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Impact of Obesity on Maternal and Neonatal Outcomes in Insulin-Resistant Pregnancy

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Abstract

Objective—To determine the impact of obesity on pregnancies complicated by insulin resistance.

Study Design—Secondary analysis of prospective cohort of women with gestational diabetes (GDM) and type 2 diabetes (DM). Exclusion criteria were type 1 DM, multiple gestation, fetal anomalies, unknown prepregnancy body mass index (BMI). Primary maternal outcome was a composite of any: severe preeclampsia, eclampsia, 3rd-4th degree laceration, readmission, wound infection, or antepartum hospitalization. Primary neonatal outcome was a composite of any: hypoglycemia, preterm delivery, admission to level 3 nursery, oxygen requirement >6 hours after birth, shoulder dystocia, 5-minute Apgar 3, cord pH<7.0, and cord base excess <-12 mmol/L. Obese women (BMI ≥30.0 kg/m²) were compared to non-obese women (BMI <30.0 kg/m²).

Results—Of 356 subjects with DM, 233 (66%) were obese. Obese women were not at further increased risk of the composite maternal outcome (adjusted odds ratio (aOR) 0.68, 95% confidence interval (CI) 0.43–1.09), the composite neonatal outcome (aOR 0.76, 95% CI 0.48–1.21), or cesarean (58.8% vs 52.9%, p=0.28, aOR 1.47, 95% CI 0.91–2.39).

Conclusion—We did not find evidence that obesity worsened pregnancy outcomes in women with GDM and type 2 DM, suggesting that obese women may not require more stringent antepartum treatment strategies.

Keywords

obesity; pregestational diabetes; gestational diabetes; type 2 diabetes

Introduction

According to the CDC, approximately 36% of women in the United States 20 years and older are currently obese, defined as a body mass index of 30 kg/m² or greater.¹ Obesity is

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associated with an increased risk of pregnancy complications, including stillbirth, preeclampsia, fetal growth disorders, cesarean delivery, and diabetes.²⁻⁶ Obese women are also at increased risk of pregestational diabetes, which may or may not have been diagnosed at the time of conception.⁶

Simultaneously, pregestational and gestational diabetes increase the risk of preterm delivery, preeclampsia, fetal growth disorders, and cesarean delivery.^{7, 8} It is currently unclear if obesity increases the risk for adverse perinatal outcomes in pregnancies already complicated by diabetes. In this study, we aimed to compare the perinatal outcomes of obese and non-obese women with type 2 and gestational diabetes.

Materials and Methods

This is a planned secondary analysis of a prospective, 4-year cohort of women with gestational diabetes (GDM) and type 2 pregestational diabetes mellitus (DM). Institutional review board approval was obtained from Washington University School of Medicine.

Women were approached for enrollment at entry to prenatal care (type 2 DM) or upon diagnosis (GDM). Exclusion criteria were type 1 DM (as reported by patient and clinical records), multiple gestation and known fetal anomalies. Women with unknown prepregnancy body mass index (BMI) and incomplete delivery records were excluded from this secondary analysis. All subjects were followed at the Center for Diabetes in Pregnancy, a clinic managed by Maternal-Fetal Medicine specialists at Washington University School of Medicine/Barnes Jewish Hospital, St. Louis, MO. Upon entry to care, women received diabetic education and dietary counseling. The standard of care at the Center for Diabetes in Pregnancy is to follow fasting and post-prandial blood sugars with a treatment goal of maintaining fasting blood sugar <95 mg/dL and one-hour post-prandial blood sugar <140 mg/dL. These goals are achieved with the use of diet, glyburide or insulin. Indication for treatment escalation is >50% of blood glucose measures at any given time point above goal.

For this analysis, women were classified according to their prepregnancy BMI, which was calculated from a self-reported prepregnancy weight and height measurement at entry to care. Obese women, defined as a BMI ≥ 30.0 kg/m², were compared to non-obese women, defined as BMI <30.0 kg/m².

A woman was considered to have the maternal composite outcome if she had at least one of the following: preeclampsia, eclampsia, 3rd or 4th degree laceration as documented by the delivery physician, readmission within 6 weeks of delivery (for any reason), wound infection, or antepartum hospitalization. Cesarean delivery (CD) and primary CD was a secondary maternal outcome. Insulin requirement in the subgroup of women with GDM was also considered as a secondary outcome. Preeclampsia was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg on two occasions at least 6 hours apart and associated with proteinuria ($>1+$ on urine dip or ≥ 300 mg/24 hours). Severe preeclampsia was defined as meeting the criteria for preeclampsia with one of the following: systolic blood pressure ≥ 160 , diastolic blood pressure ≥ 110 , proteinuria $>3+$ on urine dip or ≥ 5 -g in 24-hours, oliguria (<30 mL urine/hour), pulmonary edema, transaminitis (aspartate

aminotransferase >1.5 normal), thrombocytopenia (platelets < 120,000), or intrauterine growth restriction (estimated fetal weight 10th percentile). Neonates were considered to have the composite outcome if they had any one of the following: hypoglycemia (blood sugar <40 mg/dL), preterm delivery (<37 wks), admission to level 3 nursery, oxygen requirement >6 hours after birth, shoulder dystocia (diagnosed clinically by the delivering attending physician), 5-minute Apgar 3, umbilical cord arterial pH <7.0, or base excess <-12 mmol/L.

Obese and non-obese subjects were compared with descriptive and bivariate statistics using unpaired Student's *t* or Mann-Whitney U tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables as appropriate. Normal distribution of continuous variables was tested using the Kolmogorov-Smirnov test. Potentially confounding variables of the exposure-outcome association were identified in the stratified analyses. Variables considered were gestational versus pregestational diabetes, gestational age at delivery, race, parity, and prior vaginal delivery. Multivariable logistic regression models for the composite outcomes were then developed to better estimate the effect of obesity on perinatal outcomes while adjusting of potentially confounding effects. Clinically relevant covariates for initial inclusion in multivariable statistical models were selected using results of the stratified analyses, and factors were removed in a backward step-wise fashion, based on significant changes in the exposure adjusted odds ratio or significant differences between hierarchical models using likelihood ratio test. Covariates considered included type of diabetes, chronic hypertension, birth weight, prior vaginal delivery, maternal age, and race. All analyses were completed using Stata SE, version 11 (College Station, Texas).

Results

Of 435 women in the cohort, 79 were excluded from this analysis (18 excluded for undocumented prepregnancy body mass index, 41 excluded for incomplete delivery records, and 20 excluded for congenital anomaly). Of the remaining 356 women, 233 (65.5%) were obese and 123 were non-obese (34.5%) (Table 1). Obese and non-obese subjects were similar with respect to age, gravidity, class of diabetes, gestational age at diagnosis for gestational diabetes, prior cesarean delivery, one hour glucose challenge test values, and hemoglobin A1c. Obese women were more likely to be African American or to have chronic hypertension. The median BMI for obese women was 39.5 kg/m², and for non-obese women it was 26 kg/m².

Incidence of the composite maternal outcome was generally high, but was not increased for obese compared to non-obese women (40.8% vs 43.8%, relative risk (RR) 0.93, 95% confidence interval (CI) 0.72–1.2) (Table 2). After adjusting for gestational versus pregestational diabetes and black race, the risk of the composite maternal outcome was not significantly different between groups (adjusted odds ratio (AOR) 0.75, 95% CI 0.46–1.2). The risk of cesarean delivery (58.8% vs 52.9%, AOR 1.47, 95% CI 0.91–2.39) and primary cesarean delivery (46.4% vs 37.5%, AOR 1.47, 95% CI 0.84–2.57) was not significantly higher in the obese versus non-obese groups. When components of the maternal outcome were examined individually, obese women were not at increased risk of severe preeclampsia/eclampsia (AOR 0.95, 95% CI 0.53–1.70), postpartum readmissions (RR 0.89,

95% CI 0.36–2.21), third and fourth degree laceration (RR 0.53, 95% CI 0.03–8.37), or antepartum hospitalizations (AOR 0.63, 95% CI 0.38–1.07). Only 4 women were diagnosed with wound infections, all in the obese group ($p=0.16$). In women with gestational diabetes, obese women were not more likely to require insulin than non-obese women (37.3% vs 27.1%, RR 1.38, 95% CI 0.81–2.36).

Obese women were not at increased risk of the composite neonatal outcome compared to non-obese women (58.4% vs 65.0%, RR 0.90, 95% CI 0.75–1.07) (Table 3). After adjusting for gestational versus pregestational diabetes, the composite neonatal outcome was not increased in obese women (AOR 0.76, 95% CI 0.48–1.21). Gestational age at delivery was not significantly different between the two groups (median 38.1 versus 37.9 weeks, $p=0.60$), nor was birth weight (median 3410 g vs 3279 g, $p=0.36$). Obese women were not at an increased risk of any of the individual components of the neonatal composite outcome.

Comment

In this prospective cohort of women with gestational diabetes and type 2 pregestational diabetes, obesity did not significantly worsen maternal and neonatal outcomes. These findings suggest that obese women with treated GDM or type 2 DM can be counseled on anticipated neonatal outcomes in a fashion similar to non-obese women. An approximately 50% incidence of the composite maternal outcome and 60% incidence of the composite neonatal outcome in both obese and non-obese women demonstrates the high risk nature of diabetic pregnancies in this cohort.

The cause of adverse outcomes in the obese gravida is unclear; the increased risk is not explained solely by the presence of comorbidities such as diabetes and hypertension. However, a significant body of research has revealed that adipose tissue is very active in regulating glucose homeostasis.^{9, 10} Excessive adipose tissue results in the dysregulation of adipokines that ultimately increases peripheral insulin resistance. It is possible that we did not find an increased risk of adverse maternal and neonatal outcomes in diabetes complicated by obesity because the effects of both diseases are mediated by peripheral insulin resistance: the additional peripheral insulin resistance caused by obesity did not worsen outcomes in women who were already insulin resistant.

Catalano et al performed a secondary analysis of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) data to examine the independent effects of obesity and of hyperglycemia on pregnancy outcomes.¹¹ In this study over 23,000 women, they found that at the same levels of hyperglycemia, obesity resulted in significantly greater risks of primary cesarean, preeclampsia, large for gestational age, and shoulder dystocia than either GDM or obesity alone. Although this study provides insight into the impact of insulin resistance on these outcomes, the fact that women were not treated for diabetes as defined by this study reduces its clinical generalizability for counseling and managing patients.

A retrospective study by Roman et al demonstrated an increased risk of cesarean delivery, preeclampsia, macrosomia, stillbirth, neonatal hypoglycemia, and jaundice in obese compared to non-obese women with GDM.¹² Interestingly, this study appeared to uncover a

dose-response relationship of weight to adverse outcomes in GDM patients, with morbidly obese women having worse outcomes than obese women, who also had worse outcomes than overweight women. A limitation of this study was that outcomes were self-reported by patients, who may be unreliable for reporting certain outcomes. Additionally, although all patients were identified through a diabetes referral center, patients were diagnosed and managed by their primary obstetricians, suggesting a lack of uniformity in the diagnostic criteria and management strategies applied to the cohort, which could have resulted in differential outcomes.

Langer and colleagues described the results of a cohort of 4,000 women; obese women with GDM who achieved good glycemic control with insulin had similar pregnancy outcomes compared to normal weight women who achieved good glycemic control with insulin.¹³ However, when glycemic control was achieved through diet alone, obese women had worse outcomes than normal weight women. These findings may be due to an unrecognized difference in these groups of women, such as dietary differences. Morbidly obese women ($\text{BMI} > 35 \text{ kg/m}^2$) did not have worse pregnancy outcomes than obese women ($\text{BMI} 30\text{--}34.9 \text{ kg/m}^2$); this subgroup is most similar to the obese group in the present study.

The main strength of our study lies in the prospective data collection. As this was a study focused on diabetes and outcomes, specific attention was given to diabetic class, medications used for the treatment of diabetes, and the outcomes of interest. Furthermore, we had detailed neonatal data available such as hypoglycemia and umbilical cord gas information, enabling us to examine the effect of obesity on important infant outcomes. Also, this was a high-risk population, with a high number of adverse events occurring in the population. As a result, assuming a Type 1 error of 0.05, we had 80% power to detect a 50% increase in the risk of the maternal and neonatal composite outcomes, which we would offer represents a clinically meaningful threshold. However, our power to detect a difference in individual components of the composite outcome was limited.

One of the limitations of the current study was that women with GDM and type 2 DM were considered similarly. We felt that it was important to also examine women with type 2 DM, as both GDM and type 2 DM result from peripheral insulin resistance. In addition, obese women with GDM may in fact have previously undiagnosed type 2 DM. Type 2 DM confers much higher pregnancy risks than does GDM; the fact that some obese women diagnosed with GDM may actually have previously undiagnosed type 2 DM could explain some of the findings in studies demonstrating worse outcomes in obese women with GDM. Inclusion of type 2 DM in this study reduces this as a potential source of bias in our study. Additionally, little information exists as to the impact of obesity on Type 2 DM in pregnancy related to outcomes.

Another potential limitation of our study was in the grouping of overweight women with normal weight women; indeed, the median BMI of the non-obese group was 26.0 kg/m^2 , classifying many of these women as overweight and possibly diminishing any potential differences between the two groups. On the other hand, the median BMI of the obese group was 39.5 kg/m^2 , indicating that the majority of women in this category were class II or III obese. Therefore, we feel that these two groups of women differed substantially in their

exposure, enabling us to detect an impact of prepregnancy BMI on pregnancy outcomes in insulin-resistant women. However, the degree of obesity and incidence of adverse outcomes might limit generalizability to like populations.

Despite these limitations, we feel that clinically important conclusions can be drawn. The high incidence of adverse outcomes in both obese and non-obese women with GDM or type 2 DM highlights the high risk nature of these pregnancies. Obese women with treated type 2 and gestational diabetes in this prospective cohort did not experience a significantly higher rate of adverse outcomes compared to non-obese women with these diseases. This suggests that obese women can be managed in a similar fashion to non-obese women and may not require more stringent or aggressive treatment strategies, although more research is needed in this area.

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Table 1

Characteristics of Included Subjects

	Non-Obese (n=123)	Obese (n=233)	p
Age (yrs)	28.1 ± 6.0	29.4 ± 5.6	0.04
<u>Race</u>			<0.01
Black	64 (52.0%)	174 (74.7%)	
Caucasian	44 (35.8%)	43 (18.5%)	
Hispanic	11 (8.9%)	14 (6.0%)	
Other	4 (3.2%)	2 (0.8%)	
Gravidity	3.5 ± 2.2	3.4 ± 2.1	0.71
BMI (kg/m ²)	26.0 (23.0–28.2)	39.5 (34.0–49.9)	<0.01
Chronic Hypertension	7 (5.6%)	35 (15.0%)	<0.01
Prior Cesarean	43 (35.0%)	80 (34.3%)	0.91
<u>Type of DM</u>			
Type 2 DM	75 (61.0%)	142 (61.0%)	0.28
Gestational-A1	18 (14.6%)	21 (9.0%)	
Gestational-A2	30 (24.4%)	70 (30.0%)	
Gestational Age at Diagnosis of GDM (wks)	28.1 (25.9–30.4)	28.0 (25.1–29.6)	0.47
GCT Value (mg/dL)	176 (153–209)	167 (152–200)	0.45
Hemoglobin A1c (%) upon Entry to Study	7.2 ± 1.9	7.2 ± 1.8	0.82
Hemoglobin A1c (%) Third Trimester	6.7 ± 1.2	6.5 ± 1.1	0.15

Data presented as mean ± standard deviation, n(%), or median (interquartile range) as appropriate

Table 2**Maternal Outcomes by Obesity Status**

	Non-Obese (n=123)	Obese (n=253)	RR (95% CI)	p	aOR (95% CI)
Composite	53 (43.8%)	95 (40.8%)	0.93 (0.72–1.2)	0.58	0.75* (0.46–1.2)
Cesarean Delivery	65 (52.9%)	137 (58.8%)	1.11 (0.91–1.36)	0.28	1.47 [†] (0.91–2.39)
Primary Cesarean	30 (37.5%)	71 (46.4%)	1.24 (0.89–1.72)	0.19	1.47 [†] (0.84–2.57)
Severe Preeclampsia/Eclampsia	23 (18.7%)	45 (19.3%)	1.0 (0.7–1.6)	0.89	0.95 (0.53–1.70) [‡]
Readmission	6 (5.0%)	11 (4.7%)	0.89 (0.36–2.21)	0.81	-
Antepartum Hospitalizations	39 (31.7%)	64 (27.5%)	0.87 (0.62–1.21)	0.40	0.63* (0.38–1.07)
Maternal Wound Infection	0	4 (1.72%)	-	0.16	-
Third & Fourth Degree Lacerations	1 (0.8%)	1 (0.4%)	0.53 (0.03–8.37)	0.65	-
Required Insulin [¶]	13 (27.1%)	34 (37.3%)	1.38 (0.81–2.36)	0.22	-

Data Presented as n, % unless otherwise specified

* Adjusted for type of diabetes (gestational versus pregestational), black race

[†] Adjusted for prior vaginal delivery, macrosomia[‡] Adjusted for type of diabetes (gestational versus pregestational), maternal age[¶] Gestational diabetes only

Table 3

Neonatal Outcomes by Obesity Status

	Non-Obese (n=123)	Obese (n=253)	RR (95% CI)	p	aOR (95% CI)
Composite Outcome	78 (65.0%)	135 (58.4%)	0.90 (0.75–1.07)	0.23	0.76 (0.48–1.21)*
Neonatal Weight (g, Interquartile Range)	3279 (2795–3835)	3410 (2930–3875)	-	0.36	-
Macrosomia	24 (19.5%)	40 (17.2%)	0.88 (0.56–1.39)	0.58	0.81 [†] (0.46–1.43)
Growth Restriction	7 (5.8%)	13 (5.6%)	0.78 (0.36–1.69)	0.53	0.76* (0.32–1.76)
Shoulder Dystocia	7 (5.8%)	12 (5.2%)	0.96 (0.39–2.33)	0.75	0.96* (0.37–2.49)
Gestational Age at Delivery (wks, Interquartile Range)	37.9 (36.3–39.0)	38.1 (36.7–39.0)	-	0.60	-
Preterm Delivery	40 (32.5%)	67 (28.8%)	0.88 (0.63–1.22)	0.46	0.73 [‡] (0.44–1.22)
Cord pH < 7.0	13 (10.6%)	21 (9.0%)	0.85 (0.44–1.64)	0.86	0.84* (0.40–1.75)
Cord Base Excess < -12 mmol/L	15 (12.2%)	25 (10.7%)	0.88 (0.48–1.61)	0.68	0.86* (0.43–1.72)
5-Minute Apgar 3	5 (4.1%)	7 (3.0%)	0.74 (0.24–2.28)	0.60	-
Neonatal Respiratory Distress Syndrome	21 (17.8%)	51 (22.4%)	1.23 (0.78–1.95)	0.54	1.31 [§] (0.69–2.46)
Neonatal Hypoglycemia	37 (30.1%)	66 (28.3%)	0.94 (0.67–1.32)	0.73	0.92* (0.57–1.48)
Admission to Neonatal Intensive Care Unit	3 (2.4%)	13 (5.6%)	2.29 (0.66–7.88)	0.17	-

Data Presented as n, % unless otherwise specified

* Adjusted for type of diabetes (gestational versus pregestational)

[†] Adjusted for parity[‡] Adjusted for black race, type of diabetes (gestational versus pregestational)[§] Adjusted for gestational age at delivery