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Cardiovascular Stress Hyperreactivity in Babies of Smokers and in Babies Born Preterm

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Background—Being born preterm, small, and to a mother who smokes are common perinatal complications with major public health implications. Evidence suggests that each affects the body's structure and function in ways that could increase susceptibility to cardiovascular dysfunction later in life. Here, we used 2 routine stress reactivity tests to identify incipient “silent” programming of cardiovascular dysfunction associated with adverse perinatal events.

Methods and Results—We studied 29 control babies born at term to nonsmokers, 18 term-born babies of mothers who smoked throughout pregnancy (mean, 15 cigarettes a day), and 31 babies born preterm to nonsmokers. All infants were compared at the same age after conception (ie, at 40 to 42 weeks), during sleep. We analyzed blood pressure (BP) and heart rate responses to breathing 4% CO₂ for 4 minutes or to passive head-up tilt to 60°. BP was measured continuously from a wrist cuff. CO₂ exposure raised heart rate and BP in controls by 10%, and tilt increased their BP by 5%. CO₂ elicited the expected BP but no heart rate response from preterm infants but a much-greater-than-expected BP and heart rate response from babies of smokers. Tilt elicited a 3- to 4-fold greater rise in BP from preterm and tobacco-exposed babies.

Conclusions—Vascular, cardiac, and blood pressure reactivity is heightened in babies born preterm or to smokers. The findings are consistent with in utero and early postnatal “programming” of human cardiovascular dysfunction by adverse circumstances. This incipient dysfunction may be an early manifestation of processes that lead to other problems or complications later on (eg, higher BP or sudden infant death syndrome). (*Circulation*. 2008;118:1848-1853.)

Key Words: blood pressure ■ postnatal development ■ nervous system, autonomic ■ pediatrics
■ physiology ■ tobacco

The evidence is compelling that events early in life have an enduring impact on development and health. Being born too early, too small, and to a mother who smokes are 3 such common events with major public health implications. Preterm birth, currently accounting for nearly 8% of all deliveries, is the leading cause of neonatal death and disability and is a risk factor for elevated blood pressure later in life.¹⁻³ Nearly 10% of all babies grow poorly in utero (growth restriction) and are born small for gestational age (SGA). These babies are more susceptible to diseases such as hypertension later in life.⁴⁻⁶ Smoking is the most common preventable cause of poor infant outcome; 20% to 50% or more of mothers, depending on age, nationality, and ethnicity, smoke during pregnancy.^{7,8} Babies of these women are more at risk of dying of sudden infant death syndrome and have raised systolic blood pressure in childhood, findings that suggest, among other things, an adverse effect of tobacco products on the immature cardiovascular system.⁹⁻¹² All 3 entities also may go hand in hand; smoking increases the odds of a baby being born preterm and/or SGA.¹³ Despite the

strong epidemiology linking early events to later dysfunction, we do not know when pathophysiological changes first appear, how they evolve over time, or what mechanisms and pathways are involved. The answers to these questions may provide new opportunities for the early diagnosis, treatment, and prevention of cardiovascular disease.

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To address the first of these questions, we compared babies from uneventful and “adverse” pregnancies at the same age after conception for signs of incipient dysfunction in heart rate and blood pressure control in the latter. We analyzed reactivity to mild stress because stress may unmask physiological anomalies long before clinical symptoms such as elevated blood pressure at rest appear.^{14,15} Blood pressure and heart rate were recorded continuously while infants either breathed a low concentration of CO₂ for several minutes or were passively repositioned (“tilted”) several times from horizontal to upright then back to lying. Both methods are routinely used to test autonomic responses, including cardio-

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Table. Characteristics of the Study Population

Study Group (n)	GA, wk	PNA, d	PMA, wk	Birth Wt, g	Study Wt, g	Tests, n	Pretest Baseline			
							HR, bpm	MBP, mm Hg	SBP, mm Hg	DBP, mm Hg
Term-control (29)	40±1	7±6	40±1	3547±412	3584±418	H, 16	124±15	74±11	87±12	62±9
						T, 53	115±12	75±10	88±11	65±9
Term-tobacco (18)	39±2	12±10	41±2	3230±590	3364±501	H, 12	123±20	74±11	87±12	62±11
						T, 30	126±12	71±10	83±11	60±9
Preterm-AGA (15)	31±2*	67±19*	40±1	1755±531*	3179±311	H, 11	143±15*	68±9*	84±12	54±10*
						T, 20	136±10*	65±8*	79±10	52±7*
Preterm-SGA (16)	32±2*	53±10*†	40±1	1313±578*†	2361±522*†	H, 16	145±13*	67±9*	83±10	52±7*
						T, 18	142±8*	61±6*	76±6	49±5*
Omnibus P	<0.0001	<0.0001	0.8	<0.0001	<0.0001	H	0.001	0.005	0.4	0.001
						T	0.001	0.004	0.05	0.002

GA indicates gestation age at birth; PNA, postnatal age; PMA, postmenstrual age (GA+PNA); Wt, weight; HR, heart rate at rest (bpm); MBP, mean blood pressure at rest; SBP, systolic blood pressure at rest; and DBP, diastolic blood pressure at rest. Pretest baseline was the 1 minute immediately preceding each test (mean of all periods for each protocol is shown). All infants were studied during a routine daytime nap. Half in each group breathed 4% CO₂ for 4 minutes (H), and the other half were tilted (head-up to 60° for 1 minute [T]). The total number of tests is indicated in column 7. Data are mean±SD.

*Significant difference from control and tobacco-exposed infants; †significant difference from preterm-AGA infants (ANOVA).

vascular and control, especially during sleep. Each engages different mechanisms and elicits slightly different response profiles. The first boosts sympathetic drive to the heart, blood vessels, and adrenal, resulting in a slow escalation-deescalation in heart rate and blood pressure.¹⁶ The second tests short latency, including baroreflex mechanisms that resist (buffer) sudden rises or falls in blood pressure.^{17,18} Analyzing the pattern of responses to each challenge reveals how vascular and cardiac mechanisms contribute to hemodynamic stability. We looked for unusual stress reactivity patterns as evidence of early underlying, “silent” cardiovascular dysfunction consistent with the known epidemiological risks associated with being born small, early, or to a smoker.

Methods

Subjects

Our study cohort (the Table) consisted of 4 groups: (1) control infants born at term to nonsmokers (n=29), (2) infants born at term to women who smoked (n=18), (3) infants born preterm (27 to 34 weeks) and appropriately grown for gestational age (AGA) to nonsmokers (n=15), and (4) infants born preterm and SGA (or growth restricted) to nonsmokers (n=16). Term infants were born at 38 to 41 weeks, all were AGA, and all were breastfed from birth. Preterm infants were fed either expressed breast milk or a combination of expressed breast milk and formula. Smokers estimated the number of cigarettes smoked per day during each trimester of pregnancy (via questionnaire). Preterm-born infants suffered no major neonatal complications (no respiratory abnormalities except for transient tachypnea, no persistent ductus arteriosus, and no evidence of intraventricular hemorrhage or septicemia during the neonatal period). Preterm-born infants classified as SGA were below the 10th birth weight percentile for gestational age. All preterm infants were studied after discharge at a corrected age of 1 to 2 weeks (ie, at term-equivalent age). Half the term-born infants were studied just before discharge (postnatal day 2 to 3); the remainder were studied 1 to 2 weeks later.

The study complied with the Declaration of Helsinki. The relevant Institutional Ethics Review committees approved all procedures, and written informed consent was obtained from the parents of all infants who participated.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Procedures

Infants were studied during a routine daytime nap lying supine, lightly dressed, in a warm (20°C to 21°C) room during periods of behaviorally determined quiet sleep.¹⁹ We tested the response to either mild hypercapnia or passive head-up tilt.

Physiological Measurements

Blood pressure was recorded from a wrist cuff (Finometer, FMS, Amsterdam, the Netherlands) as described previously.¹⁶ During the hypercapnic but not the tilt protocol, we also recorded chest and abdominal breathing movements (Respirtrace, Ambulatory Monitoring Inc, Ardsley, NY), ECG, and transcutaneous PCO₂ (Radiometer TCM3, Copenhagen, Denmark). A detailed description of the hypercapnic protocol can be found elsewhere.¹⁶ Briefly, a 10-L polycarbonate head box was continuously flushed with gas (air or 4% CO₂ in air). Tests were made up of a 2-minute baseline (the box was flushed with air), followed by 4% CO₂ in air for 4 minutes and then back to air for 4 minutes (total, 10 minutes); test were repeated twice. For the tilt tests, the infant slept supine on a custom-built tilt table. Babies were comfortably padded and secured in a harness to maintain the baby’s head in the midline and to prevent limb or body movements during tilt. To eliminate hydrostatic gradients when upright, the cuffed wrist was always kept at the level of the heart. Once heart rate and blood pressure had been steady for 30 seconds, baby was tilted head up to 60° within 5 seconds, held in this position for 1 minute, and then returned to horizontal. Tilts were repeated after a 5- to 6-minute interval.

Analysis

Tests interrupted by a change in state, sigh, or arousal (movement of the head or limbs for ≥2 seconds accompanied by transient loss of the blood pressure waveform) were discarded. The arterial waveform was digitized and stored at 200 Hz. We used peak-and-valley detector software (Beatscope version 1.1, FMS) to calculate instantaneous systolic, diastolic, and mean blood pressures and heart rate (peak-to-peak interval). Data were expressed as relative changes from pretest baseline (30 seconds preceding each test), averaged each 5 seconds, and plotted against elapsed time to generate hemodynamic profiles. For CO₂ tests, respiratory rate (RR), breath amplitude (tidal volume, V_T), and ventilation (V=RR×V_T) were plotted against changes in transcutaneous PCO₂ to estimate the strength (slope) of the hypercapnic ventilatory response.¹⁶

Statistical Analysis

Data from successful tests were pooled, and an average tilt/CO₂ response was calculated for each infant. One-way ANOVA was used

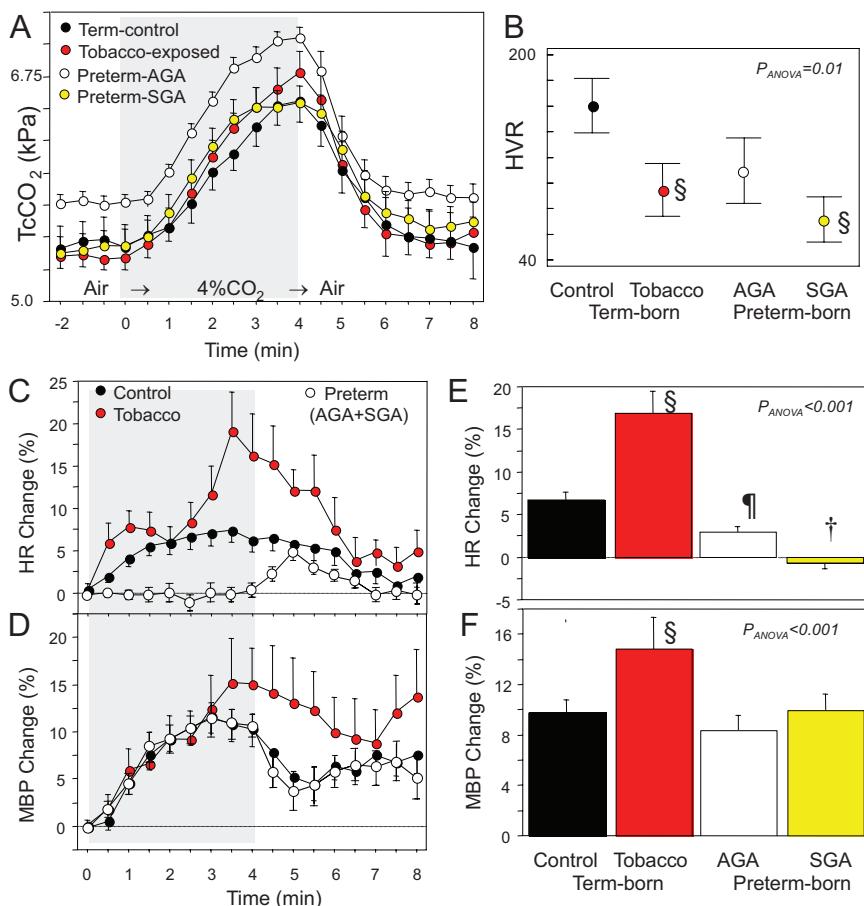


Figure 1. The CO_2 response test. A, Preterm AGA infants had mild CO_2 retention at rest, but the relative increase in tissue CO_2 levels (TcCO_2) was the same for all babies. B, Babies born preterm SGA or to mothers who smoked had the weakest hypercapnic ventilatory response (HVR; change in ventilation divided by change in PCO_2 in arbitrary units). Babies of smokers also had exaggerated and prolonged heart rate (HR; C) and mean blood pressure (MBP; D) responses to CO_2 . Comparisons at minutes 3 through 4, when CO_2 levels peaked, illustrate the heightened reactivity of these infants (E, F). Preterm infants had little or no heart rate response to CO_2 (C and E). For clarity, data for preterm AGA and preterm SGA are combined in C and D. Omnibus ANOVA P values for group comparisons are shown in B, E, and F. Significant differences from all other groups (§), from term controls (¶), and from term controls and preterm AGA (†) are indicated (multiple-range tests). Data are mean \pm SD.

to compare means across the 4 infant groups; when the global “omnibus” ANOVA was significant, pair-wise comparisons of means were undertaken with multiple-range tests adjusted with the Bonferroni correction.

We tested for differences between hypercapnic ventilatory responses using the Kruskal-Wallis test. Spearman rank correlations were used to test whether postnatal age influenced the circulatory stress reactivity of babies of smokers and nonsmokers (ie, to determine whether those tested before and after discharge home were different). Measurement error is presented as SD; values of $P \leq 0.05$ indicate significant differences/correlations with 95% confidence intervals.

Results

Characteristics of the study population are shown in the Table. At term-equivalent age, preterm SGA infants weighed 13% less than preterm AGA infants and 24% less than their AGA counterparts born at term. All preterm infants regardless of weight at birth or study had higher heart rates and lower blood pressures at rest than babies born at term (the Table). Smokers consumed 10 to 15 cigarettes a day (self-reported average throughout entire pregnancy and during breastfeeding). Babies of these mothers were slightly smaller than control infants at birth (not significant), but resting blood pressure and heart rate were within normal limits.

Maternal Smoking Exaggerates the Newborn’s Circulatory Response to CO_2

Breathing 4% CO_2 raised blood CO_2 levels of all 4 infant groups by ≈ 1 kPa (Figure 1A). Control infants had the most

and tobacco-exposed and SGA infants had the least vigorous ventilatory response to this classic breathing stimulus (Figure 1B), which normally (in control babies) also increased heart rate and blood pressure by $\approx 10\%$. Babies of mothers who smoked had exaggerated and prolonged rises in blood pressure and heart rate. Peak responses were 50% to 100% above age-matched controls, and both parameters remained elevated long after CO_2 levels returned to baseline (Figure 1C through 1F). Premature infants regardless of size at birth had a normal pressor but little or no heart rate response to CO_2 .

Complications of Pregnancy Exaggerate Sympathetic Responses to Tilt

Normally (control infants), head-up tilt while asleep caused systolic pressure to fall slightly and heart rate to rise transiently, with the peak in heart rate occurring 8 to 10 heartbeats, or about 5 seconds, after the start (ie, on reaching and stopping at 60° vertical). Subsequently, systolic, diastolic, and mean blood pressures gradually increased and settled slightly above baseline while upright and then fell slowly back to baseline on returning to horizontal (Figure 2A through 2C). For babies born to mothers who smoked or those born preterm-SGA, vertical repositioning elicited the expected rise in heart rate (Figure 2B and 2C) but an unusually exaggerated (several times greater than in control infants) and long-lasting rise in systolic, diastolic, and mean blood pressures (Figure 2A, 2D, and 2E). The pressor response of preterm-AGA infants was “intermediate” between preterm-

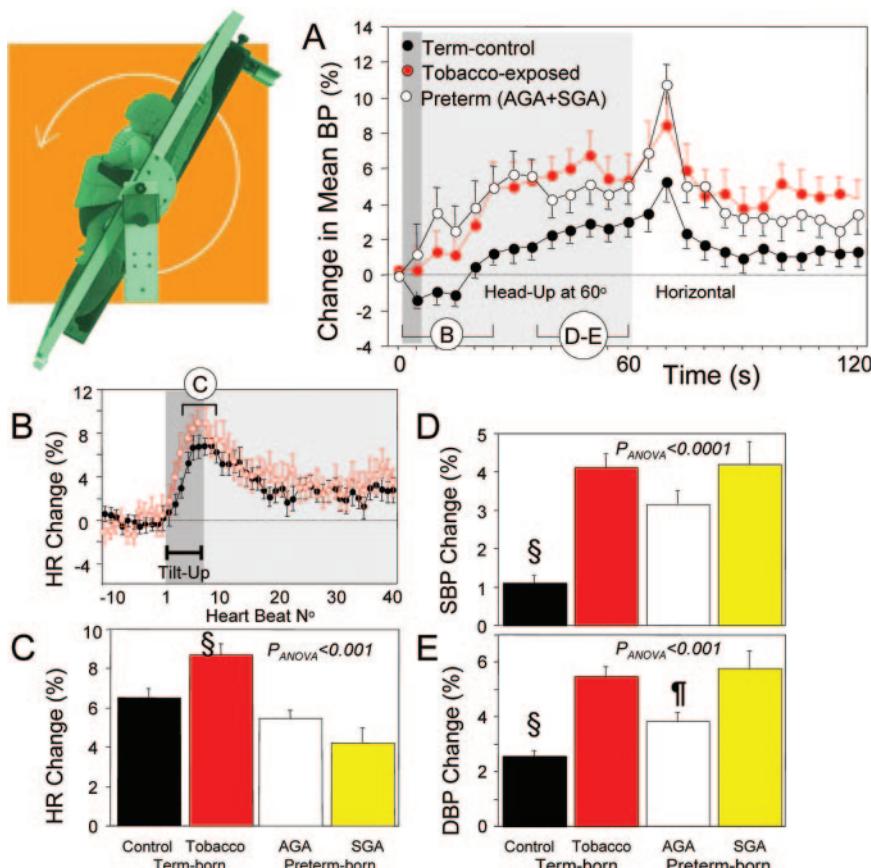


Figure 2. The head-up tilt test. Infants were tilted to 60° while comfortably immobilized. Babies born preterm and to smokers responded with an exaggerated and prolonged rise in mean blood pressure (BP; A [segments marked are expanded in B, D, and E, respectively]). The heart rate (HR) of all infants increased transiently within 8 to 10 heartbeats of tilting up (B; peak HR response is shown in C). Systolic (SBP) and diastolic (DBP) BPs always increased proportionately (D and E; means during final 30 seconds upright). Note that AGA infants had an intermediate pressor response (D and E). For clarity, an overall profile for preterm infants (AGA and SGA combined) is shown in A; only HR changes for controls and tobacco-exposed babies are compared in B. Omnibus ANOVA *P* values for group comparisons are shown in C through E. Significant differences from all other groups (§) and from tobacco-exposed or SGA infants (¶) are indicated (multiple-range tests). Data are mean \pm SD.

SGA and control babies. Brief arousals occurred at the onset of 20% of tilts; this proportion was the same for all groups, as was arousal duration estimated from movement artifact.

No significant associations were found between reactivity (heart rate and diastolic, systolic, and mean blood pressures) and postnatal age for babies of smokers ($P=0.25$ to 0.6), suggesting that stress hyperreactivity did not change during the first postnatal weeks.

Discussion

Here, we provide physiological evidence confirming what epidemiological reports of modest elevations in resting blood pressure suggest: that being born too soon, too small, or to a mother who smokes alters cardiovascular control from an early age.^{3,6,9,10} Our findings are entirely consistent with the concept of developmental “programming”²⁰ and moreover suggest that functional consequences of programming may be present much sooner than previously thought (ie, within days or weeks of birth).

Evidence for the adverse impact of passive smoking on the adult cardiovascular system began to emerge nearly 20 years ago.²¹ Our data suggest that the immature cardiovascular system also is exquisitely vulnerable to secondhand smoke exposure, despite the considerable first-pass “filtering” of toxic combustion products that must occur in the mother’s placenta and breast. Some of the physiological changes we observed in babies of smokers—cardiac, vascular, and blood pressure hyperreactivity—resemble those seen in smokers themselves. These are all classic actions of nicotine in the

autonomic system.^{22,23} Although only one of many components of cigarette smoke, nicotine is a powerful developmental toxin. Animal studies indicate that chronic exposure to nicotine before birth weakens adrenergic excitation of the heart, blunts adrenal catecholamine release, and depresses cardiovascular stress reactivity after birth.^{24–26} We cannot explain why reactivity is paradoxically heightened in babies exposed to nicotine via maternal smoking. One important difference, however, may be that babies are not continuously exposed to nicotine as are experimental animals but probably experience adult smoker-like patterns of nicotine exposure: intermittent daytime surges followed by overnight “abstinence/withdrawal.” These different patterns of nicotine exposure may have quite different cellular and behavioral side effects.^{27,28}

The effects of prenatal smoke and nicotine tend to be strongest soon after birth and then fade,²⁴ yet we found no differences between babies of smokers tested before or after hospital discharge, an interval of \approx 2 weeks at most. Two weeks may be far too soon to expect changes in such a small cohort of babies, bearing in mind that all received ongoing nicotine exposure via milk (all smokers breastfed) and perhaps environmental smoke at home. Both pathways could prolong and exacerbate changes that begin in utero. This raises the issue of whether incipient dysfunction may improve if a nursing mother who smokes abstains from breastfeeding.

Preterm birth is known to accentuate sympathetic drive (high resting heart rate and powerful peripheral vasoconstrictor reflex),²⁹ but how this sympathetic bias affects hemody-

namics and the parallels with gestational tobacco exposure are new and unexpected findings. Prematurity and growth restriction are distinct clinical entities, yet SGA and AGA infants were not dramatically different from each other in our study. The former is the classic risk factor for cardiovascular diseases in later life, but premature birth also independently increases the risk of developing high blood pressure.^{1,3} Because poor growth is an additional cardiovascular stress in utero, SGA infants could be more susceptible to circulatory failure after birth than their AGA counterparts.^{5,6} In fact, our data from infants born at ≈32 weeks and tested at term suggest that low birth weight may not be as important a cause of circulatory dysfunction as prematurity, at least for the first few months after birth. This may not be so if a baby is born small at full term (ie, if the fetus grows poorly during the final trimester of pregnancy).³ We do not know whether preterm-born infants, at the same corrected age, differ from their counterparts born at term because of something that happens in utero³⁰ or because early adaptation to the outside world delays, accelerates, or otherwise alters, perhaps permanently, their developmental trajectory.^{1,3}

We do not yet understand what our findings mean in the longer term; that may become clear by tracking the physiological development of different groups. Some of the anomalies we identified may fade over time as counterbalancing mechanisms, including the baroreflex, gradually strengthen.^{31,32} However, arterial pressure is kept within narrow limits for good reasons, and there may be consequences if that does not happen.^{33,34} Our data suggest that if hemodynamic control is weak, even routine maneuvers such as repositioning a baby (which the tilt test mimics) could trigger overcompensation and frequent, undesirable surges in pressure. Pressor effects caused by other circumstances (medication, arousal, or changes in sleep position or breathing pattern) also may be magnified.^{11,35,36} Mechanical forces such as friction resulting from flowing blood and pulsatile stretch of the arterial wall help to shape the immature vascular trees.³⁷ Too much (or indeed too little) of either or both over a long period of time may lead to structural and functional remodeling of the microcirculation, with developmental, physiological, and pathological consequences. Both maternal smoking and preterm birth also substantially increase the risk of a baby dying of sudden infant death syndrome.^{8,12,38,39} A malfunction in blood pressure and/or heart rate control during sleep has long been suspected but never identified. Our data provide intriguing evidence of incipient, sleep-related cardiovascular dysfunction in both of these high-risk groups. Could dysfunction that allows blood pressure to surge too high also let it to fall too low, allowing a momentary loss of blood pressure to spiral out of control?¹¹

Study Limitations

Active smoking is strongly associated with preterm delivery and intrauterine growth restriction, with an incremental increase in the prevalence of preterm birth and reduction in birth weight as the number of cigarettes smoked rises.¹³ We did not, however, explore whether effects from tobacco are modified by a combination of risk factors. That is a complex undertaking, given that most infants born after exposure to

tobacco are not born preterm or small for dates. We did not independently verify tobacco exposure but relied on maternal self-reporting. Consequently, we are unable to comment on whether nicotine affects circulatory dynamics in a threshold or dose-response manner. Is self-reporting reliable? Comparisons between serum and urinary cotinine levels and self-reported smoking have consistently found self-reporting by active smokers to be accurate in early and in late pregnancy.^{40,41} We did not enroll ex-smokers who quit or abstained from smoking before or during pregnancy because these women tend to understate tobacco use. We recognize that babies of smokers may have been exposed to smoke via the environment and breast milk after hospital discharge and must assume that nonsmokers kept their babies in a smoke-free environment after discharge.⁴²

Conclusions

Smoking during pregnancy and preterm birth both measurably alter cardiovascular reflex function in the weeks after birth. We suggest that these changes are a direct consequence of physiological programming by adverse circumstances and that they could plausibly be early markers of underlying processes that lead to or are involved in other changes or complications later on (eg, raised blood pressure and sudden infant death syndrome).⁴³

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Disclosures

None.

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CLINICAL PERSPECTIVE

Large-scale epidemiological studies convincingly indicate that the seeds of cardiovascular and other diseases may be planted very early in life, before or around the time of birth. Events or insults that occur during this formative developmental period are thought to alter ("program") the body's structure and physiology, which in turn increases vulnerability to stress and accelerates disease onset. The developmental programming concept has broad public health implications because it raises the prospect of improving the early diagnosis, treatment, and perhaps prevention of disease. This article provides some of the first direct evidence of perinatal programming of human cardiovascular physiology by revealing distinct vascular reactivity patterns in infants born preterm, small for dates, and to mothers who smoked during pregnancy. These are the 3 most common complications of pregnancy and causes of poor infant outcome in the world today. Signs of subtle cardiovascular dysfunction can be spotted surprisingly early in these groups of infants, within days or weeks (rather than months or years) of birth. The long-term significance of this dysfunction is uncertain at present, but it could plausibly be an early marker of later susceptibility to complications such as raised blood pressure.