Perinatal Factors Associated with Blood Pressure during Childhood

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This study aims to determine whether variables reflecting an adverse intrauterine environment are associated with childhood blood pressure. The authors conducted a secondary analysis of data from a prospective cohort of children born to healthy, nulliparous women enrolled in a randomized controlled trial. A total of 518 children were traced in 1995-1996 from 614 eligible children born in a clinic in Rosario, Argentina. The outcome was systolic blood pressure at 5–9 years. Hemoglobin during pregnancy was positively associated with children's pressure. Other maternal characteristics during pregnancy (blood pressure, smoking, weight gain, weight at 20 weeks' gestation, and glycemia) and size at birth (birth weight, ponderal index, head circumference/length ratio, and small for gestational age) were not associated with children's pressure. Among children in the upper quartile of body mass index, there was a weak inverse correlation between birth weight and systolic pressure, and systolic pressure was 14.8 mmHg (95 percent confidence interval: 3.3, 26.4) higher in low birth weight children than in others. The main predictors of childhood pressure were childhood body mass index and maternal pressure outside pregnancy. In this healthy population, the authors found weak support for an association between variables reflecting an adverse fetal environment and childhood blood pressure. Low birth weight was a risk factor for high blood pressure only in overweight children. Am J Epidemiol 2000;151:594–601.

Epidemiologic studies have suggested that an adverse fetal environment leads to a greater risk of adult chronic disease (1). Evidence of an inverse association between birth weight and later blood pressure has been observed in both adults and children (2). Other anthropometric indicators at birth were also found to be related to blood pressure in later life (3). In addition, studies have reported an association between diet and nutritional status of the mother during pregnancy on the one hand and blood pressure of the offspring during adulthood on the other (4, 5).

Mechanisms underlying an inverse association between birth weight and subsequent blood pressure are still obscure. The hypothesis that fetal nutrition, through fetal growth patterns, "programs" the risk of adult cardiovascular disease has challenged the paradigm that adult lifestyle is the main determinant of coronary heart disease (1, 6). This has stimulated considerable debate (7–9). The most common approach to testing the "fetal origin hypothesis" has been to use observational follow-up studies, which relate anthropometric measures in early life to subsequent disease. The results of some of these studies are methodologically controversial, since their conclusions are based on a small proportion of the subjects in the original cohort (8, 9) and detailed information from pregnancy characteristics is usually not available or is not reliable. In addition, newborn anthropometry is used as a proxy for fetal nutrition although many other factors can affect these measures (7). Some authors have already suggested that the association between low birth weight and high blood pressure may be confounded by parental blood pressure (10). Maternal high blood pressure is associated with both intrauterine growth retardation (11) and children's blood pressure (12). Moreover, the association between birth weight and children's blood pressure can also be explained by genetic or environmental factors shared by mother and offspring.

In this study, we have prospective, detailed information on both pregnancy characteristics and children's and mother's characteristics at follow-up in a healthy, socioeconomically and ethnically homogeneous population. This design allowed us to explore the association between perinatal variables and blood pressure in
MATERIALS AND METHODS

Study population

Mothers of the enrolled children had participated in a randomized, controlled trial of calcium supplementation during pregnancy (13). Children born of these pregnancies were followed up to ages 5–9 years (14). Women eligible for the trial were those seeking prenatal care in three clinics in Rosario, Argentina, before the 20th week of gestation, who had no past or present disease, a normal oral glucose tolerance test, and a blood pressure below 140/90 mmHg at enrollment. Only nulliparous women with a singleton pregnancy were included in the trial. Deliveries of children whose mothers were enrolled in the trial occurred between August 1987 and November 1990. Only children born to mothers enrolled at the private clinic affiliated with the Centro Rosario de Estudios Perinatales were eligible for the follow-up study. This follow-up study was conducted between January 1995 and March 1996 (14). Among the 614 livebirths eligible, a total of 518 children (84 percent) could be traced. These children constitute the population analyzed for this study.

Newborn anthropometry and maternal characteristics during pregnancy

Newborn anthropometric measurements used as independent variables were birth weight as a continuous variable, low birth weight (defined as birth weight below 2,500 g), small for gestational age (defined as a birth weight below the tenth percentile of expected weight for gestational age), head circumference, head circumference/length at birth ratio, ponderal index (weight/height$^3$), and low ponderal index (defined as ponderal index below the tenth percentile by gestational age at birth). Gestational age at delivery was determined by the date of the last menstrual period and confirmed or corrected by an early ultrasound examination. Maternal health and nutrition indicators included blood pressure after 30 weeks' gestation (mmHg), pregnancy-induced hypertension, weight gain during pregnancy (kg/week), weight at 20 weeks' gestation, fasting glycemia at 20 weeks' gestation, lowest hemoglobin during pregnancy, maternal anemia (defined as lowest hemoglobin during pregnancy ≤ 10 g/dl), serum albumin at 20 weeks' gestation, and smoking during pregnancy. All data were collected prospectively by trained personnel working for the study, using data collections forms that were developed for the study. Information from hospital clinical records was used for data validation procedures. Data quality was assured by routinely performed procedures that verify data consistency during patients' recruitment and follow-up. Women were scheduled for clinical examination, collection of urine and blood samples, and blood pressure measurements at 23, 25, 27, 31, and 35 weeks and then weekly until delivery. Hypertension during pregnancy was strictly monitored. During each visit, blood pressure was measured five times with the patient seated after 10 minutes of rest by using a random zero sphygmomanometer. The mean value of the five measurements was used in the analysis, and a standardized procedure was utilized to classify women as having hypertensive disorders of pregnancy (13).

Measurement of children's blood pressure at follow-up

Children of the index pregnancy aged 5–9 years and their mothers were invited to attend the study clinic. Trained nurses measured children's blood pressure. Measurement was performed on the right arm with the child seated in a quiet room after 15 minutes of rest. A standard mercury sphygmomanometer with cuff bladder 17.0 x 9.0 cm was used for all measurements. The mean value of three measurements taken at 1-minute intervals was used in the analysis. The same nurses visited at home the 236 children who did not attend the study clinic and measured their blood pressure at home using the same method.

Covariates

At follow-up, maternal blood pressure was measured three times with the same method as during pregnancy by using a random zero sphygmomanometer. The weights of the children and the mothers were measured to the nearest 100 g, with the children undressed and barefoot. The children's height was measured to the nearest cm.

Statistical analysis

Univariate, stratified, and multivariate analyses were used to assess the association between independent variables (anthropometric measurements at birth and maternal characteristics during pregnancy) on one hand and subsequent children's blood pressure on the other. We undertook stratified analysis to examine the association between independent variables and children's blood pressure according to level of the children's body mass index, categorized in quartiles. If an interaction between the independent variable and children's body mass index was found, further analysis of this associa-
ation was performed within strata of body mass index. The same procedure was applied in a search for an interaction between independent variables on one hand and sex and age category on the other. Potential confounders used in the multiple linear regression models were established determinants of children's blood pressure that may also be related to independent variables, namely, age, sex, children's body mass, and height. Treatment status (calcium vs. placebo) and maternal blood pressure were also used as potential confounders in the multivariate analysis. Regression coefficients were standardized (standardized regression coefficient = regression coefficient/standard deviation of the independent variable). These transformations allowed the comparison of regression coefficients between variables with different scales of measurement since the standardized coefficient represents the change in the children's systolic blood pressure (in mmHg) for 1 standard deviation shift in the value of the independent variable. These regression coefficients can be converted to regular regression coefficients by multiplying them by the standard deviation of the independent variable. Statistical analyses were performed by using SPSS (Statistical Data Analysis, SPSS, Inc., Chicago, Illinois) and SAS (Cary, North Carolina) packages for IBM-PC.

RESULTS

Table 1 describes the 518 children enrolled in this study. In this low-risk population, the proportions of low birth weight were only 5.0 and 6.8 percent in boys and girls, respectively.

<table>
<thead>
<tr>
<th>Child's characteristics</th>
<th>Boys (n = 274)</th>
<th>Girls (n = 244)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)*</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Child's characteristics at follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>7.1 (0.7)</td>
<td>7.1 (0.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>25.7 (5.3)</td>
<td>24.4 (5.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>125.5 (6.8)</td>
<td>122.7 (6.9)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>16.2 (2.3)</td>
<td>16.1 (2.4)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>104.9 (10.2)</td>
<td>104.2 (11.5)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>65.2 (9.4)</td>
<td>66.0 (9.1)</td>
</tr>
<tr>
<td>Characteristics at birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3,277.3 (469.0)</td>
<td>3,196.7 (455.8)</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>50.3 (2.4)</td>
<td>49.8 (2.1)</td>
</tr>
<tr>
<td>Low birth weight†</td>
<td>13 (5.0)‡</td>
<td>16 (6.8)‡</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>24 (9.2)‡</td>
<td>27 (11.4)‡</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.4 (1.6)</td>
<td>39.6 (1.5)</td>
</tr>
<tr>
<td>Preterm birth§</td>
<td>13 (4.9)¶</td>
<td>6 (2.5)¶</td>
</tr>
<tr>
<td>Ponderal index ((g/cm²) x 100)</td>
<td>2.6 (0.3)</td>
<td>2.6 (0.3)</td>
</tr>
</tbody>
</table>

* SD, standard deviation.
† Birth weight <2,500 g.
‡ Data on birth weight missing for 12 boys and eight girls.
§ Less than 37 completed weeks gestation.
¶ Data on gestational age at birth missing for 11 boys and eight girls.

In univariate analysis, the only variables potentially reflecting intrauterine environment that were significantly and positively associated with children's systolic pressure at ages 5–9 years were maternal weight at 20 weeks' gestation and lowest hemoglobin value during pregnancy (figure 1). There was no association or a very weak nonstatistically significant association between the children's systolic pressure and the mother's blood pressure after 30 weeks' gestation, pregnancy-induced hypertension, smoking during pregnancy, fasting glycemia at 20 weeks' gestation, serum albumin at 20 weeks' gestation, weight gain during pregnancy, birth weight, low birth weight, small for gestational age, head circumference, head circumference/length at birth ratio, and ponderal index (figure 1). A similar pattern was found for children's diastolic blood pressure, although the associations were weaker (data not shown).

Characteristics of mothers and children at follow-up were strongly associated with the children's blood pressure (figure 1). Children's body mass index was the strongest predictor of systolic pressure. One standard deviation increase in children's body mass index was associated with an increase of 5.0 mmHg in the children's systolic pressure at follow-up. While maternal blood pressure during pregnancy was not associated with children's blood pressure, we found a strong association between maternal blood pressure at follow-up and children's blood pressure (figure 1). Maternal weight at follow-up and children's height were also positively correlated with children's blood pressure.
higher in low birth weight children than in others. Mean with higher blood pressure only among children in the are shown in table 2. Low birth weight was associated of birth weight within each quartile of body mass index, group, with subjects divided into four categories mmHg (95 percent confidence interval: 3.3, 26.4) quartile of body mass index, systolic pressure was 14.8 between this variable and birth weight In the upper mass index showed a statistically significant interaction systolic pressure adjusted for age, sex, height, and treat- In line with the hypothesis that birth weight and maternal blood pressure outside pregnancy are linked

We further examined the association between perinatal variables and children’s blood pressure by conducting multivariate modeling. After adjustment for children’s sex, age at follow-up, children’s body mass index and height, and treatment status, the only perinatal variable that was significantly associated with children’s systolic pressure was hemoglobin at 20 weeks’ gestation (figure 1). The association between maternal weight at 20 weeks’ and childhood blood pressure was not apparent anymore (figure 1).

A stratified analysis by quartiles of children’s body mass index showed a statistically significant interaction between this variable and birth weight. In the upper quartile of body mass index, systolic pressure was 14.8 mmHg (95 percent confidence interval: 3.3, 26.4) higher in low birth weight children than in others. Mean systolic pressure adjusted for age, sex, height, and treatment group, with subjects divided into four categories of birth weight within each quartile of body mass index, are shown in table 2. Low birth weight was associated with higher blood pressure only among children in the upper quartile of body mass index (table 2). Table 3 shows standardized regression coefficients for the relation between children’s blood pressure and variables reflecting size at birth, stratified by category of body mass index. Birth weight as a continuous variable and small for gestational age showed a pattern similar to that of low birth weight, but with smaller effects (table 3). No other significant interaction was found between body mass index and the other perinatal variables. Among children in the upper quartile of body mass index, the strong association between low birth weight and children’s blood pressure decreased after adjustment for maternal blood pressure outside pregnancy (standardized regression coefficient = 2.2 mmHg, 95 percent confidence interval: 0.1, 4.3). Further adjustment for maternal blood pressure during pregnancy did not modify these results. The association between birth weight and blood pressure did not vary according to sex or age category (data not shown).

In line with the hypothesis that birth weight and maternal blood pressure outside pregnancy are linked
by inherited factors (10), we found that birth weight was inversely associated with maternal blood pressure at follow-up (Pearson correlation coefficient, -0.1; \( p = 0.03 \)). The association did not change substantially after adjustment for maternal blood pressure during pregnancy.

**DISCUSSION**

Factors related to maternal nutrition and well being, including weight gain during pregnancy, glycemia, serum albumin, smoking during pregnancy, maternal blood pressure after 30 weeks' gestation, and pregnancy-induced hypertension, showed weak and inconsistent relations with children's blood pressure. Only two pregnancy characteristics that could reflect an adverse intrauterine environment, maternal weight at 20 weeks' gestation and lowest hemoglobin during pregnancy, were associated with systolic pressure in children aged 5-9 years in univariate analysis. Hemoglobin during pregnancy was the only independent predictor of systolic pressure. These associations were positive, and hence, in the opposite direction of what was expected according to the fetal origin hypothesis. Evidence that low birth weight is a predictor of high blood pressure in children was present only in the upper quartile of body mass index, but the effect became weaker and nonsignificant after adjustment for maternal blood pressure at follow-up. There was no consistent association between other neonatal anthropometric measures (small for gestational age, ponderal index, head circumference and head circumference/length ratio) and blood pressure in these children. By far the best predictor of children's blood pressure was current body mass index, followed by maternal blood pressure at follow-up.

A weakness of this study is that the sample size is not very large compared with several earlier reports. However, power calculation shows that the sample size is large enough to detect a clinically important difference in blood pressure. Our study had a 70 percent power to detect a difference of at least 3 mmHg in systolic pressure between low birth weight and non-low birth weight babies. A strength of this study is that it had detailed and reliable information on pregnancy.
characteristics and maternal characteristics at follow-up not available in previous reports. Information was collected prospectively by trained personnel working for the study; thus, we do not rely on data from routine clinical records. In comparison with other studies, loss to follow-up was small, and lost patients were very similar to those included (14), making selection bias unlikely. Another strength of this study lies in the homogeneity of the study population. Enrolled women were healthy, nulliparous women attending a single hospital covering a population homogeneous with regard to socioeconomic, ethnic, and lifestyle variables. Women with chronic hypertension were excluded from the study. Study of such a population allowed minimization of the risk of spurious association resulting from residual confounding by unmeasured environmental or genetic variables or by underlying diseases, such as chronic hypertension. A possible drawback of studying such a homogeneous, healthy population of medium-to-high socioeconomic level who shared a similar environment and lifestyle is that it could restrict external validity of our study. It is entirely possible that environmental factors capable of adversely affecting the developing cardiovascular system were not prevalent enough in our study population to produce an important overall effect. In such a population, the contribution of antenatal environment to blood pressure in childhood may thus be limited, whereas the contribution of genetic and/or postnatal environment may be more important than in other populations.

Several studies found a positive association between maternal blood pressure during pregnancy and children's blood pressure (3, 15–20), while, in accordance with our data, others found no relation between these two variables (21–22). This study differs from previous research in two important aspects. First, our study was designed to obtain accurate and detailed blood pressure measures during pregnancy, and women were classified as having hypertensive disorder of pregnancy using a standardized procedure (13). In contrast, not many of the previous studies were cohort studies with quantitative data on blood pressure during pregnancy, and in most of them, data were collected retrospectively. Second, in our study, women with a history of hypertension or renal disease were not enrolled, and since maternal blood pressure outside pregnancy is a strong predictor of children's systolic pressure, chronic hypertension rather than pregnancy-induced hypertension might have been responsible for the finding in previous studies.

Law et al. (3) and Godfrey et al. (23) found no consistent relations between these variables, and our study suggests a positive association. Thus, the previous assumption that nutritional deficiency may be associated with both anemia and raised blood pressure in offspring (3) demands more evidence. In our study smoking during pregnancy did not increase the risk for high blood pressure in children. Accordingly, three studies found no association between these variables (3, 20, 24).

Delayed intrauterine growth has been implicated in the development of high blood pressure in childhood (1). Furthermore, it has been proposed that undernutrition in the first, second, or third trimester may result, respectively, in a symmetrically small baby, a thin and light baby, or a baby with a normal birth weight who is short in relation to its head circumference. It was proposed that particular patterns of size at birth predicted raised blood pressure in later life (1). In our study, as in a number of previous reports, no consistent association was found between blood pressure in children and variables reflecting fetal growth patterns (such as ponderal index, small for gestational age, head circumference, and head circumference/length ratio) (25, 26).

Several previous studies in children found no association between birth weight and children’s blood pressure before adjustment or stratification of the analysis for children’s current weight or body mass index (16, 25, 27–29). Consistently, we found no overall association between birth weight and blood pressure at ages 5–9 years. Nevertheless, among overweight children, blood pressure was higher in low birth weight babies than in other children. This finding of an interaction between birth weight and body mass index is consistent with studies of birth weight and adult blood pressure (30, 31) and also with several studies among children (27, 32–33). Therefore, our data are in agreement with the suggestion that rapid postnatal growth may yield a rise in blood pressure (21). This interaction effect between body mass index and birth weight has not been universal, however (15, 28, 34, 35). Moreover, several studies among adults (5) or children (23, 36) and most studies among adolescents (2, 35) do not show any consistent association between birth weight and subsequent blood pressure. A possible explanation is that the rapid growth that occurs during adolescence may perturb blood pressure tracking (37). We have explored the hypothesis that the age range in our study was broad enough that some children may be close to the adolescent growth spurt, resulting in weaker association in this subgroup. However, the associations found did not differ between children's age categories (results not shown). In addition, the association was similar for boys and girls, whereas some previous studies found stronger associations among girls.

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In agreement with Walker et al. (10), in our study maternal blood pressure outside pregnancy was inversely associated with birth weight. Furthermore, our study showed that this association persisted even after adjustment for blood pressure during pregnancy. These findings suggest that the association between maternal blood pressure outside pregnancy and low birth weight may not be entirely mediated by a direct effect of high blood pressure during pregnancy on the fetus and that genetic or environmental factors shared by mother and child may link low birth weight and maternal hypertension. Since maternal blood pressure outside pregnancy is one of the main predictors of children's blood pressure, this variable needs to be considered when the fetal origins hypothesis is explored. In previous research, body mass index was almost universally included as a potential confounder (2, 7), while maternal blood pressure was almost always absent (10). This is of particular concern, since adjustment for body mass index allows the effect of birth weight on blood pressure in the direction favored by the hypothesis, while adjustment for maternal blood pressure corrects the measure of association in the opposite direction. Furthermore, the association between birth weight and children's blood pressure might be confined to overweight children. Thus, adjustment for body mass index might not be appropriate if the interaction effect between body mass index and birth weight is not taken into account, as is the case in a large proportion of published studies (2).

In summary, in the homogeneous, healthy population, we found weak support for an association between perinatal variables reflecting an adverse fetal environment and subsequent high blood pressure in children. In overweight children, however, there was an inverse association between low birth weight and high blood pressure. This finding, if confirmed by future research, may have important public health implications for many developing countries with a high incidence of low birth weight and an increasing prevalence of obesity (38). Children's body mass index and maternal blood pressure outside pregnancy were much stronger independent predictors of children's blood pressure than were pregnancy and newborn characteristics. Future research exploring the association between size at birth and subsequent high blood pressure should attempt to control for these two variables that might otherwise confound such association.

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