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ORIGINAL ARTICLE

Maternal diabetes mellitus and birth defects in Taiwan: A 5-year nationwide population-based cohort study

Lih-Ju Chen[a,b,c], Chih-Huang Chiu[d], Jing-Yang Huang[a,e], Ping-Ju Chen[a,d,f], Pen-Hua Su[a], Shun-Fa Yang[a,e,*], Jia-Yuh Chen[a,b,d,*]

[a]Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan, ROC; [b]Division of Neonatology, Changhua Christian Children's Hospital, Changhua, Taiwan, ROC; [c]Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan, ROC; [d]Division of Metabolism and Endocrinology, Yunlin Christian Hospital, Changhua, Taiwan, ROC; [e]Department of Medical Research, Chung Shan Medical University Hospital, Taichung, Taiwan, ROC; [f]Division of Dentistry, Changhua Christian Hospital, Changhua, Taiwan, ROC

Abstract

Background: Birth defects (BDs) are the main causes of mortality and disability in infants and children. Associations between maternal diabetes mellitus (DM), including gestational DM (GDM) and pregestational DM (type 1 or type 2), and the risk of BDs have been reported. This study aims to determine the relationship between maternal DM and BDs and to investigate whether reducing the incidence of DM can decrease the incidence of BDs.

Methods: We identified all births in Taiwan from the National Birth Defects Surveillance Program between January 1, 2010, and December 31, 2014. Information on the infants' characteristics (sex, gestational age, and birth weight) and mothers' characteristics (age, parity, and associated diseases, including DM) were obtained from the National Birth Registry and National Health Insurance Research Database (NHIRD) in Taiwan. BDs were coded according to the International Classification of Diseases, 9th Revision—Clinical Modification (ICD-9-CM) codes 740-759.

Results: Multiple logistic regression analysis with adjusted odds ratio (aOR) and 95% confidence interval (95% CI) for all BDs showed that the aOR (95% CI) was 1.002 (0.965-1.041), and the *p*-value was 0.9139 in the GDM group. In the type 1 DM group, the aOR (95% CI) was 1.748 (1.110-2.754), and the *p*-value was 0.016. In the type 2 DM group, the aOR (95%CI) was 1.175 (1.005-1.375), 1.331 (1.196-1.482), and 1.391 (1.216-1.592), and the *p*-value was 0.0437, <0.0001, and <0.0001 for the duration of mothers with type 2 DM <2, 2 to 5, >5 years, respectively.

Conclusion: Mothers with pregestational DM (type 1 or type 2) increase the incidence of BD. Appropriate maternal glycemic control may achieve good pregnancy and perinatal outcomes.

Keywords: Birth defects; Gestational DM; Pregestational DM; Prevalence

1. INTRODUCTION

Birth defects (BDs) are structural or functional abnormalities present at or before birth. These defects can be caused by genetic abnormalities and/or environmental exposure. The epidemiology and prevalence of BDs have been reported previously.[1–6] BDs have been reported to affect approximately 3% of all infants in the United States.[2] The prevalence of all BDs diagnosed at birth in Europe is about 2.5%.[7] It has been reported by Chen et al that the prevalence of BDs is 271.66 per 10 000 births (2.7%) in Taiwan.[8] Many risk factors have been associated with BDs, including maternal age,[9,10] environmental pollution,[11] medications,[12–16] diabetic mothers,[17–23] maternal chronic diseases,[24] genitourinary infection,[25] maternal overweight, and obesity.[26] Mothers with hypertension, cardiovascular diseases, renal diseases, genitourinary infections, anemia, mental diseases, and DM having a higher prevalence of BDs in Taiwan have been reported by Chen et al.[8]

The aims of this study are to determine the relationship between maternal DM, including gestational DM (GDM) and pregestational (type 1 or type 2) DM, and BDs and to explore whether reducing the incidence of maternal DM can decrease the prevalence of BDs.

2. METHODS

2.1. Study population

We identified all births (including live and stillbirths) in Taiwan from the National Birth Defects Surveillance Program between January 1, 2010, and December 31, 2014 (n = 1 017 984). Figure 1

* *Address correspondence. Dr. Shun-Fa Yang, Institute of Medicine, Chung-Shan Medical University, 110, Section 1, Chien-Kuo North Road, Taichung 402, Taiwan, ROC. E-mail address: ysf@csmu.edu.tw (S.-F. Yang); Dr. Jia-Yuh Chen, Division of Neonatology, Changhua Christian Children's Hospital, 320, Xuguan Road, Changhua 500, Taiwan, ROC. E-mail address: 182288@cch.org.tw (J.-Y. Chen).*

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shows the flow diagram of the study cohort. Stillbirths or abortus (n = 11 664), unknown status of offspring (n = 125 129), and missing data (n = 2468) were excluded. A total of 24 204 infants with BDs were diagnosed during the 5-year study period. Among these infants with BDs, 20 236 (83.61%) were born to non-DM mothers, 3197 (13.21%) were born to mothers with GDM, 20 (0.08%) were born to mothers with type 1 DM, 165 (0.68%) were born to mothers with type 2 DM for <2 years, 358 (1.48%) were born to mothers with type 2 DM for 2 to 5 years, and 228 (0.94%) were born to mothers with type 2 DM for >5 years. A total of 854 519 infants without BDs served as the control group. Among these infants without BDs (no BDs), 722 424 (84.54%) were born to non-DM mothers, 112 909 (13.2%) were born to mothers with GDM, 347 (0.04%) were born to mothers with type 1 DM, 4570 (0.53%) were born to mothers with type 2 DM for <2 years, 8956 (1.05%) were born to mothers with type 2 DM for 2 to 5 years, and 5313 (0.62%) were born to mothers with type 2 DM for >5 years. We defined "gestational DM" as maternal DM diagnosed during pregnancy and mothers who had clinical visits with International Classification of Diseases (ICD)-9 codes 648.8 or 250.0-250.9 during the second or third trimester of pregnancy, respectively. The "pregestational DM" is defined as mothers who had a clinical visit for diabetes, as identified by ICD-9 codes 250.0-250.9 before pregnancy. Furthermore, the pregestational type 1 DM is defined as ICD-9 codes 250.1 or 250.3, and the pregestational type 2 DM is defined as ICD-9 codes 250.0 or 250.2. Information on infants' characteristics (sex, gestational age, and birth weight) and mothers' characteristics (age, parity, singleton or multiple births, educational level, and associated diseases) were obtained from the National Birth Registry and National Health Insurance Research Database in Taiwan. BDs were coded according to the International Classification of Diseases 9th Revision—Clinical Modification (ICD-9-CM) codes 740-759. Each infant was followed up for one year. BDs were diagnosed as an infant with ≥2 outpatient visits or ≥1 admission record, which were recommended by an advisory committee including many pediatric and genetic professors. By using the classification of the European Surveillance of Congenital Anomalies (EUROCAT) study,[7] if an infant had one or more BDs, it was recorded that one infant had a BD. However, if an infant had two or more BDs, every BD was recorded in the data of diseases or systems. Atrial septal defect (ASD), ventricular septal defect (VSD), congenital laryngomalacia, undescended testis, and patent ductus arteriosus were diagnosed when the infants were >6 months of age. The diagnosis of patent ductus arteriosus was excluded when the infant's gestational age was <37 weeks. This study was approved by the Ethical Committee at Chung Shan Medical University Hospital.

2.2. Statistical analysis

The chi-square test was used to compare differences in nominal variables between the BD and control (non-BD) groups. A logistic regression model was used to estimate the odds ratio with a 95% confidence interval (95% CI) for the BDs. A p-value of <0.05 was considered to be statistically significant. SAS 9.4 software was used to perform the analysis in the study. The population attributable risk percentage (PAR%) of BDs was calculated according to the following formula: PAR% = [proportion of diseases in population × relative risk – 1]/[1 + proportion of diseases in population × (relative risk – 1)].

3. RESULTS

Between January 1, 2010, and December 31, 2014, there were 1 017 984 births and 24 204 infants with BDs in Taiwan. Figure 1 shows the flow diagram of the study cohort. A total of 24 204 infants with BDs were diagnosed during the 5-year study period. Among these infants with BDs, 20 236 (83.61%) were born to non-DM mothers, 3197 (13.21%) were born to mothers with GDM, 20 (0.08%) were born to mothers with type 1 DM, 165 (0.68%) were born to mothers with type 2 DM for <2 years, 358 (1.48%) were born to mothers with type 2 DM for 2 to 5 years, and 228 (0.94%) were born to mothers with type 2 DM for >5 years. A total of 854 519 infants without BDs served as the control group. Among these infants without BDs (no BDs), 722 424 (84.54%) were born to non-DM mothers, 112 909 (13.2%) were born to mothers with GDM, 347 (0.04%) were born to mothers with type 1 DM, 4570 (0.53%) were born to mothers with type 2 DM for <2 years, 8956 (1.05%) were born to mothers with type 2 DM for 2 to 5 years, and 5313 (0.62%) were born to mothers with type 2 DM for >5 years.

By using the classification of the European Surveillance of Congenital Anomalies (EUROCAT) study,[7] if an infant had one or more BDs, it was recorded that one infant had a BD. However, if an infant had two or more BDs, every BD was recorded in the data of diseases or systems. Table 1 lists the main BDs of infants born to mothers with non-DM, GDM, and type 1 or type 2 DM. Patients' numbers <30 in the non-DM group or <3 in the GDM group are not listed in Table 1. The most common BDs were ASD and VSD. Table 2 shows the logistic regression for BDs by system. Mothers with type 1 DM or type 2 DM for >2 years increased the prevalence rate of BDs on eyes, ears, face, and neck (p < 0.05). Mothers with type 2 DM increased BDs in the cardiovascular system (p < 0.05). Mothers with type 1 DM increased BDs in the respiratory system (p < 0.05). Mothers with GDM or type 2 DM for <5 years increased BDs in the musculoskeletal system (p < 0.05). The odds ratio (95% CI) for musculoskeletal system defects in patients with type 2 DM for >5 years was 1.125 (0.779-1.625), p-value = 0.5289. This might be due to too few cases of BDs in this group to provide enough statistical significance.

Supplementary Table S1, http://links.lww.com/JCMA/A191, shows the number and prevalence of BDs classified by system in the non-DM, GDM, and pregestational DM groups. Supplementary Table S2, http://links.lww.com/JCMA/A192, shows the number and prevalence of multiple BDs in the non-DM, GDM, and pregestational DM groups.

Table 3 summarizes the number of controls or infants of diabetic mothers and the univariate analysis of BDs according to the maternal type of DM. Mothers with pregestational type 1 or type 2 DM had a higher rate (p < 0.05) of BDs than mothers without DM.

Table 4 shows multiple logistic regression, adjusted odds ratio (aOR), and 95% CI for BDs. Mothers with type 1 DM and type 2 DM were risk factors for BDs. After adjusting the covariates, including maternal age, infant sex, multiple birth, and maternal co-morbidity, compared with nondiabetic mothers, the adjusted ORs of any BD were 1.002 (95% CI = 0.965-1.041) for GDM, 1.748 (1.110-2.754) for type 1 DM, 1.175 (1.005-1.375) for type 2 DM for <2 years, 1.331 (1.196-1.482) for type 2 DM for 2 to 5 years, and 1.391 (1.216-1.592) for type 2 DM for >5 years.

The mothers with DM were older than the mothers without DM. The mean ± standard deviation of maternal age was 31.1 ± 5.1, 32.1 ± 5.6, 32.9 ± 5.0, and 33.6 ± 5.0 years in the non-DM, type 1 DM, type 2 DM, and GDM groups, respectively. Table 5 shows maternal age as a factor in determining the relationship between DM and BDs. The maternal age of 30 to 40 and ≥45 years showed a higher infantile BD rate (p < 0.0001) than the maternal age of 18 to 29 years.

The prevalence of BDs was 270.22 per 10 000 births in Taiwan in 2014. The population of Taiwan was about 23 million in 2014. Using the population attributable risk percentage

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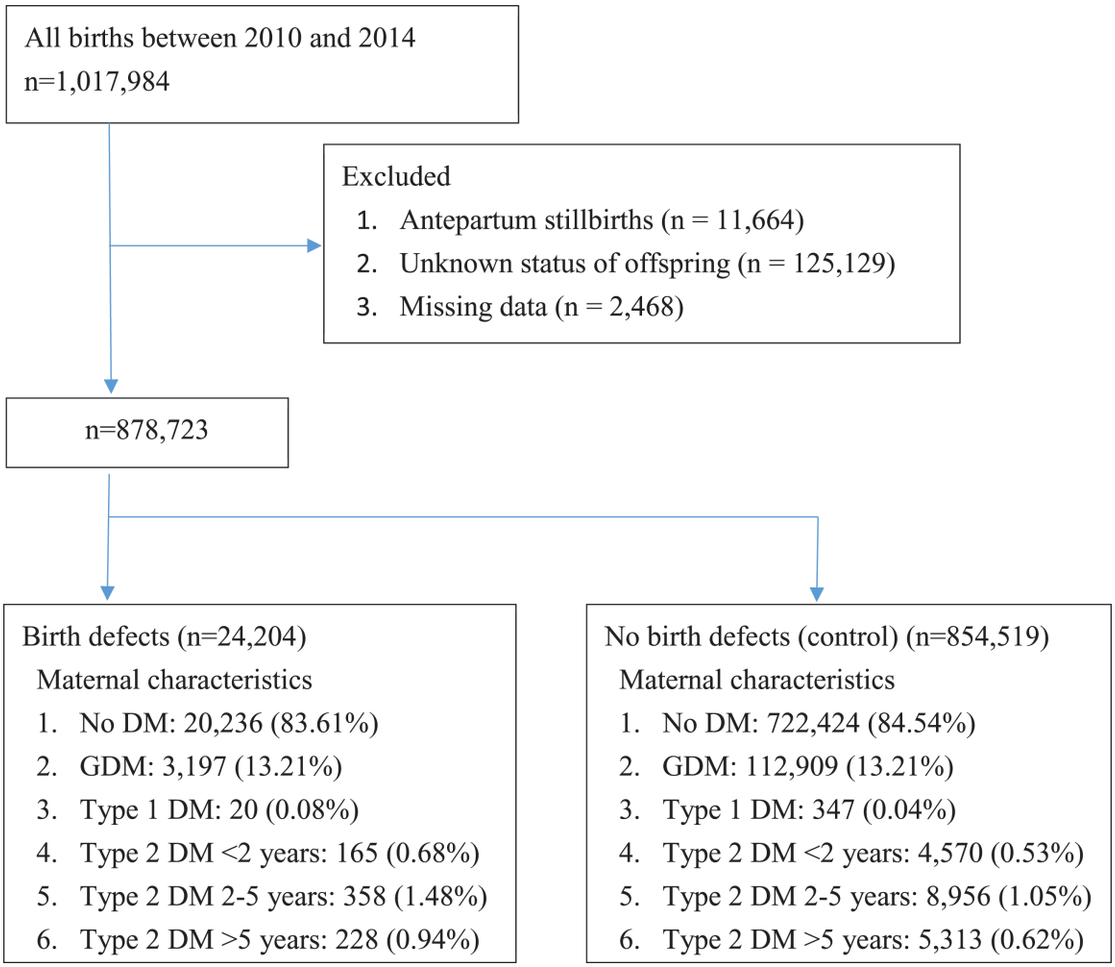

Fig. 1 Flow diagram of the study cohort.

(PAR%) of BDs, the prevalence of BDs will be 257.54 per 10 000 births in Taiwan in 2034. PAR% in GDM was 0.48% and in pregestational (type 1 and type 2) DM was 0.24%. If the percentage decrease (*y*) is 1%, 5%, and 10% for mothers with GDM, the number of patients with BDs will reduce by 17, 86, and 172 cases, respectively, in Taiwan in 2034. If the percentage decrease (*y*) is 1%, 5%, and 10% for mothers with pregestational DM, the number of patients with BDs will reduce by 8, 43, and 86 cases, respectively, in Taiwan in 2034.

4. DISCUSSION

DM in pregnancy is associated with an increased risk of fetal, neonatal, and long-term complications in the offspring. Maternal DM may be pregestational (type 1 or type 2 DM) diagnosed before pregnancy with a prevalence rate of 1.1% to 1.5%[8,27] or gestational DM (diabetes diagnosed during pregnancy) with a prevalence rate of 5.4% to 12%.[8,27,28] It was reported by Chen et al that the incidence of pregestational DM (type 1 or type 2 DM) was 1.1% and the incidence of GDM was 12% for pregnant women in Taiwan between 2005 and 2014 according to a national population-based cohort study.[8] Neonatal complications in infants of diabetic mothers included congenital anomalies, prematurity, perinatal asphyxia, macrosomia, which increases the risk of birth injury, respiratory distress, metabolic complications including hypoglycemia and hypocalcemia, hematologic complications including polycythemia and hyperviscosity, low iron stores, hyperbilirubinemia, and cardiomyopathy.[29,30] A previous report showed that the most common BDs were VSD and ASD in Taiwan.[8] In this study, the most common BDs were ASD and VSD for infants born to diabetic mothers. The same as our previous report[8] that the most common system of BDs was the cardiovascular system and the second most common system of BDs was the genitourinary system in this study.

Wren et al reported that preexisting maternal diabetes was associated with a fivefold increase in the risk of cardiovascular malformation.[31] It was also reported that higher thickness valves ($p < 0.0001$) for the interventricular septum and right and left myocardial wall were found in uncontrolled maternal DM than in the controlled diabetic cases.[32]

The crude and aOR and 95% CI showed that pregestational DM (including type 1 and type 2 DM) was associated significantly ($p < 0.05$) with BDs; however, GDM was not associated significantly ($p > 0.05$) with BDs in this study. The same findings were reported by previous reports that there was a two- to threefold increase in malformations in infants of insulin-dependent diabetic mothers.[22] This increase was not seen in infants of gestational diabetics.[22] Becerra et al reported the increased risk for major malformations among infants of mothers with insulin-dependent DM and infants of mothers with GDM who required insulin during pregnancy; however, no statistically

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Table 1

Main birth defects of infants born to nondiabetic and diabetic mothers

Birth defects	Number of patients (%)		
	Non-DM	GDM	Pregestational DM (type 1, type 2 DM)
Cardiovascular system			
Atrial septal defect[a]	2699 (0.36%)	388 (0.33%)	119 (0.60%)
Ventricular septal defect[a]	2325 (0.31%)	362 (0.31%)	98 (0.49%)
Pulmonary valve atresia/stenosis	1190 (0.16%)	174 (0.15%)	34 (0.17%)
Patent ductus arteriosus[a,b]	670 (0.09%)	110 (0.09%)	38 (0.19%)
Coarctation of aorta	416 (0.06%)	50 (0.04%)	29 (0.15%)
Tetralogy of Fallot	385 (0.05%)	67 (0.06%)	15 (0.08%)
Transposition of the great arteries	163 (0.02%)	20 (0.02%)	10 (0.05%)
Atrioventricular septal defect	163 (0.02%)	20 (0.02%)	7 (0.04%)
Double outlet right ventricle	148 (0.02%)	25 (0.02%)	13 (0.07%)
Aortic valve stenosis	92 (0.01%)	12 (0.01%)	4 (0.02%)
Complex congenital heart diseases	70 (0.01%)	7 (0.01%)	4 (0.02%)
Single ventricle	64 (0.01%)	7 (0.01%)	4 (0.02%)
Common truncus arteriosus	45 (0.01%)	3 (0.00%)	3 (0.02%)
Interrupted aortic arch	46 (0.01%)	9 (0.01%)	4 (0.02%)
Genitourinary system			
Undescended testis	1529 (0.21%)	240 (0.21%)	37 (0.19%)
Urinary obstruction, congenital hydronephrosis	1079 (0.15%)	245 (0.21%)	43 (0.22%)
Hypospadias	938 (0.13%)	140 (0.12%)	39 (0.20%)
Cloacal exstrophy	353 (0.05%)	51 (0.04%)	13 (0.07%)
Renal agenesis/hypoplasia	308 (0.04%)	46 (0.04%)	17 (0.09%)
Multicyclic dysplastic kidney	107 (0.01%)	21 (0.02%)	5 (0.03%)
Polycystic kidney	106 (0.01%)	26 (0.02%)	3 (0.02%)
Musculoskeletal system			
Polydactyly	1222 (0.16%)	233 (0.20%)	47 (0.24%)
Congenital dislocation of the hip	825 (0.11%)	150 (0.13%)	26 (0.13%)
Club foot	453 (0.06%)	78 (0.07%)	21 (0.11%)
Syndactyly	361 (0.05%)	68 (0.06%)	20 (0.10%)
Congenital anomalies of the skin	42 (0.01%)	6 (0.01%)	3 (0.02%)
Limb deficiencies	95 (0.01%)	18 (0.02%)	3 (0.02%)
Digestive system			
Congenital megacolon	571 (0.08%)	86 (0.07%)	18 (0.09%)
Imperforated anus	447 (0.06%)	94 (0.08%)	21 (0.11%)
Congenital pyloric stenosis	440 (0.06%)	62 (0.05%)	16 (0.08%)
Biliary atresia	276 (0.04%)	35 (0.03%)	6 (0.03%)
Choledochal cyst	235 (0.03%)	32 (0.03%)	5 (0.03%)
Intestinal atresia/stenosis	209 (0.03%)	40 (0.03%)	7 (0.04%)
Esophageal atresia, tracheoesophageal fistula	123 (0.02%)	27 (0.02%)	7 (0.04%)
Omphalocele, gastroschisis	93 (0.01%)	7 (0.01%)	3 (0.02%)
Mouth defects			
Cleft lip with or without cleft palate	806 (0.11%)	96 (0.08%)	34 (0.17%)
Cleft palate without cleft lip	635 (0.09%)	91 (0.08%)	21 (0.11%)
Chromosomal abnormalities			
Trisomy 21	237 (0.03%)	34 (0.03%)	6 (0.03%)
Turner syndrome	42 (0.01%)	6 (0.01%)	3 (0.02%)
Nervous system			
Congenital hydrocephalus	273 (0.04%)	35 (0.03%)	8 (0.04%)
Microcephaly	264 (0.04%)	33 (0.03%)	12 (0.06%)
Spinal bifida	184 (0.02%)	32 (0.03%)	7 (0.04%)
Myelomeningocele	140 (0.02%)	21 (0.02%)	5 (0.03%)
Holoprosencephaly	137 (0.02%)	18 (0.02%)	6 (0.03%)
Eye, ears, face, and neck defects			
Congenital malformation of ear	439 (0.06%)	67 (0.06%)	29 (0.15%)
Congenital cataract	94 (0.01%)	19 (0.02%)	0 (0.00%)
Microphthalmia/anophthalmia	39 (0.01%)	4 (0.00%)	3 (0.02%)
Respiratory system			
Pulmonary hypoplasia	167 (0.02%)	19 (0.02%)	5 (0.03%)
Congenital diaphragmatic hernia	160 (0.02%)	18 (0.02%)	7 (0.04%)
Congenital cystic adenomatoid malformation	120 (0.02%)	11 (0.01%)	3 (0.02%)
Pulmonary sequestration	30 (0.00%)	3 (0.00%)	0 (0.00%)

DM = diabetes mellitus.

[a]Patients were diagnosed at >6 months of age.

[b]Preterm infants with a gestational age of <37 weeks were excluded.

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Table 2

Logistic regression for birth defects by system

System	aOR (95% CI)	*p*
Cardiovascular system (n = 13 782)		
Non-DM	Reference	…
Type 1 DM	1.709 (0.804-3.635)	0.1639
GDM	0.940 (0.880-1.004)	0.0658
Type 2 DM for <2 y	1.298 (1.012-1.666)	0.0401
Type 2 DM for 2-5 y	1.387 (1.165-1.652)	0.0002
Type 2 DM for >5 y	1.618 (1.315-1.992)	<0.0001
Genitourinary system (n = 4880)		
Non-DM	Reference	…
Type 1 DM	2.216 (0.983-4.996)	0.0551
GDM	1.080 (0.998-1.168)	0.0562
Type 2 DM for <2 y	1.196 (0.863-1.657)	0.2835
Type 2 DM for 2-5 y	1.210 (0.953-1.537)	0.1168
Type 2 DM for >5 y	1.068 (0.777-1.468)	0.6860
Musculoskeletal system (n = 3939)		
Non-DM	Reference	…
Type 1 DM	0.598 (0.084-4.262)	0.6079
GDM	1.117 (1.021-1.221)	0.0155
Type 2 DM for <2 y	1.437 (1.001-2.062)	0.0496
Type 2 DM for 2-5 y	1.535 (1.191-1.977)	0.0009
Type 2 DM for >5 y	1.125 (0.779-1.625)	0.5289
Digestive system (n = 2203)		
Non-DM	Reference	…
Type 1 DM	<0.001 (<0.001->999.999)	0.9414
GDM	1.057 (0.944-1.183)	0.3354
Type 2 DM for <2 y	0.939 (0.554-1.590)	0.8136
Type 2 DM for 2-5 y	1.042 (0.725-1.497)	0.8246
Type 2 DM for >5 y	1.228 (0.797-1.892)	0.3518
Mouth defects (n = 1664)		
Non-DM	Reference	…
Type 1 DM	1.501 (0.21-10.718)	0.6854
GDM	0.866 (0.737-1.018)	0.0811
Type 2 DM for <2 y	1.399 (0.791-2.475)	0.2489
Type 2 DM for 2-5 y	1.360 (0.898-2.058)	0.1466
Type 2 DM for >5 y	1.205 (0.681-2.132)	0.5226
Chromosomal abnormalities (n = 1317)		
Non-DM	Reference	…
Type 1 DM	<0.001 (<0.001->999.999)	0.9834
GDM	0.915 (0.703-1.191)	0.5093
Type 2 DM for <2 y	1.516 (0.625-3.675)	0.3572
Type 2 DM for 2-5 y	0.923 (0.411-2.071)	0.8455
Type 2 DM for >5 y	1.054 (0.392-2.833)	0.9166
Nervous system (n = 1200)		
Non-DM	Reference	…
Type 1 DM	<0.001 (<0.001->999.999)	0.9433
GDM	0.929 (0.774-1.114)	0.4242
Type 2 DM for <2 y	0.939 (0.420-2.100)	0.8786
Type 2 DM for 2-5 y	1.474 (0.922-2.355)	0.1052
Type 2 DM for >5 y	1.231 (0.637-2.379)	0.5372
Eyes, ears, face, and neck defects (n = 659)		
Non-DM	Reference	…
Type 1 DM	8.703 (2.757-27.474)	0.0002
GDM	1.005 (0.804-1.258)	0.9620
Type 2 DM for <2 y	0.246 (0.035-1.752)	0.1614
Type 2 DM for 2-5 y	1.899 (1.133-3.184)	0.0150
Type 2 DM for >5 y	2.589 (1.454-4.611)	0.0012
Respiratory system (n = 403)		
Non-DM	Reference	…
Type 1 DM	3.354 (1.246-9.033)	0.0166
GDM	0.946 (0.836-1.069)	0.3705
Type 2 DM for <2 y	0.807 (0.457-1.427)	0.4615
Type 2 DM for 2-5 y	1.091 (0.763-1.559)	0.6335
Type 2 DM for >5 y	1.487 (0.999-2.212)	0.0506

aOR (95% CI) = adjusted odds ratio (95% confidence interval); DM = diabetes mellitus; GDM = gestational diabetes mellitus.

significant difference was found among infants of mothers with GDM who did not require insulin during pregnancy.[20] Correa et al reported that pregestational DM was associated with BDs (aOR was 3.17, 95% CI: 2.20-4.99); GDM was associated with a limited group of BDs (aOR was 1.42, 95% CI: 1.17-1.73) (limited to women with a pregnancy body mass index of ≥25 kg/m^2).[18] Billionnet et al reported that GDM was associated with a moderately increased risk of adverse perinatal outcomes, which was higher in insulin-treated GDM than in noninsulin-treated GDM.[33] It was also reported that both pregestational and gestational DM were risk factors for severe neonatal morbidity.[27] The causes of the fetal and neonatal sequelae of maternal diabetes were likely multifactorial; however, many of the perinatal complications could be traced to the effect of maternal glycemic control on the fetus and could be prevented by appropriate periconceptional and prenatal care.[34] Prepregnancy counseling, multidisciplinary team management, and appropriate maternal glycemic control were the key in achieving good pregnancy and perinatal outcomes.[35]

The prevalence of BDs was 270.22 per 10 000 births in Taiwan in 2014. Using population attributable risk percentage (PAR%) of BDs, the prevalence of BDs will be 257.54 per 10 000 births in Taiwan in 2034.[36] PAR% in GDM was 0.48%, and in pregestational (type 1 and type 2) DM was 0.24%. If the percentage decrease (*y*) is 1%, 5%, and 10% for mothers with GDM, the number of patients with BDs will reduce by 17, 86, and 172 cases, respectively, in Taiwan in 2034. If the percentage decrease (*y*) is 1%, 5%, and 10% for mothers with pregestational DM, the number of patients with BD will reduce by 8, 43, and 86 cases, respectively, in Taiwan in 2034. If we can reduce the incidence of GDM or pregestational DM, we will be able to reduce the prevalence of BDs.

The definition and classification of DM are based on the recommendations of the American Diabetes Association.[37] Criteria for diagnosis of diabetes are fasting plasma glucose (PG) ≥126 mg/dL (7.0 mmol/L) (fasting is defined as no caloric intake for 8 hours), 2-hour PG ≥200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT) (75 g glucose), hemoglobin A1C ≥ 6.5% (48 mmol/mol), or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random PG ≥ 200 mg/dL (11.1 mmol/L).[37–39] Type 1 DM is due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency. Type 2 DM is due to the progressive loss of adequate β-cell insulin secretion frequently on the ground of insulin resistance. Gestation DM is diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes prior to gestation.[37–39] Patients with type 1 DM usually have positive pancreatic autoantibodies and lower fasting insulin and C-peptide levels. Glucagon-stimulated C-peptide is usually <0.2 nmol/L in type 1 DM. Patients with type 2 DM usually decreased insulin sensitivity, with overweight or obesity (BMI ≥ 25 kg/m^2). Patients with type 2 DM may have insulin levels that appear normal or elevated, yet decreased insulin sensitivity and acanthosis nigricans is found in 50% to 90% of patients with type 2 DM. Screening for GDM is usually performed at 24 to 28 weeks of gestation in pregnant women not previously found to have diabetes. GDM diagnosis can be accomplished using a 75-g OGTT. The diagnosis of GDM is made when any of the following PG values are met or exceed: (1) fasting: 92 mg/dL (5.1 mmol/L), (2) 1 hour: 180 mg/dL (10 mmol/L), and (3) 2 hours: 153 mg/dL (8.5 mmol/L).[37–39] As this is a 5-year nationwide population-based cohort study, a total of 1 017 984 births and 24 204 infants with BDs were included in this study. Pregestational DM was defined as mothers who had a clinical visit for diabetes, as identified by ICD-9 codes 250.0-250.9 before pregnancy. Furthermore, the pregestational type 1 DM was defined as ICD-9 codes 250.1 or 250.3, and type 2 DM was defined as IDC-9 codes 250.0 or 250.2.

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Table 3

Number of infants in control and BD groups and univariate analysis of BDs

Type of maternal DM	Number (%) of infants		Odds ratio (95% CI)	*p*
	Control	BDs		
Non-DM	722 424 (84.54%)	20 236 (83.61%)	Reference	…
GDM	112 909 (13.2%)	3197 (13.2%)	1.01 (0.97-1.05)	0.5765
Type 1 DM	347 (0.04%)	20 (0.08%)	2.06 (1.31-3.23)	0.0017
Type 2 DM for <2 y	4570 (0.53%)	165 (0.68%)	1.29 (1.10-1.51)	0.0014
Type 2 DM for 2-5 y	8956 (1.05%)	358 (1.48%)	1.43 (1.28-1.59)	<0.0001
Type 2 DM for >5 y	5313 (0.62%)	228 (0.94%)	1.53 (1.34-1.75)	<0.0001

BDs = birth defects; GDM = gestational diabetes mellitus; DM = diabetes mellitus.

Table 4

Multiple logistic regression for birth defects

Maternal type of DM	aOR (95% CI)	*p*
Non-DM	Reference	…
GDM	1.002 (0.965-1.041)	0.9139
Type 1 DM	1.748 (1.110-2.754)	0.0160
Type 2 DM for <2 y	1.175 (1.005-1.375)	0.0437
Type 2 DM for 2-5 y	1.331 (1.196-1.482)	<0.001
Type 2 DM for >5 y	1.391 (1.216-1.592)	<0.001

aOR (95% CI) = adjusted odd ratio (95% confidence interval); GDM = gestational diabetes mellitus; DM = diabetes mellitus.

Table 5

Maternal age between non-BD and BD groups

Maternal age (y)	No BDs (control) (n = 854 519)	BDs (n = 24 204)	aOR (95% CI)	*p*
<18	2712 (0.32%)	81 (0.33%)	1.058 (0.847-1.322)	0.6199
18-29	280 611 (32.84%)	7578 (31.31%)	Reference	
30-44	570 085 (66.71%)	16 482 (68.10%)	1.072 (1.042-1.103)	<0.0001
≥45	1111 (0.13%)	63 (0.26%)	1.753 (1.353-2.270)	<0.0001

95% CI = 95% confidence interval; aOR = adjusted odds ratio; BDs = birth defects.

GDM was defined as maternal DM diagnosed during pregnancy and mothers who had clinical visits with ICD-9 codes 648.8 or 250.0-250.9 in this study.

There were several limitations to this study. First, this was a retrospective cohort study, not a prospective study. Second, we did not have a detailed date for each mother or infant. Third, we did not have data on maternal glucose levels; therefore, we could not evaluate the relationship between DM control and BDs. Fourth, definitions of type 1 DM, type 2 DM, and GDM were based on ICD-9 codes 250.0-250.9. We did not have fasting PG, 2-hour PG during OGTT, or hemoglobin A1C levels for each mother. However, this was a 5-year nationwide population-based cohort study, and the sample size was very large, including 1,017,984 births and 24,204 infants with BDs.

In conclusion, mothers with pregestational (type 1 or type 2) DM significantly increased the incidence of BDs. Appropriate maternal glycemic control may achieve good pregnancy and perinatal outcomes.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A191 and http://links.lww.com/JCMA/A192.

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