Impact of Preeclampsia and Gestational Hypertension on Birth Weight by Gestational Age

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The predominant etiologic theory of preeclampsia is that reduced uteroplacental perfusion is the unique pathogenic process in the development of preeclampsia. Decreased uteroplacental blood flow would result in lower birth weights. To date, no study has assessed the effect of preeclampsia on birth weight by gestational age. Thus, the authors conducted a retrospective cohort study based on 97,270 pregnancies that resulted in delivery between 1991 and 1996 at 35 hospitals in northern and central Alberta, Canada. Differences in mean birth weight between women with preeclampsia and normotensive women ranged from –547.5 g to 239.5 g for gestational age categories ranging from ≤32 weeks to ≥42 weeks. The birth weights were statistically significantly lower among mothers with preeclampsia who delivered at ≤37 weeks, with an average difference of –352.5 g. However, the birth weights were not lower among preeclamptic mothers who delivered after 37 weeks (average difference of 49.0 g). In Alberta, 61.2% of preeclamptic patients gave birth after 37 weeks of gestation. The authors conclude that babies born to mothers with preeclampsia at term have fetal growth similar to that of babies born to normotensive mothers. This finding does not endorse the currently held theory that reduced uteroplacental perfusion is the unique pathophysiologic process in preeclampsia. Am J Epidemiol 2002;155:203–9.

birth weight; gestational age; hypertension; pre-eclampsia; pregnancy

Hypertensive disorders in pregnancy, especially preeclampsia, remain a major cause of maternal and infant morbidity and mortality worldwide (1). Despite numerous basic, clinical, and epidemiologic studies that have been conducted over the past half-century, knowledge of the etiology and pathogenesis of preeclampsia remains elusive (2). Because the pathophysiology of preeclampsia has not yet been elucidated, clinical trials have failed to demonstrate any effective prevention or treatment strategies, apart from early delivery in cases where the disorder is severe (2, 3).

A prevailing hypothesis regarding the pathogenesis of preeclampsia is the “ischemic model.” Decreased uteroplacental perfusion is hypothesized to be the primary step and the point of convergence of diverse pathogenic processes in the development of preeclampsia (4–6). It is intuitive that reduced placental blood flow should result in decreased fetal growth, with an increased risk of intrauterine growth restriction and low birth weight. However, epidemiologic studies have not conclusively established an association between preeclampsia or gestational hypertension and poor fetal growth (7).

Birth weight is determined by both duration of gestation and rate of fetal growth. Preeclampsia significantly increases the risk of iatrogenic preterm birth (delivery) for maternal indications. To study the effect of preeclampsia and gestational hypertension on fetal growth, it is important to compare the fetal growth of babies born to mothers with preeclampsia or gestational hypertension with that of babies born to mothers without these conditions at the same gestational ages. To our knowledge, no study to date has examined the impact of preeclampsia and gestational hypertension on mean birth weight by gestational week, and no previous study has examined whether the effect of preeclampsia or gestational hypertension on fetal growth differs according to gestational age. Using an existing perinatal database, we conducted a study to assess the effect of preeclampsia and gestational hypertension on fetal growth according to gestational age.

MATERIALS AND METHODS

Study population

The Northern and Central Alberta Perinatal Audit and Education Program commenced data collection in 1991 to monitor the impact of educational strategies designed to decrease the incidence of obstetric interventions (8, 9). The
database is derived directly from the standard labor and delivery record used in Alberta. Every effort is made to ensure accuracy of the data. Records received in paper format from participating hospitals are reviewed by an audit coordinator to check for discrepancies before being entered into the database by a data clerk. Data validation is performed at three levels: The registry is checked for missing or incomplete data; programmed computer checks and cross-tabulations are used to reduce the risk of typing errors; and an ongoing manual review of a random sample of charts is performed to check the accuracy of information. A minimum of one out of every 20 records is verified against the actual data entered.

Data included in this study were collected from 35 Alberta hospitals in which 97,270 deliveries occurred between July 1, 1991, and December 31, 1996. Women with the following characteristics were excluded from the analysis: multiple pregnancies (2,528 cases); preeclampsia (695 cases); gestational diabetes (2,456 cases); cardiovascular disease (546 cases); and chronic renal disease (102 cases). Women who had had transient hypertension during labor but had experienced no hypertension during pregnancy were also excluded (809 cases). These conditions were excluded mainly because they are potentially confounding variables known to be associated with both preeclampsia or gestational hypertension and birth weight. After exclusion of an additional 1,375 cases with missing antenatal information, 87,798 pregnancies remained for the analysis.

Definition of exposure and outcome

The Northern and Central Alberta Perinatal Audit and Education Program defines gestational hypertension (8, 9) as a blood pressure of ≥140/90 mmHg without or with proteinuria of no greater than trace levels after 20 weeks of gestation. Preeclampsia is defined as a blood pressure of ≥140/90 mmHg with proteinuria of 1+ on dipstick in two samples taken 6 hours apart, or >0.3 g in a 24-hour urine collection. Eclampsia is diagnosed when convulsions occur in a woman with preeclampsia. Because we restricted our focus to gestational hypertension and preeclampsia, pregnancies complicated by chronic hypertension and preeclampsia superimposed on chronic hypertension were not studied.

Birth weight was measured shortly after delivery. Gestational age was based on the last menstrual period, confirmed by early pelvic examination, and verified by first-trimester or early second-trimester ultrasound when available. If the date of the last menstrual period was not thought to be accurate, gestational age was based solely on the first-trimester or early second-trimester ultrasound findings.

Definition of potentially confounding variables

Potentially confounding variables were selected on the basis of our review of the literature and the biologic plausibility of an association with both exposure and outcome. The potentially confounding variables included in the analysis were maternal smoking, maternal age, parity, obesity (maternal prepregnancy weight ≥91 kg), maternal prepregnancy weight ≤45 kg, prior spontaneous and induced abortion, prior small-for-gestational-age (SGA) newborn, prior large-for-gestational-age (LGA) newborn, anemia, and premature rupture of membranes.

Statistical analysis

Analysis of variance was performed to compare mean birth weights by gestational week between women with gestational hypertension or preeclampsia and normotensive women. Post hoc pairwise multiple comparisons that assessed which specific mean values differed significantly from the others were performed using Tukey and Bonferroni procedures (10). To adjust for confounding effects, we applied multiple linear regression using birth weight as the dependent variable and preeclampsia (preeclampsia = 1, normotensive = 0), gestational hypertension (gestational hypertension = 1, normotensive = 0), and other confounding variables as the independent variables. The regression (β) coefficients for preeclampsia, gestational hypertension, and other variables were estimated by the method of least squares (10, 11). For example, the β coefficient for the variable “preeclampsia” represents the average change in birth weight (g) associated with a change from preeclampsia (code 1) to normotensive status (code 0) adjusted for all other variables included in the regression (10). Finally, we also analyzed the impact of preeclampsia and gestational hypertension on birth weight by gestational age by separating nulliparous and multiparous women to examine whether the effect differed by parity. The statistical significance (p value) of the β coefficients was also tested by t test; the p value was two-tailed, and 0.05 was the critical alpha level. All statistical analyses were performed with SPSS 10.0 for Windows (SPSS, Inc., Chicago, Illinois).

RESULTS

The initial population in the database consisted of 97,270 women. Table 1 shows the characteristics of the study population before exclusions. Overall, 8.2 percent of the women were teenagers and 37.4 percent were over 30 years old; 40.5 percent were nulliparous, and 26.6 percent smoked during pregnancy. The incidences of gestational hypertension, preeclampsia, and chronic hypertension were 3.9 percent, 1.7 percent, and 0.9 percent, respectively. The incidences of preterm birth, low birth weight, and stillbirth were 9.0 percent, 6.9 percent, and 0.3 percent, respectively.

Figure 1 and table 2 show the impact of gestational hypertension and preeclampsia on birth weight by gestational age. Babies born to women at gestational ages ≤32 weeks were pooled, as were those born at gestational ages ≥42 weeks, producing categories of sufficient sample size to allow meaningful comparisons. With respect to the gestational age categories from ≤32 weeks to ≥42 weeks, differences in mean birth weight between the gestational hypertension and normotensive groups ranged from −434.2 g to 55.1 g. For
women delivering before 37 weeks, birth weights were statistically significantly lower among women with gestational hypertension than among women with normal blood pressure. However, for women delivering at ≥37 weeks, the birth weights were generally higher among women with gestational hypertension than among women with normal blood pressure. After adjustment for confounding factors, for women delivering before 37 weeks, birth weights remained significantly lower among babies born to women with gestational hypertension than among babies born to women with normal blood pressure (β < 0, p < 0.01). For women delivering at ≥37 weeks, there was no statistically significant difference in mean birth weights between women with gestational hypertension and normal blood pressure.

The differences in mean birth weight between the preeclamptic and normotensive groups ranged from −547.5 g to 239.5 g. For women delivering at ≤37 weeks, birth weights were statistically significantly lower among women with preeclampsia than among women with normal blood pressure, both prior to and after adjustment for confounding variables (β < 0, p < 0.01). The average unadjusted birth weight difference at ≤37 weeks was −352.5 g. However, for women delivering after 37 weeks, the differences in mean birth weights between women with preeclampsia and women with normal blood pressure were not statistically significant. In fact, mean birth weights were higher among women with preeclampsia than among women with normal blood pressure at 41 and ≥42 weeks, but the differences were not statistically significant (β > 0, p > 0.05). The average unadjusted birth weight difference after 37 weeks was 49.0 g.

In Alberta, 38.8 percent of women with preeclampsia gave birth at 37 weeks or less, and 61.2 percent gave birth after 37 weeks.

Table 3 shows the results of multivariable analyses of the impact of preeclampsia and gestational hypertension on birth weight by gestational age among nulliparous and multiparous women separately. There was no significant difference in the effect of preeclampsia and gestational hypertension on birth weight between nulliparous and multiparous women. However, in the upper gestational age categories (41 and ≥42 weeks), the effects pointed in different directions.

**DISCUSSION**

To our knowledge, no previous study has examined the effect of preeclampsia and gestational hypertension on mean birth weight by gestational week. These results contrast with our previous findings, in which, on the basis of the same data, we observed that the overall mean birth weight was markedly lower among babies born to mothers with preeclampsia than among babies born to normotensive mothers (8). In the present study, 61.2 percent of babies born to mothers with preeclampsia were delivered after 37 weeks. When we compared the birth weight of babies born to mothers with preeclampsia after 37 weeks to that of babies born to normotensive mothers at the same gestational age, there was no statistically significant difference. Thus, most babies born to mothers with preeclampsia at term actually have normal birth weight for their expected gestational age. The effect of gestational hypertension on birth weight by gestational age was similar to that of preeclampsia.

This study demonstrates that the effect of preeclampsia and gestational hypertension on birth weight is a function of gestational age. The effect of decreased birth weight is found mostly among preterm births. This may explain the contradictory findings of previous epidemiologic studies that have examined the relation between preeclampsia or gestational hypertension and birth weight (7, 8, 12). For example, we recently reported results from two separate studies of the effects of preeclampsia on birth weight (8, 12). These studies were carried out in separate populations. The first study, in which we found no difference in mean birth weight between
FIGURE 1. Impact of preeclampsia and gestational hypertension on birth weight (n = 87,798), Alberta, Canada, 1991–1996.

The finding that most babies born to preeclamptic women at term have normal fetal growth cannot be reconciled with the currently held belief that reduced uteroplacental perfusion is the unique pathophysiologic process in preeclampsia (4–6). There is increasing literature supporting the hypotheses of considerable pathophysiologic heterogeneity in preeclampsia. The limitations of the “ischemic model” as the sole genesis of preeclampsia have been discussed (13). In longitudinal studies, Easterling et al. (14) demonstrated an increase in blood flow among preeclamptic patients secondary to increased maternal cardiac output. By studying

TABLE 2. Impact of preeclampsia and gestational hypertension on birth weight, by week of gestation, in univariable analysis and multivariable linear regression analysis (n = 87,798), Alberta, Canada, 1991–1996

<table>
<thead>
<tr>
<th>Week of gestation</th>
<th>Study sample</th>
<th>Gestational hypertension (n = 2,395) versus normotensive status (n = 84,658)</th>
<th>Preeclampsia (n = 745) versus normotensive status (n = 84,658)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. with gestational hypertension</td>
<td>No. normotensive</td>
<td>Mean birth weight difference (g)</td>
</tr>
<tr>
<td>≤32</td>
<td>41</td>
<td>1,676</td>
<td>−248.1</td>
</tr>
<tr>
<td>33</td>
<td>29</td>
<td>417</td>
<td>−434.2***</td>
</tr>
<tr>
<td>34</td>
<td>22</td>
<td>668</td>
<td>−312.8*</td>
</tr>
<tr>
<td>35</td>
<td>43</td>
<td>1,097</td>
<td>−317.2***</td>
</tr>
<tr>
<td>36</td>
<td>107</td>
<td>2,293</td>
<td>−189.7***</td>
</tr>
<tr>
<td>37</td>
<td>238</td>
<td>5,007</td>
<td>−19.7</td>
</tr>
<tr>
<td>38</td>
<td>432</td>
<td>12,617</td>
<td>5.9</td>
</tr>
<tr>
<td>39</td>
<td>632</td>
<td>20,841</td>
<td>55.1***</td>
</tr>
<tr>
<td>40</td>
<td>622</td>
<td>26,642</td>
<td>45.3*</td>
</tr>
<tr>
<td>41</td>
<td>418</td>
<td>11,929</td>
<td>22.4</td>
</tr>
<tr>
<td>≥42</td>
<td>31</td>
<td>1,471</td>
<td>−59.3</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01.
† Adjusted for maternal smoking, maternal age, parity, maternal prepregnancy weight of ≥91 kg, maternal prepregnancy weight of ≤45 kg, prior spontaneous and induced abortions, prior small-for-gestational-age newborn, prior large-for-gestational-age newborn, anemia, and premature rupture of membranes.
‡ SE, standard error.
the placental clearance of dehydroisoandrosterone sulfate, an indicator of uteroplacental perfusion, Gant et al. (15) noted that women who became preeclamptic in the third trimester had substantially greater uteroplacental blood flows throughout most of their pregnancies than those who remained normotensive. In a study of 1,650 Caucasian women, Kingdom et al. (16) found that 85 percent and 94 percent of women who developed preeclampsia at term had normal uterine Doppler flow indices as measured at 20 weeks and 30–34 weeks, respectively. In our recent studies (8, 12), we observed a significant association between gestational hypertension and preeclampsia and LGA infants. Indeed, approximately 90 percent of babies born to preeclamptic mothers were appropriate-for-gestational-age or LGA, which suggests that uteroplacental blood flow may be normal or increased in the majority of preeclamptic patients (8).

A further challenge to the “ischemic model” in preeclampsia arises from the findings of a reduced risk of cerebral palsy among preterm or low birth weight infants born to mothers with preeclampsia (17). Cerebral palsy risk is markedly increased in infants born significantly preterm or in those of very low birth weight. If uteroplacental hypoperfusion were the sole pathophysiologic mechanism, then infants born to preeclamptic mothers, under such “ischemic conditions,” would be expected to be at higher risk of developing cerebral palsy. However, the results of our recent meta-analysis suggest that preeclampsia may be protective against cerebral palsy in preterm and low birth weight infants (17). Finally, most previous studies on the etiology of preeclampsia were of a cross-sectional or case-control design in which women selected for study have already had preeclampsia. It is therefore difficult to know whether decreased uteroplacental perfusion was the cause of the disease or the result of the disease. Uteroplacental hypoperfusion may be the result of preeclampsia occurring after the clinical expression of the disease. In order to detect changes in uteroplacental perfusion before the onset of preeclampsia, prospective or longitudinal studies are warranted.

Mean birth weight is influenced by both the right and left tails of the birth weight curve. Although preeclampsia significantly increases the risk of low birth weight and SGA babies (the left tail of the birth weight curve), preeclampsia also increases the risk of high birth weight and LGA babies (the right tail of the birth weight curve) (8, 12). The lower weights on the left side of the curve may be offset by higher weights on the right side of curve, resulting in a flattening out of the normal distribution, without displacement of the mean birth weight (12). The group of preeclamptic women who have LGA babies are probably mostly among those who gave birth after 37 weeks. The phenomenon of LGA and high birth weight infants born to preeclamptic patients may be the result of earlier growth-enhancing effects by an increased uteroplacental blood flow due to higher blood pressure (8, 18).

Another possible explanation for these findings is that preeclampsia that is of early onset (≤37 weeks) may be more likely to be severe, more likely to have a detrimental effect on fetal growth, and more likely to lead to “iatrogenic” prematurity delivery. Preeclampsia that is of late onset (>37 weeks) may be more likely to be mild and less likely to lead to “iatrogenic” prematurity delivery. Uteroplacental hypoperfusion, if present, may be of too short a duration to affect fetal size (8). Indeed, it would seem likely that preterm birth is a marker of disease severity and fetal growth restriction. Early-onset preeclampsia and late-onset preeclampsia may be different diseases. Unfortunately, our data set did not

### Table 3. Impact of preeclampsia and gestational hypertension on birth weight, by week of gestation and parity, in multivariable linear regression analysis (n = 87,798), Alberta, Canada, 1991–1996

<table>
<thead>
<tr>
<th>Week of gestation</th>
<th>Gestational hypertension (n = 2,395) versus normotensive status (n = 84,668)</th>
<th>Preeclampsia (n = 745) versus normotensive status (n = 84,668)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nulliparous women (n = 34,929)</td>
<td>Multiparous women (n = 52,124)</td>
</tr>
<tr>
<td></td>
<td>β†</td>
<td>SE†</td>
</tr>
<tr>
<td>≤32</td>
<td>-451.5</td>
<td>192.6**</td>
</tr>
<tr>
<td>33</td>
<td>-396.7</td>
<td>121.7**</td>
</tr>
<tr>
<td>34</td>
<td>-304.3</td>
<td>140.3*</td>
</tr>
<tr>
<td>35</td>
<td>-254.4</td>
<td>82.4**</td>
</tr>
<tr>
<td>36</td>
<td>-244.0</td>
<td>55.9**</td>
</tr>
<tr>
<td>37</td>
<td>-29.3</td>
<td>38.4</td>
</tr>
<tr>
<td>38</td>
<td>0.1</td>
<td>27.0</td>
</tr>
<tr>
<td>39</td>
<td>27.7</td>
<td>22.3</td>
</tr>
<tr>
<td>40</td>
<td>33.0</td>
<td>21.5</td>
</tr>
<tr>
<td>41</td>
<td>67.9</td>
<td>37.3</td>
</tr>
<tr>
<td>≥42</td>
<td>-137.7</td>
<td>103.8</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01.
† Adjusted for maternal smoking, maternal age, maternal prepregnancy weight of ≥91 kg, maternal prepregnancy weight of ≤45 kg, prior spontaneous and induced abortions, prior small-for-gestational-age newborn, prior large-for-gestational-age newborn, anemia, and premature rupture of membranes.
‡ SE, standard error.

include information on the onset and severity of preeclampsia or on whether the preterm births were spontaneous or medically induced. Further studies are needed to examine this hypothesis.

As is true for other studies based on a large database, our data were subject to nondifferential misclassification bias. To limit the number of false-positive cases in the preeclampsia and gestational hypertension groups, we excluded women with hypertension that occurred only during labor. Many of these women may not have had true hypertensive disorders but rather may have represented the normal response to stress at the time of delivery. Because the sample size was so large for the normotensive group, the false-negative cases were unlikely to have biased our findings.

It should be noted that the control group for preterm births does not necessarily represent a “normal” control group and that patients who deliver their babies prematurely from causes other than preeclampsia probably have a higher proportion of SGA infants than women whose babies remain in utero. The data presented here may underestimate the detrimental effects of preeclampsia on birth weight among preterm births.

The incidence of preeclampsia in our data was 1.7 percent, which is lower than a previously reported rate of 5 percent (1, 2). The incidence of preeclampsia varies greatly according to the characteristics of the population studied and the criteria used for the diagnosis of preeclampsia. There is also great geographic variation in the incidence of preeclampsia (19). Indeed, few previous studies reporting the incidence of preeclampsia have been population-based. Most of these studies originated from one or a few tertiary hospital(s) where women who have preeclampsia or are at high risk of developing preeclampsia are more likely to be referred. Other studies have been limited to primiparous women, who are at greater risk. Thus, the incidence of preeclampsia is often overstated. Our data captured more than 80 percent of the births that had occurred in northern and central Alberta since 1992 and 90 percent of those that had occurred after 1994. From 1991 to 1996, the incidence of preeclampsia ranged from 1.6 percent to 2.0 percent, with an average rate of 1.7 percent. Finally, the overall incidence of hypertensive disorders, including chronic hypertension in pregnancy, in Alberta is 6.5 percent (table 1). This figure is comparable to the recently updated estimate of 6–8 percent for hypertensive disorders in pregnancy, including gestational hypertension, preeclampsia, and chronic hypertension, published by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (20, 21).

Our data support the hypothesis that preeclampsia is a heterogeneous disorder (13) and that it may appear in at least two forms (8): restricted fetal growth preeclampsia and normal fetal growth preeclampsia. Patients with restricted fetal growth preeclampsia often deliver prior to term, and among these patients preeclampsia may follow the “ischemic model.” Patients with normal fetal growth preeclampsia often deliver at term. It is less likely that the pathogenesis of preeclampsia follows the “ischemic model” in these patients. Future epidemiologic and basic scientific studies of preeclampsia may be needed to study these two subsets of preeclampsia separately. In particular, future studies are needed to examine whether there is a difference between these two possible subtypes of preeclampsia in terms of onset and severity.

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