Association of Maternal Prepregnancy Diabetes and Gestational Diabetes Mellitus With Congenital Anomalies of the Newborn

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Diabetes Care 2020;43:2983–2990 | https://doi.org/10.2337/dc20-0261

OBJECTIVE

To examine the association of maternal prepregnancy diabetes, gestational diabetes mellitus (GDM), and 12 subtypes of congenital anomalies of the newborn.

RESEARCH DESIGN AND METHODS

We included 29,211,974 live births with maternal age ranging from 18 to 49 years old documented in the National Vital Statistics System in the U.S. from 2011 to 2018. Information on prepregnancy diabetes, GDM, and congenital anomalies was retrieved from birth certificates. Log-binomial regression was used to estimate risk ratios (RRs) and 95% CIs for congenital anomalies overall and by subtypes.

RESULTS

Of the 29,211,974 live births, there were 90,061 infants who had congenital anomalies identified at birth. The adjusted RRs of congenital anomalies at birth were 2.44 (95% CI 2.33–2.55) for prepregnancy diabetes and 1.28 (95% CI 1.24–1.31) for GDM. The associations were generally consistent across subgroups by maternal age, race/ethnicity, prepregnancy obesity status, and infant sex. For specific subtypes of congenital anomalies, maternal prepregnancy diabetes or GDM was associated with an increased risk of most subtypes. For example, the adjusted RRs of cyanotic congenital heart disease were 4.61 (95% CI 4.28–4.96) for prepregnancy diabetes and 1.50 (95% CI 1.43–1.58) for GDM; the adjusted RRs of hypospadias were 1.88 (95% CI 1.67–2.12) for prepregnancy diabetes and 1.29 (95% CI 1.21–1.36) for GDM.

CONCLUSIONS

Prepregnancy diabetes and, to a lesser extent, GDM were associated with several subtypes of congenital anomalies of the newborn. These findings suggest potential benefits of preconception counseling in women with preexisting diabetes or at risk for GDM for the prevention of congenital anomalies.

Congenital anomalies, also known as birth defects or congenital malformations, are defined as structural or functional anomalies (e.g., metabolic disorders) that occur during intrauterine life. These conditions can be identified prenatally, at birth, or later in life. Congenital anomalies are the second leading cause of infant mortality after prematurity, accounting for at least 20% of infant deaths (1). In addition, congenital anomalies also comprise a leading cause of death in early childhood (2). The etiology of

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Received 5 February 2020 and accepted 23 September 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.13017422.

congenital anomalies is multifactorial; they can be caused by single gene defects, chromosomal disorders, multifactorial inheritance, environmental teratogens, or micronutrient deficiencies.

Biologically, an intrauterine hyperglycemic environment may cause oxidative stress and increase the risk of congenital anomalies in developing fetuses. The incidence of diabetes among women of reproductive age is increasing worldwide (3,4). Prepregnancy diabetes was reported to be associated with increased adverse maternal and neonatal outcomes (3,5,6). Previous epidemiological studies have identified prepregnancy diabetes as a risk factor for congenital anomalies such as congenital heart disease, oral clefts, and anomalies of the central nervous system, digestive system, genitourinary system, and musculoskeletal system (7–16). However, the influence of prepregnancy diabetes on specific types of congenital anomalies remains inconclusive (13,17,18).

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first recognition during pregnancy, is a common metabolic complication during pregnancy. Because screening for GDM occurs between 24 and 28 weeks of gestation, critical periods of fetal development have already occurred. Increasingly, it has been recognized that women who develop GDM during pregnancy usually have chronic β-cell dysfunction and/or insulin resistance prior to pregnancy. Therefore, women with GDM likely have impaired glucose metabolism before or during early pregnancy, although not as severe as those with overt diabetes before pregnancy (19).

The association between GDM and congenital anomalies remains unclear. Previous studies linking GDM to congenital anomalies are sparse and have yielded conflicting findings. For example, the research from the National Birth Defects Prevention Study (NBDPS) concluded that GDM was only associated with a limited group of congenital anomalies such as cleft lip with or without cleft palate and cleft palate alone (15). A study conducted in Washington state also found that GDM was not related to hypospadias (20). However, a study using Danish and Swedish register-based data from 1978 to 2012 found that GDM was associated with slightly increased risks of genital anomalies (21). A Texas population-based case-control study concluded that GDM may increase the risk of congenital anomalies in the central nervous system (22). The conflicting findings from previous studies underscored an urgent need for a large population-based study to establish the relationships of maternal prepregnancy diabetes and GDM with congenital anomalies.

In this population-based study with 29 million mother-infant pairs in the United States, we aimed to examine the associations of maternal prepregnancy diabetes and GDM with 12 subtypes of congenital anomalies of the newborn, including cyanotic congenital heart disease, hypospadias, cleft lip with or without cleft palate, Down syndrome, gastroschisis, suspected chromosomal disorder, cleft palate alone, meningomyelocele/spina bifida, congenital diaphragmatic hernia, limb reduction defect, anencephaly, and omphalocele.

RESEARCH DESIGN AND METHODS

Study Population

The data resource for this study is the 2011–2018 natality data files of the National Vital Statistics System (NVSS). The NVSS natality data file includes information on a wide range of maternal and infant demographic and health characteristics for all births registered in 50 states and the District of Columbia in the U.S. The Centers for Disease Control and Prevention's National Center for Health Statistics receives these data as electronic files, prepared from individual records processed by each registration area, through the Vital Statistics Cooperative Program (23).

In this analysis, we included all live births from 2011 to 2018 in the U.S. for which information on maternal diabetes and congenital anomalies was available. The analysis was restricted to mothers aged from 18 to 49 years.

Data Collection

All live birth data were retrieved from the U.S. Standard Certificate of Live Birth. It is issued by the U.S. Department of Health and Human Services and was revised in 2003. Implementation of the 2003 U.S. Standard Certificate of Live Birth (revised) by the states and independent reporting areas was phased in from 2003 to 2016. All states and the District of Columbia had implemented the revised birth certificate as of 1 January 2016. Maternal prepregnancy diabetes was defined as having type 1 or type 2 diabetes diagnosed prior to the pregnancy, and maternal GDM was defined as having newly diagnosed diabetes during the pregnancy (24).

Maternal age was defined as maternal age at the time of the birth and classified as 18–24, 25–29, 30–34, 35–39, and 40 years or older. Maternal race/ethnicity was classified as Hispanic, non-Hispanic White, non-Hispanic Black, and other, according to the U.S. Office of Management and Budget Standards for the Classification of Federal Data on Race and Ethnicity. Maternal education levels were categorized as lower than high school, high school, higher than high school, and unknown. Maternal prepregnancy BMI (kg/m^2) was calculated as prepregnancy weight in kilograms divided by the square of height in meters and classified as underweight ($<$18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obesity I (30.0–34.9 kg/m^2), obesity class II (35.0–39.9 kg/m^2), and obesity class III ($\geq$40.0 kg/m^2). Smoking before and during pregnancy were categorized as "yes," "no," and "missing." Infant sex was categorized as male and female. Marital status was categorized as married, unmarried, and unknown. Parity in this study indicated how many live births a mother has had including this delivery, and it was categorized as 1, 2, 3, $\geq$4, and unknown. Timing of initiation of prenatal care was categorized based on the trimester of first prenatal visit as no prenatal care, 1st–3rd month, 4th–6th month, 7th–final month, and unknown. Prepregnancy hypertension was identified from the facility worksheet for the live birth certificate as "yes" and "no."

Twelve subtypes of congenital anomalies identified at birth were reported on the revised 2003 birth certificate, each with a checkbox. These congenital anomalies included cyanotic congenital heart disease, hypospadias, cleft lip with or without cleft palate, Down syndrome, gastroschisis, suspected chromosomal disorder, cleft palate alone, meningomyelocele/spina bifida, congenital diaphragmatic hernia, limb reduction defect, anencephaly, and omphalocele. In this analysis, we defined having any type of congenital anomalies at birth as having any one type of these listed congenital anomalies. In NVSS, it is recommended that information on congenital anomalies

be collected directly from the medical record (23). Data for the congenital anomaly "hypospadias" was restricted to male infants. For Down syndrome and suspected chromosomal disorder, the 2003 birth certificate includes a general checkbox question about whether each of these two anomalies is present. They were categorized as "confirmed," "pending," "no," and "unknown." It meant that there were some cases of these two congenital anomalies that needed to be further confirmed. We only included the cases that were confirmed at birth.

Statistical Analysis

Comparisons in descriptive statistics across groups were tested by χ^2 analysis and Fisher exact test, where appropriate. Log-binomial regression analysis was used to calculate crude and adjusted risk ratios (RRs) and 95% CIs for congenital anomalies overall and by subtypes. Covariates in the multivariable models included age, race/ethnicity, education levels, marital status, parity, smoking before pregnancy, smoking during pregnancy, timing of initiation of prenatal care, prepregnancy BMI, infant sex, and prepregnancy hypertension.

All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC). For most analyses in this study, $P < 0.05$ was considered statistically significant. For the analyses of 12 subtypes of congenital anomalies, we performed Bonferroni correction to account for multiple comparisons; in this case, $P < 0.0045$ was considered statistically significant.

RESULTS

Of the 29,211,974 mother-infant pairs, 242,600 mothers had prepregnancy diabetes, 1,685,479 mothers had GDM, and 27,283,895 mothers did not have diabetes; 90,061 infants were reported to have congenital anomalies identified at birth. Compared with mothers who had no diabetes before and during pregnancy, mothers with prepregnancy diabetes and GDM tended to be older, less educated, more likely to have multiple parities and prepregnancy hypertension, and more likely to be overweight or obese. Detailed statistical description for other variables are shown in Table 1.

Compared with infants born to mothers without diabetes, those born to mothers with prepregnancy diabetes or GDM had a greater likelihood of having congenital anomalies of the newborn (Table 2). After adjustment, the RRs of congenital anomalies were 2.44 (95% CI 2.33–2.55) for maternal prepregnancy diabetes and 1.28 (95% CI 1.24–1.31) for maternal GDM. The association was generally consistent across subgroups by age, race/ethnicity, maternal prepregnancy obesity status, and infant sex (Table 3). Moreover, for specific subtypes of congenital anomalies, maternal prepregnancy diabetes or GDM was associated with an increased risk of most subtypes. For example, the adjusted RRs of cyanotic congenital heart disease were 4.61 (95% CI 4.28–4.96) for maternal prepregnancy diabetes and 1.50 (95% CI 1.43–1.58) for maternal GDM, the adjusted RRs of hypospadias were 1.88 (95% CI 1.67–2.12) for maternal prepregnancy diabetes and 1.29 (95% CI 1.21–1.36) for maternal GDM, the adjusted RRs of cleft lip with or without cleft palate were 2.06 (95% CI 1.82–2.33) for maternal prepregnancy diabetes and 1.28 (95% CI 1.20–1.36) for maternal GDM, the RRs for cleft palate alone were 2.35 (95% CI 1.97–2.79) for prepregnancy diabetes and 1.40 (95% CI 1.28–1.53) for GDM, the adjusted RRs of Down syndrome were 1.34 (95% CI 1.10–1.63) for maternal prepregnancy diabetes and 1.38 (95% CI 1.27–1.50) for maternal GDM, the RRs for meningomyelocele/spina bifida were 2.00 (95% CI 1.59–2.51) for prepregnancy diabetes and 1.13 (95% CI 1.00–1.28) for GDM, and the adjusted RRs of suspected chromosomal disorder were 1.38 (95% CI 1.06–1.81) for prepregnancy diabetes and 1.01 (95% CI 0.89–1.14) for GDM.

CONCLUSIONS

In this large nationwide population-based study, we found that prepregnancy diabetes and GDM were associated with the majority of the 12 congenital anomalies of the newborn. These findings have important clinical and public health implications. In parallel with the increasing trends of adult obesity, the prevalence of prepregnancy diabetes and prevalence of GDM are both increasing among pregnant women in the U.S. (24). This increase in maternal diabetes prevalence may undermine the historical achievement in the prevention of congenital anomalies by improvement of periconception care and genetic counseling.

Our study extended the findings from previous population-based studies. First, we have reaffirmed maternal prepregnancy diabetes as a strong risk factor for congenital anomalies, as reported in previous studies (7–13). More importantly, with a very large sample size, this study showed a significant association of GDM with several types of congenital anomalies. Findings in previous studies on the relation of GDM to congenital anomalies remained inconclusive. For example, a retrospective study using birth registry data ($N = 650,914$) in upstate New York from 2004 to 2016 (17) showed a relatively strong association of prepregnancy diabetes with cyanotic congenital heart disease, cleft lip and palate, cleft palate alone, hypospadias, and limb reduction defect, but no significant association between GDM and congenital anomalies except cyanotic congenital heart disease. In the current study, maternal GDM was associated with an increased risk of most of the 12 subtypes of congenital anomalies of the newborn. The reasons for which maternal GDM was inversely associated with the risk of gastroschisis and anencephaly are currently unknown, which warrants confirmation and further investigation in future studies.

The potential biological mechanisms for the association between maternal diabetes and congenital anomalies remain to be elucidated. Both clinical investigations and animal studies have clearly demonstrated that the main characteristics of maternal hyperglycemia-associated defects are organ agenesis and underdevelopment (25,26). The organ systems most commonly affected include the central nervous, cardiovascular, gastrointestinal, craniofacial, genitourinary, and skeletal systems (25,27,28). Animal studies have revealed that prepregnancy diabetes induces oxidative stress, which activates cellular stress signaling leading to dysregulation of gene expression and increased apoptosis in the target organs (17,29). Multiple studies have confirmed that excess cell death in the environment of maternal high concentrations of glucose, at least in the central nervous system, contributes to the abnormal development of structures in the embryos of diabetic animals (26,30–33). These observations strongly suggest that high levels of glucose cause damage to the neural progenitor cells,

Table 1—Population characteristics according to different types of maternal diabetes: NVSS, 2011–2018 (N = 29,211,974)

	No diabetes	Prepregnancy diabetes	GDM	*P*
Total population, *n*	27,283,895	242,600	1,685,479	
Age, years, mean (SD)	28.5 (5.7)	31.0 (5.9)	31.1 (5.6)	
Age, years, *n* (%)				<0.001
<25	7,471,163 (27.4)	37,576 (15.5)	226,676 (13.4)	
25–29	8,096,385 (29.7)	58,940 (24.3)	426,411 (25.3)	
30–34	7,444,579 (27.3)	74,382 (30.7)	553,408 (32.8)	
35–39	3,493,313 (12.8)	53,880 (22.2)	368,770 (21.9)	
≥40	778,455 (2.9)	17,822 (7.3)	110,214 (6.5)	
Race/ethnicity, *n* (%)				<0.001
Hispanic	6,283,153 (23.0)	62,402 (25.7)	426,056 (25.3)	
Non-Hispanic White	14,609,438 (53.5)	107,169 (44.2)	809,117 (48.0)	
Non-Hispanic Black	3,910,753 (14.3)	47,472 (19.6)	196,090 (11.6)	
Other	2,480,551 (9.1)	25,557 (10.5)	254,216 (15.1)	
Education levels, *n* (%)				<0.001
Lower than high school	3,661,699 (13.4)	41,914 (17.3)	244,258 (14.5)	
High school	6,883,714 (25.2)	65,642 (27.1)	390,738 (23.2)	
Higher than high school	16,407,872 (60.1)	132,439 (54.6)	1,030,134 (61.1)	
Unknown	330,610 (1.2)	2,605 (1.1)	20,349 (1.2)	
Marital status, *n* (%)				<0.001
Married	15,973,161 (58.5)	138,098 (56.9)	1,084,180 (64.3)	
Unmarried	10,459,295 (38.3)	98,007 (40.4)	540,196 (32.0)	
Unknown	851,439 (3.1)	6,495 (2.7)	61,103 (3.6)	
Parity, *n* (%)				<0.001
1	10,385,435 (38.1)	81,060 (33.4)	560,088 (33.2)	
2	8,806,993 (32.3)	74,064 (30.5)	529,818 (31.4)	
3	4,639,524 (17.0)	45,058 (18.6)	318,794 (18.9)	
≥4	3,337,674 (12.2)	41,450 (17.1)	271,892 (16.1)	
Unknown	114,269 (0.4)	968 (0.4)	4,887 (0.3)	
Smoking before pregnancy, *n* (%)				<0.001
Yes	2,708,246 (9.9)	28,369 (11.7)	162,116 (9.6)	
No	23,876,609 (87.5)	208,553 (86.0)	1,489,997 (88.4)	
Unknown	699,040 (2.6)	5,678 (2.3)	33,366 (2.0)	
Smoking during pregnancy, *n* (%)				<0.001
Yes	1,417,302 (5.2)	14,434 (5.9)	78,401 (4.7)	
No	24,484,089 (89.7)	214,190 (88.3)	1,532,855 (90.9)	
Unknown	1,382,504 (5.1)	13,976 (5.8)	74,223 (4.4)	
Timing of initiation of prenatal care, *n* (%)				<0.001
No prenatal care	424,068 (1.6)	2,861 (1.2)	9,717 (0.6)	
1st–3rd month	20,144,489 (73.8)	183,714 (75.7)	1,296,143 (76.9)	
4th–6th month	4,660,467 (17.1)	39,307 (16.2)	273,868 (16.2)	
7th–final month	1,176,852 (4.3)	8,986 (3.7)	66,344 (3.9)	
Unknown	878,019 (3.2)	7,732 (3.2)	39,407 (2.3)	
Prepregnancy BMI, kg/m^2, *n* (%)				<0.001
Underweight: <18.5	968,978 (3.6)	2,326 (1.0)	27,037 (1.6)	
Normal: 18.5–24.9	12,195,886 (44.7)	46,061 (19.0)	436,919 (25.9)	
Overweight: 25.0–29.9	6,833,728 (25.0)	54,392 (22.4)	433,402 (25.7)	
Obesity I: 30.0–34.9	3,580,222 (13.1)	51,326 (21.2)	343,910 (20.4)	
Obesity II: 35.0–39.9	1,668,383 (6.1)	38,298 (15.8)	211,418 (12.5)	
Obesity III: ≥40.0	1,118,851 (4.1)	41,651 (17.2)	183,296 (10.9)	
Unknown	917,847 (3.4)	8,546 (3.5)	49,497 (2.9)	
Infant sex, *n* (%)				<0.001
Male	13,947,717 (51.1)	124,342 (51.3)	873,163 (51.8)	
Female	13,336,178 (48.9)	118,258 (48.7)	812,316 (48.2)	
Prepregnancy hypertension, *n* (%)				<0.001
Yes	382,039 (1.4)	38,262 (15.8)	72,098 (4.3)	
No	26,901,856 (98.6)	204,338 (84.2)	1,613,381 (95.7)	

leading to apoptosis and, ultimately, abnormal organogenesis. GDM is a condition usually diagnosed after 24 weeks of pregnancy, whereas most of the structural morphogenesis occurs during the first 12 weeks of pregnancy, when developing fetuses have higher risk of teratogenic effects. Intuitively, this conflicts with a biological plausibility of the association between GDM and observed congenital anomalies in this study. However, women who develop GDM during

Table 2—Association of prepregnancy diabetes and GDM with any type or major subtypes of congenital anomalies identified at birth

Congenital anomalies	No diabetes	Prepregnancy diabetes	*P*	GDM	*P*
Any type[a]					
Cases/no. of participants	81,599/27,283,895	1,914/242,600		6,548/1,685,479	
Model 1	1.00 (ref)	2.70 (2.58–2.83)	<0.001	1.32 (1.28–1.35)	<0.001
Model 2	1.00 (ref)	2.58 (2.46–2.70)	<0.001	1.29 (1.26–1.32)	<0.001
Model 3	1.00 (ref)	2.44 (2.33–2.55)	<0.001	1.28 (1.24–1.31)	<0.001
Cyanotic congenital heart disease					
Cases/no. of participants	17,680/27,283,895	804/242,600		1,691/1,685,479	
Model 1	1.00 (ref)	5.07 (4.73–5.45)	<0.001	1.52 (1.44–1.59)	<0.001
Model 2	1.00 (ref)	5.01 (4.66–5.39)	<0.001	1.52 (1.44–1.60)	<0.001
Model 3	1.00 (ref)	4.61 (4.28–4.96)	<0.001	1.50 (1.43–1.58)	<0.001
Hypospadias[b]					
Cases/no. of participants	15,879/13,947,717	289/124,342		1,300/873,163	
Model 1	1.00 (ref)	2.17 (1.93–2.43)	<0.001	1.37 (1.29–1.45)	<0.001
Model 2	1.00 (ref)	2.01 (1.79–2.26)	<0.001	1.30 (1.23–1.38)	<0.001
Model 3	1.00 (ref)	1.88 (1.67–2.12)	<0.001	1.29 (1.21–1.36)	<0.001
Cleft lip with or without cleft palate					
Cases/no. of participants	13,891/27,283,895	273/242,600		1,145/1,685,479	
Model 1	1.00 (ref)	2.36 (2.09–2.66)	<0.001	1.38 (1.30–1.47)	<0.001
Model 2	1.00 (ref)	2.12 (1.88–2.40)	<0.001	1.29 (1.21–1.37)	<0.001
Model 3	1.00 (ref)	2.06 (1.82–2.33)	<0.001	1.28 (1.20–1.36)	<0.001
Gastroschisis					
Cases/no. of participants	7,206/27,283,895	37/242,600		187/1,685,479	
Model 1	1.00 (ref)	0.83 (0.60–1.14)	0.25	0.61 (0.53–0.71)	<0.001
Model 2	1.00 (ref)	1.00 (0.72–1.38)	0.98	0.76 (0.65–0.88)	<0.001
Model 3	1.00 (ref)	0.98 (0.71–1.37)	0.92	0.76 (0.65–0.88)	<0.001
Cleft palate alone					
Cases/no. of participants	6,166/27,283,895	139/242,600		543/1,685,479	
Model 1	1.00 (ref)	2.74 (2.32–3.24)	<0.001	1.48 (1.36–1.62)	<0.001
Model 2	1.00 (ref)	2.48 (2.09–2.94)	<0.001	1.41 (1.29–1.55)	<0.001
Model 3	1.00 (ref)	2.35 (1.97–2.79)	<0.001	1.40 (1.28–1.53)	<0.001
Down syndrome					
Cases/no. of participants	5,487/27,283,895	105/242,600		688/1,685,479	
Model 1	1.00 (ref)	1.44 (1.19–1.75)	<0.001	1.41 (1.31–1.53)	<0.001
Model 2	1.00 (ref)	1.42 (1.16–1.73)	<0.001	1.39 (1.28–1.51)	<0.001
Model 3	1.00 (ref)	1.34 (1.10–1.63)	0.004	1.38 (1.27–1.50)	<0.001
Meningomyelocele/spina bifida					
Cases/no. of participants	3,938/27,283,895	80/242,600		288/1,685,479	
Model 1	1.00 (ref)	2.45 (1.97–3.06)	<0.001	1.26 (1.11–1.42)	<0.001
Model 2	1.00 (ref)	2.11 (1.68–2.65)	<0.001	1.14 (1.01–1.29)	0.03
Model 3	1.00 (ref)	2.00 (1.59–2.51)	<0.001	1.13 (1.00–1.28)	0.05
Suspected chromosomal disorder					
Cases/no. of participants	3,548/27,283,895	57/242,600		275/1,685,479	
Model 1	1.00 (ref)	1.46 (1.12–1.89)	0.01	1.03 (0.91–1.16)	0.69
Model 2	1.00 (ref)	1.46 (1.12–1.91)	0.01	1.02 (0.89–1.15)	0.81
Model 3	1.00 (ref)	1.38 (1.06–1.81)	0.02	1.01 (0.89–1.14)	0.92
Congenital diaphragmatic hernia					
Cases/no. of participants	3,538/27,283,895	59/242,600		272/1,685,479	
Model 1	1.00 (ref)	1.97 (1.52–2.54)	<0.001	1.29 (1.14–1.46)	<0.001
Model 2	1.00 (ref)	1.86 (1.43–2.41)	<0.001	1.24 (1.09–1.41)	<0.001
Model 3	1.00 (ref)	1.75 (1.35–2.27)	<0.001	1.23 (1.08–1.39)	0.002
Limb reduction defect					
Cases/no. of participants	3,507/27,283,895	92/242,600		251/1,685,479	
Model 1	1.00 (ref)	3.14 (2.55–3.86)	<0.001	1.24 (1.09–1.41)	0.001
Model 2	1.00 (ref)	2.87 (2.33–3.54)	<0.001	1.18 (1.04–1.35)	0.01
Model 3	1.00 (ref)	2.80 (2.27–3.46)	<0.001	1.18 (1.03–1.34)	0.02
Anencephaly					
Cases/no. of participants	2,782/27,283,895	67/242,600		144/1,685,479	
Model 1	1.00 (ref)	2.87 (2.25–3.65)	<0.001	0.88 (0.75–1.04)	0.15
Model 2	1.00 (ref)	2.68 (2.10–3.43)	<0.001	0.85 (0.72–1.01)	0.07
Model 3	1.00 (ref)	2.66 (2.07–3.42)	<0.001	0.85 (0.72–1.01)	0.07

Continued on p. 2988

Table 2—Continued

Congenital anomalies	No diabetes	Prepregnancy diabetes	*P*	GDM	*P*
Omphalocele					
Cases/no. of participants	2,723/27,283,895	48/242,600		206/1,685,479	
Model 1	1.00 (ref)	1.97 (1.48–2.62)	<0.001	1.24 (1.08–1.43)	0.003
Model 2	1.00 (ref)	1.78 (1.32–2.40)	<0.001	1.23 (1.06–1.42)	0.01
Model 3	1.00 (ref)	1.71 (1.27–2.31)	<0.001	1.22 (1.05–1.41)	0.01

Data are RR (95% CI) or *n*. Model 1: adjustment for maternal age and race/ethnicity. Model 2: model 1 adjustments plus adjustment for maternal education levels, marital status, parity, smoking before pregnancy, smoking during pregnancy, timing of initiation of prenatal care, prepregnancy BMI, and infant sex. Model 3: model 2 adjustments plus adjustment for prepregnancy hypertension. ref, reference. [a]Any type of congenital anomaly in all 12 types of congenital anomalies of the NVSS data set. [b]Only in boys.

pregnancy usually have evidence of metabolic dysfunction before pregnancy, such as pancreatic β-cell defects and increased insulin resistance (34,35). Therefore, these women may have mild or moderate hyperglycemia before and during pregnancy. In this study, the magnitude of the associations between maternal prepregnancy diabetes and congenital anomalies was, in general, stronger than the associations between maternal GDM and congenital anomalies, indicating that the increased risk of congenital anomalies may differ according to the degree of impairment in glucose metabolism. These findings are in line with several previous studies that showed a dose-response relation between hemoglobin A_{1c} levels during early pregnancy and risk of birth defects (14,36,37). These results were also consistent with previous studies regarding the association of prepregnancy diabetes and GDM with the risk of congenital anomalies (17,38,39).

Strengths and Limitations

The strengths of this study include virtually full coverage of a nationwide population of mother-infant pairs, a large sample size, information about many subtypes of congenital anomalies, and low levels of missing data. Because some subtypes of both maternal GDM and congenital anomalies are rare conditions, it is key to examine their associations in a population-based study with a large sample size. The 29,211,974 participants in our study include all live births that occurred in the U.S. from 2011 to 2018 and had information on maternal diabetes and congenital anomalies, which not only ensured a large sample size but also made our findings generalizable.

There are several limitations in this study. First, we did not have information to distinguish type 1 versus type 2 diabetes before pregnancy. Further investigation on the association of type 1 diabetes and type 2 diabetes before pregnancy with congenital anomalies is needed. Second, it is possible that in some women, pregnancies with newly

Table 3—Stratified analysis for the association of prepregnancy diabetes and GDM with any type of congenital anomalies identified at birth

Variables	No diabetes	Prepregnancy diabetes		GDM		$P_{interaction}$
		RR (95% CI)	*P*	RR (95% CI)	*P*	
Age, years						<0.001
<25	1.00 (ref)	2.71 (2.44–3.02)	<0.001	1.20 (1.12–1.28)	<0.001	
25–29	1.00 (ref)	2.68 (2.44–2.94)	<0.001	1.23 (1.17–1.30)	<0.001	
30–34	1.00 (ref)	2.25 (2.05–2.47)	<0.001	1.29 (1.23–1.35)	<0.001	
35–39	1.00 (ref)	2.40 (2.17–2.65)	<0.001	1.31 (1.24–1.38)	<0.001	
≥40	1.00 (ref)	1.81 (1.55–2.11)	<0.001	1.28 (1.18–1.38)	<0.001	
Race/ethnicity						0.004
Hispanic	1.00 (ref)	3.27 (2.98–3.59)	<0.001	1.38 (1.30–1.46)	<0.001	
Non-Hispanic White	1.00 (ref)	2.12 (1.98–2.26)	<0.001	1.24 (1.20–1.28)	<0.001	
Non-Hispanic Black	1.00 (ref)	2.39 (2.12–2.69)	<0.001	1.38 (1.27–1.50)	<0.001	
Other	1.00 (ref)	2.43 (2.09–2.83)	<0.001	1.24 (1.15–1.34)	<0.001	
Prepregnancy BMI, kg/m^2						0.18
Underweight: <18.5	1.00 (ref)	2.12 (1.30–3.47)	0.003	1.14 (0.92–1.41)	0.23	
Normal: 18.5–24.9	1.00 (ref)	2.61 (2.35–2.89)	<0.001	1.22 (1.16–1.29)	<0.001	
Overweight: 25.0–29.9	1.00 (ref)	2.46 (2.23–2.71)	<0.001	1.29 (1.22–1.36)	<0.001	
Obesity I: 30.0–34.9	1.00 (ref)	2.49 (2.25–2.75)	<0.001	1.24 (1.17–1.31)	<0.001	
Obesity II: 35.0–39.9	1.00 (ref)	2.19 (1.94–2.48)	<0.001	1.26 (1.17–1.36)	<0.001	
Obesity III: ≥40.0	1.00 (ref)	2.12 (1.89–2.38)	<0.001	1.29 (1.20–1.39)	<0.001	
Unknown	1.00 (ref)	3.09 (2.47–3.86)	<0.001	1.51 (1.32–1.74)	<0.001	
Infant sex						<0.001
Male	1.00 (ref)	2.25 (2.12–2.39)	<0.001	1.29 (1.25–1.33)	<0.001	
Female	1.00 (ref)	2.75 (2.56–2.96)	<0.001	1.25 (1.20–1.31)	<0.001	

Maternal age, race/ethnicity, education levels, marital status, parity, smoking before pregnancy, smoking during pregnancy, timing of initiation of prenatal care, prepregnancy BMI, infant sex, and prepregnancy hypertension were adjusted for in models, except when the variable was a stratified variable. ref, reference.

diagnosed overt diabetes are misclassified as pregnancies complicated by GDM. Given that >50% of pregnancies in the U.S. are unplanned and that screening for diabetes among women of childbearing age who are not planning a pregnancy may not be done regularly (particularly among those with no health insurance), it is likely that some pregnancies classified as GDM in this study may actually be pregnancies complicated by undiagnosed preexisting diabetes. This data set did not have information about glucose screening and tests that were performed in early pregnancy. Future large population-based studies with detailed assessments of glucose metabolism parameters (such as fasting glucose levels and hemoglobin A_{1c}) before and during pregnancy are warranted. Third, the NVSS only collects information on congenital anomalies that are present and identifiable at the time of birth. Some types of congenital anomalies may not be determined at that time. For example, among congenital heart diseases, cyanotic congenital heart disease is a condition present at birth, but most (75%) other types of congenital heart disease are usually identified in childhood or even adulthood. Therefore, in this study, we only included cyanotic congenital heart disease as a subtype of congenital anomalies. Our findings could not be generalized to all congenital anomalies, particularly the subtypes of congenital anomalies that cannot be identified at birth. In addition, as we only included live births, congenital anomalies among pregnancy terminations and stillbirths were not captured. Lastly, although we have adjusted many potential confounders in this study, we cannot rule out the possibility of residual confounding from unmeasured and unknown factors, such as folic acid supplementation, dietary and lifestyle habits, and medication use before and during pregnancy (40). Moreover, given that prepregnancy BMI was based on maternal self-reports in this study, recall bias could be introduced. Although in the stratification analysis we found that prepregnancy BMI did not change the magnitude of the association—i.e., the associations of either prepregnancy diabetes or GDM with congenital anomalies identified at birth were similar across different BMI categories—it is still possible there is residual confounding due to metabolic disorders associated with obesity or undiagnosed prepregnancy diabetes.

Conclusion

In conclusion, our findings from a nationwide population-based study showed that prepregnancy diabetes and, to a lesser extent, GDM were associated with several subtypes of congenital anomalies of the newborn. Our study expands the understanding of the potential effects of maternal diabetes on congenital anomalies and suggests potential benefits of preconception counseling in women with preexisting diabetes or at risk for GDM for the prevention of congenital anomalies.

Funding. This work was partly supported by a research grant from the National Institute of Child Health and Human Development, National Institutes of Health (R21 HD091458).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. W.B. and Y.W. conceived the idea. Y.W. and B.L. analyzed the data. Y.W. wrote the manuscript. B.L., Y.S., Y.D., M.K.S., D.A.S., L.G.S., and W.B. reviewed and edited the manuscript. All authors approved the current version of the manuscript. W.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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