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Original Contribution

Maternal Catecholamine Levels in Midpregnancy and Risk of Preterm Delivery

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Associations between stress hormones and preterm delivery have not been fully explored. In this study, pregnant women enrolled from 52 clinics in 5 Michigan communities (1998–2004) provided urine samples for 3 days (waking and bedtime) during midpregnancy. Urinary catecholamine levels (epinephrine, norepinephrine, and dopamine) were measured in a subcohort (247 preterm and 760 term deliveries), and a 3-day median value was calculated. Polytomous logistic regression models assessed relations between catecholamine quartiles (of the median) and a 4-level outcome variable (i.e., term (referent) and 3 preterm delivery subtypes: spontaneous; premature rupture of membranes; and medically indicated). Final models incorporated other relevant covariates (e.g., creatinine, demographic, behavior). The risk of spontaneous preterm delivery was increased in the highest versus lowest quartile of norepinephrine and dopamine: norepinephrine, waking (adjusted odds ratio (AOR) = 3.7, 95% confidence interval (CI): 1.8, 7.9) and bedtime (AOR = 2.5, 95% CI: 1.3, 4.9); dopamine, waking (AOR = 2.6, 95% CI: 1.4, 5.1) and bedtime (AOR = 2.3, 95% CI: 1.2, 4.6). Adjusted odds ratios were further strengthened after removing women whose placentas showed evidence of acute infection or vascular pathology. High catecholamine levels in maternal urine may be indicative of excess stressors and/or predisposition to elevated sympathetic activation that contributes to increased risk of spontaneous preterm delivery.

catecholamines; dopamine; epinephrine; gestational age; norepinephrine; pregnancy; pregnancy outcome; premature birth

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; MSAFP, maternal serum α-fetoprotein; POUCH, Pregnancy Outcomes and Community Health.

Preterm births, that is, delivery at <37 weeks' gestation, account for a substantial proportion of infant mortality and long-term disability in developed countries (1, 2). Over the last decade, rates of very early preterm delivery have not declined, and rates of late preterm delivery have increased among both singleton- and multiple-gestation pregnancies (3). Disparities in risk of preterm delivery continue, with higher rates among African-American women (4) and women of lower socioeconomic status (5–7).

Spontaneous and medically indicated preterm deliveries have many causes that act alone or in combination. The most frequently identified causes include infection/inflammation, premature rupture of fetal membranes, and vascular complications such as preeclampsia, gestational hypertension, bleeding/placental abruption, and decreased placental perfusion (8). These causes are identified through various forms of evidence that span clinical signs/symptoms, biomarkers, and placental pathology. The term ''idiopathic'' is frequently used to refer to preterm deliveries that are initiated by spontaneous labor; these represent an estimated 20%–50% of preterm delivery depending on the extent of prematurity and inclusion/exclusion criteria (9–11).

Maternal stress, variably defined, has also been hypothesized to play a role in preterm delivery. Proposed mechanisms include stress-induced alterations in immune function leading to infection, stress effects contributing to vascular complications, stress-related behaviors (e.g., poor diet, smoking, substance abuse), and hormonal pathways

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triggered by stress (12–14). Prospective studies testing the stress and/or anxiety-preterm delivery hypothesis have typically measured maternal stressors and stress/anxiety through self-report, and there are examples of both positive (15–17) and null (18–20) findings. Fewer studies have evaluated biomarkers of maternal stress, primarily cortisol, in relation to preterm delivery, and again results have been mixed (21–24).

In this prospective study of pregnant women, midpregnancy urine levels of catecholamines, key stress/arousal biomarkers, were assessed in relation to the risk of preterm delivery. Placental pathology was used to define 2 common preterm delivery pathways (infection, vascular complications) and to determine whether a catecholamine-preterm delivery association is observed outside these pathways.

MATERIALS AND METHODS

Study design and eligibility

The Pregnancy Outcomes and Community Health (POUCH) Study prospectively enrolled women in their 15th−27th weeks of pregnancy from 52 clinics in 5 Michigan communities from September 8, 1998, through June 15, 2004 (25). Eligibility criteria included a singleton pregnancy with no known chromosomal abnormality or birth defect, maternal serum α-fetoprotein (MSAFP) screening at 15–22 weeks, maternal age of ≥15 years, no prepregnancy diabetes mellitus, and proficiency in English. The study received institutional review board approval at Michigan State University, the Michigan Department of Community Health, and 9 community hospitals.

Sampling for the cohort and subcohort

Women who met the eligibility criteria, expressed interest in the study, and had normal MSAFP levels were stratified by race/ethnicity and randomly sampled into the cohort. In addition, all interested women with unexplained MSAFP levels of ≥2 multiples of the mean were invited to participate (7% of the cohort but typically 3%–5% of the screened population), because this biomarker had been linked to preterm delivery previously (26, 27) and was of particular interest in the POUCH Study. A total of 3,038 women were enrolled, and follow-up through delivery was completed for 3,019 (99.5%) cohort women.

A subcohort was assembled ($n = 1{,}371$) and studied in greater detail to maximize resource efficiency. The subcohort included the following: 1) all women who delivered preterm (<37 weeks); 2) all women with unexplained elevated MSAFP (≥2 multiples of the mean); and 3) a race-stratified random sample of women with normal MSAFP levels and term deliveries, with an oversampling from the African-American stratum. The sampling scheme was designed to optimize statistical power for studying at-risk subgroups within a subcohort (i.e., preterm, African Americans, and women with high MSAFP). All subcohort analyses use sampling weights that account for the cohort and subcohort sampling scheme and thereby remove any bias due to oversampling from certain strata.

Because of Health Insurance Portability and Accountability Act (HIPAA) regulations, it was not possible to determine an exact participation rate or to compare characteristics between cohort participants and nonparticipants. However, race/ethnic-specific comparisons between POUCH Study data and birth file data from the 5 communities showed that the POUCH Study sample was very similar to community mothers on most factors measured (i.e., parity, educational levels, and the proportions of women with Medicaid insurance, preterm delivery, previous stillbirth, previous preterm infant, and previous low birth weight infant).

Study protocol

At enrollment, POUCH Study cohort women met with a study nurse, signed consent forms, completed in-person interviews and self-administered questionnaires, and had biologic samples collected. Shortly after recruitment was underway in each community, the POUCH Study added an optional at-home data collection protocol (28) aimed at measuring stress biomarkers (cortisol and catecholamines) and blood pressure. As part of this protocol, women collected urine (for catecholamine levels) twice a day for 3 consecutive days immediately upon waking and just before bedtime, and they recorded waking, sleeping, and sample collection times.

Subcohort sample for catecholamine analyses

Approximately 85% of the eligible subcohort women agreed to complete the at-home protocol (Figure 1), and 79% ($n = 1{,}016$) successfully returned urine samples and diary data. An additional 9 women were excluded because their urine catecholamine levels were extreme outliers (6 standard deviations above the mean), leaving a sample of 1,007 women (247 preterm, 760 term). Of the 1,007 women, placental pathology was completed to date on 773 (176 preterm, 597 term).

Measurement of catecholamines

Urine samples collected at home were frozen (−20°C) during storage and shipping. At the laboratory, frozen urine was thawed within 1 week of receipt, acidified with hydrochloric acid to a pH of 3–5, and refrozen (−20°C). Samples were later thawed and assayed for levels of epinephrine, norepinephrine, and dopamine by using high-performance liquid chromatography (29). A solvent extraction method was used with 3,4-dihydroxybenzylamine hydrobromide as an internal standard. A heptane/octanol solution was used for extraction followed by an acetic acid extraction. The mobile phase consisted of 0.175 mM decanesulfonic acid, 0.1 mM ethylenediaminetetraacetic acid, 0.15 mM sodium hydride × peroxidase, and 5% methanol (pH 5.1) for catecholamine analysis (flow rate, 1.2 mL/minute). The electrode potential was set to 850 mV versus a Ag/AgCl reference electrode. At the same time, urine creatinine was measured by using a colorimetric assay kit (Assay Designs, Ann Arbor, Michigan). Intraassay coefficients ranged from 5% to 13% and interassay coefficients ranged from

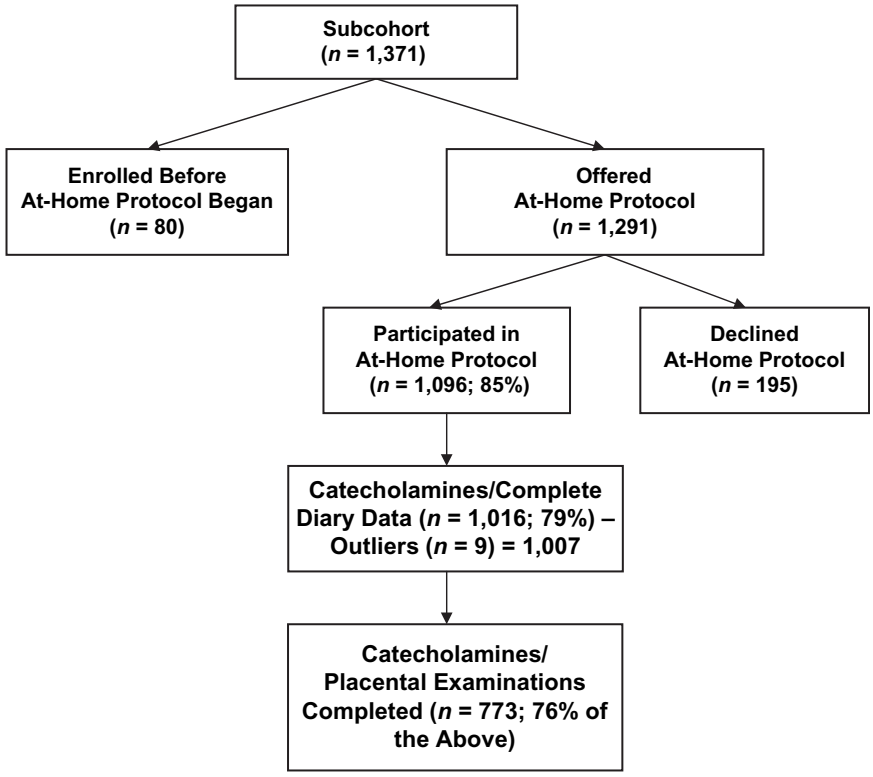

Figure 1. Flow chart of data on catecholamine levels in maternal urine at midpregnancy, Pregnancy Outcomes and Community Health Study, 1998–2004.

10% to 14% with epinephrine assays being at the top of the range.

Outcome measures

Preterm delivery. Gestational age at delivery was calculated by using the date of the last menstrual period or gestational age from an early ultrasound (<22 weeks' gestation) if the 2 estimates differed by more than 2 weeks. Two abstractors, a physician and a labor and delivery nurse, independently reviewed subcohort prenatal and labor and delivery records to identify clinical circumstances leading to preterm delivery. Disagreements were resolved through reexamination of medical records by an expert team. Preterm delivery was divided into 3 groups: 1) Spontaneous preterm delivery included women with regular contractions that led to cervical changes (≥2 cm of dilatation); 2) premature rupture of membranes preterm delivery included women with rupture of membranes before or simultaneously with onset of contractions; and 3) medically indicated preterm delivery included women induced or given cesarean sections before either preterm labor or premature rupture of membranes.

Placental pathology. Placentas were formalin fixed and received gross examination by using standard protocols that included recording of gross hemorrhage accompanied by compression (evidence of abruption). Nine tissue samples from each placenta were embedded in paraffin blocks, sectioned, and stained with hematoxylin and eosin for microscopic assessment. Details of the sampling and microscopic evaluation have been described elsewhere (30). The study pathologist, who was blinded to gestational age at delivery, all clinical data, and gross examination findings, recorded placental findings in a structured, computer-based descriptive instrument adapted from one developed by Dr. Carolyn Salafia (Placental Analytics LLC, Larchmont, New York, and Institute for Basic Research, Staten Island, New York). Evidence of significant infection/inflammation, referred to here as "histologic chorioamnionitis," was defined as an advanced maternal inflammatory response or fetal inflammatory response, both of which were found to be related to preterm delivery in previous POUCH Study analyses (30). A total of 29 placental vascular findings were divided into 5 conceptual groups or pathology-based latent constructs: 1) maternal vascular-obstructive (MV-O) (e.g., villous infarcts and atherosis); 2) maternal vascular-disturbance of integrity (MV-I) (e.g., evidence of retroplacental, retromembranous, and decidual hemorrhage); 3) maternal vascular-developmental (MV-D) (e.g., unaltered/abnormal decidual vessels); 4) fetal vascular-obstructive (FV-O) (e.g., thrombi and avascular villi); and 5) fetal vascular-disturbance of integrity (FV-I) (e.g., villous stromal hemorrhage and intervillous thrombi). The POUCH Study placental vascular groups were adapted from the Placental Diagnostic Coding Tool of Dr. Raymond Redline (P. K. Senagore, Michigan State University, personal communication, 1999) and have been described elsewhere

in greater detail (31). For each of the 5 groups, findings were summed, and a score was assigned to each woman. The distributions of these scores among the term, normal MSAFP deliveries formed the basis for 2 cutoff values, very high (approximately the top decile) and high (approximately the top quintile), within each vascular pathology group.

Covariate data

Information on demographics, medical and reproductive history, prepregnancy weight and height, levels of substance use (i.e., cigarette smoking and use of alcohol, marijuana, or other illicit drugs) before and during pregnancy, and levels of caffeinated beverage intake during pregnancy was gathered at enrollment. Maternal prepregnancy weight and height were used to calculate a body mass index (weight (kg)/height $(m)^2$). Data on medication use during pregnancy up through the time of enrollment were obtained through maternal interview and by abstracting prenatal/labor and delivery records. Medical records were also the source of information on maternal hypertensive complications (chronic, gestational, preeclampsia) and clinically diagnosed placental abruption.

Analytical strategy

For descriptive purposes, Spearman's rank correlation coefficients were used to measure correlations among 1) catecholamine levels across the 3 days; 2) waking and bedtime catecholamine levels on a specific day; and 3) levels of the different catecholamines within the same urine sample. Median (from the 3 days) waking and bedtime epinephrine, norepinephrine, and dopamine levels were calculated for each woman. These median values were divided into quartiles. Cutpoints for the quartiles were based on distributions in women delivering at term with normal MSAFP.

Waking and bedtime epinephrine, norepinephrine, and dopamine were each evaluated as exposure measures in separate models. Polytomous regression was used to assess relations between catecholamine quartiles and a 4-level pregnancy outcome variable (i.e., term (referent), spontaneous preterm delivery, premature rupture of membranes preterm delivery, and medically indicated preterm delivery). We also conducted a homogeneity test for equivalence to examine whether the preterm delivery clinical subtypes each had significantly different associations with the catecholamines. We compared the log-likelihoods of 2 polytomous logistic models (chi-square test statistic), one that constrained all the catecholamine odds ratios so that they were identical for each preterm delivery subtype and one that allowed the odds ratios to vary by preterm delivery subtype (32). After observing that catecholamines were specifically associated with spontaneous preterm delivery, we further subdivided this category by gestational week at delivery (i.e., <35 weeks and 35–36 weeks) to consider the relations with timing of spontaneous preterm delivery.

All regression models included urinary creatinine levels to adjust for urine concentration. In a second series of models, other potential confounders were incorporated, that is, maternal age, week of pregnancy when urine was sampled, race/ethnicity, Medicaid insurance status, parity, and body mass index. Later models also tested confounding by exposures that might alter maternal catecholamine levels, that is, maternal smoking, marijuana use, illicit drug use, caffeinated beverage intake, psychotropic medications, and tocolytics.

A final set of analyses was aimed at identifying the biologic pathways linked to elevated maternal catecholamine levels. In logistic regression models, catecholamine quartiles (independent variable) were evaluated in relation to histologic chorioamnionitis (dependent variable, yes/no) and then in relation to each of the 5 placental vascular pathology groups (dependent variable, high score vs. not high score). Null findings in these models motivated a repeat of the polytomous regression models described above to test the persistence of the catecholamine-spontaneous preterm delivery association after exclusion of women with common causes of preterm delivery, that is, histologic chorioamnionitis and a very high score (top decile) for any of the 5 vascular pathology groupings.

Weights were incorporated in all regression models to reflect oversampling of high MSAFP into the cohort and the subcohort sampling scheme. All regression analyses were conducted by using PROC SURVEYLOGISTIC procedures with SAS, version 9.1, software (33).

RESULTS

Maternal characteristics in the subcohort sample with urinary catecholamines ($n = 1{,}007$) were similar to those in the entire subcohort, with the exception that a larger percentage, 26% versus 13%, was enrolled at 25–27 weeks' gestation (Table 1). As expected, the study sample had higher percentages of African-American women (39%) and women who delivered preterm (25%) than those in the original cohort (25% and 11%, respectively), because these groups were oversampled for the subcohort, the source of the study sample.

Distributions of median catecholamine levels (median from across the 3 days) were skewed to the right (Table 2). The percentage of median catecholamine values below the limit of detection was considerable for waking and bedtime epinephrine (about 27%) but negligible (<3%) for the other catecholamines. For each catecholamine, day-to-day correlations and waking-to-bedtime correlations were moderate, with Spearman's rank correlation coefficients in the range of 0.44–0.59. Within a single sample of urine, the range of correlations varied for epinephrine and norepinephrine levels (waking, 0.09–0.10; bedtime, 0.14–0.22), norepinephrine and dopamine levels (waking, 0.27–0.31; bedtime, 0.30–0.37), and epinephrine and dopamine levels (waking, 0.03–0.06; bedtime, 0.08–0.15).

In polytomous regression models with adjustment for creatinine levels, urinary catecholamine levels were positively associated with spontaneous preterm delivery (Table 3). Top quartile adjusted odd ratios were statistically significant for waking norepinephrine (adjusted odds ratio (AOR) = 3.4, 95% confidence interval (CI): 1.6, 7.0), bedtime

Table 1. Maternal Characteristics and Pregnancy Outcome in the Study Subcohort With Urinary Catecholamines Measured at Midpregnancy ($n = 1,007$) and in the Entire Subcohort, Pregnancy Outcomes and Community Health Study, 1998–2004

Maternal Characteristics	Study Sample ($n = 1,007$)		Entire Subcohort ($n = 1,371$),
	No.	%	%
Maternal age, years			
<20	178	18	18
20–29	563	56	56
≥30	266	26	26
Race/ethnicity[a]			
White	543	54	51
African American	391	39	42
Others	73	7	7
Maternal education, years			
<12	218	22	23
12	285	28	29
>12	504	50	48
Medicaid insured			
No	450	45	43
Yes	557	55	57
Week of pregnancy at enrollment			
<20	159	16	16
20–24	584	58	71
25–27	264	26	13
Parity/preterm delivery history			
No previous livebirth	424	42	42
Previous livebirth without preterm delivery	534	53	53
Previous livebirth with preterm delivery	49	5	5
Pregnancy outcome[a]			
Term	760	75	75
Preterm medically indicated	75	7	8
Preterm PROM	67	8	7
Preterm spontaneous preterm labor	105	10	10

Abbreviation: PROM, premature rupture of membranes.

[a] Percentages reflect oversampling of African Americans and preterm into the subcohort.

norepinephrine (AOR = 2.3, 95% CI: 1.2, 4.5), waking dopamine (AOR = 2.6, 95% CI: 1.3, 5.0), and bedtime dopamine (AOR = 2.4, 95% CI: 1.3, 4.6). The homogeneity test for equivalence of models showed that the model allowing catecholamine odds ratios to vary by preterm delivery subtype produced a better fit (chi-square values, $P < 0.001$) than the model that constrained odds ratios to be identical across preterm delivery subtypes. These results persisted for all catecholamines, waking and bedtime, and reinforced the specificity of the relation between catecholamines and spontaneous preterm delivery.

The addition of other covariates (age, pregnancy week at urine sampling, race/ethnicity, Medicaid insurance status, parity, body mass index) had little impact on the association between catecholamines and preterm delivery (Table 4). After further subdivision of spontaneous preterm delivery by weeks of gestation, the upper quartiles of waking and bedtime epinephrine were associated primarily with an increased risk of spontaneous preterm delivery at <35 weeks (Table 4). Other potential confounders were added to these models one by one, that is, levels of cigarette smoking, alcohol, marijuana and other illicit drugs before and during pregnancy, levels of caffeinated beverage intake during pregnancy, psychotropic medications, and tocolytics. These covariates did not alter catecholamine-adjusted odds ratios by greater than 10% (results not shown). Analyses were repeated after exclusion of the 103 women who reported illicit substance use before or during pregnancy, and the results remained unchanged. Similar catecholamine results were observed when the data were modeled separately for Medicaid and non-Medicaid insured, women with high and low educational levels, and African Americans and whites/others.

Separate logistic regression models were used to evaluate quartiles of waking and bedtime epinephrine, norepinephrine, and dopamine in relation to histologic chorioamnionitis (no/yes) and each of the 5 placental vascular pathology groups (dichotomized as high/not high). There were no significant associations between any of the catecholamine measures and these placental pathology findings (data not shown). Polytomous regression models with adjustment for urinary creatinine levels (discussed above) were repeated after exclusion of all cases of histologic chorioamnionitis. The relation between spontaneous preterm delivery and both norepinephrine and dopamine persisted with fourth quartile adjusted odds ratios ranging from 2.3 to 5.5 (Table 5). Similarly, the association between high levels of catecholamines and spontaneous preterm delivery remained after exclusion of women with a vascular pathology score in the top 10th percentile among any of the 5 pathology groups (Table 5), and after exclusion of women with evidence of abruption (gross, microscopic, or clinical diagnosis) or hypertensive complications (data not shown). A final series of models excluded women with either histologic chorioamnionitis or high vascular pathology scores. Although sample sizes were markedly reduced, the exclusion of these pathways to preterm delivery further strengthened the fourth quartile adjusted odds ratios for waking norepinephrine (AOR = 8.3, 95% CI: 1.1, 60.7), bedtime norepinephrine (AOR = 3.4, 95% CI: 1.0, 12.2), and waking dopamine (AOR = 6.1, 95% CI: 1.7, 22.1) in relation to spontaneous preterm delivery.

DISCUSSION

We found that women with higher levels of urinary catecholamines at midpregnancy were at greater risk of spontaneous preterm delivery, and the association was strengthened after exclusion of women with placental evidence of infection/inflammation and vascular complications. These

Table 2. Urinary Catecholamine Levels at Midpregnancy in the Entire Study Subcohort[a] ($n = 1,007$), Pregnancy Outcomes and Community Health Study, 1998–2004

	Mean[b]	Median[b]	SD[b]	% Below the Level of Detection[b]	Day-to-Day Correlation[c] Range (Days 1–3)	Waking-to-Bedtime Correlation[c] Range (Days 1–3)
Epinephrine, nm/dL						
Waking	43.5	21	66.4	26.2	0.49–0.50	
Bedtime	43.1	21	67.5	27.8	0.44–0.48	0.44–0.48
Norepinephrine, nm/dL						
Waking	86.1	53	104.5	2.9	0.50–0.59	
Bedtime	105.8	68	116.2	2.7	0.51–0.55	0.49–0.58
Dopamine, nm/dL						
Waking	539.9	439	355.0	0.2	0.51–0.54	
Bedtime	546.6	426	385.0	0.2	0.49–0.50	0.46–0.51

Abbreviation: SD, standard deviation.
[a] Descriptive statistics not weighted for subcohort sampling scheme.
[b] Based on the distribution of the median catecholamine level from the 3-day samples.
[c] Spearman's rank correlation coefficients.

findings provide compelling evidence of a potential link between a stress-related biomarker and some cases of preterm delivery.

Catecholamine release is under the control of the central nervous system (34, 35). Epinephrine is released primarily by the adrenal glands and acts as a circulating hormone (35). Norepinephrine and dopamine are neurotransmitters released into the circulation as a result of overflow from adrenergic and dopaminergic nerve endings and, to a lesser degree, following adrenal gland stimulation (35). The mechanisms that link catecholamine levels with preterm delivery may be indirect, as catecholamines affect constriction/dilatation of blood vessels, mobilization of fatty acids, and insulin secretion (36). Through more direct pathways, catecholamines can influence uterine contractions by binding to α_1 (contraction) and β_2 (relaxation) adrenergic receptors in the uterus (37) and, perhaps, by upregulating oxytocin receptors (38) or increasing prostaglandin production in the amnion, decidua, and myometrial tissues (39, 40). Early studies have demonstrated increased uterine contractility following administration of dopamine or norepinephrine to pregnant women at term (41, 42). β_2-Adrenergic receptor agonists are used to treat premature labor, but they only delay delivery by up to 48 hours and have not proven successful in preventing preterm delivery (43). This may be due to a subsequent down regulation of β_2 receptors in most women treated and, for some, underlying complications that are not adrenergic in origin. A lack of synchrony between catecholamine release and regulation of uterine adrenergic receptors might occur more often with chronic stress/arousal or in those genetically predisposed, which may account for the results presented here.

Both environmental and constitutional factors appear to influence basal catecholamine levels. Measures of allostatic load, a concept of body ''wear and tear,'' include catecholamine levels (44). Low socioeconomic status (45), stressful work (46–48), and chronic exposure to noise including traffic noise while sleeping (49) have all been associated with higher urinary catecholamine levels. Individuals experiencing anxiety symptoms (35) or posttraumatic stress disorder (50, 51), particularly when involving sexual abuse as a child and as an adult (52), have been found to have higher urinary catecholamine levels. Although early descriptions have often labeled epinephrine release a response to cognitive stressors and norepinephrine release a response to physical stressors, recent studies have shown that norepinephrine levels are increased with certain types of psychological arousal (53, 54) and a rise in all catecholamines levels is consistent with a generalized stress response (34).

Studies of catecholamines and psychological well-being in pregnant women are limited and typically small in scope. Among the more moderately sized studies, one found no significant increases in urinary catecholamine levels in relation to stress (55). Another reported higher urinary levels of epinephrine and norepinephrine but lower levels of dopamine in women with increased anxiety (56). There are few data on catecholamine levels and pregnancy outcome. Studies showing preterm delivery risk elevated in association with anxiety (15, 57), posttraumatic stress disorder episodes in pregnancy (58), and increased vascular reactivity (59) may be indirect evidence of an adrenergic-mediated pathway. In our analyses, adjustment for hypertensive disorders in pregnancy and history of previous preterm delivery did not alter the findings (data not presented), suggesting that maternal anxiety related to these conditions did not explain our results.

A limitation is that we measured catecholamines during only one point in the pregnancy and did not collect 24-hour samples of urine, yet outside a clinic setting, a 24-hour urine collection invites measurement error. We had the advantage of measuring stress hormones during the women's typical daily routine, and the 3 consecutive days of waking and bedtime samples allowed us to take account of intraindividual variability. Urinary levels of epinephrine and norepinephrine are considered a good indicator of plasma levels (60). Kidney synthesis of L-3,4-dihydroxyphenylalanine

Table 3. Associations Between Midpregnancy Urinary Catecholamine Levels and Preterm Delivery, Adjusted for Urinary Creatinine Levels ($n = 1{,}007$), Pregnancy Outcomes and Community Health Study, 1998–2004

	Term Delivery (Referent Group), no.	Preterm Delivery								
		Medically Indicated			Premature Rupture of Membranes			Spontaneous Preterm Labor		
		No.	AOR	95% Confidence Interval	No.	AOR	95% Confidence Interval	No.	AOR	95% Confidence Interval
Epinephrine										
Waking										
Quartile 1 (referent)	204	18	1.0		19	1.0		26	1.0	
Quartile 2	187	17	1.1	0.5, 2.3	10	0.6	0.3, 1.4	18	0.8	0.4, 1.6
Quartile 3	182	25	1.6	0.8, 3.2	20	1.0	0.5, 2.0	23	1.0	0.5, 1.8
Quartile 4	187	15	1.0	0.5, 2.1	18	1.1	0.5, 2.2	38	1.7	1.0, 3.0
Bedtime										
Quartile 1 (referent)	222	22	1.0		17	1.0		29	1.0	
Quartile 2	168	18	1.1	0.6, 2.2	14	1.1	0.5, 2.4	18	0.9	0.5, 1.7
Quartile 3	183	17	0.9	0.5, 1.9	15	0.9	0.4, 2.0	23	1.0	0.6, 1.9
Quartile 4	187	18	1.0	0.5, 1.9	21	1.5	0.7, 2.9	35	1.5	0.9, 2.7
Norepinephrine										
Waking										
Quartile 1 (referent)	197	17	1.0		23	1.0		11	1.0	
Quartile 2	187	24	1.7	0.8, 3.4	15	0.7	0.4, 1.5	26	2.7*	1.3, 5.9
Quartile 3	191	13	0.9	0.4, 1.9	11	0.5	0.2, 1.1	31	2.8*	1.3, 5.9
Quartile 4	185	21	1.4	0.7, 2.8	18	0.8	0.4, 1.6	37	3.4*	1.6, 7.0
Bedtime										
Quartile 1 (referent)	200	20	1.0		21	1.0		18	1.0	
Quartile 2	187	21	1.2	0.6, 2.4	18	1.0	0.5, 1.9	25	1.7	0.9, 3.4
Quartile 3	191	20	1.1	0.5, 2.2	11	0.6	0.3, 1.3	25	1.7	0.8, 3.3
Quartile 4	182	14	0.9	0.4, 1.8	17	1.0	0.5, 2.0	37	2.3*	1.2, 4.5
Dopamine										
Waking										
Quartile 1 (referent)	201	33	1.0		18	1.0		15	1.0	
Quartile 2	182	14	0.5	0.2, 1.0	21	1.5	0.8, 3.0	17	1.3	0.6, 2.8
Quartile 3	187	13	0.5	0.2, 1.0	17	1.2	0.6, 2.5	38	2.9*	1.5, 5.6
Quartile 4	190	15	0.5	0.3, 1.0	11	0.8	0.3, 1.7	35	2.6*	1.3, 5.0
Bedtime										
Quartile 1 (referent)	234	26	1.0		24	1.0		21	1.0	
Quartile 2	179	21	1.3	0.7, 2.5	17	1.0	0.5, 2.0	20	1.3	0.6, 2.6
Quartile 3	171	14	0.8	0.4, 1.8	14	0.9	0.4, 1.9	30	2.1*	1.1, 4.0
Quartile 4	176	14	0.9	0.4, 2.0	12	0.8	0.4, 1.6	34	2.4*	1.3, 4.6

Abbreviation: AOR, adjusted odds ratio.
* $P < 0.05$.

(L-DOPA) to dopamine accounts for a large amount of dopamine in the urine, but this is under the influence of sympathetic innervation via levels of the L-DOPA precursor in maternal blood. Therefore, it seems plausible to infer that chronic overactivation of the sympathetic system could result in higher urinary dopamine levels. Still we cannot rule out the possibility that unmeasured pathophysiologic changes act as confounders, increasing catecholamine levels and predisposing women to deliver preterm.

The specificity of our finding, catecholamine's link to spontaneous preterm delivery only, is consistent with a biologically plausible mechanism. By incorporating placental pathology findings, we were able to demonstrate that the link was not simply a result of infection/inflammation and vascular pathways to preterm delivery; this type of biologic data is rarely available in studies of stress hormones and preterm delivery risk. Our large sample size allowed us to test the robustness of our findings among

Table 4. Associations Between Midpregnancy Urinary Catecholamine Levels and Preterm Delivery,[a] Adjusted for Urinary Creatinine Levels, Maternal Age, Pregnancy Week at Sampling, Race/Ethnicity, Medicaid Insurance Status, Parity, and Body Mass Index ($n = 1{,}007$), Pregnancy Outcomes and Community Health Study, 1998–2004

	Preterm Delivery					
	Spontaneous Preterm Labor		Spontaneous Preterm Labor			
			At 35–36 Weeks		At <35 Weeks	
	AOR	95% Confidence Interval	AOR	95% Confidence Interval	AOR	95% Confidence Interval
Epinephrine						
Waking						
Quartile 1 (referent)	1.0		1.0		1.0	
Quartile 2	0.8	0.4, 1.5	0.7	0.3, 1.5	1.3	0.3, 6.0
Quartile 3	1.0	0.5, 1.8	0.7	0.3, 1.4	2.6	0.7, 9.6
Quartile 4	1.8*	1.0, 3.2	1.3	0.7, 2.6	4.7*	1.4, 16.3
Bedtime						
Quartile 1 (referent)	1.0		1.0		1.0	
Quartile 2	0.9	0.4, 1.7	0.6	0.3, 1.4	2.2	0.6, 8.6
Quartile 3	1.0	0.5, 1.8	0.6	0.3, 1.3	3.3*	1.0, 11.4
Quartile 4	1.6	0.9, 2.9	1.4	0.7, 2.6	3.1	0.9, 11.1
Norepinephrine						
Waking						
Quartile 1 (referent)	1.0		1.0		1.0	
Quartile 2	2.8*	1.3, 6.0	2.9*	1.2, 7.4	2.6	0.7, 9.6
Quartile 3	2.6*	1.2, 5.6	2.8*	1.1, 6.9	2.2	0.6, 8.6
Quartile 4	3.7*	1.8, 7.9	3.6*	1.5, 9.0	3.9*	1.1, 13.7
Bedtime						
Quartile 1 (referent)	1.0		1.0		1.0	
Quartile 2	1.6	0.8, 3.2	1.6	0.7, 3.7	1.6	0.5, 5.5
Quartile 3	1.6	0.8, 3.2	1.4	0.6, 3.3	2.1	0.6, 7.0
Quartile 4	2.5*	1.3, 4.9	2.6*	1.2, 5.7	2.1	0.6, 7.4
Dopamine						
Waking						
Quartile 1 (referent)	1.0		1.0		1.0	
Quartile 2	1.2	0.6, 2.7	0.9	0.3, 2.5	1.9	0.6, 6.1
Quartile 3	2.8*	1.4, 5.4	2.9*	1.3, 6.5	2.6	0.9, 7.6
Quartile 4	2.6*	1.4, 5.1	3.5*	1.6, 7.5	0.9	0.2, 3.7
Bedtime						
Quartile 1 (referent)	1.0		1.0		1.0	
Quartile 2	1.1	0.5, 2.4	1.4	0.5, 3.5	0.8	0.2, 2.7
Quartile 3	2.1*	1.1, 4.1	2.7*	1.2, 6.3	1.2	0.4, 3.9
Quartile 4	2.3*	1.2, 4.6	3.3*	1.5, 7.7	1.1	0.3, 3.4

Abbreviation: AOR, adjusted odds ratio.

* $P < 0.05$.

[a] The adjusted odds ratios for medically indicated preterm delivery and premature rupture of membranes preterm delivery were similar to those in Table 3 and are not displayed in this table.

women with different characteristics, and in all models our findings persisted. In future analyses we will probe, in greater detail, psychosocial and physiologic characteristics of POUCH Study women with higher catecholamine levels at midpregnancy in an effort to learn more about upstream factors.

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Table 5. Associations Between Catecholamine Levels and Spontaneous Preterm Labor and Delivery[a] After Exclusion of Women With Placental Pathology Related to Preterm Delivery, Pregnancy Outcomes and Community Health Study, 1998–2004

	No High HCA (n = 682)		No Top 10% Vascular Findings (n = 572)		No High HCA and No Top 10% Vascular Findings (n = 504)	
	AOR[b]	95% Confidence Interval	AOR[b]	95% Confidence Interval	AOR[b]	95% Confidence Interval
Epinephrine						
Waking						
Quartile 1	1.0		1.0		1.0	
Quartile 2	0.8	0.3, 2.0	0.9	0.4, 2.3	1.2	0.5, 3.3
Quartile 3	0.7	0.3, 1.6	0.6	0.3, 1.6	0.5	0.2, 1.5
Quartile 4	1.6	0.8, 3.2	1.1	0.5, 2.5	1.3	0.6, 3.2
Bedtime						
Quartile 1	1.0		1.0		1.0	
Quartile 2	1.0	0.4, 2.2	0.7	0.3, 1.8	1.0	0.4, 2.6
Quartile 3	0.7	0.3, 1.6	0.3	0.1, 0.9	0.3	0.1, 1.1
Quartile 4	1.2	0.6, 2.5	1.0	0.5, 2.1	1.0	0.5, 2.5
Norepinephrine						
Waking						
Quartile 1	1.0		1.0		1.0	
Quartile 2	5.3*	1.5, 18.1	5.6*	1.3, 25.3	7.2	1.0, 54.0
Quartile 3	3.9*	1.1, 13.5	4.2	0.9, 19.0	5.6	0.7, 41.8
Quartile 4	5.5*	1.6, 18.2	6.0*	1.4, 25.9	8.3*	1.1, 60.7
Bedtime						
Quartile 1	1.0		1.0		1.0	
Quartile 2	2.3	0.9, 6.5	1.9	0.7, 5.3	2.3	0.6, 8.7
Quartile 3	2.0	0.7, 5.7	1.6	0.6, 4.3	1.7	0.4, 6.4
Quartile 4	3.7*	1.4, 9.7	2.5	1.0, 6.3	3.4*	1.0, 12.2
Dopamine						
Waking						
Quartile 1	1.0		1.0		1.0	
Quartile 2	2.0	0.7, 5.7	1.5	0.4, 5.1	3.0	0.7, 12.7
Quartile 3	5.0*	2.0, 13.3	3.7*	1.3, 11.1	7.4*	2.0, 27.1
Quartile 4	3.6*	1.4, 9.1	3.8*	1.3, 10.9	6.1*	1.7, 22.1
Bedtime						
Quartile 1	1.0		1.0		1.0	
Quartile 2	1.3	0.5, 3.1	1.1	0.4, 3.2	1.3	0.4, 4.0
Quartile 3	2.4*	1.1, 5.5	2.5*	1.0, 6.3	2.1	0.7, 6.2
Quartile 4	2.3*	1.0, 5.2	2.4	0.9, 6.0	2.5*	0.9, 6.9

Abbreviations: AOR, adjusted odds ratio; HCA, histologic chorioamnionitis.

* $P < 0.05$.

[a] Results are from full polytomous regression models with 4-level outcome (term = referent, medically indicated preterm delivery, premature rupture of membranes preterm delivery, and spontaneous preterm delivery), but only results from spontaneous preterm delivery are displayed in Table 5.

[b] Adjusted for creatinine.

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