Association of Catecholamines with Blood Glucose and Severity of Illness in Infants Born Preterm

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Objective To assess whether urinary catecholamine/metanephrine concentrations correlate with illness severity and blood glucose (BG) levels during the first weeks of life among infants born preterm.

Study design This was a prospective cohort study of 33 neonates born at <32 + 0 weeks or with a birth weight <1500 g. Urine was collected 2-3x/week up to 10 weeks of age. Catecholamines/metanephrines were analyzed by an isotope dilution liquid chromatography in combination with tandem mass spectrometry. Severity of illness was estimated using the Neonatal Therapeutic Intervention Scoring System and the number of apneas/bradycardias. BG levels were measured as clinically indicated.

Results Six hundred fifteen urine samples and 3491 BG levels were analyzed. Median age at lowest BG was 686 (IQR 27, 2420) hours for infants <1000 g, 20 (IQR 1, 165) hours for infants between 1000-1499 g and 4 (IQR 1, 104) hours for infants >1500 g. Three neonates were diagnosed with transient hyperinsulinism. Urinary norepinephrine and metanephrine correlated positively with the Neonatal Therapeutic Intervention Scoring System ($F(1, 58.73) = 33.24$, $P < .001$; $F(1, 310.01) = 19.78$, $P < .001$). Norepinephrine, normetanephrine, and metanephrine correlated positively with the number of apneas/bradycardias during the last 6 hours before urine collection ($F(1, 442.69) = 22.12$, $P < .001$; $F(1, 598) = 7.40$, $P = .007$; $F(1, 591.50) = 29.05$, $P < .001$). Norepinephrine and normetanephrine concentrations correlated positively with BG levels ($F(1, 314.6) = 8.58$, $P = .004$; $F(1, 312.5) = 10.40$, $P = .001$).

Conclusion Urinary catecholamines in infants born preterm correlate with severity of illness and BG levels. Whether postnatal catecholamines directly influence beta-cell physiology in infants born preterm remains to be elucidated and should be addressed in future studies. A better understanding of the biologic mechanism might help improve glucose management in this vulnerable population. *(J Pediatr 2026;289:114897)*.

Trial Registration German Clinical Trials Register: DRKS00026230; https://drks.de/search/de/trial/DRKS00026230/details.

Hypoglycemia and hyperglycemia are common metabolic problems in preterm infants; however, optimal definitions or treatment thresholds remain unclear.[1-4] Reported frequencies of hyperglycemia in infants born preterm vary between 16 and 70%.[3,5,6] Hyperglycemia is associated with increased mortality and morbidity, including the development of necrotizing enterocolitis, intraventricular hemorrhage, and retinopathy of prematurity.[7-10] Reported frequencies of hypoglycemia vary between 9 and 63%.[1,2,5,11] Nevertheless, studies on hypoglycemia in preterm infants are rare. The majority have only investigated the occurrence of hypoglycemia during the first days or the first week of life,[2,5,12,13] although a few reports indicate that hypoglycemia can also occur beyond the first week of life.[1,14,15] Staffler et al reported delayed onset of hypoglycemia in infants with a birth weight <1500 g.[1] Pertierra-Cortada et al performed continuous glucose monitoring in 60 patients born before 32 weeks of gestation at a mean age of 65 ± 21 days, and found that 23.3% had hypoglycemia.[14] Further metabolic

BG	Blood glucose
CTG	Cardiotocography
ELBW	Extremely low birth weight
IQR	Interquartile range
IV	Intravenous
NTISS	Neonatal Therapeutic Intervention Scoring System
THI	Transient hyperinsulinism
UCB	Arterial umbilical cord blood
VLBW	Very low birth weight

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analyses regarding the underlying cause for the delayed onset of hypoglycemia were not reported. We recently reported that a frequent cause of pronounced hypoglycemia in preterm infants is delayed-onset transient hyperinsulinism (THI). In a retrospective analysis, 16 of 622 preterm infants with a birthweight <1500 g developed delayed-onset THI at a median age of 27 days (range: 6-52 days) which was not related to cessation of parenteral nutrition.[16]

Transient hyperinsulinism is often associated with perinatal stress. A possible mechanism has been established by Limesand and Rozance who showed that growth restricted fetal sheep have significantly higher catecholamines and a suppressed intrauterine insulin secretion compared with controls.[17] Once the adrenergic stimulus subsides, the beta-cells exhibit a hyper-responsive insulin secretion.[17] Correspondingly, we previously demonstrated that human neonates ≥35 + 0 weeks of gestation born with growth restriction and neonates with other forms of perinatal stress also had significantly higher catecholamines/metanephrine concentrations in arterial umbilical cord blood at the time of delivery compared with controls.[18] Furthermore, higher catecholamines correlated with postnatal hypoglycemic episodes and lower glucose levels.[18] We hypothesize that this mechanism might also be a potential explanation for delayed-onset hypoglycemia in preterm neonates, ie, that there is significant catecholamine exposure due to severity of illness or iatrogenic catecholamine application during the initial period of prematurity treatment, and catecholamine decrease after clinical stabilization then leads to subsequent hyper-responsive insulin secretion.

Thus, we here investigated if urine catecholamine/metanephrine concentrations of infants born at <32 weeks' gestation or with a birth weight <1500 g correlate with the severity of illness and glycemia during the first weeks of life.

Methods

Patient Sample and Study Design

We conducted an exploratory, prospective, single center cohort study of 33 infants born preterm. Pregnant women with their unborn child were recruited prenatally or the infants were recruited postnatally within the first 3 days of life from November 2021 to December 2022. Inclusion criteria were birth weight <1500 g or gestational age <32 + 0 weeks of gestation. Exclusion criteria were lack of consent from both parents and contraindication for noninvasive urine collection. If possible, arterial umbilical cord blood (UCB) (0.2-2.0 mL) was obtained directly after cord clamping and processed as described previously.[18] Urine samples were collected 2-3 times/wk until up to 10 weeks of life, or until discharge from the hospital, whichever was earlier. If hypoglycemia persisted, urine collection was extended until 2 weeks after normalization of blood glucose (BG) levels. Urine sampling was performed noninvasively by placing a compress in the diaper. To collect the urine, the compress was centrifuged at 2500 g for 3 minutes. If a urinary catheter was in place for routine care, urine was collected from the catheter. Urine was supplemented with 5-10 μg EDTA/mL urine (Carl Roth GmbH, Karlsruhe, Germany;) and 5-10 μg ascorbic acid/mL urine (VWR Chemicals BDH, Radnor, PA, USA). An isotope dilution liquid chromatography in combination with tandem mass spectrometry was used to analyze free catecholamines and free metanephrines in UCB and urine. For plasma, the assay was performed as previously described.[19] Urinary free catecholamines and metanephrines were analyzed using essentially the same method as for plasma free metanephrines, but fully validated for human urine. Interassay imprecision (n = 20 days) was below 6.5%, 3.1%, 3.3%, 5.1%, for urinary norepinephrine, epinephrine, normetanephrine, and metanephrine, respectively. C-peptide was measured in urine with a chemiluminescent microparticle immunoassay, on the Alinity immunoanalyzer (Abbott Laboratories). The analytical measurement range was 100-100 000 pmol/L. The assay has an imprecision of 3.3 and 2.8% at levels of 418 and 1850 pmol/L, respectively. Urine catecholamines, metanephrines, and C-peptide are expressed as ratio to urine creatinine.

Data on the pregnancy and the clinical course of each neonate, including all BG measurements, were obtained from the medical records. Voigt centiles were calculated for birth measures.[20] The Neonatal Therapeutic Intervention Scoring System[21] (NTISS, last 24 hours before urine collection) and the number of apneas and bradycardias documented in the medical records during the last 6 hours before urine collection were used to assess severity of illness. The total carbohydrate intake was calculated from the daily documentation of the electronic medical prescription program, which calculates carbohydrate content of the different components of the dietary intake (eg, breast milk or formula) and additionally accounts for the total intravenous (IV) glucose intake (parenteral nutrition and medications dissolved in glucose).

Claris FileMaker Pro Version 19 (Claris International Inc) and Microsoft Excel Version 2408 (Microsoft) were used to record the data.

The study was approved by the Ethics Committee of the Medical Faculty of the Heinrich-Heine-University Düsseldorf (2021-1458) according to the Declaration of Helsinki. Written informed consent was obtained from both parents. Participants did not receive a stipend.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 29.0 (IBM). Clinical characteristics are displayed as median and IQR. A mixed linear model was computed to test whether catecholamines/metanephrines correlate with the mean BG levels, NTISS, number of apneas and/or bradycardias and C-peptide levels, using subjects and age (in hours) as random effects. For correlation analyses between the catecholamines/metanephrines and NTISS and the number of apneas/bradycardias, 14 catecholamine/metanephrine values were excluded, as either IV epinephrine and/or norepinephrine has been administered at the time of urine sampling. Mann–Whitney U test and Kruskal–Wallis test with Bonferroni corrections were used to compare the medians of

non-normally distributed data. To adjust for multiple comparisons (4 tests) 2-sided *P* values < .0125 were considered statistically significant. Median and IQR are reported. A univariate general linear model was used to analyze "causes for delivery" (independent variables) regarding catecholamine/metanephrine concentrations in UCB (dependent variables). To minimize the impact of outliers, catecholamine/metanephrine concentrations were log-transformed for these analyses.

Results

Parents of 35 neonates were asked to participate in the study of which 33 consented. Thirteen of 33 infants were classified as ELBW (<1000 g), 12/33 as VLBW (1000-1500 g), and 8 of 33 had birth weights >1500 g. Clinical characteristics are summarized in Tables I and II. Most infants received breast or donor human milk during the first weeks. Based on weight gain, milk was fortified with human milk-based or bovine fortifier once on full or nearly full enteral feeds. 4/33 infants died before 10 weeks of age; their data were partially included in the analyses but excluded from the evaluation of whether hypoglycemia or THI occurred. A total number of 18 UCB samples, 615 urine samples, and 3491 BG levels were analyzed.

Catecholamine/Metanephrine Concentrations in UCB of Infants with Pathologic Cardiotocography and/or Doppler Abnormalities

UCB was obtained in 18 of 33 infants with a median gestational age of 30 + 1 (28 + 5, 32 + 0) weeks and a median birth weight of 1315 (IQR 1023, 1526) g, including only 4 of 13 preterm infants <1000 g. In a univariate analysis, the delivery

Table I. Clinical characteristics

	<1000 g n = 13		1000-1499 g n = 12		>1500 g n = 8	
Characteristics	**n (% of n)**	**Median (IQR)**	**n (% of n)**	**Median (IQR)**	**n (% of n)**	**Median (IQR)**
C-section	12 (92.3)		12 (100)		8 (100)	
One dose of bethamethasone before delivery	3 (23.1)		1 (8.3)		0 (0)	
Two or more doses of betamethasone before delivery	10 (76.9)		11 (91.7)		7 (87.5)	
Cause for premature delivery						
Unstoppable labor and/or premature rupture of membranes	4 (30.8)		4 (33.3)		5 (62.5)	
Triple I	5 (38.5)		0 (0)		0 (0)	
Fetal growth restriction	1 (7.7)		5 (41.7)		0 (0)	
Preeclampsia	2 (15.4)		2 (16.7)		0 (0)	
Pathologic cardiotocography	1 (7.7)		1 (8.3)		3 (37.5)	
Female	7 (53.9)		7 (58.3)		1 (12.5)	
Multiples	3 (23.1)		7 (58.3)		4 (50)	
Gestational age (d)	13 (100)	176 (172, 193)	12 (100)	218 (206, 226)	8 (100)	213 (209, 218)
Birth weight (g)	13 (100)	725 (595, 845)	12 (100)	1295 (1120, 1443)	8 (100)	1663 (1638, 1788)
Birth weight SDS	13 (100)	−0.93 (−1.55, −0.07)	12 (100)	−0.78 (−1.70, −0.24)	8 (100)	0.64 (0.12, 1.22)
Birth length SDS	13 (100)	−0.59 (−1.2, 0.13)	12 (100)	−0.67 (−2.31, −0.12)	8 (100)	0.71 (−0.33, 1.04)
Birth head circumference SDS	13 (100)	−0.61 (−1.19, 0.04)	12 (100)	−0.84 (−1.25, −0.22)	8 (100)	0.31 (0.06, 0.76)
Apgar score min 1; 5; 10	12-13 (92-100)	5; 7; 9 (3, 7; 6, 8; 7, 9)	12 (100)	6; 8; 9 (5, 8; 7, 9; 8, 10)	8 (100)	6; 8; 9 (5, 7; 7, 8; 8, 10)
Arterial cord blood pH	10 (77)	7.33 (7.26, 7.37)	10 (83)	7.30 (7.22, 7.34)	7 (88)	7.26 (7.15, 7.31)
Arterial cord blood base excess (mmol/L)	8 (62)	−4.8 (−7.08, −1.75)	11 (92)	−2.2 (−3.3, −0.20)	7 (88)	−2.8 (−8.4, −0.77)
Arterial cord blood glucose (mg/dL)	7 (54)	85 (66, 109)	6 (50)	71 (45, 87)	6 (75)	93 (65, 98)
Arterial cord blood lactate (mmol/L)	4 (31)	2.8 (1.63, 5.1)	4 (33)	2.3 (1.95, 2.80)	2 (25)	Range: 2.5-3.4
Arterial cord blood insulin (mU/L) [pmol/L]	1 (8)	3.8 [26.4]	7 (58)	5.3 (4.1, 7.3) [36.8 [28.47, 50.69]]	3 (38)	13.2 (range: 5.7-21.2) [91.7 [range: 39.6-147.2]]
Number of infants that died before discharge	5 (38.5)					
Number of infants that died before 10 wks of age	4 (31)		0 (0)		0 (0)	
Number of infants with						
Early-onset sepsis (<72 h of age)	6/13 (46)		0 (0)		1/8 (13)	
Late-onset sepsis (>72 h of age) at least one episode	6/13 (46)		0 (0)		0 (0)	
Intraventricular hemorrhage grade I-II	3/13 (23)		0 (0)		0 (0)	
Intraventricular hemorrhage grade III-IV	2/13 (15)		0 (0)		0 (0)	
Necrotizing enterocolitis	4/13 (31)		0 (0)		0 (0)	
Focal intestinal perforation	1/13 (8)		0 (0)		0 (0)	
Retinopathy of prematurity (infants that died before 10 wks excluded)	4/9 (44)		0 (0)		0 (0)	
Bronchopulmonary dysplasia (infants that died before 10 wks excluded)	2/9 (22)		0 (0)		0 (0)	

SDS, standard deviation score.

Table II. Glycemia in the study cohort

Characteristics	<1000 g n = 13		1000-1499 g n = 12		>1500 g n = 8	
	n (% of n)	Median (IQR)	n (% of n)	Median (IQR)	n (% of n)	Median (IQR)
Number of infants with at least 1 hyperglycemia ≥180 mg/dL	11 (85)		1 (8)		0 (0)	
Age at first blood glucose level ≥180 mg/dL (h)	11 (85)	35 (13, 48)		108		
Number of infants treated with insulin	4 (31)		0 (0)		0 (0)	
Highest measured blood glucose level (mg/dL)	13 (100)	259 (188, 275)	12 (100)	135 (108, 159)	8 (100)	116 (106, 154)
Age at highest blood glucose level (h)	13 (100)	101 (29, 337)	12 (100)	41 (16, 104)	8 (100)	29 (3, 129)
Number of infants with at least 1 hypoglycemia ≤45 mg/dL	7/9 (78)		4 (33)		4 (50)	
Number of blood glucose levels ≤45 mg/dL/neonate	9/9 (100)	1 (1, 7)	12 (100)	0 (0, 1)	8 (100)	1 (0, 1)
Number of infants with at least 1 hypoglycemia ≤45 mg/dL during the first 3 h of life	1 (8)		1 (8)		4 (50)	
Number of infants with at least 1 hypoglycemia ≤45 mg/dL during 4-72 h of life	2 (15)		3 (25)		0 (0)	
Number of infants with at least 1 hypoglycemia ≤45 mg/dL > 72 h of life	6/9 (67)		0 (0)		0 (0)	
Number of blood glucose levels ≤45 mg/dL (>72 h)	9/9 (100)	1 (0, 7)	12 (100)	0 (0, 0)	8 (100)	0 (0, 0)
Number of blood glucose levels 46-54 mg/dL (>72 h)	9/9 (100)	4 (1, 11)	12 (100)	0 (0, 1)	8 (100)	0 (0, 0)
Number of blood glucose levels 55-70 mg/dL (>72 h)	9/9 (100)	30 (11, 48)	12 (100)	1 (0, 4)	8 (100)	0 (0, 6)
Lowest measured blood glucose level (mg/dL)	9/9 (100)	39 (34, 48)	12 (100)	53 (38, 67)	8 (100)	49 (29, 79)
Age at lowest plasma glucose recorded (h)	9/9 (100)	686 (27, 2420)	12 (100)	20 (1, 165)	8 (100)	4 (1, 104)
Number of blood glucose measurements in total	9/9 (100)	237 (130, 414)	12 (100)	23 (15, 27)	8 (100)	17 (11, 22)
Highest measured C-peptide/Creatinine level (nmol/mmol)	9 (69)	17.9 (15.3, 36.1)	12 (100)	18.2 (9.5, 31.6)	8 (100)	23.0 (12.7, 28.7)
Age at highest C-peptide/Creatinine level (h)	9 (69)	901 (330, 1402)	12 (100)	579 (474, 761)	8 (100)	490 (309, 618)
Number of infants with diagnosis of transient hyperinsulinism	3/9 (33.3)		0 (0)		0 (0)	
Age at first critical sample (d)	3/3 (100)	27 (range: 17-32)	-	-	-	-
Plasma glucose (mg/dL)	3/3 (100)	49 (range: 34-50)	-	-	-	-
Insulin (mU/L) [pmol/L]	3/3 (100)	3.8 (range: 2.6-5.7) [26.4 [range: 18.1-39.6]]	-	-	-	-
C-peptide (ng/mL)	2/3 (67)	0.95-3.03	-	-	-	-
Maximum total carbohydrate intake (IV and enteral) (g/kg/d)	13 (100)	17.5 (14.1, 20.6)	12 (100)	16.8 (15.1, 17.2)	8 (100)	15.2 (13.7, 16.5)
Age at maximum total carbohydrate intake (d)	13 (100)	27 (10, 57)	12 (100)	22 (8, 27)	8 (100)	27 (16, 34)
Total carbohydrate intake (IV and enteral) DOL 1-7 (g/kg/d)	13 (100)	8.4 (7.0, 10.7)	12 (100)	10.5 (10.1, 10.8)	8 (100)	10.0 (9.4, 10.6)
Total carbohydrate intake (IV and enteral) DOL 8-14 (g/kg/d)	12 (92)	10.8 (8.5, 11.9)	12 (100)	12.1 (10.6, 13.5)	8 (100)	11.6 (10.7, 13.1)
Total carbohydrate intake (IV and enteral) DOL 14-21 (g/kg/d)	10 (77)	12.6 (11.2, 13.2)	12 (100)	13.0 (11.7, 13.6)	8 (100)	12.3 (11.3, 14.5)
Total carbohydrate intake (IV and enteral) DOL 22-28 (g/kg/d)	10 (77)	13.5 (12.2, 17.4)	12 (100)	13.9 (13.1, 14.8)	8 (100)	13.2 (11.2, 13.5)

DOL, day of life; IQR, interquartile range, IV, intravenous.

cause of "pathological cardiotocography and/or Doppler abnormalities" had a significant influence on UCB LgNorepinephrine, LgNormetanephrine, LgEpinephrine and LgMetanephrine (**eTable 1**; available at www.jpeds.com). Furthermore, UCB norepinephrine, normetanephrine, epinephrine and metanephrine concentrations were significantly higher in preterm infants with pathologic cardiotocography and/or Doppler abnormalities compared with preterm infants with normal findings (**Table III**). Norepinephrine, normetanephrine, epinephrine, and metanephrine concentrations correlated negatively with the venous umbilical cord blood pH (Spearman correlation coefficient $r_s = -0.814$, $P = .001$; $r_s = -0.909$, $P < .001$; $r_s = -0.811$, $P = .001$; $r_s = -0.875$, $P < .001$; n = 12) whereas negative correlation with arterial umbilical cord blood pH did not reach statistical significance ($r_s = -0.437$, $P = .090$; $r_s = -0.492$, $P = .053$; $r_s = -0.404$, $P = .135$; $r_s = -0.415$, $P = .110$; n = 15-16).

Incidence and Onset of Hyperglycemia

Eleven of 13 (85%) ELBW infants had at least one BG level ≥180 mg/dL, of which 4 required insulin (**Table II**). Only one infant >1000 g developed hyperglycemia (**Table II**).

Table III. Comparison of catecholamine/metanephrine concentrations in UCB of preterm infants with and without a pathologic CTG/Doppler*

Catecholamine/metanephrine in UCB [nmol/L]	No pathologic CTG/Doppler (n = 9)	Pathologic CTG/Doppler (n = 9)	
	Median (IQR)	Median (IQR)	*P*
Norepinephrine	5.30 (2.90, 10.24)	42.73 (12.2, 110.26)	.006†
Normetanephrine	1.05 (0.93, 1.50)	3.42 (2.31, 7.61)	.002†
Epinephrine	0.81 (0.07, 1.50)	4.98 (1.90, 12.74)	<.001†
Metanephrine	0.067 (0.054, 0.085)	0.21 (0.20, 0.43)	<.001†

CTG, cardiotocography; UCB, arterial umbilical cord blood.
*Mann–Whitney U Test with Bonferroni correction.
†*P* values < .0125 were considered statistically significant.

Table IV. Correlation of catecholamines/metanephrines, BG levels, NTISS scores, and the number of apneas/bradycardias*

	Mean BG (n = 322)		NTISS (n = 599-600)		Apneas/bradycardias in the last 6 h before urine collection (n = 599-600)	
Catecholamines/metanephrines	***P***	**F**	***P***	**F**	***P***	**F**
Norepinephrine	.004	F(1, 314.6) = 8.58	<.001	F(1, 58.73) = 33.24	<.001	F(1, 442.69) = 22.12
Normetanephrine	.001	F(1, 312.5) = 10.40	.47	F(1, 393.6) = 0.53	.007	F(1, 598) = 7.40
Epinephrine	.066	F(1, 307.58) = 3.41	.903	F(1, 312.67) = 0.015	.146	F(1, 596.61) = 2.12
Metanephrine	.027	F(1, 311.20) = 4.97	<.001	F(1, 310.01) = 19.78	<.001	F(1, 591.50) = 29.05

BG, blood glucose; NTISS, Neonatal Therapeutic Intervention Scoring System.
*Mixed linear model using subjects and age (in hours) as random effects.

eFigure 1 (available at www.jpeds.com) shows the IV glucose, BG levels and NTISS scores for neonates with and without hyperglycemia. The total carbohydrate intake (IV and enteral) was lower for ELBW compared with VLWB infants in the first week of life. Otherwise, there was no difference in total carbohydrate intake during the first weeks (**Table II**). **eFigure 2** (available at www.jpeds.com) shows the enteral, IV and total carbohydrate intake, as well as the BG levels, during the first 4 weeks of life.

Incidence and Onset of Hypoglycemia

Fifteen of 29 (52%) preterm infants developed at least one episode of hypoglycemia ≤45 mg/dL. None of the infants with a birth weight >1000 g developed hypoglycemic episodes >72 hours of life, whereas 6/9 ELBW infants developed hypoglycemic episodes >72 hours of life (**Table II**). The median onset of the lowest BG level was significantly later in the ELBW compared with the VLBW group and infants with a birth weight >1500 g (**Table II**).

In our cohort, 3 of 29 (10%) of surviving neonates developed THI (**Table II**). Birth weights ranged from 490-860 g. Two were small for gestational age. Age at critical sample for establishment of diagnosis ranged from 17 to 32 days. Lowest blood glucose levels ranged from 32 to 44 mg/dL, occurring at 17-110 days of age. Maximum total carbohydrate intake ranged from 20-29 g/kg/d. One infant received maltodextrin and IV glucose. One was treated with maltodextrin, continuous subcutaneous glucagon, and diazoxide and one received maltodextrin and diazoxide. Age at diazoxide start was 35 and 110 days. Diazoxide was stopped in one infant after 65 days, the other infant was discharged home with diazoxide.

Treatment with Intravenous Catecholamines

Ten of 33 (30.3%) infants were treated with IV norepinephrine at least once during the first 10 weeks of life. Five received IV epinephrine additionally. Median age at start was 45 (IQR 6, 342) hours, and median duration of treatment was 48 (IQR 25, 100) hours. Eight of 10 preterm infants with catecholamine treatment had BG levels ≥180 mg/dL during treatment. **eFigure 3** (available at www.jpeds.com) shows the IV norepinephrine and epinephrine dosages, BG levels, and urinary catecholamine/metanephrine concentrations during the treatment for each neonate.

Catecholamines/Metanephrine Concentrations in Urine

Norepinephrine and metanephrine correlated positively with the NTISS score and norepinephrine, normetanephrine and metanephrine correlated positively with the number of apneas/bradycardias (**Table IV**). During nasal high-flow or continuous positive airway pressure treatment, norepinephrine, normetanephrine, epinephrine and metanephrine concentrations were significantly higher compared with spontaneous breathing neonates. Furthermore, neonates with synchronized intermittent mechanical ventilation or high-frequency oscillatory ventilation had significantly higher normetanephrine, epinephrine and metanephrine concentrations compared with spontaneous breathing neonates (**Table V**).

Norepinephrine and normetanephrine concentrations correlated positively with the BG levels on the day of the urine collection. Correlation with metanephrine failed to reach statistical significance after Bonferroni correction. In case of more than one BG measurement, the mean BG level was calculated for the analyses (**Table IV**). BG levels correlated negatively with the age of the infants (F(1, 313.59) = 147.92, $P < .001$, n = 3491) (**Figure**, A). An illustrative clinical course of one preterm infant is shown in **eFigure 4** (available at www.jpeds.com).

C-Peptide Levels in Urine

In a mixed linear model, urinary C-peptide levels correlated positively with the age of the infants (F(1, 592.96) = 15.03, $P < .001$, n = 595). Median C-peptide/creatinine levels were significantly higher in week 5 of life compared with week 1 (5.70 (IQR 2.76, 10.27) vs 3.12 (IQR 1.67, 5.93) nmol/mmol, n = 97; $P = .009$) (**Figure**, B). Normetanephrine correlated negatively with the C-peptide levels (F(1, 548.60) = 4.54, $P = .034$) (**eTable 2**; available at www.jpeds.com). No correlation was found for the mean BG levels and C-peptide levels (F(1, 297.08) = 1.30 $P = .256$). C-peptide values of all preterm infants are shown in **Figure**, A.

Discussion

Hypoglycemia is a common metabolic problem in preterm infants. In the present study, >50% of preterm infants had

Table V. Comparison of catecholamine/metanephrine concentrations in urine during different ventilation modes with no ventilation*

Catecholamine and metanephrine/Creatinine (nmol/mmol)	No ventilation (n = 335-336)	CPAP or highflow (n = 196)		SIMV or HFOV (n = 68)	
	Median (IQR)	Median (IQR)	*P*	Median (IQR)	*P*
Norepinephrine	37.54 (30.26, 49.59)	42.18 (28.26, 73.11)	.008†	49.89 (21.20, 106.0)	.058
Normetanephrine	61.98 (49.36, 80.36)	75.48 (50.46, 101.47)	<.001†	91.51 (72.12, 134.65)	<.001†
Epinephrine	1.41 (0.92, 2.37)	2.21 (1.35, 4.79)	<.001†	3.09 (2.10, 6.21)	<.001†
Metanephrine	8.66 (6.24, 11.25)	12.34 (7.52, 19.26)	<.001†	17.27 (11.06, 38.58)	<.001†

CPAP, continuous positive airway pressure; HFOV, high-frequency oscillatory ventilation; IQR, interquartile range; SIMV, synchronized intermittent mechanical ventilation.
In case of treatment with intravenous norepinephrine or epinephrine during the time of urine collection, these samples were not included to the analyses.
*Mann–Whitney U Test with Bonferroni correction.
†*P* values < .0125 were considered statistically significant.

at least one episode of hypoglycemia ≤45 mg/dL with a pronounced difference in the timing of hypoglycemic episodes depending on the birth weight. Whereas none of the infants with a birth weight >1000 g had a hypoglycemic episode beyond 72 hours of life, 67% of the preterm infants with a birth weight <1000 g had hypoglycemic episodes >72 hours of life. Staffler et al reported that 44% of infants with a birth weight <1000 g and 23% of infants with a birthweight between 1000 and 1449 g developed hypoglycemia <45 mg/dL once on full enteral feeds for at least 48 hours.[1] Our study did not include standardized/routine BG screening, which may have underestimated hypoglycemia after 72 hours in the children with birthweights >1000 g as symptoms are often absent or not recognized.[22] Overall, 10.3% (3/29) of all preterm infants were diagnosed with delayed-onset THI, which is higher than our previous report.[16] These numbers underline that delayed-onset THI occurs in a considerable proportion of VLBW infants and that standardized BG screening beyond the first days of life is essential in this vulnerable group in order to detect hypoglycemia early and treat it appropriately. However, it is not clear why very small premature infants develop delayed-onset hypoglycemia or even delayed-onset THI.

A major factor in BG regulation is the composition of the infants' nutrition. As shown in **eFigure 2** (available at www.jpeds.com), preterm infants born ≥1000 g were able to tolerate a higher amount of enteral nutrition earlier compared with those born <1000 g. In addition, the combined enteral and IV carbohydrate intake during the first week of life was lower in the preterm infants <1000 g than in those >1000 g. Most preterm infants received breast milk or donor human milk. The composition of breast milk/donor milk varies individually. It is known that the breast milk of mothers of preterm infants, especially in the first days, contains less lactose than the milk of mothers of full-term infants,[23] and the galactose content might differ from glucose in terms of its capacity to stimulate insulin secretion. Furthermore, it is known that incretins (glucagon-like peptide-1 and glucose-dependent insulinotropic peptide) are released during enteral feeding and stimulate insulin secretion, which could explain our finding of fewer hyperglycemia episodes in preterm infants weighing >1000 g at birth.[24] However, a study by Shoji et al. found that preterm infants born <30 weeks of gestation, compared with those born above 30 weeks, had significantly higher incretin and insulin levels at 2 and 4 weeks of age.[25] These aspects underline the complexity of BG and insulin secretion regulation in preterm infants, indicating that clinical studies with realistic cohort sizes can only capture the major components of these systems.

In a recent study on late preterm (≥35 + 0 weeks of gestation) and term born neonates, we found that neonates with certain risk factors (eg, fetal growth restriction or perinatal stress) display higher catecholamine and metanephrine concentrations in UCB compared with neonates without any risk factors for neonatal hypoglycemia.[18] The catecholamine and metanephrine concentrations correlated with postnatal hypoglycemic episodes, lower glucose levels and higher need for treatment with IV glucose or glucose gel.[18] These results are consistent with findings in a sheep model showing that growth-restricted fetal sheep have significantly higher catecholamines, which directly suppress insulin secretion from the fetal pancreatic beta-cells.[17] Once the catecholamine concentrations decrease, pancreatic beta-cells develop a hyper-responsive insulin secretion that may then lead to hyperinsulinemic hypoglycemia.[17] Based on these data, we hypothesized that preterm infants exposed to high endogenous or exogenous catecholamines due to severity of illness during the first days to weeks of life develop hyper-responsive insulin secretion and hyperinsulinemic hypoglycemia after clinical stabilization and decrease of catecholamines.

In line with our previous study on term and late-preterm neonates,[18] we were able to show that preterm infants with perinatal stress identified by cardiotocography or Doppler abnormalities had significantly higher catecholamines and metanephrine concentrations in UCB compared with those without these findings. Furthermore, urinary norepinephrine and metanephrine levels correlated positively with the NTISS score and urinary norepinephrine, normetanephrine and metanephrine levels correlated positively with the number of apneas/bradycardias and the need for respiratory support during the first weeks of life. Our results indicate that urinary catecholamines and metanephrines reflect the clinical stress of preterm infants during the first weeks of life.

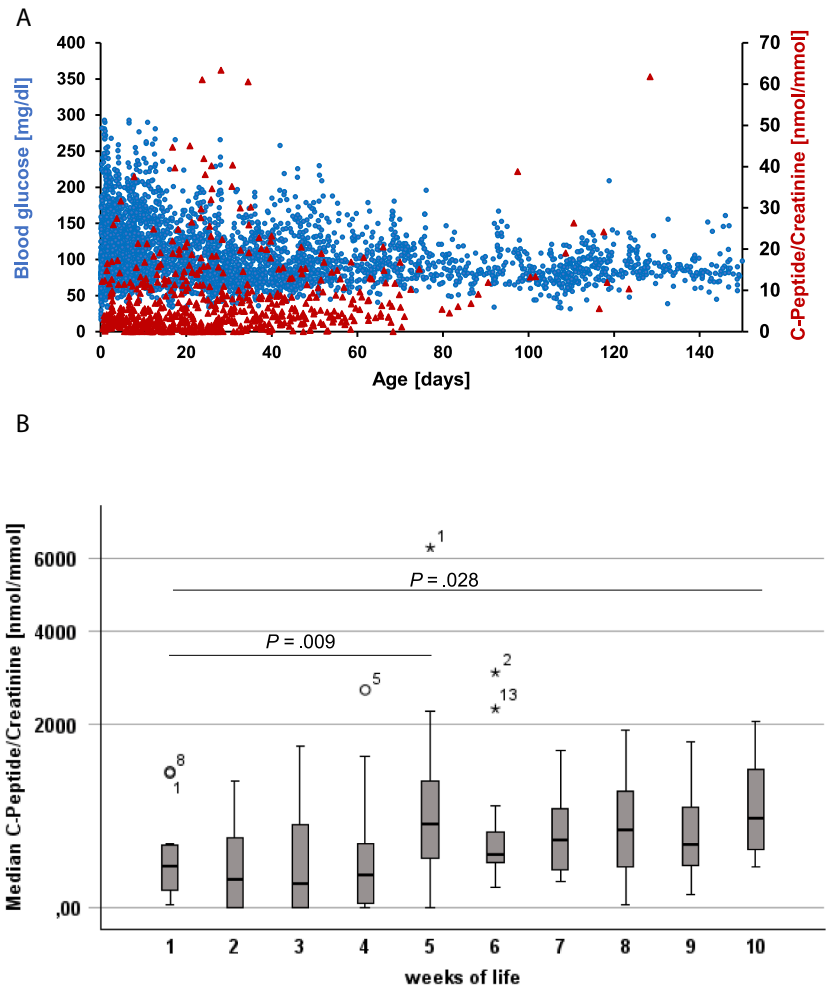

Figure. (**A**) Blood glucose and C-peptide levels from 33 preterm infants over time. Blood glucose values n = 3491 (blue dots); C-peptide values n = 615 (red triangles). (**B**) Median C-peptide values over the first 10 weeks of life. Kruskal–Wallis test with pairwise comparison was used. The circles and stars show outliers of individual patients.

Norepinephrine and normetanephrine concentrations correlated positively with BG levels on the day of the urine collection. Furthermore, BG levels correlated negatively with the age of the preterm infants. The majority of ELBW infants in our cohort (11/13 (85%)) developed hyperglycemia with a median onset at 35 hours of life, despite lower carbohydrate intake during the first week of life compared with preterm infants with a birth weight between 1000 and 1499 g. This is in line with recommendations to first reduce carbohydrate intake for hyperglycemia in preterm infants.[26] In addition, we aimed to assess whether early catecholamine concentrations at or shortly after birth were correlated with later hypoglycemia or THI. Owing to heterogeneity in gestational age, birth weight, treatment course, and timing of clinical stabilization, combined with the limited availability of cord blood catecholamine measurements, a robust statistical analysis with adequate sensitivity and specificity was not feasible.

Interestingly, C-peptide levels in urine did not correlate with BG levels. Elevated BG levels would normally be expected to result in an upregulation of insulin secretion and the associated increase in C-peptide levels. Moreover, C-peptide levels correlated positively with the age of the preterm infants. These results are consistent with findings by King et al who showed an increase of insulin response to glucose over the first 108 days of life in 18 preterm infants (26-30 weeks of gestation).[27] Furthermore, normetanephrine correlated inversely with the C-peptide levels, potentially reflecting a direct suppression of insulin secretion from the beta-cells as previously shown for fetal sheep with elevated catecholamines.[17] The suppression of insulin secretion might therefore contribute to the high incidence of hyperglycemia in very small premature babies especially during the first days of life,[26] as insulin resistance alone would be expected to result in higher insulin and C-peptide levels at elevated BG levels. The C-peptide increasing with the age of the infants

suggests that inhibition of insulin secretion is decreasing during the clinical stabilization of the premature infants, eventually leading to delayed hypoglycemia in some of the premature infants. Although transient hypoglycemia might occur if preterm infants are weaned from IV glucose before they are advanced sufficiently on enteral feeding, there are reports of delayed onset hypoglycemia in preterm infants occurring days to weeks after full enteral feeds were established.[1,14,16] We suggest the term "postnatal stress-induced hyperinsulinemic hypoglycemia" to describe this clinical phenomenon, analogous to the term perinatal stress-induced hyperinsulinemic hypoglycemia used in term and late preterm neonates.

A limitation of our study is the heterogeneity of severity of illness of the cohort. This resulted in variable numbers of BG measurements and duration of BG checks in the first weeks of life. Furthermore, the limited number of neonates unfortunately did not allow reliable analyses and/or conclusions for specific subgroups, ie, those developing pronounced hypoglycemia or THI over time, or more detailed comparisons between the smaller and the more mature participants within the cohort. In addition, to be as noninvasive as possible, the urine was collected using compresses that were left in the diaper for different lengths of time. Furthermore, other stressful procedures such as blood sampling or ultrasound examinations might have been carried out during the time of urine collection. The different duration and timing of urine collection could have influenced catecholamine concentrations and C-peptide levels. However, as these clinical factors affected all urine samples, we assume that the bias for analyses within the cohort should be limited.

Strengths of this study are the prospective design with a longitudinal approach and frequent analysis of catecholamines/metanephrines, BG values and C-peptide levels over the first 10 weeks of life. These generate a highly granular, exploratory dataset on these metabolic parameters through the treatment of prematurity. The correlation of catecholamine concentrations with the disease severity indicates that the method reliably reflects the degree of clinical stress despite measuring relatively volatile metabolites. Although these correlations with BG levels do not clearly prove causality, the consistent pattern of results fit well with the published literature/data.

In conclusion, urinary catecholamines and metanephrines correlate with severity of illness and mean BG levels over the first weeks of life. C-peptide levels increase with the age of the preterm infants and showed no correlation with the BG levels. The negative correlation of normetanephrine with C-peptide supports a direct catecholamine-mediated suppression of insulin secretion from the beta-cells and potentially contributes to higher BG levels during critical illness in preterm infants. However, further studies are needed to evaluate if delayed onset hyperinsulinism also results from direct influences of catecholamines on beta cells. Addressing these questions might help to improve glycemia management in preterm infants in the future. ■

CRediT authorship contribution statement

Henrike Hoermann: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marcia Roeper:** Writing – review & editing, Resources, Investigation, Formal analysis. **Martijn van Faassen:** Writing – review & editing, Validation, Methodology, Investigation. **Carsten Hagenbeck:** Writing – review & editing, Methodology, Investigation. **Diran Herebian:** Writing – review & editing, Methodology, Investigation. **Anneke C. Muller Kobold:** Writing – review & editing, Methodology, Investigation. **Juergen Dukart:** Writing – review & editing, Software, Methodology, Formal analysis. **Ido P. Kema:** Supervision, Methodology, Investigation. **Ertan Mayatepek:** Writing – review & editing, Supervision, Conceptualization. **Thomas Meissner:** Writing – review & editing, Supervision, Resources, Conceptualization. **Sebastian Kummer:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of Competing Interest

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Data Statement

Data sharing statement available at www.jpeds.com.

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