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ORIGINAL ARTICLE

The joint effects of obesity and pregestational diabetes on the risk of stillbirth

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ABSTRACT

Objective: Obesity and pregestational diabetes (PGDM) may interact to further increase the risk of stillbirth than either risk factors independently. The objective of this study was to determine the risk of stillbirth in pregnancies complicated by both conditions.

Method: This was a retrospective cohort analysis of singleton nonanomalous births using the updated Texas vital records database between 2006 and 2014. Gestational diabetes and hypertensive diseases were additionally excluded from analysis. Analysis was stratified into 10 strata based on BMI class: underweight, normal weight, overweight, obese and morbidly obese, and PGDM. Furthermore, gestational age was stratified into the four periods for analysis: 24–33, 34–36, 37–39, and 40–42 weeks. The rate of stillbirth per 10,000 pregnancies were calculated for each stratum. The risks of stillbirth associated with each BMI class and PGDM were compared to normal weight nondiabetic pregnancies for each gestational period using proportional hazard regression models.

Result: After all exclusions, 3,097,123 births remained for analysis, including 5997 stillbirths. The overall rate of stillbirth increased from 15.0 per 10,000 pregnancies in normal weight pregnancies to 26.7 per 10,000 pregnancies in the morbidly obese group. The rate of stillbirth further increased with coexistence of PGDM to 119.9 per 10,000 pregnancies in the normal weight group and 209.8 per 10,000 pregnancies in the morbidly obese group. Compared to normal weight nondiabetic pregnancies the overall adjusted hazard ratio (aHR) of stillbirth associated with morbid obesity without PGDM was 1.57 [1.38, 1.79]. However, when further complicated by PGDM, the aHR was 6.67 [5.05, 8.81] in normal weight pregnancies and 12.86 [9.36, 17.67] in morbidly obese pregnancies. The highest risk of stillbirth was seen between 37 and 39 weeks, when the aHR in the diabetic normal weight group was 9.63 [5.65, 16.40] and the aHR in the diabetic morbidly obese group was 25.34 [15.58, 41.22].

Conclusion: PGDM and obesity both independently increased the risk of stillbirth. The joint effect of obesity and PGDM is stronger than the summation or multiplication of the individual effects of each risk factor.

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Obesity; pregestational diabetes; stillbirth

Introduction

Obesity and maternal diabetes are known risk factors for stillbirth. Population-based studies have reported the risk of stillbirth associated with increasing maternal body mass index (BMI) to range between 2 and 14 times compared to normal weight women depending on the severity of obesity and gestational age of pregnancy [1,2]. The association between maternal obesity and stillbirths remains significant even after controlling for confounding risk factors such as diabetes and hypertension [2,3]. Maternal obesity has become one of the most impactful risk factors for stillbirth given its increasing prevalence in contrast to other modifiable factors such as smoking and advanced maternal age [4,5].

Obesity is often associated with diabetes, another known risk factor for stillbirth. Over 21% of obese adults have diabetes according to the national health and nutrition examination survey [6]. The development of gestational diabetes (GDM) in pregnancy complicated by obesity has been well characterized. Between 8% and 13% of obese women develop GDM in pregnancy [7,8]. However, the prevalence of pregestational diabetes (PGDM) among obese pregnancies is

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less clear, and ranged between 0.6% and 3.8% [2,9]. The risk of stillbirth associated with PGDM is between 2.3 and 9.0 times higher than pregnancies without diabetes based on various studies published to date [10].

The underlying pathophysiology of stillbirth appears better understood for diabetes than obesity. In PGDM, deranged glycemic control appears to be a key component in the etiology of stillbirth [10]. This does not appear to be the case in nondiabetic obese pregnancies [11]. Placenta insufficiency is another major contributor to stillbirth risk in PGDM, primarily due to poor maternal vascular disease [10]. Placenta insufficiency is also implicated in obese pregnancies by indirect evidence [12,13]. However, the underlying mechanism is still unclear.

Because the pathophysiology of stillbirth associated with obesity and PGDM share some similarities but also major differences, we hypothesize that the presence of both conditions interact to increase the risk of stillbirth more than either risk factor alone. The purpose of this study was to estimate the risks of stillbirth associated with obesity and PGDM separately and in combination using a large population-based cohort.

Materials and methods

We conducted a retrospective cohort study using data derived from the Texas vital records between the years 2006 and 2014. There were 3,579,662 total births including 17,776 stillbirths registered in this time period. The database was based on birth records electronically submitted to the Texas Electronic Registrar. Texas employs several quality control measures such as periodic data reviews and site visits to improve compliance and data quality [2]. The use of this deidentified database was reviewed and approved by the Texas Department of State Health Services Internal Review Board (IRB#17–012).

Analysis was limited to singleton births between 24 weeks 0 days and 41-week 6-day weeks of gestation based on best clinical estimate of gestational age. While the current recommendations are generally to deliver PGDM between 37 and 39 weeks unless well controlled, there were 1381 PGDM who delivered after 39 weeks in this database [14,15]. These pregnancies were therefore included in the stillbirth rate calculations. We serially excluded multifetal gestations, pregnancies outside of the gestational age range, and those complicated by severe fetal anomalies. These anomalies included: anencephaly, spina bifida, cardiac anomalies, diaphragmatic hernia, gastroschisis, omphalocele, and chromosomal abnormalities. Additionally, maternal weight less than 70 lbs. were excluded as extremely underweight. We further excluded GDM, chronic hypertension and gestational hypertension, so as to not artificially increase the baseline risk of stillbirth when assessing for the effects of PGDM and obesity.

Maternal prepregnancy weight was based on self-reporting during the first prenatal visit. BMI was calculated using the prepregnancy weight and measured height during prenatal visit using the following formula: weight (kg) divided by the square of height (m). Maternal BMI was then stratified into five categories: underweight ($<18.5\,kg/m^2$), normal weight ($18.5–24.9\,kg/m^2$), overweight ($25.0–29.9\,kg/m^2$), obese ($30.0–39.9\,kg/m^2$), or morbidly obese ($\geq 40.0\,kg/m^2$). PGDM was recorded in the birth certificates by trained personnel, which included both type I and type II diabetes diagnosed prior to pregnancy without specifying the status of diabetic control.

Baseline characteristics were tabulated across all BMI groups. Given the large sample size, statistical methods were not used for comparison between the groups. Rather, trends in baseline characteristics were assessed to determine their inclusion into regression modeling.

In order to estimate the risks of stillbirth associated with maternal obesity and PGDM, both independently and in combination, 10 strata were created. These included the five BMI strata without PGDM and five BMI strata complicated by PGDM. The overall rates of stillbirth per 10,000 pregnancies in each of the 10 strata were calculated using established methods [16]. Cox proportional hazard regression analysis was used to estimate the risks of stillbirth associated with each of the strata using normal weight nondiabetic group as the baseline for comparison. The proportional hazard assumption was checked by calculating Schoenfeld's residuals. Variables were assessed for confounding effects based on population characteristics. These variables included maternal age, parity, race/ethnicity, education, smoking, and prenatal care. Backward stepwise elimination method was performed to arrive at the final regression model, which included maternal age, race/ethnicity, education, and smoking. Because the risks of stillbirth vary by gestational age, we further stratified the above analyses by grouping GA as follows: 24–32, 33–36, 37–39, and 40–42 weeks. Finally, in order to compare the impact of obesity and diabetes on the overall population, the population attributable risks (PAR) were calculated for obesity and PGDM using the adjusted hazard ratios (aHRs) from

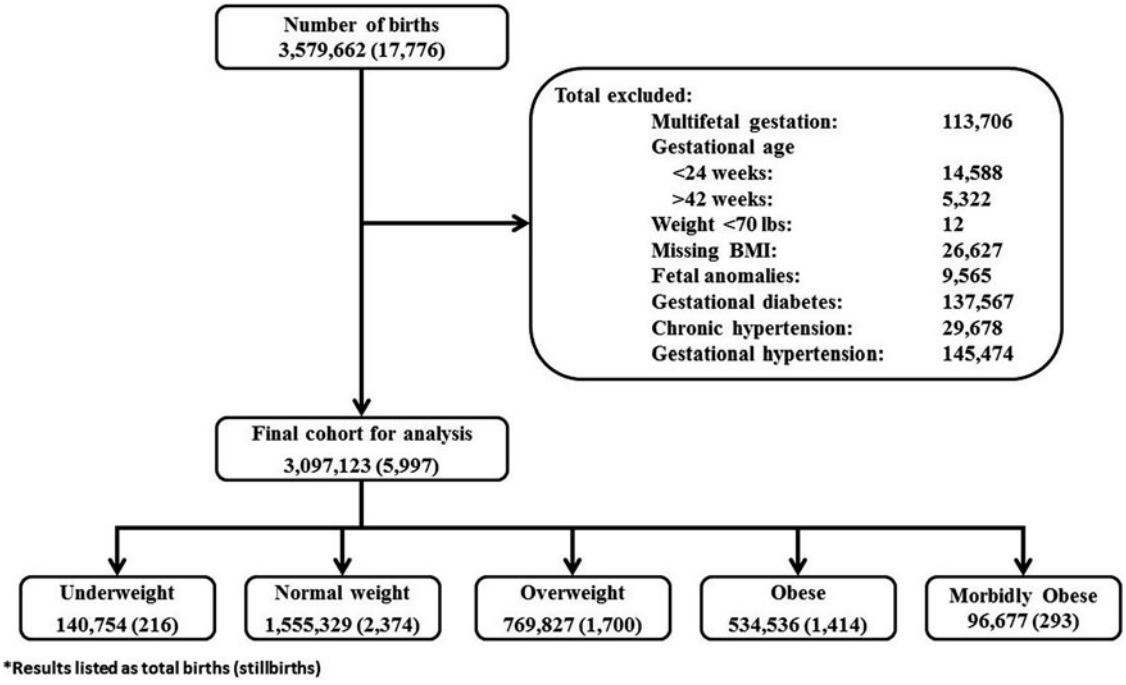

Figure 1. Cohort selection diagram.

the regression analysis. All analyses were performed using Stata 12 (College Station, TX).

Results

In the Texas database there were 3,579,662 total births including 17,776 stillbirths between 2006 and 2014. From this database, we excluded 113,706 multifetal gestations, 14,588 births earlier than 24 weeks GA, and 5322 births later than 42 weeks GA. There were 12 pregnancies with prepregnancy weight under 70 lbs., 26,627 births with missing maternal BMI, and 9565 fetal anomalies which were excluded. Furthermore, 137,567 pregnancies complicated by GDM, 29,678 complicated by chronic hypertension, and 145,474 complicated by gestational hypertension were also excluded from analysis. After all exclusions, 3,097,123 births remained for analysis including 5997 stillbirths (Figure 1).

Within this cohort 4.5% were underweight, 52.6% were normal weight, 24.9% were overweight, 17.3% were obese, and 3.1% were morbidly obese. There was a trend toward increasing maternal age with higher prevalence of advanced maternal age with higher BMI group. There were also a higher proportion of preterm delivery, African decent, and multiparity as BMI increased. In contrast, there was a trend toward decreasing levels of higher education and smoking with increasing BMI class. As expected, the prevalence of PGDM was higher with increasing BMI class. In the normal weight group, 0.4% of pregnancies were PGDM, compared to 3.4% in the morbidly obese group. In contrast, only 0.2% of underweight pregnancies were complicated by PGDM (Table 1).

The overall rate of stillbirth increased with increasing BMI. In pregnancies not complicated by PGDM, the rate increased from 15.0 per 10,000 pregnancies in the normal weight groups to 26.7 per 10,000 pregnancies in the morbidly obese groups. When pregnancies were also affected by PGDM, the rates of stillbirths were further increased, from 119.9 per 10,000 pregnancies in normal weight group to 209.8 per 10,000 pregnancies in the morbidly obese group (Table 2). The overall risks of stillbirths similarly increased with increasing BMI and PGDM. Using normal weight nondiabetics as the baseline comparison group, the aHR was 1.57 [1.38, 1.79] for the morbidly obese nondiabetic group, 6.67 [5.05, 8.81] for normal weight PGDM group, and 12.86 [9.36, 17.67] for the morbidly obese with PGDM (Table 3).

When stratified by gestational period, the rate of stillbirth decreased with increasing gestational age for every BMI-diabetes stratum. Between 24 and 33 weeks gestation, there was no obvious pattern in rate of stillbirth with increasing BMI. The rate of stillbirths in the normal weight group was 7.2 per 10,000 pregnancies in this gestational period, whereas for the morbidly obese group it was 10.9 per 10,000 pregnancies (Table 2). After adjusting for confounders, the hazard of stillbirth associated with morbid obesity compared

Table 1. Cohort characteristics.[a]

Characteristics	Underweight BMI < 18.5 kg/m^2	Normal weight BMI 18.5–24.9 kg/m^2	Overweight BMI 25.0–29.9 kg/m^2	Obese BMI 30.0–39.9 kg/m^2	Morbidly obese BMI ≥ 40.0 kg/m^2
N	140,754	1,555,329	769,827	534,536	96,677
%	4.5	52.6	24.9	17.3	3.1
Maternal age	23 [20, 29]	26 [21, 31]	27 [23, 32]	27 [23, 32]	28 [24, 32]
Maternal age ≥35 (%)	6.6	11.4	13.6	13.8	14.1
Gestational age	38 [37, 39]	38 [38, 39]	38 [38, 39]	39 [37, 39]	38 [37, 39]
Preterm <37 weeks (%)	13.8	11.2	11.3	12.3	14.2
Race (%)					
White	38.1	36.2	31.0	30.0	31.4
Black	10.5	9.9	11.7	13.3	18.8
Hispanic	41.0	47.0	53.4	54.4	48.5
Other	10.4	6.9	4.0	2.3	1.3
Education (%)					
High school diploma	48.7	46.2	48.6	54.6	62.1
>HS diploma	22.0	29.5	25.3	21.3	18.9
Nulliparous (%)	48.2	40.0	31.8	28.5	28.5
No prenatal care (%)	3.8	3.3	3.2	2.6	2.1
Smoking (%)	12.3	7.3	7.0	7.8	8.4
Pregestational diabetes	0.2	0.4	0.8	1.7	3.4

[a]Results presented as %, or median [inner quartile range].

Table 2. Rate of stillbirth.[a]

	Overall	*p* Value	24–33 weeks	*p* Value	34–36 weeks	*p* Value	37–39 weeks	*p* Value	40–42 weeks	*p* Value
Nondiabetic		<.001		<.001		<.001		<.001		<.001
Underweight	15.3		7.8		4.0		3.6		–[b]	
Normal weight nondiabetic	15.0		7.2		3.8		3.5		3.2	
Overweight	21.4		10.7		5.1		4.9		4.6	
Obese	25.1		11.3		6.0		6.9		6.2	
Morbidly obese	26.7		10.9		6.7		7.7		11.1	
Pregestational diabetic										
Underweight	48.5		–		–		–		–	
Normal weight	119.9		40.7		44.3		41.1		–	
Overweight	138.3		57.2		41.9		46.6		–	
Obese	155.8		30.1		53.1		88.5		–	
Morbidly obese	209.8		62.9		49.2		118.7		–	

[a]Results reported as: rate per 10,000 pregnancies.
[b]Incidence too low to report.

to normal weight pregnancies in this gestational period was not statistically significant. However, the aHR for the obese group was statistically significant (aHR: 1.38, 95% CI: [1.25, 1.53]) (Table 3). The added complication of PGDM increased the rate of stillbirth to 40.7 per 10,000 pregnancies in the normal weight group and 62.9 per 10,000 pregnancies in the morbidly obese group (Table 2). Similarly, however, when also complicated by PGDM, the aHR for normal weight diabetic group was 2.22 [1.39, 3.53] and 2.77 [1.57, 4.89] for morbidly obese diabetic group (Table 3).

In contrast to the gestational period between 24 and 33 weeks, the pattern of stillbirth between 34–36 weeks period and 37–39-week periods both demonstrated step-wise increase in stillbirth with increasing BMI. Specifically, between 37 and 39 weeks, the rate of stillbirth was 3.5 per 10,000 pregnancies for the normal weight group and 7.7 per 10,000 pregnancies in the morbidly obese group. When the pregnancies were further complicated by PGDM, the rates of stillbirth further increased to 41.1 per 10,000 pregnancies in the normal weight group and 118.7 per 10,000 pregnancies in the morbidly obese group (Table 2). The hazard of stillbirth was statistically significant after adjusting for confounders. Compared to normal weight nondiabetic group between 37 and 39 weeks, the aHR associated with the morbidly obese group was 1.81 [1.39, 2.35]. When further complicated by PGDM, the aHR increased to 9.63 [5.65, 16.40] in the normal weight group and 25.34 [15.58, 41.22] in the morbidly obese group (Table 3).

The trend of increasing rate of stillbirth associated with increasing BMI continues into the 40–42-week period, where the rate of stillbirth increased from 3.2 per 10,000 pregnancies in the normal weight group to 11.1 per 10,000 pregnancies in the morbidly obese group (Table 2). The corresponding adjusted hazard of stillbirth in the morbidly obese group compared to the normal weight group in the period was 3.08 [1.91, 4.95] (Table 3). The incidences of stillbirth in PGDM

Table 3. The effects of obesity and diabetes on stillbirth risk.

	Overall		24–33 weeks		34–36 weeks		37–39 weeks		40–42 weeks	
	HR (95% CI)[a]	aHR (95% CI)[b]	HR (95% CI)	aHR (95% CI)	HR (95% CI)	aHR (95% CI)	HR (95% CI)	aHR (95% CI)	HR (95% CI)	aHR (95% CI)
Underweight	1.05 (0.91, 1.21)	1.09 (0.94, 1.25)	0.77 (0.63, 0.94)	0.79 (0.65, 0.96)	0.81 (0.61, 1.07)	0.83 (0.63, 1.10)	1.04 (0.77, 1.40)	1.09 (0.80, 1.47)	–[c]	–
Normal weight	Reference-									
Non-diabetic										
Overweight	1.44 (1.35, 1.53)	1.35 (1.27, 1.67)	1.50 (1.37, 1.64)	1.48 (1.35, 1.63)	1.41 (1.24, 1.60)	1.36 (1.20, 1.56)	1.39 (1.22, 1.60)	1.30 (1.13, 1.50)	1.46 (1.11, 1.91)	1.39 (1.06, 1.83)
Obese	1.69 (1.58, 1.81)	1.56 (1.45, 1.67)	1.40 (1.27, 1.54)	1.38 (1.25, 1.53)	1.59 (1.39, 1.82)	1.55 (1.34, 1.78)	1.91 (1.67, 2.20)	1.77 (1.54, 2.04)	1.97 (1.48, 2.61)	1.87 (1.40, 2.49)
Morbidly obese	1.83 (1.61, 2.08)	1.57 (1.38, 1.79)	1.17 (0.95, 1.43)	1.13 (0.92, 1.39)	1.57 (1.21, 2.04)	1.47 (1.13, 1.93)	2.07 (1.60, 2.68)	1.81 (1.39, 2.35)	3.51 (2.23, 5.52)	3.08 (1.91, 4.95)
Diabetes (pregestational)										
Underweight	–	–	–	–	–	–	–	–	–	–
Normal weight	8.99 (6.85, 11.80)	6.67 (5.05, 8.81)	2.19 (1.37, 3.48)	2.22 (1.39, 3.53)	5.62 (3.56, 8.87)	5.53 (3.50, 8.73)	11.44 (6.85, 19.13)	9.63 (5.65, 16.40)	–	–
Overweight	10.39 (8.00, 13.48)	7.22 (5.53, 9.42)	3.68 (2.45, 5.51)	3.47 (2.29, 5.24)	4.96 (3.06, 8.03)	4.74 (2.92, 7.69)	12.78 (7.77, 21.02)	9.91 (5.91, 16.62)	–	–
Obese	11.83 (9.56, 14.63)	7.89 (6.35, 9.82)	1.68 (1.04, 2.72)	1.57 (0.95, 2.57)	6.56 (4.52, 9.52)	6.39 (4.39, 9.31)	24.08 (17.51, 33.12)	18.78 (13.49, 26.14)	–	–
Morbidly obese	16.20 (11.85, 22.14)	12.86 (9.36, 17.67)	2.91 (1.65, 5.14)	2.77 (1.57, 4.89)	5.1 (2.64, 9.85)	4.84 (2.50, 9.36)	32.79 (20.49, 52.48)	25.34 (15.58, 41.22)	–	–

[a]Hazard ratio (95% confidence interval).
[b]Adjusted hazard ratio (95% confidence interval): adjusted for maternal age, race/ethnicity, education, and smoking.
[c]Incidence too low to report.

affected pregnancies were too low for analysis in this gestational period.

Based on the regression analysis, the overall PAR of stillbirth from obesity and morbid obesity in the absence of PGDM were 18.1% and 3.9%, respectively. Whereas for isolated PGDM without obesity, the overall PAR was 2.0%. Between 37 and 39 weeks, the PAR from obesity and morbid obesity were 22.7% and 5.2% respectively, and 2.7% in isolated PGDM.

Comment

This large population-based cohort study, with over three million pregnancies analyzed, highlights several important findings. As previous published studies have noted, there was a dose-dependent effect of obesity on stillbirth independent of other risk factors. The largest impact of obesity on stillbirth was seen between 40 and 42 weeks, where the risk of stillbirth was 3 times higher in the morbidly obese group compared to the normal weight group. This effect size was smaller than other studies, likely because we excluded GDM and gestational hypertension in the analysis [14]. In comparison, the effect of PGDM on stillbirth was 6.7 times higher than nondiabetics overall in normal weight pregnancies, and 9.6 times higher in pregnancies delivered between 37 and 39 weeks.

The joint effect of obesity and PGDM is stronger than either risk factor alone. In morbidly obese women with PGDM, the overall risk of stillbirth is 12.9 times higher than normal weight nondiabetics, and 25.3 times higher between 37 and 39 weeks. These results are higher than the summation or multiplication of the individual risk factors' effects. These results suggest a synergistic effect where obesity potentiates the effects of diabetes, or *vice versa*, in the mechanisms of stillbirths.

In PGDM, deranged glycemic control appears to be a major pathway leading to stillbirth. This is evident by studies demonstrating that tight glycemic control decreased the risk of stillbirth in PGDM pregnancies, whereas poor compliance results in higher risk of stillbirth and other adverse outcomes [17,18]. A commonly accepted theory is that hyperglycemia results in fetal hyperinsulinemia, which results in accelerated fetal growth. Fetal growth may outpace the placenta's ability to support the metabolic demands, leading to the development of relative hypoxia and acidosis due to increased metabolic demands. These conditions may eventually result in stillbirth [15].

Obesity may further induce insulin overproduction through a separate biochemical pathway. One study

reported a direct relationship between maternal and fetal leptin concentration as a consequence of maternal obesity, and furthermore demonstrated an increase in insulin resistance with higher serum leptin concentrations [19]. This is in contrast to the idea of undiagnosed hyperglycemia in obese pregnancies. This may help explain the 2–4 times higher risk of macrosomia associated with maternal obesity independent of other risk factors such as diabetes [20,21]. The common pathway of insulin overproduction leading to uncontrolled fetal growth and relative placental insufficiency may explain the observed synergistic effects of both conditions on stillbirth.

In pregnancies complicated by diabetes, microvascular injuries can lead to decreased placental invasion and spiral artery remodeling [10]. These lead to decreased placental development as suggested by decreased serum placental growth factors in the second trimester [22]. In obese pregnancies, population data suggest a higher risk of adverse outcomes associated with birthweight less than the 10th percentile compared to nonobese pregnancies in similar birthweight percentiles, as well as compared to obese pregnancies greater than the 10th percentile [12,13]. The reasons for the observed pathological growth are unclear. However, sleep apnea and hypoxemia are commonly associated with obesity [23]. There is evidence that placental vasoconstriction can develop due to chronic hypoxia, which can lead to growth restriction [24]. The combined insults of chronic hypoxia and microvascular injuries restricting placental development, and of a fetus with accelerated growth and rapidly increasing metabolic demand due to hyperinsulinemia may also explain the joint effects of obesity and diabetes on stillbirth reported here.

It is also important to note, that while diabetes has a larger effect size on stillbirth than obesity, its prevalence in the general population is low. Therefore, from a population and public health stand point, PGDM's impact is relatively small as evident by a PAR of 2.7%. By comparison, obesity is much more common. Therefore, the elimination of stillbirths associated with obesity and morbid obesity would reduce the overall incidences of stillbirth by 22.0% overall, and 27.9% between 37 and 39 weeks.

The strengths of our study include the large study population. The large sample size allowed us to stratify by both BMI and GA. It also allowed us to isolate the effects of obesity and diabetes by excluding most commonly seen comorbidities associated with both conditions. Furthermore, we were able to adjust for other important confounders, such as maternal age, education, and race. Importantly, our study was adequately powered to demonstrate the effect on stillbirth when pregnancies are complicated by both obesity and PGDM, a scenario that is becoming increasingly common in clinical practice.

There are, however, limitations to this study. First, population databases are subject to coding errors, missing data, and data entry errors. We were able to minimize the effect by only including complete data. Additionally, the database recorded self-reported maternal weight, which has a tendency to be underestimated [25,26]. A falsely low maternal weight may lead to an underestimation of the effect of obesity on stillbirth and the prevalence of diabetes in each BMI group. This misclassification bias will result in underestimation of the risk of stillbirth associated with higher BMI and PGDM groups. Furthermore, we were unable to further categorize PGDM into type I or type II, or based on glycemic control status. These details should be considered as topics for future studies to further characterize the risks associated with PGDM.

It is also important to point out, that in this retrospective cohort study design, the findings reported do not establish causation of diabetes and obesity with stillbirths. However, the abundance of such published literature and the proposed biologic plausibility give weight to the likelihood that both risk factors are part of the etiologic pathway of stillbirths.

Despite these limitations, the results of this study are alarming and calls to attention the importance of managing both diabetes and obesity in pregnancy. Currently, the management of PGDM does not distinguish between individual patients' BMI class [15,27]. However, given the stark contrast in risk of stillbirth associated with PGDM in normal weight group compared to PGDM in obese groups, additionally studies are needed to determine if more intense fetal surveillance strategies or earlier delivery would be beneficial.

Disclosure statement

No potential conflict of interest was reported by the authors.

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