities, may also contribute to the recent increase.

On the other hand, the incidence of stillbirth decreased among patients with type 1 diabetes. All stillbirths observed in patients with type 1 diabetes were caused by maternal diabetic ketoacidosis in the current study. The incidence of maternal diabetic ketoacidosis decreased in our cohort; the number of deliveries with ketoacidosis was four during Period 1, one during Period 2, and zero during Periods 3 and 4. Recent advances in antidiabetic treatments would prevent diabetic ketoacidosis, potentially reducing the risk of stillbirth.

There are some limitations of this study. One limitation is the retrospective nature of the analysis. The information on pre-existing diabetes and the type of diabetes was extracted from medical records and was dependent on the diagnostic criteria and definitions used in clinical practice at the time, and changed over time. Such changes may have affected the time trends. The changes in the screening and diagnosis systems may also have influenced the trends. Furthermore, data on the number of women who underwent screening for hyperglycemia during pregnancy were unavailable, and data used for analysis were from a single center. In addition, a quarter of women were referred to our hospital during the second to third trimester. The prevalence of spontaneous miscarriage may therefore be underestimated. Lastly, the number of observed perinatal outcomes, including major congenital anomalies, stillbirth, and neonatal death, was so small that the statistical power was insufficient, and the results were inconclusive.

In conclusion, maternal HbA1c in all trimesters have decreased over recent decades in pregnant women with diabetes in Japan, although there is still room for improvement. The mean maternal age at delivery, diabetes duration, and the proportion of obesity have increased over time. Not all perinatal outcomes have improved over the decades.

ACKNOWLEDGMENTS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DISCLOSURE

There was no financial support or relationships that may be construed as conflicts of interest.

Approval of the research protocol: The study protocol was in accordance with the Helsinki Declaration of 2013 and was approved by the institutional review boards of Osaka Women's and Children's Hospital and Osaka University Hospital.

Informed consent: Since we used the existing data retrospectively, the requirement for informed consent was waived. Instead, we applied the opt-out method, offering opportunities for refusal *via* the website of Osaka Women's and Children's Hospital.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Maternal characteristics and perinatal outcomes of multipregnancy

Table S2 | Trends of the proportion of users of SMBG or insulin injection stratified by the type of diabetes mellitus

Table S3 | Overall trends of maternal characteristics and perinatal outcomes by 10 years

Table S4 | Trends of maternal characteristics and perinatal outcomes stratified by the type of diabetes mellitus by 10 years

Table S5 | Trends in HbA1c values by 10 years

Table S6 | Trends in HbA1c values (raw data)

Table S7 | Trends in HbA1c values by 10 years (raw data)

Table S8 | Trends in proportion of HbA1c values <6.5% (47 mmol/mol) after multiple imputation

Table S9 | Trends in proportion of HbA1c values <6.5% (47 mmol/mol) by 10 years after multiple imputation

Table S10 | Trends in proportion of HbA1c values <6.5% (47 mmol/mol) (raw data)

Table S11 | Trends in proportion of HbA1c values <6.5% (47 mmol/mol) by 10 years (raw data)

Figure S1 | The trend of the proportion of LGA (a and b) and major congenital anomaly (c and d). Panel a and c, the study population was divided according to the quartiles of the delivery date. Panel b and d, the study population was divided by 10 years.

Figure S2 | The trend of the mean BMI value in Japanese female population among 20s and 30s[38].