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Early Postnatal Hypotension and Developmental Delay at 24 Months of Age among Extremely Low Gestational Age Newborns

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Abstract

Objectives—To evaluate, in extremely low gestational age newborns (ELGANs), relationships between indicators of hypotension during the first 24 postnatal hours and developmental delay at 24 months of age.

Methods—The 945 infants in this prospective study were born at < 28 weeks, were assessed for 3 indicators of hypotension in the first 24 postnatal hours, and were evaluated with the Bayley Mental Development Index (MDI) and Psychomotor Development Index (PDI) at 24 months corrected age. Indicators of hypotension included: 1) mean arterial pressure (MAP) in the lowest quartile for gestational age; 2) treatment with a vasopressor; and 3) blood pressure lability, defined as the upper quartile for the difference between the lowest and highest MAP. Logistic regression was used to evaluate relationships between hypotension and developmental outcomes, adjusting for potential confounders.

Results—26% of the cohort had an MDI < 70 and 32% had a PDI < 70. Low MDI and PDI were significantly associated with low gestational age, which in turn, was associated with receipt of vasopressor treatment. Blood pressure in the lowest quartile for gestational age was associated

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with vasopressor treatment and labile blood pressure. After adjusting for potential confounders, none of the indicators of hypotension was associated with MDI < 70 or PDI < 70.

Conclusions—In this large cohort of ELGANs, we found little evidence that early postnatal hypotension is associated with developmental delay at 24 months corrected gestational age.

Keywords

hypotension; blood pressure; mean arterial blood pressure; developmental delay; Bayley Scales of Infant Development; extremely preterm infants

Introduction

The term “cerebral blood flow autoregulation” is used to indicate that compensatory mechanisms can assure normal cerebral blood flow even when systemic blood pressure is reduced. Some preterm infants have impaired cerebral autoregulation.[1, 2] However, clinical identification of this physiological impairment remains elusive. Nevertheless, clinicians are frequently advised to treat hypotension in the preterm newborn in order to avoid brain damage that might result from impaired cerebral blood flow autoregulation.

Conflicting results have been obtained in small observational studies of the association of low arterial blood pressure (variably defined) and brain damage. In some studies,[3–9] but not in others,[10–19] low blood pressure has been associated with a higher risk of intraventricular hemorrhage (IVH) or white matter damage identified by cranial ultrasound. The few studies reporting an association between hypotension and developmental delay were small and do not appear to have adequately controlled for potential confounders.[8, 20–22]

In this study, we evaluated relationships between hypotension indicators in the first 24 postnatal hours and developmental delay at 24 months, in a large multi-center cohort of infants born prior to 28 weeks gestation.

Methods

The ELGAN Study was designed to identify characteristics and exposures that increase the risk of structural and functional neurological disorders in ELGANs (Extremely Low Gestational Age Newborns). During the years 2002–2004, women whose babies were delivered before 28 weeks gestation were asked to enroll in the study. The project was overseen by the National Institutes of Health, the institutional review boards of 14 participating institutions, and an external Performance Monitoring and Safety Board (members appointed by the National Institutes of Neurologic Disorders and Stroke) at Children’s Hospital Boston. All variables and outcomes were defined *a priori*, and research personnel were trained prior to the start of the study.

Study participants

Mothers of eligible infants were approached for consent either upon antenatal admission or shortly after delivery, depending on clinical circumstance and institutional preference. One thousand two hundred forty-nine mothers consented to participate, and their 1506 infants

(1002 singletons, 504 twins or higher order) were enrolled. Two hundred sixty mothers were missed or did not consent. Infants derive from 14 institutions, 11 cities and 5 states. All infants were born at level III neonatal intensive care units, in either urban or suburban academic institutions.

Demographic, pregnancy and delivery variables

The clinical circumstances that led to each maternal admission and ultimately to each preterm delivery were operationally defined using data from a structured maternal interview and abstracted from the medical record.[23] Variables evaluated as potential confounders included, but were not limited to, pregnancy complications and exposures (*i.e.* antenatal steroids and magnesium), placental characteristics (*i.e.* chorioamnionitis, funisitis, and thrombosis), and neonatal characteristics ascertained at birth (*i.e.* gestational age, race, gender, and anthropomorphic measurements).

Newborn variables

The gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval, intrauterine insemination or fetal ultrasound before the 14th week (62%). When these were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks (29%), dates of the last menstrual period without fetal ultrasound (7%), and gestational age (1%). The birth weight Z-score and head circumference Z-score represent the number of standard deviations the infant's weight or head circumference are above or below the median of infants at the same gestational age in a standard data set.[24]

Hypotension indicators

The frequency of hypotension indicators was greater in the first 24 postnatal hours than on subsequent days. So was the severity of hypotensive episodes. Because brain damage that can be attributed to severe hypotension was most likely to have occurred then, we studied the lowest MAP measured during the first postnatal day. Because no single definition of hypotension is widely accepted,[19, 25] we examined three indicators of hypotension in the first 24 postnatal hours, including: 1) MAP in the lowest quartile for gestational age (23–24, 25–26, and 27 weeks); 2) treatment for hypotension using a vasopressor (dopamine, dobutamine, epinephrine); and 3) blood pressure lability, defined as the upper quartile for the quantity (highest MAP – lowest MAP).

Data forms were developed prior to the start of the study, and multiple training sessions were held to train research personnel in standardized approaches to data collection from the hospital chart. The lowest, highest, and mode blood pressure measurements were abstracted from the medical record, for each day. We did not collect information about the method used for measuring blood pressure (oscillometry vs. intra-arterial catheter). MAP in the lowest quartile represents the lowest quartile blood pressures for a broad sample of ELGANs. Vasopressor use served as a "functional" definition of hypotension; regardless of how the clinician arrived at the decision to treat, he/she deemed the infant hypotensive enough to require treatment. Blood pressure lability was chosen because it has been associated with intraventricular hemorrhage.[17]

Because 75% of the infants in this study received volume expansion in the first 24 hours, receipt of volume expansion was not included as a variable in analyses.

24-month developmental assessment

A developmental assessment was performed by certified examiners at 24 months corrected gestational age. Families were invited to bring their child for a developmental assessment, which included the Bayley Scales of Infant Development - Second edition (BSID-II).[26] Only 2% of examiners indicated at the time of the examination that they had more than a limited amount of information about the child. Before testing, examiners were told the child's age. After completion of testing, examiners were told the gestational age so that the Mental Development Index (MDI) and Psychomotor Development Index (PDI) could be appropriately age-adjusted.

Developmental delay was defined as either an MDI < 70 or a PDI < 70. The child was classified as non-testable on a scale if her/his impairments prohibited standardized administration, or more than 2 items were judged to be 'not applicable'. On the basis of their Vineland Adaptive Behavior Scales Composite score, 26 of 33 children considered non-testable were assigned an MDI of < 70 (N=23) or ≥ 70 (N=3).[27] On the basis of the motor scale (#4) of the Vineland Adaptive Behavior Scales, 32 of 38 considered non-testable were assigned a PDI of < 70 (N=27) or ≥ 70 (N=5).

Data analysis

We evaluated the null hypothesis that children with an indicator of hypotension during the first 24 postnatal hours were no more likely than their peers to have developmental delay at 24 months.

In order to detect potential confounders, we compared the distribution of other characteristics and exposures among children who had each indicator of hypotension to the distribution among children who did not. We then compared the distribution of these characteristics and exposures among children who did and did not have an MDI < 70 or a PDI < 70.

To be identified as a potentially important confounder, characteristics and exposures of the pregnancy, delivery, and postnatal period had to be associated with both the exposure (hypotension indicator) and the outcome (low Bayley score) with a p-value ≤ 0.25. These were entered into time-oriented risk models that allowed antenatal and perinatal antecedents of hypotension indicators to be considered before variables for hypotension indicators were added.

Outcome measures were modeled as a dichotomy, (*e.g.* MDI < 70 and MDI ≥ 70), in an effort to minimize bias associated with detecting small, perhaps clinically unimportant variations in outcome appreciated with the use of continuous variables. The contribution of relevant characteristics and exposures to the outcome of interest are presented as odds ratios with 95% confidence intervals. To account for the possibility that infants born at a particular hospital are more like each other than infants born at other hospitals, a hospital cluster term was included in all models.[28]

Here we present data adjusted for gestational age in groups of weeks, (*i.e.* 23 to 24 weeks, 25 to 26 weeks, and 27 weeks). Early analyses included an adjustment for illness severity (SNAP-II).[29] However, because lowest MAP in the first 12 hours is a component of SNAP-II, it was removed from the model. Removal of the adjustment for illness severity resulted in no difference in adjusted risk ratios (data not shown).

Results

The three indicators of hypotension were available for 1341 (89%) of the infants in the ELGAN sample. At 24 months adjusted age, 1120 (84%) of these infants were alive, and 945 (84%) were evaluated with the BSID-II (Figure 1). To evaluate the potential for bias due to surviving infants who were lost to follow up at 24 months of age, we compared characteristics of infants who returned for follow-up to those who did not (Table 1). Mothers who brought their child for a developmental assessment were more educated and more likely to be married. Their babies were born later in gestation, and were more likely to have a hypotension indicator.

Twenty-two percent of infants were hypotensive, defined as MAP in the lowest quartile for gestation, and 64% were hypotensive, defined as MAP (in mmHg) less than gestational age (in weeks). Due to the high proportion of infants with MAP < gestational age, any relationship between MAP in the lowest quartile for gestation and other characteristics, exposures, and abnormal development, would be statistically stronger than a relationship identified with MAP < than gestational age. We report only the results for hypotension defined as MAP in the lowest quartile for gestation.

Infant characteristics (Table 2, Figure 2)

Twenty-five percent of the entire cohort had blood pressure in the lowest quartile, whereas 21% of survivors had a blood pressure this low, indicating an association between blood pressure in the lowest quartile and mortality. Twenty-six percent of infants were treated with vasopressors and 24% had labile blood pressure. Twenty-six percent of infants had an MDI < 70 and 32% had a PDI < 70.

The rate of MDI < 70 was higher in males, but males were only minimally more likely than females to have a hypotension indicator. Lower gestational age was associated with higher risk of vasopressor treatment and labile blood pressure. Lower gestational age infants were also at higher risk of having an MDI or PDI < 70.

Infants who had a low birth weight Z-score were at heightened risk of a blood pressure in the lowest quartile for gestation and labile blood pressure, but not for treatment with a vasopressor. Infants with a low birth weight Z-score and low head circumference Z-score, a correlate of low birth weight Z-score, also had a heightened risk of an MDI or PDI < 70.

Social, demographic and pregnancy characteristics (Table 3)

Indicators of social disadvantage, specifically education less than 12 years and public insurance, were associated with a higher rate of MDI < 70. However, because education and

public insurance were not associated with hypotension indicators, they are not potential confounders, and therefore were not included in multivariate analyses.

Univariate relationships: hypotension indicators and developmental delay (Table 4)

Vasopressors were given to less than half of infants with MAP in the lowest quartile, and one third of infants with a labile blood pressure. However, hypotension and vasopressor therapy conveyed very little information about the risk of low MDI and PDI, and labile blood pressure conveyed even less. Univariate analyses identified black race, public insurance, primigravida, male sex, gestation 23–24 weeks, and birthweight z-score < −1 as potentially important confounders.

Multivariate relationships: hypotension indicators and developmental delay (Figure 3)

In the unadjusted models for MDI < 70, use of vasopressors approached, but did not reach, statistical significance with an odds ratio of 1.4 (95% CI: 0.98–2.0). After adjusting for confounders, none of the indicators of hypotension studied here was significantly associated with an MDI < 70 or a PDI < 70.

Discussion

After controlling for potentially important confounders, we found little evidence for an association between early postnatal hypotension and developmental delay in a large cohort of extremely preterm infants.

In this study, 78% of the infants received some treatment (vasopressor or volume expansion) for hypotension in the first 24 postnatal hours. The proportion of infants treated for hypotension varied greatly among the 14 centers, even after adjustment for maternal and neonatal risk factors.[25] Although we do not know what provoked the majority of clinicians to initiate treatment for hypotension, it is likely that the perception of harm to the central nervous system was a key motivation. To the extent that early volume expansion ameliorates the adverse effects of hypotension, our inferences apply only to cohorts that receive volume expansion liberally, as 75% of ELGANs in this study received volume expansion in the first 24 hours. If volume expansion is not beneficial, our inferences might apply more broadly.

The correlation of blood pressure and cerebral blood flow has been studied using a number of techniques, including near-infrared spectroscopy,[2, 30, 31] trans-cranial doppler,[32, 33] superior vena cava blood flow,[33–36] and ventricular output.[33, 37] While some studies have shown positive correlations between blood pressure and cerebral blood flow,[2, 30, 32, 38, 39] others have not.[31, 33, 36, 37, 40, 41] Thus, blood pressure might not be a sensitive indicator of the putative effect of insufficient cerebral perfusion on the preterm brain, which might explain why abnormalities of cerebral blood flow have been associated with cranial ultrasound lesions,[34, 35, 38, 42–46] but systemic hypotension has not.[10–19]

Our finding that early postnatal hypotension is not associated with developmental delay contrasts with conclusions from several prior studies of hypotension and developmental status assessed with the BSID-II or a similar instrument, the Griffiths Scale.[8, 20–22] Studies reporting an association between hypotension and developmental delay were small, single-

center studies, decreasing the likelihood that multiple potential confounders could be adequately controlled.[8, 20–22] Hypotensive infants are frequently treated with vasopressors, and only two of the studies reporting an association between hypotension and developmental delay adequately controlled for treatment.[21, 22] Further, two of the studies favoring an association between hypotension and developmental delay reported composite developmental outcomes.[8, 22] Since individual outcomes do not contribute equally to composite measures, the overall effect estimate for a composite measure cannot be assumed to apply equally to each of its individual outcomes.[47]

Our failure to detect an association between hypotension and developmental delay has several possible explanations. The first and perhaps most likely is that early postnatal hypotension is not associated with brain damage in preterm newborns. This is what one would expect if the physiologic transition from intra-uterine to extra-uterine life were not associated with reduced cerebral blood flow.[40, 48] If poor cerebral perfusion is associated with brain damage in preterm newborns, then our findings suggest that hypotension is not a reliable indicator of poor cerebral perfusion.

Because none of the potential confounders are in any way negatively associated with low blood pressure or low BSID, we do not consider negative confounding an explanation for our failure to detect an association between early postnatal hypotension and developmental delay.[49] Our study sample was large enough to detect the confounding influence of treatment (with vasopressors) on outcome, and our results suggest a near-significant association between vasopressor use and developmental delay. A possible explanation for this finding is that use of vasopressors could have adverse effects. An alternative explanation is that the severe physiologic abnormalities that prompted therapy provide information about the risk of brain damage. This would occur if clinicians provided therapy to those infants at highest risk of morbidities, e.g. infants born at lower gestational age,[50] a bias referred to as confounding by indication.[51–53]

The strengths of our study include the use of prospectively collected data from a large multicenter cohort, defined by gestational age (rather than birth weight),[54] and the use of follow up data collected by examiners who were trained in the standardized administration of the BSID-II. Examiners were masked to infants' medical histories, including the infant's corrected gestational age at the follow-up visit.

A potential limitation of our study is the lack of a consistent method for obtaining MAP. Some MAP measurements were obtained by intra-arterial catheters, others by oscillometry. The latter method overestimates blood pressure.[55, 56] The direction of the resulting bias would depend on whether an association exists between the method by which infants' blood pressures were measured and their risks of developmental delay. Other limitations include the intermittent collection of MAP data, and the possibility that we missed the lowest MAP during the first 24 hours. Since a large proportion of ELGANs in this study received volume expansion, we are unable to speculate regarding the effects of hypotension on developmental status for cohorts in which volume expansion is used sparingly. We also acknowledge that the agreement between early developmental assessments (20 to 24 months) and school-age outcomes (5 to 8 years) is not strong.[57]

We did not report on the presence or absence of acidosis for two reasons. First, the available data did not permit a temporal correlation between recorded blood pressure and blood gas measurements. Second, hypotension is only one of a number of events that contribute to acidosis in the early postnatal period. These factors include, but are not limited to, utero-placental insufficiency, abruptio-placenta, maternal medications, and chorioamnionitis. Consequently, acidosis reflects much more than poor systemic perfusion in the early postnatal period, and cannot be viewed as a surrogate for poor perfusion. Therefore, we chose to address only the contribution of early postnatal hypotension to developmental outcomes.

Despite these limitations, our study has implications for researchers interested in preventing developmental delay in extremely preterm infants. Specifically, our study casts doubt on the concept that early postnatal hypotension is an important risk factor for such delays, and the corollary that interventions to increase blood pressure can prevent such delays.

The implications for clinicians are important as well, as ELGANs are frequently given treatments to increase blood pressure under the assumption that these treatments decrease the risk of brain injury. This assumption is not supported by observational studies,{Kuint, 2008 #101;Dempsey, 2009 #125} and there is a paucity of support for therapies widely used to treat hypotension.{Pellicer, 2009 #127;Dempsey, 2007 #41} Treatment for hypotension has been associated with abnormal development,{Kuint, 2008 #101;Greenough, 2002 #50;Fanaroff, 2006 #42} hearing loss,{Kuint, 2008 #101;Fanaroff, 2006 #42} and severe brain ultrasound abnormalities in low birth weight infants.{Kuint, 2008 #101;Goldberg, 1980 #51;Salafia, 1995 #43;O'Shea, 1998 #90;Synnes, 2001 #94;Greenough, 2002 #50;Batton, 2007 #44} Thus, while it is possible that the decision to treat reflects the physician's perception that the infant is vulnerable, it is also suggests the possibility that these therapies are harmful.

In conclusion, we found that hypotension and therapy for hypotension during the first 24 postnatal hours is associated with a small increased risk for a low MDI, which despite our large sample of 945 infants did not achieve statistical significance.

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Abbreviations

BSID-II	Bayley Scales of Infant Development – Second Edition
ELGAN	extremely low gestational age newborn
GMFCS	Gross Motor Function Classification System
IVH	intraventricular hemorrhage

M-CHAT	Modified Checklist for Autism in Toddlers
MAP	mean arterial pressure
MDI	Mental Development Index
PDI	Psychomotor Development Index

Hypotension.BSID Bibliography

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What is already known on this topic

The available literature contains conflicting results regarding the association of low arterial blood pressure and brain damage in ELGANs. In some studies, low blood pressure has been associated with an increased risk of brain damage identified by cranial ultrasound, while in other studies these associations were not found. The few studies reporting an association between hypotension and developmental delay were small, and do not appear to have adequately controlled for potential confounders.

What this study adds

This study casts some doubt on the concept that early postnatal hypotension is associated with developmental delay, and the corollary that treatment for hypotension improves developmental outcomes. Contrary to the findings of others, we found little evidence for an association between early postnatal hypotension and developmental delay in a large cohort of extremely preterm infants. Our findings should provide some motivation for the development of clinical trials that address questions regarding hypotension and developmental outcomes.

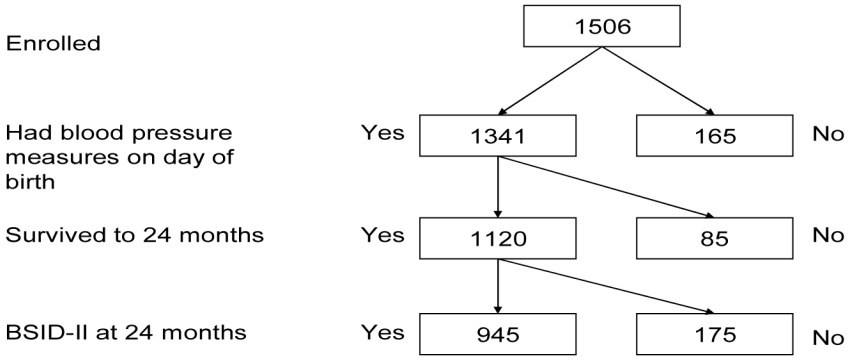

Figure 1.
Sample for analyses of hypotension and developmental delay

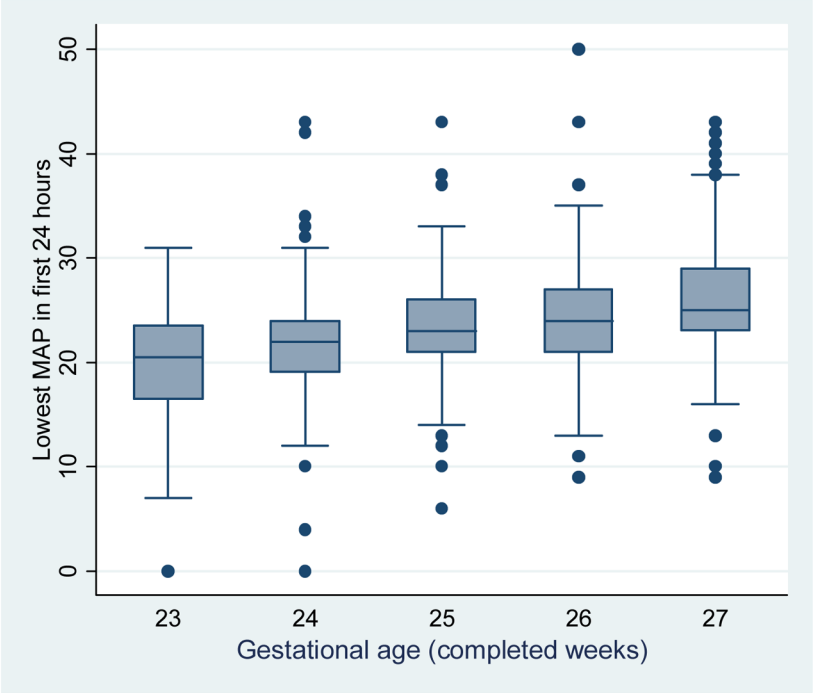

Figure 2.

Lowest MAP (mmHg) in the first 24 hours and Gestational Age (weeks). The bottom of each dark box marks the upper boundary of the lowest quartile, and measures below this boundary are those that were included in our analysis as a hypotension indicator. Asterisks represent outliers.

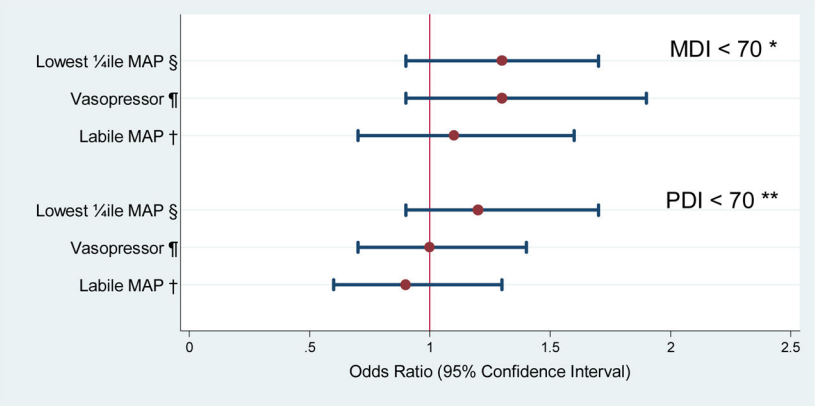

Figure 3.

Odds ratios (and 95% confidence intervals) of the risk of MDI <70 and PDI <70 obtained with logistic regression models that incorporate indicators of hypotension during the first 24 postnatal hours and potential confounders.

* Adjustedfor black race, public insurance, primagravida, male sex, gestational age 23–24 weeks, birth weight Z-score < −1, and center

** Adjusted for public insurance, male sex, multiple birth, gestational age 23–24 weeks, birth weight Z-score < −1, and center

§Lowest ¼ile MAP: lowest MAP recorded in the first 24 hours, in the lowest quartile for gestational age

¶Vasopressor: treatment for hypotension in the first 24 hours, using any vasopressor (dopamine, dobutamine, epinephrine)

†Labile MAP: labile blood pressure, defined as the upper quartile of the difference in the lowest and highest MAP

MDI Mental Developmental Index

PDI Psychomotor Developmental Index

Table 1

Comparison of characteristics of mothers and children who were followed to those of mothers and children who were not. Presented as column percents.

Maternal or infant characteristic		Followed	Not followed
Maternal education	< 12	18	24
	12 (High school)	26	28
	>12 to <16	23	28
	College grad	18	14
	> 16	14	6
Married	Yes	56	44
Public insurance	Yes	41	50
Delivery complication	Preterm labor	43	43
	pPROM	22	22
	Preeclampsia	15	11
	Abruption	11	10
	Cerv insufficiency	5	7
	Fetal Indication	3	6
Sex	Male	53	55
Black race	Yes	27	27
Gestational age (wks)	23–24	20	26
	25–26	47	46
	27	33	29
Birth weight Z-score	< −2	6	3
	≥ −2, < −1	12	11
	> −1	82	86
Head circumference Z-score	< −2	8	5
	≥ −2, < −1	23	20
	> −1	69	75
Lowest ¼ile MAP[§]	Yes	22	15
Vasopressor [¶]	Yes	26	19
Labile MAP[†]	Yes	24	17
Max number of infants		945	175

[*] Yudkin standard [24]

[§] Lowest ¼ile MAP: lowest MAP recorded in the first 24 hours, in the lowest quartile for gestational age

[¶] Vasopressor: treatment for hypotension in the first 24 hours, using any vasopressor (dopamine, dobutamine, epinephrine)

[†] Labile MAP: labile blood pressure, defined as the upper quartile of the difference in the lowest and highest MAP

Table 2

Infant characteristics, indicators of hypotension, and developmental delay (row percents).

Characteristics of the infant		Lowest ¼ile MAP[§]	Vasopressor[¶]	Labile MAP[†]	BSID < 70		N
					MDI	PDI	
Sex	Male	22	28	25	32	34	497
	Female	22	24	23	20	29	448
Black race	Yes	27	26	31	40	35	253
	No	20	26	21	22	30	677
Type of gestation	Singleton	22	23	26	25	30	632
	Multiple	21	32	20	27	36	313
Gestational age (weeks)	23–24	19	37	28	37	40	190
	25–26	20	24	23	26	31	443
	27	26	21	22	21	27	312
Birth weight (grams)	≤750	21	31	28	35	39	346
	751–1000	24	25	23	24	28	421
	1001–1250	19	17	18	15	25	162
	> 1250	13	44	18	19	31	16
Birth weight Z-score [*]	< −2	26	23	32	38	51	53
	≥ −2, < −1	24	27	29	32	36	117
	≥ −1	21	26	22	25	30	775
Birth head circumference Z-score [*]	< − 2	27	30	26	36	45	73
	≥ −2, < −1	22	23	24	31	31	207
	≥ −1	22	26	23	25	30	634
Max number of infants		206	244	225	250	300	945
Row percent		22	26	24	26	32	

[*] Yudkin standard [24]

[§] Lowest ¼ile MAP: lowest MAP recorded in the first 24 hours, in the lowest quartile for gestational age

[¶] Vasopressor: treatment for hypotension in the first 24 hours, using any vasopressor (dopamine, dobutamine, epinephrine)

[†] Labile MAP: labile blood pressure, defined as the upper quartile of the difference in the lowest and highest MAP

BSID: Bayley Scales of Infant Development; MDI: Mental Developmental Index; PDI: Psychomotor Developmental Index

Table 3

Maternal characteristics, indicators of hypotension, and developmental delay (row percents).

Maternal characteristics		Lowest ¼ile MAP[§]	Vasopressor[¶]	Labile MAP[†]	BSID < 70		N
					MDI	PDI	
Years of education	< 12	27	25	23	43	33	147
	12 (High school)	23	23	24	32	38	244
	>12 to <16	20	22	28	26	30	214
	College grad	19	27	24	16	28	172
	> 16	24	34	21	15	26	137
Married	Yes	20	26	21	22	30	560
	No	25	26	27	33	35	385
Self supported	Yes	21	28	21	25	33	623
	No	25	21	30	31	29	302
Public insurance	Yes	26	24	29	36	36	352
	No	20	26	21	21	29	574
Primagravida	Yes	24	29	22	20	32	371
	No	21	24	26	32	32	549
Any conception assistance	Yes	18	33	17	18	34	201
	No	23	24	26	29	31	718
Pre-pregnancy BMI	< 18.5	26	27	26	23	33	66
	18.5 to 25	21	26	23	23	29	456
	25.1 to 30	23	26	27	23	28	188
	≥30	24	24	23	38	41	197
Vaginitis	Yes	21	21	30	37	38	126
	No	22	26	23	25	30	792
Aspirin	Yes	21	31	21	35	37	52
	No	22	25	24	26	31	863
Pregnancy complication	Preterm labor	21	27	22	25	33	427
	pPROM	23	25	25	27	32	206
	Preeclampsia	20	20	26	32	33	123

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Maternal characteristics		Lowest ¼ile MAP[§]	Vasopressor[¶]	Labile MAP[†]	BSID < 70		N
					MDI	PDI	
	Abruption	24	25	30	18	23	104
	Cerv insufficiency	25	36	21	34	39	53
	Fetal Indication	25	28	25	44	34	32

[§]Lowest ¼ile MAP: lowest MAP recorded in the first 24 hours, in the lowest quartile for gestational age

[¶]Vasopressor: treatment for hypotension in the first 24 hours, using any vasopressor (dopamine, dobutamine, epinephrine)

[†]Labile MAP: labile blood pressure, defined as the upper quartile of the difference in the lowest and highest MAP

BSID: Bayley Scales of Infant Development; MDI: Mental Developmental Index; PDI: Psychomotor Developmental Index; BMI: body mass index; pPROM: preterm premature rupture of membranes; Cerv insufficiency: Cervical insufficiency

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Table 4

Frequencies of indicators of hypotension and developmental delay (row percents).

Exposures and BSID outcomes		Lowest ¼ile MAP[§]	Vasopressor[¶]	Labile MAP[†]	BSID < 70		N
					MDI	PDI	
Lowest ¼ile MAP[§]	Yes		45	42	30	34	206
	No		20	19	25	31	739
Vasopressor [¶]	Yes	38		30	31	35	244
	No	16		22	25	31	701
Labile MAP [†]	Yes	39	32		28	30	225
	No	17	24		26	32	720
BSID MDI < 70	Yes	25	30	26		70	250
	No	21	24	23		20	695
BSID PDI < 70	Yes	24	28	22	58		300
	No	21	25	25	12		645
Maximum number of infants		206	244	225	250	300	945
Row percent		22	26	24	26	32	

[§]Lowest ¼ile MAP: lowest MAP recorded in the first 24 hours, in the lowest quartile for gestational age

[¶]Vasopressor: treatment for hypotension in the first 24 hours, using any vasopressor (dopamine, dobutamine, epinephrine)

[†]Labile MAP: labile blood pressure, defined as the upper quartile of the difference in the lowest and highest MAP

BSID: Bayley Scales of Infant Development; MDI: Mental Developmental Index; PDI: Psychomotor Developmental Index