Obesity Subtypes and Risk of Spontaneous versus Medically Indicated Preterm Births in Singletons and Twins

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Using data from the Missouri maternally linked files (1989–1997), the authors examined the association among maternal obesity, obesity subtypes, and spontaneous and medically indicated preterm (<37 weeks) and very preterm (<33 weeks) births in singletons and twins. Adjusted odds ratios were obtained with correction for intracluster correlation. The prevalence of obesity increased by 77% over the study period (p trend < 0.001). Obese mothers had a lower risk for spontaneous preterm birth, and this was more pronounced among twins (odds ratio = 0.68, 95% confidence interval: 0.62, 0.75) than singletons (odds ratio = 0.84, 95% confidence interval: 0.82, 0.87). However, this association was present only among obese women who gained less than 0.69 kg/week for singletons and between 0.23 and 0.69 kg/week for twins. By contrast, obese mothers with singleton gestation had about 50% greater odds of medically indicated preterm (odds ratio = 1.46, 95% confidence interval: 1.39, 1.54) and very preterm (odds ratio = 1.49, 95% confidence interval: 1.34, 1.65) births, and the risk increases with ascending severity of obesity (p trend < 0.01). For extreme obesity, the risk of medically indicated preterm and very preterm births was almost double that for nonobese women. Similar findings were observed in twins. These data suggest that obesity increases the risk for medically indicated but not spontaneous preterm birth in both singletons and twins.

Abbreviations: BMI, body mass index; SD, standard deviation.

Over the previous two decades, the prevalence of obesity (body mass index (BMI): >30) has doubled, while that of morbid or extreme obesity (BMI: ≥40) has quadrupled (1, 2). The area of reproductive health is one domain where the burden of the obesity epidemic is strongly felt. Obesity has been associated with a myriad of adverse pregnancy outcomes including birth defects, fetal death, miscarriages, fetal macrosomia and shoulder dystocia, and increased rates of cesarean births, preeclampsia, and gestational diabetes (3–11). An important adverse birth outcome for which the linkage to obesity has been inconclusive is that of preterm birth. Although some investigators have reported no association between obesity and preterm birth (3, 4, 7, 9), others found reduced (5, 6, 8, 10, 12) or increased (5) risk of preterm birth. These conflicting results may be explained by the fact that preterm birth is a heterogeneous event, and any association of this outcome with maternal obesity may depend on the subtype of preterm being considered, as shown recently (13).

Another point that is noteworthy is that previous studies have considered the relation between obesity and preterm birth among singleton gestations only and, to our knowledge,
the impact of high body mass index on preterm delivery among twins has not been investigated. This is a domain that merits study, because the burden of preterm birth is considerably greater among twins than among singletons; about 50–60 percent of twins are delivered preterm (14) compared with an incidence of about 10 percent in singletons (15). Further, the epidemic of obesity in the United States has coincided to some extent with a sustained rise in the incidence of twins in the past two decades (16). Thus, it becomes logical and important to include twins in analyses that seek to delineate the impact of maternal obesity on preterm birth. Accordingly, we undertook this study to assess the association between maternal obesity and spontaneous and medically indicated preterm birth in singletons and twins.

MATERIALS AND METHODS

We utilized the Missouri maternally linked cohort data files covering the period from 1989 through 1997. In this data set, siblings are linked to their biologic mothers by use of unique identifiers. The methods and algorithm used in linking birth data into sibships and the process of validation have been described in detail previously (17). The Missouri vital records system is a reliable one that has been adopted as “gold standard” to validate US national data sets that involve matching and linking procedures (18).

For the purpose of this study, we selected livebirths for singletons and twins within the gestational age range of 20–44 weeks. Body mass index (weight (kg)/height (m)) was used to define maternal prepregnancy weight groups. Height, measured at the first prenatal visit, and prepregnancy weight, as reported at the first prenatal visit, were used to calculate prepregnant body mass index (19). On the basis of previously published reports (20, 21), we assigned women to the following body mass index-based categories: 18.5–24.9 (normal), 30.0–34.9 (class I obesity), 35.0–39.9 (class 2 obesity), and ≥40 (morbid/extreme or class 3 obesity). In a subanalysis, we defined weight gain during pregnancy as weight gained in kilograms divided by the gestational age in weeks. We then categorized the rates into five groups across body mass index classes: <0.12 kg/week (very low), 0.12–0.22 kg/week (low), 0.23–0.68 kg/week (moderate), 0.69–0.79 kg/week (high), and ≥0.79 kg/week (very high) (22). We used mothers with normal weight and moderate weight gain during pregnancy as referent.

The main outcome of interest was preterm birth at less than 37 weeks and very preterm birth at less than 33 weeks among singleton and twin gestations. Gestational age was based largely on the interval between the last menstrual period and the date of delivery of the baby (95 percent of cases). When the menstrual estimate of gestational age was inconsistent with the birth weight (e.g., very low birth weight at term), a clinical estimate of gestational age based on the vital records was used instead (23, 24).

We examined preterm births on the basis of two clinical subtypes: spontaneous and medically indicated preterm births. Because the data did not denote whether women experienced labor, we therefore considered labor to have been present if the birth record contained the presence of one or more of the following, as we previously reported (15): vaginal birth without an induction of labor; tocolysis; cephalopelvic disproportion; precipitated, prolonged, or dysfunctional labor; or vaginal birth after cesarean. If labor was present and if the women delivered preterm, then we classified that preterm birth as spontaneous. Additionally, if women experienced premature rupture of membranes, they were also combined with the spontaneous labor group. We then defined a medically indicated preterm birth as one that required either an induction of labor or prelabor cesarean or both.

The distribution of the following selected maternal sociodemographic characteristics was compared between obese and nonobese mothers to assess differences in baseline characteristics: maternal age, parity, race, education, marital status, smoking habits, and adequacy of prenatal care. Adequacy of prenatal care was assessed by use of the revised graduated index algorithm, which has been found to be more accurate than several others, especially in describing the level of prenatal care utilization among groups that are high risk (25, 26). This index assesses the adequacy of care on the basis of the trimester when prenatal care began, the number of visits, and the gestational age of the infant at birth. In this study, inadequate prenatal care utilization refers to women who had missing prenatal care information, who had prenatal care but the level was considered suboptimal, or who had no prenatal care at all. We performed crude frequency comparisons between the two groups for the presence of common obstetric complications, namely, anemia, insulin-dependent diabetes mellitus, other types of diabetes mellitus, chronic hypertension, preeclampsia, eclampsia, abruptio placenta, and placenta previa.

Regarding statistical analysis, the chi-square test was used to determine differences in sociodemographic characteristics and maternal pregnancy complications between the two groups (obese/nonobese). We used logistic regression models to generate adjusted odd ratios and their 95 percent confidence intervals. The covariates included in our model are maternal age, maternal education, marital status, maternal race, maternal prenatal smoking, adequacy of prenatal care, weight gain during pregnancy, maternal height, gender of the infant, and year of birth. Adjusted estimates were derived in all cases by using normal-weight gravidas (BMI: 18.5–24.9) as the referent category. Because the inclusion of interaction terms did not improve model fit, we retained the model without interaction terms.

Because the data set contained siblings of successive pregnancies as well as twins, we estimated regression parameters by taking into account the presence of intracluster correlation using the methodology of generalized estimating equations (27). We constructed the regression models and assessed their goodness of fit using the −2 log likelihood ratio test. We estimated the significance of main effects by means of the Wald test and assessed dose response using the chi-square test for linear trend (28).

All tests of hypothesis were two tailed with a type 1 error rate fixed at 5 percent. SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina) was used to perform all analyses. This study was approved by the Office of the Institutional Review Board at the University of South Florida.

RESULTS

Our analysis covered the years from 1989 through 1997, a period for which information on maternal pregnancy complications was routinely documented on birth certificates in the United States. A total of 686,834 singleton births were available for analysis. We excluded pregnancies before 20 weeks or beyond 44 weeks of gestation (31,517 pregnancies or 4.6 percent) and records for which body mass index could not be computed because of either missing or implausible values (17,980 pregnancies or 2.7 percent). The data set was also limited to the records for 80,236 obese mothers (17.5 percent) and nonobese mothers (the referent group comprising normal-weight gravidas only), totaling 459,913 singleton records. For twins, we had 18,770 individual records for analysis. By application of the same aforementioned exclusion criteria to twins, a total of 12,899 twin individuals were included in the final analysis, of which 2,748 (21.3 percent) were obese. The excluded cases among singletons were more likely to be Black, of lower educational status, and unmarried and to have smoked during pregnancy. Similar findings were observed for twins. The prevalence of obesity increased by 77 percent over the study period (from 12.3 percent at baseline to 21.8 percent at the end of the study period) (p<0.001).

Table 1 shows the comparison of obese and nonobese mothers with respect to selected sociodemographic characteristics. Obese gravidas giving birth to singletons were more likely to be older, multiparous, and Black and more likely to have received adequate prenatal care than were nonobese gravidas. Obese mothers were also slightly more educated than were their nonobese counterparts. However, obese mothers were less likely to be married and to be smokers during pregnancy. Similar results were obtained for mothers with twin gestation with the following exception: Nonobese mothers of twins were older and more likely to have received adequate prenatal care during pregnancy than were obese gravidas. Obese and nonobese mothers of twins had equivalent levels of educational attainment.

Table 2 displays the prevalence of common medical and obstetric complications among mothers in the study. Medical complications traditionally known to be associated with high body mass index were documented in greater frequency among obese mothers with singleton births. Of the obstetric complications, preeclampsia and eclampsia were more common among obese mothers, while placental abruption and placenta previa were slightly higher in nonobese mothers. The prevalence of anemia was also slightly more likely among nonobese mothers. Similar differences between the two groups of mothers were noted among twin births with the following exception: The levels of eclampsia and placenta previa were equivalent for both maternal categories among twin births.

Singleton infants born to obese mothers had a slightly greater mean gestational age than did their counterparts (mean = 39.1 weeks, standard deviation (SD): 2.4) born to nonobese mothers (mean = 39.0 weeks, SD: 2.5) (p < 0.01). Obese mothers were also found to have a higher mean birth weight (3.467 g, SD: 628) than nonobese mothers had (3.350 g, SD: 562) (p < 0.01). Similar differences were also noted in twins.

Among singleton births, 44,340 (9.6 percent) infants were born preterm, of which 36,203 (81.7 percent) were classifiable as spontaneous preterm births while the remaining 8,137 (18.3 percent) were medically indicated preterm deliveries. There were 7,066 (54.8 percent) twins born at less than 37 weeks of gestation. Of these, 4,630 (65.5 percent) were spontaneous preterm births, while 2,436 (34.5 percent) were medically indicated preterm births. Among singleton births, 8,427 (1.8 percent) were born very preterm. Of these, 1,927 (22.9 percent) were medically indicated, while 6,500 (77.1 percent) were spontaneous. For twin births, 2,029 (15.7 percent) were born very preterm. Of these, 582 (28.7 percent) were medically indicated, while 1,447 (71.3 percent) were spontaneous.

In table 3, we present the results of the association between obesity severity and the risk of preterm and very preterm births by obesity subtype. For spontaneous preterm

<table>
<thead>
<tr>
<th>Complication</th>
<th>Singletons</th>
<th>Twins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obese (n = 80,236)</td>
<td>Nonobese (n = 379,677)</td>
</tr>
<tr>
<td>Anemia, yes</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Insulin-dependent diabetes, yes</td>
<td>488</td>
<td>0.6</td>
</tr>
<tr>
<td>Other forms of diabetes, yes</td>
<td>6,734</td>
<td>8.4</td>
</tr>
<tr>
<td>Chronic hypertension, yes</td>
<td>148</td>
<td>0.2</td>
</tr>
<tr>
<td>Eclampsia, yes</td>
<td>897</td>
<td>1.1</td>
</tr>
<tr>
<td>Placental abruption, yes</td>
<td>1,299</td>
<td>1.6</td>
</tr>
<tr>
<td>Chronic hypertension, yes</td>
<td>3,776</td>
<td>4.7</td>
</tr>
<tr>
<td>Other forms of diabetes, yes</td>
<td>2,387</td>
<td>3.0</td>
</tr>
<tr>
<td>Preeclampsia, yes</td>
<td>6,734</td>
<td>8.4</td>
</tr>
<tr>
<td>Placenta previa, yes</td>
<td>488</td>
<td>0.6</td>
</tr>
<tr>
<td>Placental abruption, yes</td>
<td>263</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* Adjusted estimates were generated after controlling for the effects of maternal age, parity, race, smoking, education, marital status, adequacy of prenatal care, weight gain during pregnancy, maternal height, gender of the infant, and year of birth.

† Obesity subtype, body mass index (kg/m²): nonobese (18.5–24.9); obese (≥30); class I (30.0–34.9); class 2 (35.0–39.9); class 3 (≥40).

TABLE 3. Adjusted odds ratios* for spontaneous and medically indicated preterm singleton and twin births among gravidas by obesity subtype,† Missouri, 1989–1997

<table>
<thead>
<tr>
<th>Complication</th>
<th>Preterm births</th>
<th>Very preterm births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All preterm</td>
<td>Spontaneous preterm</td>
</tr>
<tr>
<td></td>
<td>Singletons (n = 44,340)</td>
<td>Twins (n = 7,066)</td>
</tr>
<tr>
<td>Anemia, yes</td>
<td>Nonobese</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Class 1</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Class 2</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>Class 3</td>
<td>0.98</td>
</tr>
</tbody>
</table>

* Adjusted estimates were generated after controlling for the effects of maternal age, parity, race, smoking, education, marital status, adequacy of prenatal care, weight gain during pregnancy, maternal height, gender of the infant, and year of birth.

† Obesity subtype, body mass index (kg/m²): nonobese (18.5–24.9); obese (≥30); class I (30.0–34.9); class 2 (35.0–39.9); class 3 (≥40).
indicated preterm birth with increasing severity of obesity ($p_{\text{trend}} < 0.01$). However, significant risk elevation for medically indicated very preterm birth among twins was observed for class 2 and class 3 obesity subtypes only.

For singleton births with medically indicated preterm delivery, 20 percent were diagnosed with preeclampsia, which was far more than the overall prevalence of preeclampsia in the study population (3.9 percent). Among obese mothers with medically indicated preterm delivery, about one third had a diagnosis of preeclampsia compared with a similar diagnosis among only 16 percent of nonobese mothers ($p < 0.01$). Among twin births, the overall prevalence of preeclampsia was 10.3 percent, with 24 percent versus 15 percent of medically indicated preterm births bearing the diagnosis of preeclampsia in obese and nonobese mothers, respectively. We further assessed whether the preponderance of preeclampsia could be the pathway that could explain the heightened risk for medically indicated preterm births among obese mothers. Introduction of the preeclampsia variable into the adjusted model caused a substantial drop in the point estimates for the association between obesity and obesity subclasses and medically indicated preterm and very preterm births, especially among singleton births (table 4). The findings for all preterm and spontaneous preterm births remained, however, unchanged.

The amount of weight gain during pregnancy could impact pregnancy outcome independently of the prepregnancy body mass index. We, therefore, examined the data for the association between spontaneous preterm births and body mass index categories stratified by maternal weight gain during pregnancy (table 5). Obesity was associated with a reduced risk of spontaneous preterm birth among women with low or moderate weight gain but not among women with high weight gain. Normal-weight mothers with very low pregnancy weight gain were at greatest risk of spontaneous preterm birth. Similar findings were observed for twin births.

**DISCUSSION**

In this study, we found an elevated risk of medically indicated preterm birth among obese mothers of both singletons and twins but a reduction in risk of spontaneous preterm birth. These contrasting findings suggest that preterm birth is a heterogeneous rather than a homogeneous entity. If we had limited our analysis to preterm birth as an overall and homogeneous diagnosis, our findings would have masked the elevated risk for medically indicated preterm birth associated with obesity. Both findings are in tandem with the results of a recent population-based study conducted among
singleton births in Scotland (13) but differ from other findings (5). The observation of risk reduction for spontaneous preterm birth in obese women is also in agreement with that of another study performed in the United States in 10 medical centers under the umbrella of the Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development (29).

When we further stratified obese and normal-weight mothers according to the rate of weight gain during pregnancy, we observed that the decrease in adjusted risk for preterm delivery among obese mothers was restricted to those with a weight gain of less than 0.69 kg/week for singletons and between 0.23 and 0.69 kg/week for twins. This finding is noteworthy because, to our knowledge, it is the first time that a specific optimal rate of weight gain during pregnancy in relation to risk reduction for spontaneous preterm birth among obese mothers has been clearly defined for both singletons and twins. This has important implications in terms of policy recommendations and nutritional intervention for obese mothers with singleton or twin gestations.

Some hypotheses have been suggested to explain the risk reduction for spontaneous preterm birth among obese mothers. Obese women are reported to have, on average, a longer cervix than do nonobese women in diverse populations (29, 30), and this could explain the lower rate of spontaneous preterm birth with an increase in body mass index. Another explanation is the role of malnutrition in inducing spontaneous preterm delivery. Noggers eand Goldenberg (31) have found decreased intakes of calories, proteins, vitamins, and minerals, which are frequently associated with thin women or low body mass index, to be a likely factor in the genesis of spontaneous preterm birth. This could explain our findings of reduced risk for spontaneous preterm birth with ascending body mass index.

Maternal obesity has been consistently shown to be a risk factor for preeclampsia (32). Similar pathologic features of oxidative stress, inflammation, and altered vascular function have been reported in both preeclamptic women and obese women (32), lending credence to the existence of a common pathway linking the two conditions. In nulliparous and multiparous women with singleton gestations and a high body mass index (e.g., >35) who had undergone an indicated preterm delivery, 40.2 percent and 18.0 percent, respectively, were concomitantly diagnosed with preeclampsia (13). This yields an unweighted average prevalence of preeclampsia of around 30 percent and is considerably greater than the overall prevalence of preeclampsia in the entire studied population (2.6 percent). This is concordant with our findings among singletons. We further assessed the mediating role of preeclampsia among the participants in our study. Our results provide evidence that the excess risk for medically indicated preterm and very preterm births among women with high body mass index levels was, to a substantial degree, mediated via preeclampsia.

Unique in our analysis is the inclusion of twin births, a population that is more susceptible to prematurity than singletons. The consistent findings among singletons and twins may be suggestive of a common causality pathway for the relation between high body mass index and spontaneous and medically indicated preterm birth in both singleton and twin gestations. An implication of these results for practice is that counseling for obese women regarding risk for preterm birth need not be modified on the basis of fetal number. We were, however, unable to provide maternal obesity-associated risk estimates stratified by zygosity, because information on this variable is not available in the data set, an important limitation for our analysis on twin births. Nevertheless, our findings on twins are unique and should be regarded as an impetus for further and more refined studies in this direction.

Our study depended on self-report of prepregnancy body weight, and the validity of the computed body mass index as an accurate estimate of the true population prevalence of obesity over the long period covered by the study may be in question. However, the observed prevalence of obesity in this study (17.5 percent in singletons and 21.3 percent in twins) is comparable to the 20.5 percent prevalence noted in a recent multicenter study covering 10 medical centers under the umbrella of the Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development (29).

### TABLE 5. Adjusted odds ratios* for spontaneous preterm births among mothers giving birth to singletons and twins by obesity status and weight gain during pregnancy, Missouri, 1989–1997†

<table>
<thead>
<tr>
<th>Weight gain in pregnancy (kg/week)</th>
<th>Singleton (n = 30,505)</th>
<th>Obese (n = 5,698)</th>
<th>Twin (n = 811)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted odds ratio</td>
<td>95% confidence interval</td>
<td>Adjusted odds ratio</td>
</tr>
<tr>
<td>&lt;0.12</td>
<td>1.98</td>
<td>1.83, 2.14</td>
<td>0.89</td>
</tr>
<tr>
<td>0.12–0.22</td>
<td>1.09</td>
<td>1.08, 1.10</td>
<td>0.96</td>
</tr>
<tr>
<td>0.23–0.68</td>
<td>1.0</td>
<td>Referent</td>
<td>0.94</td>
</tr>
<tr>
<td>0.69–0.79</td>
<td>1.01</td>
<td>1.00, 1.02</td>
<td>0.96</td>
</tr>
<tr>
<td>&gt;0.79</td>
<td>1.03</td>
<td>1.00, 1.03</td>
<td>1.07</td>
</tr>
</tbody>
</table>

* Adjusted estimates were generated after taking into account the confounding effects of maternal age, parity, race, smoking, education, marital status, adequacy of prenatal care, gender of the infant, and year of birth.
† n = total number of spontaneous preterm births.
Network of the National Institute of Child Health and Human Development (29). This is further evidence of the validity of our findings.

In the majority of cases, gestational age derived from the last menstrual period was used in classifying preterm status in our study. Errors in recall regarding the last menstrual period may induce some misclassification bias that is more likely to be nondifferential, because it is improbable that obese mothers will recall their last menstrual period in a pattern different from nonobese gravidas. Hence, the misclassification induced will be nondifferential, shifting our estimates toward the null.

Similarly, clinical indicators (e.g., tocolysis, cephalopelvic disproportion, prolonged or dysfunctional labor, and so on) used in classifying medically indicated preterm birth may be incompletely reported on the birth certificate, and it is logical that the resulting misclassification bias will also be nondifferential because there is no reason to believe that underreporting of these clinical indices will discriminate against the body mass index status of the mother. Consequently, it is likely that the estimates being reported for both singletons and twins in this study represent underestimates.

In summary, we found obesity to be a risk factor for medically indicated but not spontaneous preterm birth in both singletons and twins. Although interventions that aim to reduce maternal obesity preconceptionally may potentially impact medically indicated preterm birth, such interventions may not necessarily be effective in reducing spontaneous preterm delivery.

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Conflict of interest: none declared.

REFERENCES

17. Herman AA, McCarthy BJ, Bakewell JM, et al. Data linkage methods used in maternally-linked birth and infant death surveillance data sets from the United States (Georgia, Missouri, Utah and Washington State), Israel, Norway, Scotland and Western Australia. Paediatr Perinat Epidemiol 1997;11(suppl 1):5–22.


