Glucocorticoid-Remediable Aldosteronism and Pregnancy

Jennifer A. Wyckoff, Ellen W. Seely, Shelley Hurwitz, Bruce F. Anderson, Richard P. Lifton, Robert G. Dluhy

Abstract—Glucocorticoid-remediable aldosteronism (GRA) is a hereditary form of primary hyperaldosteronism that presents with hypokalemia and hypertension from childhood onward. GRA is characterized by the ectopic production of aldosterone in the cortisol-producing zona fasciculata under the regulation of adrenocorticotrophic hormone. Despite the early age of onset, no previous reports of pregnancy and GRA exist. Therefore, we set out to describe the maternal and fetal outcomes of pregnancy in women with GRA. Data regarding the blood pressure and pregnancy outcomes were collected in a retrospective chart review of prenatal and hospital records of 35 pregnancies in 16 women with genetically proven GRA. A total of 6% of pregnancies in women with GRA (GRA+) were complicated by preeclampsia. The published rates of preeclampsia in general obstetric populations vary from 2.5% to 10%. Despite the lack of an apparent increase in the rate of preeclampsia, GRA+ women with chronic hypertension had a high rate (39%) of pregnancy-aggravated hypertension. Starting with a higher baseline blood pressure, maternal blood pressure plotted over the time course of pregnancy followed a quadratic curve similar to that previously described in normal pregnancy. Mean gestational age at delivery was 39.1 weeks. Mean birth weight, excluding the 3 sets of twins, was 3219 g. However, infants of GRA+ mothers with pregnancy-aggravated hypertension tended to have lower birth weights than those that did not (3019 g versus 3385 g, respectively; P = 0.08). The primary cesarean section rate was 32%, which is approximately double that seen in other general or hypertensive obstetric populations. In summary, GRA+ women did not seem to have an increased risk of preeclampsia. However, GRA+ women with chronic hypertension seem to be at an increased risk for an exacerbation of their hypertension during pregnancy. (Hypertension. 2000;35:668-672.)

Key Words: hypertension, chronic • pregnancy • blood pressure • hyperaldosteronism • renin-angiotensin system • glucocorticoids

Glucocorticoid-remediable aldosteronism (GRA) is an increasingly recognized form of hereditary primary hyperaldosteronism.1 Presenting from childhood onward, GRA is clinically characterized by severe hypertension, variable hypokalemia, volume expansion, and suppressed plasma renin activity.2 GRA is caused by a chimeric gene duplication that results from an unequal crossing over between the 11β-hydroxylase and aldosterone synthase genes.1 Pregnancy outcomes in women with GRA have not been previously reported; they are of interest for several reasons. First, pregnancy-related hypertensive disorders are one of the leading causes of maternal and perinatal mortality and morbidity in the United States.3 Chronic hypertensive disorders like GRA are considered risk factors for the development of preeclampsia and poor fetal outcomes.4 Therefore, studying pregnancy outcomes provides essential information for the clinician caring for a patient with GRA. Second, because GRA is a state of endogenous suppression of the renin-angiotensin-aldosterone system (RAAS) secondary to primary hyperaldosteronism, it is possible that the study of pregnancy outcomes in such women might provide insight into the importance of the RAAS in regulating blood pressure (BP) in normal pregnancy and in preeclampsia. Third, adrenocorticotropic hormone (ACTH) levels are elevated in normal pregnancy due to the placental production of corticotropin-releasing hormone.5 Because aldosterone production in GRA is solely under the control of ACTH, it is possible that the hyperaldosteronism in pregnancy could be exacerbated, which implies that GRA could be a very specific risk factor for preeclampsia or the worsening of hypertension.

Methods

Subjects and Data Collection

A retrospective chart review of 39 mothers identified as having the GRA genotype (GRA+) in the International GRA Registry provided sufficient outcome information for 16 women (35 pregnancies occurring between 1950 and 1996). Data collected from prenatal and hospital records included BP, medications, urine protein, gestational age at delivery, birth weight, Apgar score, type of delivery, and delivery complications. Informed consent was obtained from all subjects and this study was approved by the institutional review board at the Brigham and Women’s Hospital.
Analysis of Maternal BP Outcomes in All 35 Pregnancies

We used the classification scheme for hypertension during pregnancy developed by the Joint National Commission (JNC) on Hypertension. Categories are as follows.

1. Normal BP ($<140/90$ mm Hg)
2. Transient hypertension (BP $<140/90$ mm Hg before pregnancy and a $\geq 30$ mm Hg increase in systolic BP [SBP] or a $\geq 15$ mm Hg increase in diastolic BP [DBP] during pregnancy)
3. Chronic hypertension (BP $\geq 140/90$ mm Hg or mother requiring antihypertensive medication before pregnancy)
4. Chronic hypertension with superimposed preeclampsia (BP $\geq 140/90$ mm Hg before pregnancy and an increase of $\geq 30$ mm Hg in SBP or $\geq 15$ mm Hg in DBP and a grade of $\geq 2$+ in proteinuria during pregnancy)
5. Preeclampsia (BP $<140/90$ mm Hg before pregnancy and an increase of $\geq 30$ mm Hg in SBP or $\geq 15$ mm Hg in DBP and a grade of $\geq 2$+ in proteinuria during pregnancy)

One limitation of the JNC criteria is the failure to distinguish between women with chronic hypertension who have an exacerbation of their hypertension during pregnancy and those whose hypertension remains controlled or even improves during pregnancy. Therefore, we added the diagnosis of (6) pregnancy-aggravated hypertension (PAH) to our criteria. PAH is defined as a $\geq 30$ mm Hg increase in SBP or a $\geq 15$ mm Hg increase in DBP from a baseline BP $\geq 140/90$ mm Hg before pregnancy.

Summary statistics are presented as means $\pm$ SD. Maternal outcomes were compared between groups within this study population on the basis of infant genotype and gender using Student’s $t$ test or Fisher’s exact test, where appropriate. All statistics were performed using the SAS software package.

Analysis of Maternal BP Patterns During Pregnancy in a Subset of 14 Pregnancies

We used a subset of 14 pregnancies, which were defined as each woman’s first pregnancy for which $\geq 3$ recorded BP measurements during pregnancy were available, for the analysis of BP patterns. This analysis addressed the longitudinal effect of pregnancy on the BP of women with GRA. Mixed models analyses allowed a general specification of the covariance matrix in this repeated measures analysis to allow for nonlinearity in the trajectory of the BPs for different patients. Polynomial mixed models analyses were conducted to allow for nonlinearity in the trajectory of the BPs through the study period.

To characterize the time course of BP in pregnancy for all subjects, the duration of gestation was standardized to 9 months. The month during the pregnancy in which the BP was obtained was calculated as follows: $9.0 \times$ (examination date – conception date)/(delivery date – conception date). Conception date was assumed to be 14 days after the first day of the last menstrual period and 266 days before the estimated date of confinement reported by the obstetrician. In the 1 case in which a discrepancy between these 2 dates existed, the estimated date of confinement was used to calculate the conception date. For each subject, the nonpregnant baseline BP was calculated by averaging the subject-specific BPs before conception and those $\geq 2$ weeks after delivery. The analysis was repeated without the baseline data to assess the pattern of observed BP during pregnancy.

Analysis of Fetal Outcomes for All 38 Infants

For the analyses of fetal outcomes, all 38 infants were included. Fetal outcomes were compared between groups within this study population on the basis of maternal hypertension and infant genotype using Student’s $t$ test or Fisher’s exact test, where appropriate.

Results

Maternal Outcomes

Maternal Characteristics and BP

The general characteristics of the GRA+ mothers are presented in Table 1. The mean maternal age at conception was 25±6 years. All study participants were white. The mean maternal weight before pregnancy was 61.8±11.8 kg. The mean maternal body mass index before pregnancy was 23 kg/m². The average maternal weight gain during pregnancy was 16.4±4.5 kg. A total of 26% of the pregnancies were primigravidas. Smoking complicated 20% of the pregnancies. A total of 54% of the GRA+ women were known to be hypertensive before conception, and the mean duration of hypertension in the GRA+ mothers was 8.6 years.

BP Outcomes in All 35 Pregnancies

Hypertension was present in 26 of the 35 pregnancies (74%). Of these pregnant subjects, 23 (66%) were classified as chronic hypertension, 1 (3%) as transient hypertension, and 2 (6%) as chronic hypertension with superimposed preeclampsia. None of the mothers who were normotensive before pregnancy developed preeclampsia. When only the GRA+ women who were hypertensive before pregnancy were included, the rate of preeclampsia was 8%. Of the 23 pregnancies in women with chronic hypertension, 39% demonstrated a $\geq 30$ mm Hg increase in SBP or a $\geq 15$ mm Hg increase in DBP during pregnancy (PAH), without preeclampsia. Four of the 23 pregnancies (17%) complicated by chronic hypertension had a resolution of the hypertension during the pregnancy. No cases of eclampsia or the syndrome of hemolysis, elevated liver function tests, and low platelets (HELLP) were reported.

Eight pregnancies (23%) required $\geq 1$ antihypertensive medications. All of the women who required medication during pregnancy were hypertensive before pregnancy, and 6 of these women were on medication from the onset of pregnancy. Antihypertensive medications used included methyldopa (2 cases), potassium-sparing diuretics (3 cases), $\beta$-blockers (2 cases), and thiazide diuretics (5 cases).

<table>
<thead>
<tr>
<th>TABLE 1. Maternal Characteristics of 35 Pregnancies</th>
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<tbody>
<tr>
<td>Demographics</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Mean maternal age at conception, y</td>
</tr>
<tr>
<td>Mean pregnancy BMI, kg/m²</td>
</tr>
<tr>
<td>Mean SBP before conception, mm Hg</td>
</tr>
<tr>
<td>Mean DBP before conception, mm Hg</td>
</tr>
<tr>
<td>Primigravida, %</td>
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<tr>
<td>Smoking during pregnancy, %</td>
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<tr>
<td>Mean maternal weight gain, kg</td>
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<tr>
<td>Mean SBP at term, mm Hg</td>
</tr>
<tr>
<td>Mean DBP at term, mm Hg</td>
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<tr>
<td>Antihypertensive Rx during pregnancy, %</td>
</tr>
<tr>
<td>PAH, %</td>
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<tr>
<td>Preeclampsia, %</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; Rx, treatment.
Risk Factors and Impact of Infant Gender and GRA Status on Maternal BP

The mean age (24.7 ± 6.2 years) and weight (68.6 ± 10.9 kg) of the women who developed PAH were not significantly different from the mean age (24.1 ± 5.0 years) and weight (64.1 ± 13.6 kg) of the women who did not develop PAH (P = 0.45 and P = 0.61, respectively).

Infant gender predicted PAH. A total of 64% of the pregnancies in mothers with chronic hypertension who were carrying male infants were complicated by PAH compared with only 17% of the pregnancies in mothers who were carrying female infants (P = 0.036). Infant GRA genotype status was not predictive of maternal PAH (P = 0.97).

Maternal BP Patterns in the Subset of 14 Pregnancies

The predicted quadratic curves resulted from fitting the data in the polynomial mixed models analysis (Figure). The relationship for both SBP and DBP as a function of pregnancy had a significant quadratic trend (P = 0.0001). SBP could be characterized by the following equation: SBP = 139.5 – 8.0 × month + 0.86 × month². Similarly, DBP could be characterized by the following equation: DBP = 90.2 – 7.5 × month + 0.78 × month². To avoid bias, the analysis was repeated without delivery or baseline observations. The equations that characterize “pregnancy-only” BP are similar and the linear and quadratic trends remained significant (SBP, P < 0.01; DBP, P < 0.05). Five of the pregnancies included in this subset were complicated by PAH. The pattern of BP during pregnancy in these patients also seemed to follow a roughly quadratic curve, but the group was too small to allow meaningful statistical analysis. Similar curves have been described in the pregnancies of both normal and hypertensive women.9–12

Other Maternal Outcomes

A total of 43% of these 35 pregnancies were delivered by cesarean section; 9 were primary cesarean sections and 6 were repeat cesarean sections. The primary cesarean section rate was 32% (9 of 28 pregnancies, excluding repeat cesarean sections). Hypertension did not seem to play a major role in the high cesarean rate. The cesarean section rate was similar in hypertensive (45%) and normotensive (48%) mothers.

Indications for the 9 primary cesarean sections included the following (some cases had > 1 complication): 4 cases of fetal distress; 3 cases of failure of labor to progress; 2 cases each of severe hypertension, breech presentation, fever, and partial placenta previa; and 1 case each of prolapsed cord, nuchal cord, twin pregnancy, and head entrapment. Indications for the remaining 6 cesarean sections were the following: 5 cases of repeat cesarean section and 1 case each of twin pregnancy and fetal distress. No cases of gestational diabetes occurred. Maternal complications included 1 case of chorioamnionitis, 1 failure of placental separation, and 2 women who lost > 500 cc of blood during delivery.

Fetal Outcomes

Fetal outcome measurements are summarized in Table 2. The mean gestational age at delivery was 38.9 ± 2.4 weeks, including twin pregnancies. Four pregnancies (11.4%) were delivered before 37 weeks. The 4 premature deliveries in the GRA + women included 2 spontaneous vaginal deliveries, 1 scheduled cesarean section for a twin pregnancy, and 1 emergent cesarean section for hypertension and fetal distress. The average birth weight, including the 3 sets of twins, was 3124 ± 619 g. When twins were excluded, the mean birth weight was 3219 ± 586 g. The Apgar scores were > 7 at 1 minute and > 9 at 5 minutes for 95% of the 38 infants. No fetal malformations, prolonged neonatal hospitalizations, or neonatal deaths were reported.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Infants (n=38)</th>
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<tbody>
<tr>
<td>Total cesarean rate, %</td>
<td>43</td>
</tr>
<tr>
<td>Primary cesarean rate, %</td>
<td>32</td>
</tr>
<tr>
<td>Mean gestational age, wk</td>
<td>38.9 ± 2.4</td>
</tr>
<tr>
<td>Gestational age &lt; 37 wk, %</td>
<td>11.4</td>
</tr>
<tr>
<td>Mean birth weight, g</td>
<td>3124 ± 619</td>
</tr>
<tr>
<td>APGAR1 &lt; 6, %</td>
<td>8</td>
</tr>
<tr>
<td>APGAR5 &lt; 8, %</td>
<td>13</td>
</tr>
</tbody>
</table>

APGAR1 indicates Apgar score at 1 minute; APGAR5, Apgar score at 5 minutes.
Effect of Maternal Hypertension on Fetal Outcomes

The mean gestational age of infants whose chronically hypertensive mothers had PAH during pregnancy was 39.6±1.5 weeks, which was similar to the age of 39.1±1.6 weeks for infants whose mothers did not have PAH (P=0.99). However, the mean birth weight of infants whose chronically hypertensive mothers had PAH (3019±659 g) tended to be lower (P=0.08) than those infants whose chronically hypertensive mothers did not have PAH (3385±374 g).

Effect of Infant Characteristics on Fetal Outcomes

The effect of fetal GRA status on fetal outcome was analyzed in the 29 nontwin pregnancies in which the infant’s genotype was known. GRA+ infants had a mean gestational age at delivery of 39.0 weeks and a mean birth weight of 3138 g. GRA− infants had a mean gestational age of 39.7 weeks and a mean birth weight of 3361 g. Mothers carrying GRA+ infants had a cesarean section rate of 33%, compared with a rate of 25% in those carrying GRA− infants. No significant difference existed between GRA+ and GRA− infants in any outcome measurement (Apgar at 1 minute, P=0.53; Apgar at 5 minutes, P=0.29; birth weight, P=0.25; gestational age, P=0.3; and maternal cesarean section rate, P=0.72).

Discussion

We hypothesized that women with GRA would be at an increased risk of preeclampsia during pregnancy for 4 reasons. (1) Because the RAAS is thought to play a role in the development of preeclampsia, the dysregulation of volume homeostasis by the RAAS seen in GRA might influence a woman’s risk of developing preeclampsia. (2) Because aldosterone production is solely under the control of ACTH in the placenta and the placenta produces corticotropin-releasing hormone, it is possible that hyperaldosteronism would be exacerbated during pregnancy. (3) Hyperaldosteronism per se could affect the risk of preeclampsia. And (4) 57% of the GRA+ mothers had chronic hypertension, which is felt, regardless of cause, to be a risk factor for developing preeclampsia. However, the BP outcomes in GRA+ women did not support this hypothesis. The 6% rate of preeclampsia in GRA+ women is not greater than the rates of 2.5% to 10% reported for the general obstetric population. Even if only those women with GRA who were hypertensive before pregnancy were included in the analyses, the preeclampsia rate was only 8%. Thus, GRA+ women do not seem to have an increased risk of preeclampsia compared with the general obstetric population.

Several factors limit the conclusions drawn in this study. First, studies of preeclampsia are complicated by the wide variability of the definition of preeclampsia in the literature. A second potential confounder is the number of twin pregnancies, because twin pregnancy itself is a risk factor for preeclampsia. The 6% incidence of preeclampsia in GRA+ women did not exclude twin pregnancies. When twin pregnancies were excluded, the incidence of preeclampsia dropped to only 3%. Finally, our sample size is small and the study is largely descriptive, which limits the extent to which statistical conclusions can be drawn.

In addition to preeclampsia, a lack of consensus exists on the definitions of other hypertensive syndromes during pregnancy. For example, the JNC criteria for hypertensive disorders of pregnancy do not include the possibility that pregnancy may improve or aggravate chronic hypertension. We evaluated the prevalence of PAH in GRA+ mothers; our definition of PAH was an increase of 30 mm Hg in SBP or of 15 mm Hg in DBP in women with known chronic hypertension. A total of 39% of the GRA+ women with chronic hypertension in this study had PAH. Sibai et al reported a 17% incidence of a worsening of BP control in their chronically hypertensive population during pregnancy. However, in contrast to the present study, PAH in Sibai et al’s study was defined as an exacerbation of mean arterial pressures and the need to begin BP medication. Thus, the 2 studies are not strictly comparable. Nevertheless, the fact that GRA+ women with chronic hypertension seem to be at risk for an exacerbation of their hypertension during pregnancy is important for 2 reasons. First, it lends support to the hypothesis that the some of the mechanisms underlying chronic hypertension predispose a woman to pregnancy-aggravated hypertension but that others do not. Second, it is clinically relevant in light of the tendency toward lower birth weights observed in the infants of the GRA+ mothers with PAH. This association of hypertension during pregnancy with lower birth weights is well known, both in women with chronic hypertension and with preeclampsia. It is unclear whether the treatment of maternal hypertension improves fetal outcomes.

Infant gender predicted which mothers developed PAH, with the mothers of male infants more likely to develop PAH than the mothers of female infants. Some studies examining the relationship between infant gender and maternal BP have found a similar association, but it has not been consistent. Infant GRA status did not impact maternal BP. Other risk factors for the development of preeclampsia and PAH include primigravida, age, and obesity. A significant association was not demonstrated between any of these factors and the development of PAH in the present study. However, because of the small sample size, such factors may not have achieved statistical significance.

Evaluation of maternal BP during the time course of 14 pregnancies in GRA+ women revealed a pattern similar to that reported for normal pregnancies. In normal pregnancy, a decrease in maternal BP is noted during the first trimester, and the second trimester is characterized by BPs lower than those before pregnancy. Finally, during the third trimester, most women experience an increase in BP back to the levels seen before pregnancy.

One interesting finding of the present study was the high rate of cesarean sections: 43% compared with 15.2% for the general obstetric population or 21% for the chronically hypertensive population. Because women with prior cesarean sections are more likely to have repeat cesarean sections, the use of a total cesarean section rate is biased. Thus, the primary cesarean section rate is a more appropriate indicator. The primary cesarean section rate was 32% in this study, in contrast to the 13.1% reported in Sibai et al’s study of chronic hypertensives. However, the cesarean section rate is highly...
variable over decades, institutions, and individual practices. No obvious explanation for the high rates in GRA+ mothers was evident.

Overall, the mean birth weight and gestational age of infants of GRA+ mothers were comparable to those published for general obstetric populations. However, when we divided the GRA+ women into 2 groups: mothers with PAH during pregnancy and those without, the infants of the mothers with PAH demonstrated a trend toward a lower birth weight. Although no neonatal mortality was reported, our study was not designed to assess rates of fetal loss before 20 weeks of gestation.

The role of the RAAS in BP regulation during pregnancy and in the pathogenesis of preeclampsia is unclear. The BP outcomes and the pattern of BP during pregnancy in our GRA+ women question the hypothesis that the RAAS is a major regulator of BP during pregnancy. Because the RAAS was not assessed in these GRA+ mothers, it would be of interest to prospectively study the RAAS during pregnancy in GRA+ mothers and correlate hormonal changes with BP. Levels of aldosterone secretion during pregnancy would also be of particular interest in GRA mothers because the elevation of ACTH seen in normal pregnancy would be predicted to exacerbate this ACTH-regulated aldosterone excess state.

The present study was not designed to address the optimum treatment of the pregnant woman with GRA. Management of hypertension must be individualized for each patient. How treatment of the pregnant woman with GRA. Management of hypertension in childhood.

In conclusion, GRA+ women did not seem to have an increased risk of preeclampsia. However, GRA+ women with chronic hypertension do seem to be at risk for an exacerbation of their hypertension during pregnancy. Maternal BP during pregnancy follows patterns similar to those found in normal pregnancy, with the exception of higher baseline pressures. The mean gestational age and mean birth weights of infants born to GRA+ mothers were not remarkable, but a tendency toward low birth weights was noted in infants of mothers with PAH. A high primary cesarean section rate was noted. Careful assessment of BP in pregnant women with GRA is necessary.

References
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