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MATERNAL AGE AND OTHER PREDICTORS OF NEWBORN BLOOD PRESSURE

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Objective   To investigate perinatal predictors of newborn blood pressure.

Study design   Among 1059 mothers and their newborn infants participating in Project Viva, a US cohort study of pregnant women and their offspring, we obtained five systolic blood pressure readings on a single occasion in the first few days of life. Using multivariate linear regression models, we examined the extent to which maternal age and other pre- and perinatal factors predicted newborn blood pressure level.

Results   Mean (SD) maternal age was 32.0 (5.2) years, and mean (SD) newborn systolic blood pressure was 72.6 (9.0) mm Hg. A multivariate model showed that for each 5-year increase in maternal age, newborn systolic blood pressure was 0.8 mm Hg higher (95% CI, 0.2, 1.4). In addition to maternal age, independent predictors of newborn blood pressure included maternal third trimester blood pressure (0.9 mm Hg [95% CI, 0.2, 1.6] for each increment in maternal blood pressure); infant age at which we measured blood pressure (2.4 mm Hg [95% CI 1.7, 3.0] for each additional day of life); and birth weight (2.9 mm Hg [95% CI, 1.6, 4.2] per kg).

Conclusion   Higher maternal age, maternal blood pressure, and birth weight were associated with higher newborn systolic blood pressure. Whereas blood pressure later in childhood predicts adult hypertension and its consequences, newborn blood pressure may represent different phenomena, such as pre- and perinatal influences on cardiac structure and function.

Development of risk for adult cardiovascular disease begins very early in life, even before birth.[1] Data are scarce, however, regarding blood pressure in the newborn period, which may reflect pre- and perinatal influences on cardiac structure and function. The few studies that have examined determinants of newborn blood pressure suggest a direct association with birth weight,[2-10] in contrast to the inverse association seen with older infants, children, and adults.[11] However, most of these studies have at least one important limitation, such as a relatively small sample size of term newborns, lack of data on potentially confounding variables, and limited data on maternal predictors. Maternal age is of particular interest given the known associations of advanced age with adverse reproductive outcomes, including reduced fertility, preterm birth, impaired fetal growth, multiple birth, and congenital anomalies.[12-14] The additional associations of advanced maternal age with diabetes and hypertension,[15,16] with possible diminished uterine vascular and placental function,[17,18] and in at least two reports with blood pressure level in childhood and in adolescence[19,20] warrant examination of its influence on newborn blood pressure.

The purpose of this analysis was to investigate associations of pre- and perinatal factors, including maternal age, with systolic blood pressure level during the first few days of life among members of Project Viva, a cohort study of pregnant women and their children.

METHODS

Subjects

Participants are recruited into Project Viva at eight offices of Harvard Vanguard Medical Associates, a large multispecialty urban/suburban group practice in eastern

Massachusetts. At the first study visit (Visit 1), which immediately follows the woman's initial clinical prenatal visit, we obtain informed consent, administer a brief interview, provide a take-home self-administered questionnaire, and obtain a blood sample. At the second study visit, at 26 to 28 weeks' gestation (Visit 2), we again administer a brief interview, provide a questionnaire, and obtain a blood sample. Project Viva participants deliver in one of two study hospitals: Brigham and Women's Hospital or Beth Israel Deaconess Medical Center. Within 3 days after delivery, we briefly interview the mother and perform measurements on the newborn (Visit 3). As part of Project Viva, we also collect umbilical cord blood and follow up the children at 6 months and at 1, 2, and 3 years, but those data are not part of the present analysis.

Exclusion criteria include multiple gestation (twins, triplets, etc), inability to answer questions in English, plan to move out of the area before delivery, and gestational age >22 completed weeks at initial prenatal clinical appointment. We enrolled 2671 pregnant women (64% of those eligible) between April 22, 1999, and July 31, 2002, of whom 330 subsequently became ineligible because of multiple gestation (n = 19), transferring obstetric care to a nonstudy site (n = 115), or because they were no longer pregnant (n = 196). Of the 2341 remaining participants, 195 (8%) withdrew, and 18 (<1%) were lost to follow-up, leaving 2128 who delivered a live infant.

Our goal was to visit the 5/7 (71%) of mothers who delivered on weekdays and to measure blood pressure on their newborns. In fact, of the 2128 delivered mothers, we visited 1714 (81%), and we measured blood pressure on 1129 (66%) of their newborns. Reasons for not obtaining measurements were admission to the neonatal intensive care unit (n = 78), infant too fussy to perform measurements (n = 32), infant not available when staff present (n = 104), parents not giving consent for measurements (n = 328), and other reasons (n = 45). For this analysis, we also excluded 70 of the 1129 participants for whom there were missing data for certain covariates. Thus, 1059 newborns with blood pressure readings and their mothers form the study sample for this analysis.

Compared with participants in this analysis, the group of mothers of newborns on whom we did not obtain blood pressure readings comprised fewer whites (64% versus 69%) but were similar in age, prepregnancy body mass index, gravidity, education status, household income, marital status, and financial security. Human subjects committees of Harvard Pilgrim Health Care, Brigham and Women's Hospital, and Beth Israel Deaconess Medical Center approved the study protocols.

Measurements

We obtain data for Project Viva from multiple sources. Table I shows the name, source, and type of each variable used in the analysis.

Data Analysis

Our main outcome was newborn systolic blood pressure, which we measured on each infant up to 5 times at 1-minute intervals on a single occasion. We obtained 5 readings on 1020 infants, 4 readings on 17 infants, 3 readings on 7 infants, 2 readings on 5 infants, and 1 reading on 10 infants, for a total of 5209 readings on the 1059 participants. For bivariate analyses, we averaged all measurements for each newborn. Although the first measurement is generally higher than the second through fifth, including it in the average tends to improve precision when absolute levels are not as important as differences.[21]

To assess the multivariate associations between predictors and newborn systolic blood pressure, we used mixed models that incorporated each of the up to 5 blood pressure measurements from each infant as repeated outcome measures.[22] Some advantages of this modeling approach, compared with using the average of available measures for each child as the outcome, are that persons with more measurements and less variability among those measurements receive more weight than those with fewer measurements and/or more variability. We assessed the confounding effect of covariates by examining the association of predictors of interest with newborn blood pressure before and after adding the covariates to the model. From the models we present effect estimates and 95% CIs. Although we used exact maternal age as a linear term in the models, for ease of interpretation we present the effects of maternal age in 5-year increments. All models, including the base ("unadjusted") model, were controlled for blood pressure measurement conditions, including an indicator for the sequence number (first through fifth) of each reading, cuff size, the arm on which we obtained the readings, body position (supine or held by mother), and infant state (quiet sleep, active sleep, quiet awake, crying).

RESULTS

Thirty-one percent of the 1059 women classified themselves as racial/ethnic minorities (Table II). Reflective of a generally employed and insured managed care population, few subjects had less than a high school education or had annual household incomes below $20,000. To assess financial security independent of income, we asked the women how long they could maintain their standard of living if they suddenly lost all sources of income. Of the women who responded, 294 (32%) said more than 6 months (Table II).

Mean gestational age at birth was 39.7 weeks (Table III). Fewer than 5% of newborns were born at less than 37 completed weeks gestation, but we did not obtain blood pressure measurements on babies admitted to the neonatal intensive care unit, a large proportion of whom are premature infants. Approximately 2.5% were born at 42 or more weeks' gestation. Mean systolic blood pressure, 72.6 mm Hg, was comparable to estimates from other studies of children of this age.[3,4,6,7,9,10,23]

The Figure shows that unadjusted mean systolic blood pressure rose monotonically with category of maternal age. Blood pressure of offspring born to women aged 40 to 44 years was approximately 4 mm Hg higher than that of women under aged 20 years. In other bivariate analyses, maternal age was

Table I. Sources of information for variables used in analysis

	Maternal variables	
Variable name	**Source**	**Specific measure, if not standard**
Maternal variables		
Maternal age, race/ethnicity, education, marital status, number of previous pregnancies; household income	V1 interview	
Prepregnancy weight	V1 interview	Prepregnancy body mass index is weight in kg divided by the square of height in meters.
Height	V1 interview	
Smoking	V1 and V2 questionnaires	
Financial security	V1 questionnaire	"If you suddenly lost all sources of your household income right now, how long would you be able to maintain your standard of living: <3, 3-6, 7-12, >12 months"
3rd trimester systolic blood pressure	HVMA automated medical record	Average of all readings 28-32 weeks' gestation
Gestational weight gain	HVMA automated medical record	Uses last prenatal recorded weight; difference between that measure and self-reported prepregnancy weight
Glucose tolerance	HVMA automated medical record	Standard 1-hour 50-g oral glucose challenge test at 26-28 weeks gestation for most participants. If abnormal (ie, serum glucose >140 mg/dL), it is followed by a fasting 100-g 3-hour glucose tolerance test. For the 3-hour test, 2 of the 4 cutpoints—fasting (95 mg/dL), 1-hour (180), 2-hour (155), and 3-hour (140)—must be met or exceeded to diagnose gestational diabetes.[33] We formed 5 categories for our analyses: a) Normal glucose tolerance—either normal results of the 50-g glucose challenge test or test not done because of low risk status;[33] b) Impaired glucose tolerance—an intermediate category, ie, failing only 0 or 1 cutpoint on the 100-g test; c) Failed initial challenge but no fasting oral test offered; d) Gestational diabetes; and e) Pre-existing diabetes.
Newborn variables		
Birth weight, sex	Hospital vital statistics record	
Gestational age	V1 interview	Last menstrual period
	V2 interview	Updated self-reported due date based on ultrasound data Gestational age calculated from LMP unless updated due date from 16-20 week ultrasound differed by more than 10 days; then use updated due date
Infant age at time of measurements	Recorded at V3	
Blood pressure	Measured at V3	Dinamap 8100 (or, since 2/21/01, Pro 100) oscillometric recorder; baby supine or in mother's lap; state of baby recorded for each measurement (quiet sleep, active sleep, quiet awake, crying); 5 readings, each 1 minute apart
Heart rate	Measured at V3	Dinamap; average of 5 readings

V1, Visit 1, at the first clinical prenatal visit, mean gestational age 10.6 weeks; *V2*, Visit 2, at 26 to 28 weeks' gestation; *V3*, Visit 3, in hospital after delivery; *HVMA*, Harvard Vanguard Medical Associates, medical group practice, site of enrollment.
Questionnaires at Visits 1 and 2 are self-administered at home and mailed to the study office.

modestly correlated with birth weight (Pearson r = 0.12) and with number of previous pregnancies (r = 0.30) but minimally correlated with prepregnancy body mass index (r = −0.01), third trimester systolic blood pressure (r = −0.06), infant heart rate (r = 0.01), or age at which we measured newborn blood pressure (r = 0.04).

Table II. Characteristics of 1059 participating mothers from Project Viva

Characteristic	Mean (SD, range)	
Age (y)	32.0 (5.2, 14.8-44.8)	
Pre-pregnancy BMI (kg/m^2)	25.0 (5.5, 15.2-49.2)	
3rd trimester systolic blood pressure (mm Hg)	111.1 (8.1, 89.3-150.0)	
Gestational weight gain (kg)	15.5 (6.0, −23.4-33.3)	
Gestational age at enrollment (wk)	10.6 (2.6, 5.1-23.7)	
	No. subjects	%
Race/Ethnicity		
White	728	69
Black or African American	181	17
Hispanic or Latina	65	6
Asian	46	4
>1 race	39	4
Highest grade level completed		
Less than high school or high school diploma	115	11
Some college/tech school	233	22
College graduate	385	36
Postgraduate degree	326	31
Marital status		
Married	861	81
Divorced/Separated/Cohabitating/ Never married/Other	198	19
Number of previous pregnancies		
0	314	30
≥1	745	70
Household income		
$20,000 or less	42	4
20,001-40,000	104	10
40,001-70,000	234	22
>70,000	593	56
Don't know	36	3
Missing data	50	5
Financial security (duration of standard of living if lost income)		
<6 months	526	50
>6 months	294	28
Don't know	100	9
Missing data	139	13
Glucose tolerance status		
Normal	613	58
Impaired glucose tolerance	80	8
Failed glucose challenge test but no fasting test	18	2
Gestational diabetes	29	3
Pre-existing diabetes	14	1
No test result	305	29

Table IV shows the effects of maternal age in multivariate models, expressed as predicted increment of newborn systolic blood pressure for each increase of 5 years of maternal age. The base model, not including any covariates

Table III. Characteristics of 1059 participating newborns from Project Viva

Characteristic	Mean (SD, range)	
Gestational age at birth (wk)	39.7 (1.4, 33.6-43.3)	
Birth weight (kg)	3.51 (0.50, 1.42-5.53)	
Systolic blood pressure (mm Hg)	72.6 (9.0, 46.2-120.3)	
Heart rate (bpm)	122.4 (14.0, 79.8-171.2)	
	No. subjects	%
Age at blood pressure measurement		
<24 h	426	40
24-<48 h	482	46
48-<72 h	108	10
≥72 h	43	4

except blood pressure measurement conditions, estimated an increase of 0.8 mm Hg (95% CI 0.3, 1.3). The addition of several confounding variables in models 2 and 3 did not materially change this estimate. Additional control for maternal third trimester systolic blood pressure and measures of glucose tolerance, which could be construed as part of the biological pathway instead of true confounding variables, likewise did not alter the estimate (0.8 mm Hg [95% CI 0.2, 1.4]).

Because studies of newborn blood pressure are few, it is also of interest to examine the independent associations of several variables with this outcome. Table V shows that in this sample, increasing birth weight was related to higher newborn systolic blood pressure (2.9 mm Hg [95% CI 1.6, 4.2] for each kg increment in birth weight). Maternal prepregnancy body mass index was not associated with the outcome. Although maternal third trimester blood pressure did not appear to mediate the association between maternal age and newborn blood pressure, it was a strong independent predictor of the outcome. For every 10-mm Hg rise in third trimester systolic blood pressure, the model estimated a 0.9-mm Hg increase (95% CI 0.2, 1.6) in newborn systolic blood pressure. We also observed, as others have, that blood pressure rose swiftly during the first few days of life; every 24 hours of life was associated with a 2.4-mm Hg rise (95% CI 1.7, 3.0) in systolic blood pressure. In addition, heart rate appeared to be related to blood pressure level, with an estimated increase of 0.3 mm Hg (95% CI -0.04, 0.7) for each increment of 10 beats per minute.

Variables that were not associated with newborn blood pressure include maternal race/ethnicity, education, income, financial security, level of glucose tolerance, gestational weight gain, and infant sex.

DISCUSSION

Findings from this study show that systolic blood pressure among newborns was approximately 0.8 mm Hg higher for each increase of 5 years in maternal age, even after controlling for potentially confounding factors. Our model thus predicts that babies of mothers in their early 40s would have average systolic blood pressure approximately 4 mm Hg
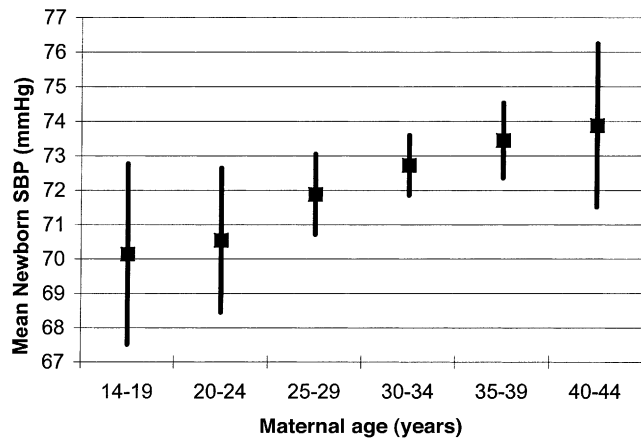
Figure. Mean and 95% CI for newborn systolic blood pressure (SBP) by maternal age group. Data from 1059 mothers and newborns participating in Project Viva.

Table IV. Increment in newborn systolic blood pressure (mm Hg) for each increase of 5 years of maternal age, from mixed linear models

Model covariates	Change in SBP (mm Hg) per 5 y of maternal age	95% CI
1. None (maternal age and blood pressure measurement conditions only)	0.8	0.3, 1.3
2. Model 1 + maternal BMI, gravidity, birth weight, infant heart rate, infant age when BP measured	0.6	0.1, 1.1
3. Model 2 + race/ethnicity, education, household income, financial security, marital status	0.8	0.2, 1.4
4. Model 3 + 3rd trimester SBP, glucose tolerance status	0.8	0.2, 1.4

BMI, Body mass index; *SBP*, systolic blood pressure; *CI*, confidence interval.
Data from 1059 mothers and newborns participating in Project Viva.

Table V. Predictors of newborn systolic blood pressure (mm Hg) from a mixed linear regression model that included all variables shown in the table

Model covariates	Change in SBP (mm Hg)	95% CI
Maternal age (5 y)	0.8	0.2, 1.4
Birth weight (kg)	2.9	1.6, 4.2
Primigravida vs not	0.2	−1.0, 1.4
Prepregnancy BMI (kg/m^2)	0.01	−0.1, 0.1
3rd trimester SBP (10 mmHg)	0.9	0.2, 1.6
Infant age when BP measured (24 h)	2.4	1.7, 3.0
Heart rate (10 bpm)	0.3	−0.04, 0.7

BMI, Body mass index; *SBP*, systolic blood pressure; *CI*, confidence interval.
Data from 1059 mothers and newborns participating in Project Viva. Estimates also adjusted for race/ethnicity, education, financial security, household income, marital status, glucose tolerance status, and newborn blood pressure measurement conditions.

higher than babies born to women younger than aged 20 years. This is a substantial difference in the newborn period, when mean systolic blood pressure is <80 mm Hg. In addition, although maternal third trimester blood pressure was a strong independent predictor of newborn blood pressure, it did not explain the effect of maternal age. Other predictors of higher newborn blood pressure included higher maternal blood pressure in late pregnancy and higher infant birth weight.

Blood pressure in the newborn period may reflect phenomena different than blood pressure only a few months later in infancy. Starting as early as aged 6 months, blood pressure levels correlate with levels measured later in childhood, suggesting that the precursors of essential hypertension may be present in late infancy.[24,25] However, tracking from birth to aged 6 months appears to be weaker.[25,26] In addition,

unlike blood pressure measured at older ages, birth weight is not inversely associated with newborn blood pressure.[2-10] Among 476 Dutch infants, Launer et al[6] showed a direct association at age 1 week and an inverse association at age 3 months, suggesting that the birth weight-blood pressure association reverses direction sometime between these two ages. One might speculate that underlying this reversal are the profound changes in the cardiac circulation during the first few weeks of life, with the right heart giving way to the left as the major supplier of the systemic circulation. The rapid rise in blood pressure during the first days to weeks of life, shown in this and in previous studies,[24-26] is consistent with this speculation.

If newborn blood pressure is not a predictor of later hypertension, perhaps it reflects instead the development of cardiac structure and function during fetal life. Evidence is accumulating that the fetal environment affects newborn cardiac structure and function in humans. Hornberger et al[27] and Lipshultz et al[28] have found that HIV-negative children born to HIV-positive mothers have higher placental vascular resistance than do children born to uninfected mothers, and that they show evidence of ventricular dysfunction in infancy. Although these findings do not pertain directly to newborn blood pressure, they do suggest that an insult occurring solely in utero can profoundly affect cardiovascular health in the offspring.

Our results do not explain why older mothers would deliver newborns with higher blood pressure. It is possible that older mothers have poorer blood flow to the placenta, perhaps because of a larger average burden of cardiovascular risk factors. Decreased uteroplacental blood flow could lead to placental dysfunction and elevated blood pressure in the offspring through hormonal changes[29] or through some other means. Empirical data linking maternal age with placental dysfunction, however, are few. Yamada et al[18] did find advanced maternal age to be associated with higher proliferative activity

of trophoblasts. Other published evidence is indirect, as it links maternal age not with placental dysfunction itself but with various conditions associated with placental dysfunction, such as risk of preterm delivery, abruptio placentae, and need for neonatal intensive care.[30-32] In addition, although maternal third trimester blood pressure predicted offspring blood pressure in our data, neither it nor measures of glucose tolerance appeared to mediate the maternal age affect. Examination of placental material in future studies might shed light on these hypothesized biological explanations for our findings.

Our study has several strengths, including a relatively large sample size, carefully measured blood pressure, and information on a large number of covariates. However, we had no physiological information on fathers, and the relatively high socioeconomic position of our participants could limit the ability to generalize.

At present, there is no need to conclude that older mothers have children at high risk for hypertension. Nor should clinicians use these results to recommend that women avoid becoming pregnant at older ages. Rather, the findings suggest that newborn blood pressure may provide clues to fetal cardiac development, possibly unrelated to later hypertension, that have implications for lifelong risk of cardiovascular disease.

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