Effect of Uncomplicated Chronic Hypertension on the Risk of Small-for-Gestational Age Birth

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This study assesses the effect of chronic hypertension on fetal growth. A cohort of 1,938 pregnant women attending five prenatal clinics in France between August 1991 and May 1993 were enrolled in a prospective study. Chronic hypertension was defined according to blood pressure at enrollment and past history, and cases complicated by preeclampsia were excluded. Adjusted odds ratios of small-for-gestational age birth were estimated by logistic regression. The independent effect of chronic hypertension on mean birth weight was examined through multiple linear regression analysis adjusting for gestational age at delivery and potential confounders. Uncomplicated chronic hypertension was associated with an increased risk of small-for-gestational age birth. Odds ratios increased with age. In women over age 30 years, the association was strong (adjusted odds ratio = 8.5, 95% confidence interval 2.9-24.5). Multiple linear regression showed that mean birth weight was 161 g (95% confidence interval 66-256 g) less in women with chronic hypertension compared with normotensive women. The authors conclude that mean birth weight is reduced and the risk of small-for-gestational age birth is increased in uncomplicated chronic hypertension compared with normotensive pregnancies. Results further suggest that the magnitude of this association increases with age. Am J Epidemiol 1997;145:689–95.

birth weight; cohort studies; gestational age; hypertension; multivariate analysis; pregnancy; risk factors

Chronic hypertension accompanies 0.5-5 percent of all pregnancies (1-3), a frequency in the same range as that of preeclampsia (4, 5). Hypertensive disorders during pregnancy are known to be related to poor fetal outcome (1, 6). The adverse effect of preeclampsia on the fetus is well established. Studies consistently show a link between preeclampsia and impaired fetal growth (7-9), with both disorders probably being the consequence of a common placental disorder (10, 11). Several old, but few recent, studies have addressed the effect of chronic hypertension on fetal outcome. All of these studies showed that among pregnancies complicated by chronic hypertension, the worst perinatal outcome is found in superimposed preeclampsia (1, 6, 8, 12). Studies were contradictory regarding the issue of pregnancies without superimposed preeclampsia (1). On one hand, some authors stated that the excess of morbidity and mortality in pregnancies complicated by chronic hypertension is entirely due to superimposed preeclampsia (3). According to them, the risk of perinatal mortality and fetal growth restriction in pregnancies accompanied by uncomplicated chronic hypertension is similar to the risk in normotensive pregnancies (3, 13, 14). On the other hand, some studies found an increased risk of perinatal mortality and fetal growth restriction in pregnancies accompanied by uncomplicated chronic hypertension, at least in severe cases (8, 12, 15-18). Except for a few recent studies, most papers on fetal outcome in chronic hypertension did not take into account the effect of potential confounders, and sometimes no control group was used. Our prospective cohort study evaluates the effect of chronic hypertension uncomplicated by superimposed preeclampsia on fetal growth and on the risk of small-for-gestational age birth.

MATERIALS AND METHODS

Study population

An analysis of data from a prospective cohort study on hypertensive disorders of pregnancy was performed. The population of this study (n = 2,185) consisted of women followed by a participating midwife in five prenatal clinics in France—Lille Salengro, Lille Victor Olivier, Strasbourg, Paris Port-Royal, and
cases were analyzed. Because the cutoff of 20 weeks
population, only uncomplicated essential hypertension
secondary hypertension (i.e., hypertension due to an un-
definition of chronic hypertension is similar to that of
Haelterman et al.
seem arbitrary, we have performed a subgroup analy-
to separate chronic from gestational hypertension may
the American College of Obstetricians and Gynecolo-
pregnancy who received treatment for this condition
with a prior history of hypertension independent of
pregnancy who received treatment for this condition.
Definition of outcome
Small-for-gestational age birth was defined as a
birth weight below the tenth percentile of expected
weight for gestational age according to the tables of
Leroy and Lefort (20). Gestational age at delivery was
originally determined by the date of the last menstrual
period, which was then either confirmed or corrected
by an early ultrasound examination.
Other variables
At the initial visit, women were interviewed regard-
ing ethnic group of origin, socioeconomic status,
smoking habits, and medical and obstetric histories.
Data on maximal blood pressure recorded, drug intake
during pregnancy, mother’s height, and her weight at
initial visit were collected.
Statistical analyses
Crude odds ratios of small-for-gestational age birth
were estimated for chronic hypertension relative to
normotensive women. Exact confidence intervals
around crude odds ratios (21) were determined. Un-
paired t tests were performed to compare mean birth
weights in exposed and unexposed women.
Stratified and multivariate analyses were performed
to assess the presence of interaction with age and
parity as well as the effect of potential confounders.
Interactions were tested in stratified analysis by a
Woolf test for homogeneity of the odds ratios (22). In
multivariate analysis, a global test of the interactions
was first performed. If this log-likelihood ratio test
proved to be significant, nonsignificant interaction
terms were eliminated by using a backward procedure
based on the likelihood ratio (23). Potential confound-
ers were entered into the model based on the literature
without considering their association with the outcome
or exposure in univariate analyses. Parity, age, socio-
economic status, ethnic group of origin, weight at
initial visit, smoking status, and mother’s height are all
established as direct or indirect determinants of intra-
uterine growth (24, 25). These factors may also be
related to hypertension (26–28). Since all women had
prenatal care very early in pregnancy, weight at the
initial visit was considered as a proxy variable of
prepregnancy weight. Aspirin intake during pregnancy
and maternity center were also considered a priori as
potential confounders. We did not adjust for history of
small-for-gestational age birth because bias can result
when adjustment is made for a factor that is caused in
part by the exposure and is also correlated with the

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outcome (29). Adjusted odds ratios of small-for-gestational age birth for chronic hypertension and their 95 percent confidence intervals were derived from the logistic regression model. If an interaction with age or parity had to be included in the logistic models, odds ratios adjusted for the other variables were estimated for different categories of age or parity.

A multiple linear regression model was used to determine the independent effect of chronic hypertension on birth weight adjusted for gestational age at delivery. We controlled simultaneously for all of the potential confounders. Conditions of application and adequacy of the model were verified through the analysis of residuals and collinearity detection (30).

All p values were two-tailed, and the significance level chosen was 0.05. Statistical analyses were performed using the SPSS 4.0 package (Statistical Data Analysis, SPSS, Inc., Chicago, Illinois) for IBM-PC and Epi-Info 6.0.

RESULTS

The prevalence of uncomplicated chronic hypertension was 4.2 percent (n = 82) in our cohort of 1,938 women. Of these 82 cases, 18 had a diastolic pressure over 100 mmHg at least once, and 36 received treatment for hypertension during pregnancy. The prevalence of chronic hypertension increased with age: 3.1, 4.1, and 5.3 percent for women aged 25 years or less, 26–30 years, and more than 30 years, respectively (p = 0.16). After 73 women who were lost to follow-up were excluded, mean birth weight was 3,265 g (standard deviation = 514), and the risk of small-for-gestational age birth was 7.6 percent (n = 142). Characteristics of the study population are detailed in table 1.

We compared women who developed chronic hypertension during pregnancy (n = 82) with normotensive women (n = 1,856). Hypertensive women were at increased risk of small-for-gestational age birth compared with normotensive women (crude odds ratio (OR) = 2.0, 95 percent confidence interval (CI) 0.9–3.8). Among the 82 women with chronic hypertension, 21 reported that they had been treated for this condition outside pregnancy. Small-for-gestational age birth was more frequent in these women than in chronic hypertensives who did not have such a previous history (19.0 vs. 11.5 percent, p = 0.4). Among previously nulliparous women, chronic hypertension was not related to an increased risk of small-for-gestational age birth (crude OR = 0.8, 95 percent CI 0.1–3.2). In multiparous women, however, the crude odds ratio of small-for-gestational age birth for chronic hypertension was 3.1 (95 percent CI 1.3–6.9). The effect of chronic hypertension on small-for-gestational age birth was further examined within categories of age. The category-specific crude odds ratios were found to increase with age (table 2). The risk of small-for-gestational age birth decreased with age in normotensive women and increased with age in chronic hypertensives (figure 1).

Both interactions between age and chronic hypertension and between parity and chronic hypertension were entered in a logistic regression model to verify their interdependence. The global test of the interactions was statistically significant (p = 0.02). When a backward procedure of selection of the interaction terms was performed with a model including parity, age, and chronic hypertension and its interaction with parity and age, only the interaction with age remained.

Table 2 presents the adjusted odds ratios of small-for-gestational age birth for chronic hypertension by age.
age category with age entered as a categorical variable in the logistic regression model. Further control for aspirin intake during pregnancy and maternity center did not substantially modify the odds ratios. This result corroborates the finding of the stratified analysis and was confirmed when age was entered as a continuous variable in the logistic regression model. Similar results were obtained with the exposure variable limited to women with a previous history of hypertension independent of a pregnancy who received treatment for this condition; adjusted odds ratios were 2.6 (95 percent CI 0.5–14.5), 4.4 (95 percent CI 1.1–17.3), and 7.4 (95 percent CI 1.8–30.6) in women under age 26, ages 26–30, and over age 30 years, respectively. Mean birth weight increased with age in normotensive term pregnancies. In term pregnancies with chronic hypertension, there was a nonsignificant tendency of mean birth weight to decrease in women over age 30 years compared with younger women. In women age 30 years or under, mean birth weight was similar for chronic hypertensives and normotensives (3,237 vs. 3,249 g). Univariate analysis showed that mean birth weight tended to be lower in chronic hypertensive women compared with normotensive women only in the older age category (over age 30 years) (3,155 vs. 3,315 g). This difference was not statistically significant, however ($p = 0.3$).

Multiple linear regression pointed to an association between birth weight and chronic hypertension after adjustment for gestational age at delivery and for all potential confounders. Mean birth weight was 161 g (95 percent CI 66–256 g) less in women with chronic hypertension compared with normotensive women (table 3). No statistically significant interaction between chronic hypertension and age or parity was found in the multiple linear regression model used to predict birth weight.

**DISCUSSION**

In this study, the risk of small-for-gestational age birth was greater and mean birth weight was reduced in pregnancies with uncomplicated chronic hypertension compared with normotensive pregnancies. The magnitude of the association between chronic hypertension and small-for-gestational age birth increased progressively with age. In women over age 30 years, the adjusted odds ratio of small-for-gestational age birth for chronic hypertension was 8.5.

Women enrolled in our study were at lower risk of hypertensive disorders of pregnancy than were those of many other populations. The risk of gestational hypertension (with or without proteinuria) is usually estimated to be 9–13 percent of all pregnancies (1, 4), whereas in our population it was only 4.7 percent. In studies by Sibai et al., the risk of superimposed preeclampsia was 10 percent in moderate chronic hypertension (14) and 52 percent in severe chronic hypertension (13), whereas we found a risk of superimposed preeclampsia of 3.5 percent in chronic hypertension. There are two explanations for these findings. Criteria for the diagnosis of hypertensive disorders of pregnancy are many and varied (3, 12); unlike in other classification systems, the definition of gestational hypertension used in our study does not take edema into account (19). In addition, only women at low risk of pregnancy complications are followed by midwives,
and all cases of secondary hypertension were excluded from the study population, whereas most previous studies on hypertensive disorders of pregnancy are carried out in high-risk populations of referral hospitals. Other studies of low-risk populations found results comparable with ours. For example, by studying birth certificates in North Carolina, Ananth et al. (2) found a risk of pregnancy-induced hypertension of 3.9 percent.

This was a prospective cohort study specially designed to investigate hypertensive diseases of pregnancy. This warranted a high reliability and completeness of the data, particularly regarding hypertension history and blood pressures. Nevertheless, the definition of chronic hypertension used in this study might have resulted in some degree of misclassification between gestational hypertension and chronic hypertension. On the one hand, since the normal physiology of pregnancy leads to decreased blood pressure beginning in the first trimester and peaking in the early third trimester (1), some chronic hypertensives with later elevations in blood pressure would be classified as having gestational hypertension if their hypertension was masked by the normal physiology of pregnancy. On the other hand, hypertension appearing before the 21st week of gestation might sometimes be the early sign of gestational hypertension. However, there is no reason to believe that misclassification occurred differentially according to outcome status. Moreover, the relation between chronic hypertension and the risk of small-for-gestational age birth did not change substantially when the definition of chronic hypertension was restricted to women with a previous history of hypertension requiring treatment, demonstrating that misclassification bias was limited.

The magnitude of the association between uncomplicated chronic hypertension and small-for-gestational age birth was larger than expected from the literature. Table 2 also suggests that the independent effect of chronic hypertension on mean birth weight was greater than that for cigarette smoking. Since chronic renal diseases were excluded and no secondary hypertension was present in the study population, the association found in this study cannot be explained by the presence of any known underlying disease. The finding that small-for-gestational age births were more frequent in uncomplicated chronic hypertension compared with normotensive pregnancies is in disagreement with studies that showed an increased risk of small-for-gestational age birth only if superimposed preeclampsia was present (13, 14, 31). Some studies, however, have produced findings consistent with ours. They indicate that uncomplicated chronic hypertension is associated with an increased risk of fetal growth restriction, at least among severe hypertension (2, 8, 15–18). The flaw of most studies on the effect of hypertension on fetal growth is the lack of control for potential confounders and sometimes the absence of control group. The necessary adjustments were achieved in only a few investigations. Ananth et al. (2) and Shoham-Vardi et al. (32) also found an association between uncomplicated chronic hypertension and small-for-gestational age birth. Moreover, even though their study was not designed specifically to investigate hypertensive disorders of pregnancy, Shoham-Vardi et al. showed an interaction between parity and chronic hypertension on fetal growth restriction, with an increased risk in hypertensive compared with normotensive women only in those who were multiparous. In their recent large retrospective study, McCowan et al. (18) found that women with chronic hypertension without preeclampsia had an increased risk of delivering a small-for-gestational age baby. The discrepancies between our findings and those of Ananth et al., Shoham-Vardi et al., and McCowan et al. on one hand and those of Sibai (13, 14) on the other could possibly be explained by the use of distinct definitions of superimposed preeclampsia and a subsequent misclassification between superimposed preeclampsia and uncomplicated hypertension. We believe, however, that the low frequency of superimposed preeclampsia in our population is due to the fact that all eligible women were at low risk of pregnancy complications. Since antihypertensive medication has not been shown to prevent small-for-gestational age birth (33), differences between the medication used in our study population and other study populations would be an unlikely explanation of the differences between our findings and theirs. In our study, data were carefully recorded on potential confounders. All established determinants of fetal growth (24, 25) that might also be related to hypertension (26–28) were considered as potential confounders except history of small-for-gestational age birth in a previous pregnancy. After adjusting for these potential confounders, we found odds ratios considerably greater than the crude odds ratios. Consistently, in univariate analysis there was no difference in mean birth weight between normotensive women and women with chronic hypertension, whereas in multiple linear regression analysis mean birth weight was reduced in chronic hypertension compared with normotensive women. Women who exhibited chronic hypertension were less likely to smoke than were normotensive women, and their weight at initial visit was greater than that of normotensive women (data not shown). Both smoking during pregnancy and mother’s low weight are related to an increased risk of small-for-gestational age birth (24, 25).
Most former studies on the relation between chronic hypertension and small-for-gestational age birth did not control for potential confounders. Therefore, the inverse confounding effect of smoking and mother’s weight might have partially masked the main effect in many of these studies. This probably is the main reason for differences between our findings and those of some other authors.

For reasons of both statistical significance and physiopathologic plausibility, the final model we have considered is that including the interaction with age and not the interaction with parity. We hypothesized that the interaction with age was the most meaningful from a biologic standpoint and that the interaction with parity was due to the interaction with age. The interaction between chronic hypertension and age on small-for-gestational age birth could not be explained by an increasing hypertension magnitude with age. As a matter of fact, within the group of chronic hypertension, the proportion of women exhibiting high diastolic (>100 mmHg) or systolic (>160 mmHg) pressure did not increase with age, and median diastolic and systolic pressures were not higher in older women. Likewise, the risk of small-for-gestational age birth did not increase according to blood pressure magnitude (data not shown). Our findings might be explained if there were a higher proportion of undiagnosed superimposed preeclampsia in older women. However, there is no reason to believe that measurements of proteinuria were performed less frequently in these women; on the contrary, data on proteinuria were missing less often in older women. Chronic hypertension is a risk factor for arterial atherosclerosis (34). It produces the same lesions in the placental bed vessels as in blood vessels of other organs (35). These lesions are distinct from those of preeclampsia (35). A subsequent reduction of the uteroplacental blood flow may be responsible for the impairment of fetal growth. The extent of blood vessel damage might be related to the duration of disease. Hence, the more intense reduction of uteroplacental flow in older women might account for the interaction between age and chronic hypertension on small-for-gestational age birth found in our analysis. Accordingly, among chronic hypertensives, small-for-gestational age birth was more frequent in women who reported an history of hypertension than in women without such a history.

Chronic hypertension is more likely in older women. In addition, our data suggest that fetal outcome in chronic hypertension worsens with age. The average age of conception is increasing steadily in developed countries (36, 37). In France, the proportion of livebirths from mothers over age 30 years was 37 percent in 1991 (38). It was 34 percent in our population study. Later childbearing is associated with a number of complications mainly due to underlying chronic disorders (39). Chronic hypertension may occur with 10–20 percent of pregnancies in women over age 35 years (39). In our study population, which consisted of very low risk women, the prevalence of chronic hypertension was 5.3 percent over age 30 years. Our findings, if confirmed in other studies, point to an important rise in the risk of small-for-gestational age birth in these older women. In addition to being subject to immediate morbidity, small-for-gestational age babies might also have an increased risk of cardiovascular disease and diabetes as adults (40). For now, no effective means of preventing small-for-gestational age birth in pregnant women with chronic hypertension has been established. Antihypertensive drugs do not preclude fetal growth restriction in these women (33). Low-dose aspirin might be a promising way of preventing fetal growth restriction in high-risk women if it were administered early in pregnancy (10, 41). Further experimental studies have to be conducted before it can be concluded whether babies of older hypertensive women might benefit from low-dose aspirin during pregnancy.

In conclusion, our data indicate a reduction in mean birth weight and a higher risk of small-for-gestational age birth in fetuses of women presenting with uncomplicated essential hypertension compared with normotensive women. In addition, this study suggests that the association between small-for-gestational age birth and chronic hypertension increases progressively with age and is strong over age 30 years.

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