Association of Maternal Hypoglycemia With Low Birth Weight and Low Placental Weight: A Retrospective Investigation

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Context: The effects of maternal hypoglycemia on birth weight, placental weight, and placental ratio are unclear. A reliable indicator for increased risk of low birth weight or associated low placental weight could prove invaluable in caring for newborns who are small for gestational age.

Objective: To retrospectively review 2 years of hospital obstetric records for evidence of an association between maternal hypoglycemia (< fifth percentile at 24-week 1-hour glucose challenge test) and birth weight, placental weight, or placental ratio.

Methods: Medical center records were reviewed for women who delivered a term newborn between July 1, 2005, and July 31, 2007. Women included in the study were younger than 35 years and had completed a 1-hour glucose challenge test during pregnancy. Excluded were women with comorbid conditions that may be associated with abnormal birth weight and women with serum glucose levels greater than 135 mg/dL.

Results: Newborns of women with hypoglycemia weighed, on average, significantly less than newborns of women with normal blood glucose levels ($t$ test $P=.011$). Relative risk was 5.81 (95% confidence interval, 1.25-27.03). Placentas of women with hypoglycemia were also lighter than those of the women in the control group, but the difference was not significant ($t$ test $P=.1089$). Differences in placental ratios between the 2 groups were not statistically significant ($P=.8171$).

Conclusion: Lower serum glucose levels during pregnancy might be a causative factor, rather than merely a risk factor, for lower birth weights. (ClinicalTrials.gov number NCT00614094)

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During pregnancy, rising estrogen levels stimulate insulin production by the pancreas beta cells, causing changes in glucose metabolism. As the fetus draws on maternal fat stores, ketosis can develop and lead to hypoglycemia, particularly during periods of fasting.1

Several studies have addressed the possible effects of maternal hypoglycemia on birth weight, placental weight, or placental ratio (ratio of placental weight to birth weight). The most common finding is that maternal hypoglycemia is associated with an increased risk of intrauterine growth retardation (IUGR) or a small for gestational age (SGA) newborn.2-8 However, some reports have contradicted that association.9-11 Although few studies have examined a potential association between maternal hypoglycemia and altered placental weight or placental ratio,12 reports of some studies have indicated an association between SGA newborns and increased placental weight or placental ratio.13-14 Other studies, however, have found just the opposite.15,16

Confounding the interpretation of data on the effects of maternal hypoglycemia are variability in values used to define hypoglycemia, timing of serum glucose measurement (ie, whether it was measured at 1 hour or 3 hours after administration of oral glucose solution), and consideration of comorbid factors such as smoking or drug abuse, which in themselves would help to explain SGA newborns.2,5

In short, the effects of maternal hypoglycemia on birth weight, placental weight, and placental ratio are still unclear. However, a reliable indicator for increased risk of low birth weight or associated low placental weight could prove invaluable in light of outcomes for SGA newborns. In addition to being at increased risk for hypoglycemia, sepsis, seizure, stillbirth, respiratory distress, and meconium aspiration, SGA newborns are at risk for long-term outcomes such as poor school performance, hyperactivity, hypertension, and cardiovascular disease.17,18
The purpose of the present retrospective study was to assess whether maternal hypoglycemia is a contributing cause of decreased birth weight, altered placental weight, or altered placental ratio.

**Methods**

For the present retrospective study, we examined obstetric records of women who delivered a term newborn (ie, ≥37 weeks gestation) at Oklahoma State University Medical Center between July 1, 2005, and July 31, 2007. Women included in the study were typically patients of a resident clinic located in a low-income, urban setting. The study was registered with ClinicalTrials.gov (number NCT00614094) and approved by the Oklahoma State University Center for Health Sciences Institutional Review Board. Patient confidentiality was closely guarded.

Included in the study were women who were younger than 35 years and who had completed a 1-hour screening glucose challenge test, typically given at the first prenatal appointment between 24 weeks and 28 weeks gestation. This test was chosen because it is the only oral glucose tolerance test that we recorded in patient charts. Excluded were women with comorbid conditions that may be associated with abnormal birth weight (Figure) and women with serum glucose levels greater than 135 mg/dL. The value of the upper range cutoff was chosen to avoid an artificial increase in the birth weight of newborns in the control group, because test results more than 135 mg/dL are considered positive for gestational diabetes.

At clinics associated with Oklahoma State University Center for Health Sciences, 100 g of Glucola is routinely administered orally for the glucose challenge test at 24 weeks gestation or after; gestation is calculated on the basis of the last menstrual period and findings at ultrasonography. Patients are instructed not to eat anything for 2 or 3 hours prior to the test; beverages are limited to water, coffee, or unsweetened tea. The test can be performed at any time of day. Blood is drawn 1 hour after the Glucola is administered for a serum glucose measurement. Maternal hypoglycemia was defined as a serum glucose level less than or equal to 88 mg/dL, equal to a range in the fifth percentile or less.2.9,10 Women in the control group had a 1-hour serum glucose result greater than 88 mg/dL and less than 136 mg/dL.

Data collected for each patient included age, date of delivery, newborn birth weight, result of 1-hour screening glucose challenge test, placental weight, and any of the formerly mentioned exclusion criteria.

**Statistical Analysis**

All statistical analyses were conducted with the use of PC SAS statistical software (Version 9.1; SAS Institute Inc, Cary, North Carolina). Both the relationship of birth weight to maternal hypoglycemia and the relationship of placental weight to maternal hypoglycemia were investigated with 2 different statistical procedures: a t test and a contingency table. The placental ratio was analyzed by a t test but not with a Fisher exact test. The contingency table and Fisher exact test required categorization of all variables. Although it is known that a normal placental ratio is 1:6, or 0.167,19 reference ranges are not yet well established, so each woman’s placental ratio could not be objectively labeled as “normal” or “not normal.”

For t test analysis, birth weight and placental weight were defined according to continuous and meaningful numeric values rather than categories such as “low,” “normal,” or “high.” These values were used to determine whether statistically significant differences existed between the study group (ie, women with hypoglycemia) and the control group (ie,
women with normal blood glucose levels) with regard to the mean birth weight, the mean placental weight, and the mean placental ratio.

Categories for birth weight included “SGA” and “not SGA.” For analysis, SGA was defined as birth weight below the 10th percentile for gestational age.20,21 In the majority of cases, gestational age was confirmed with first trimester ultrasonography. Most women included in this study underwent ultrasonography before 20 weeks gestation, making the recorded gestational ages of the newborns reliable and accurate. To compare the birth weight category (ie, “SGA” vs “not SGA”) with the maternal hypoglycemia category (ie, study group vs control group), a contingency table was constructed. Because the sample number for births was relatively small, a Fisher exact test was used to assess the relationship.

The weight of small placenta was also categorized as less than the 10th percentile for gestational age.21 Like the birth weight analysis, the placental weight category (ie, “low” vs “normal”) and the maternal hypoglycemia category (ie, study group vs control group) were compared using a contingency table, and a Fisher exact test was used to assess the relationship.

As was previously explained, no contingency table was created for placental ratio.

Table 1. Fisher Exact Test Analysis of Birth Weight, Placental Weight, and Placental Ratio in Newborns of Women With Hypoglycemia and Women With Normal Blood Glucose Levels (N=157)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Mean (SD)</th>
<th>Placental Weight to Birth Weight Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Birth</td>
<td>Placental Weight</td>
</tr>
<tr>
<td></td>
<td>Weight, g</td>
<td>Weight, g</td>
</tr>
<tr>
<td>Women With Hypoglycemia,*</td>
<td>3483 (39.6)</td>
<td>607 (12.6)</td>
</tr>
<tr>
<td>(n=59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women With Normal Blood</td>
<td>3303 (56.4)</td>
<td>574 (16.6)</td>
</tr>
<tr>
<td>Glucose Levels,*†</td>
<td>(n=98)</td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>.011</td>
<td>.109</td>
</tr>
</tbody>
</table>

*Serum glucose level < 88 mg/dL
†Serum glucose level > 88 mg/dL and < 136 mg/dL.

Table 2. Fisher Exact Test Analysis of Placental Weight and Birth Weight of Newborns of Women With Hypoglycemia and Women With Normal Blood Glucose Levels (N=157)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Placental Weight</th>
<th>Birth Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low*</td>
<td>Not Low</td>
</tr>
<tr>
<td>Women With Hypoglycemia*</td>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td>Women With Normal Blood</td>
<td>3</td>
<td>95</td>
</tr>
<tr>
<td>Glucose Levels*†</td>
<td>.4265</td>
<td>.0271</td>
</tr>
<tr>
<td>P Value</td>
<td>.8171</td>
<td></td>
</tr>
</tbody>
</table>

*Less than the 10th percentile for gestational age
†Serum glucose level > 88 mg/dL and < 136 mg/dL.

Results

One hundred fifty-seven records met the inclusion criteria. Sixty women were younger than 20 years, 87 women were aged 20 years to 29 years, and 10 women were aged 30 years to 34 years. The mean age was 21.75 years. Fifty-nine women (37.6%) had maternal hypoglycemia on the basis of findings from their prenatal glucose challenge test (serum glucose level <88 mg/dL) (ie, the study group), and 98 women (62.4%) had normal blood glucose levels (serum glucose level >88 mg/dL and <136 mg/dL) (ie, the control group).

The results of the t tests revealed that mothers with hypoglycemia were significantly more likely than mothers with normal blood glucose levels to have newborns that were SGA (P=.011 (Table 1). Conversely, mothers with hypoglycemia had lighter placentas than mothers with normal blood glucose levels, but the difference did not reach statistical significance (P=.1089) (Table 1). The difference between the 2 groups’ placental ratios was also not statistically significant (P=.8171) (Table 1).

Results of the contingency tables identified 9 newborns with birth weights that could be labeled SGA according to the standards in the present study. Because of the small number of newborns identified as SGA, a Fisher exact test rather than a χ² test was used to make comparisons. The 2-tailed P value from the Fisher exact test was .0271 (Table 2). The percentage of newborns with low birth weight in the study group was 11.9%, which was almost 6 times greater than that of the control group (2.0%). Women with hypoglycemia had a relative risk of 5.81 (95% confidence interval, 1.25-27.03) for having a low–birth weight newborn.

The contingency table results also revealed 7 low-weight placentas. Again, due to the low number of low-weight placentas in the study, a Fisher exact test rather than a χ² test was used to make comparisons. The 2-tailed P value from the Fisher exact test was .4265 (Table 2). The percentage of women with low placental weights in the study group was 6.78%, which was more than twice than that for the control group (3.06%). This difference was not statistically significant, however. Women with hypoglycemia had a relative risk of 5.81 (95% confidence interval, 0.51-9.55) for having a low-weight placaenta. The relative risk ratio was not statistically significant. For the t tests performed, the sample sizes were powerful enough to detect a departure from the baseline of 1 standard deviation with 99% likelihood.
Comment

The present data agree with data from other studies that have found a relationship between low birth weight and maternal hypoglycemia.2,3 Although our birth weight results agreed with results in the majority of former reports we reviewed on the subject,2,3 these previous studies did not typically control for other factors that are known to be associated with SGA newborns. Some of the former studies based their findings of hypoglycemia on serum glucose measurements taken 3 hours after oral glucose intake,2,5,8 rather than 1 hour after intake, as we did. Other studies found no statistically significant association between hypoglycemia and SGA newborns,6,11 and 2 of those reports did control for such SGA-associated conditions as preterm birth, hypertension, smoking, and drug abuse.9,11 The present data suggest that maternal hypoglycemia could be a causative agent, lending support to an unsubstantiated previous claim.2

It should be noted, however, that some unknown third factor could also be the cause of both SGA newborns and hypoglycemia. In addition, SGA newborns and hypoglycemia could be merely coincidental. For these reasons, causality cannot be established with certainty.

Some past studies have noted a relationship between SGA newborns or IUGR and increased placental weight or placental ratio,13,14 which the authors presumed was due to placental attempts to compensate for low nutrient uptake by the fetus. However, one study15 reported just the opposite: SGA newborns had placentas that were 45% smaller than the control patients. Nevertheless, this particular relationship was not the focus of our study, and a possible association with hypoglycemia was not considered or discussed in any of those articles.3

Studies that actually examine placental weight in relation to maternal hypoglycemia, rather than only SGA or IUGR, are scant. Aldoretta et al12 found that hypoglycemic sheep mothers had lighter placentas than control sheep. The $t$ test $P$ value of our work appears to trend toward agreement with the $P$ value obtained by Aldoretta et al. The accepted value for a normal placental ratio is about 1.6, or 0.167.19 The ratios of both the mothers with hypoglycemia and the mothers with normal blood glucose levels in the present study were very close to that value at 0.17. Consequently, due to low sample size—even though the $P$ value of the $t$ test was close to statistical significance—it seems unlikely that repeated tests would reveal a lower value, particularly in light of the fact that the $t$ test result was not corroborated by a near statistically significant $P$ value in the Fisher exact test.

Just as hyperglycemia is associated with larger birth weight newborns, hypoglycemia might hinder fat-storing or growth-promoting aspects of the fetus’ environment, which could result in smaller birth weight newborns.5,6 Further, the same mechanism that results in an SGA infant might also be responsible for a smaller placenta. A good follow-up study might have larger numbers of patients and a more stringent definition of hypoglycemia. The present study included too few women whose serum glucose levels were below 60 to make the study group any more exclusive than less than or equal to the fifth percentile. This less rigorous definition of hypoglycemia corresponded to the protocol of some previous research2,8,10 and strengthens our conclusions about the relationship between maternal hypoglycemia and low birth weight.
Conclusion
Our results support a cause-and-effect relationship between maternal hypoglycemia and low birth weight. The present findings impact clinical practice because newborns with SGA could be at risk for a host of difficulties later in life.18,19 Advance notice of heightened risk for maternal hypoglycemia by means of the prenatal glucose challenge test could be a valuable tool for physicians. Physicians could counsel their patients to moderate the condition with diet or search for other ways by which it might be effectively controlled. A firm establishment of maternal hypoglycemia as a cause of SGA or IUGR would raise the important question of whether prenatal intervention for maternal hypoglycemia by means of screening could lead to decreased health risks for the child later in life. If so, hypoglycemia may become as closely moderated in the prenatal period as hyperglycemia.

Acknowledgments
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References