Plasma midregional proadrenomedullin in newborn infants: impact of prematurity and perinatal infection

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INTRODUCTION: Adrenomedullin (ADM) is one of the strongest endogenous vasodilating hormones. Its stable by-product midregional-proADM (MR-proADM) is an established indicator of systemic infection and cardiovascular compromise in adult patients.

METHODS: A prospective cross-sectional study was performed to investigate the perinatal factors affecting MR-proADM plasma concentrations in 328 newborn infants with a gestational age (GA) between 24 and 41 wk.

RESULTS: Blood samples were obtained in 270 infants from umbilical veins (with additional 108 paired samples from umbilical arteries), and at 2–3 d of life in 183 infants. Paired venous and arterial umbilical cord MR-proADM concentrations were closely related (Spearman's rank order correlation coefficient (R_s) = 0.825, $P < 0.001$). MR-proADM concentrations at birth and at 2–3 d were inversely related to GA (R_s = -0.403 and R_s = -0.541, respectively) and birth weight (BW; R_s = -0.421 and R_s = -0.530, respectively; all $P < 0.001$). On stepwise regression analysis, clinical chorioamnionitis and umbilical arterial blood base excess retained a significant impact on MR-proADM cord venous blood concentrations. At 2–3 d of life, histologic chorioamnionitis and GA at delivery were significantly associated with MR-proADM levels.

DISCUSSION: As compared with adults, MR-proADM concentrations are elevated in neonates, especially those born very preterm. Immaturity and infection, which both feature low systemic vascular resistance, are related to increased MR-proADM concentrations.

The vasoactive peptide adrenomedullin (ADM) is produced by vascular endothelial cells, epithelial cells of various origins, and some other tissue-specific cell types (1,2). ADM is involved in a variety of processes, including embryogenesis, normal and malignant growth, inflammation, and immunity (3,4). Plasma concentrations of ADM and its stable by-product, midregional-proADM (MR-proADM), are increased in various disease processes, such as arterial hypertension, heart failure, acute coronary syndromes, renal failure, and septic shock (3,5,6).

In infants, various perinatal stressors are known to increase ADM concentrations in umbilical cord blood or fetal membrane samples, including vaginal delivery, low umbilical cord pH (7), and preeclampsia (8). In two studies, it has been demonstrated that intrauterine growth restriction in response to reduced uteroplacental blood flow increases ADM concentrations in umbilical cord blood at birth (9,10), whereas another study reported unchanged ADM concentrations (11). This discrepancy might be explained by different study settings and the fact that reliable quantification of ADM concentrations is hampered by its short half-life and the existence of a binding protein (12). ADM synthesis, as assessed by mRNA and protein levels, was found to be unchanged or even decreased in the placentas of women with preeclampsia (13–16). Preterm infants and infants with asphyxia who developed intraventricular hemorrhage also showed higher plasma ADM concentrations in the first days of life (17,18).

Recently, reference values for MR-proADM venous cord blood concentrations have been established for healthy, term newborn infants ($n = 194$, reference range: 0.55–1.38 nmol/l; ref. 19). Infants with risk factors for early-onset sepsis (EOS; $n = 73$), including intrapartum maternal fever ($n = 5$), maternal carriers of group B streptococci ($n = 35$), preterm spontaneous delivery ($n = 6$), and prolonged rupture of membranes ($n = 27$), had similar values, but no reference was made to previously identified stressors, including delivery mode, low umbilical cord pH, or intrauterine growth restriction (19).

In this cross-sectional prospective study, we measured MR-proADM levels in plasma samples of 328 infants born between 24 and 41 wk gestational age (GA). Samples were obtained from venous and arterial umbilical cord blood, and repeat samples were drawn at 2–3 d of life concomitant with metabolic screening. The findings were related to indexes of pregnancy, parturition, placental histology, and postnatal course.

RESULTS

Patients

Patient characteristics are given in Table 1.

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Table 1. Clinical details of infants grouped according to gestational age

	<i>n</i>	GA 24–31 wk		GA 32–36 wk		GA 37–41 wk		<i>P</i>
		<i>M</i> (P10/P90) or <i>n</i> (%)	<i>N</i>	<i>M</i> (P10/P90) or <i>n</i> (%)	<i>n</i>	<i>M</i> (P10/P90) or <i>n</i> (%)	<i>N</i>	
Maternal characteristics								
Age (y) at delivery	328	32 (26/39)	86	34 (26/40)	99	32 (24/39)	143	NS
BMI before pregnancy	284	23 (19/28)	73	22 (19/29)	91	23 (20/28)	120	NS
Preeclampsia	328	26 (30)	86	24 (24)	99	3 (2)	143	<0.001
Gestational diabetes mellitus	328	3 (3)	86	2 (2)	99	10 (7)	143	NS
PPROM	328	32 (37)	86	39 (39)	99	15 (11)	141	<0.001
Antenatal steroids, full course	328	75 (87)	86	35 (35)	99	2 (1)	143	<0.001
Antenatal steroids, any	328	84 (98)	86	46 (46)	99	0 (0)	143	<0.001
At delivery								
CRP (mg/l)	191	6 (2/36)	79	4 (2/17)	87	3 (1/20)	25	<0.01
Leukocyte count (1,000/μl)	236	13 (9/19)	82	11 (8/17)	89	10 (7/13)	65	<0.001
Clinical chorioamnionitis	328	21 (28)	86	13 (13)	99	1 (1)	143	<0.001
Placenta								
Histologic chorioamnionitis	168	16 (19)	85	3 (5)	65	0 (0)	18	<0.01
Maternal reaction only	168	10 (12)	85	2 (3)	65	0 (0)	18	<0.05
Maternal + fetal reaction	168	6 (7)	85	1 (2)	65	0 (0)	18	<0.05
Compromised perfusion	168	35 (41)	85	26 (40)	65	9 (50)	18	NS
Fetal characteristics								
Small for gestational age (<P5)	328	14 (16)	86	21 (21)	99	14 (10)	143	NS
Suspect CTG just before birth	328	30 (35)	86	27 (27)	99	48 (34)	143	NS
Infants								
Sex (m/f)	328	44/42	86	57/42	99	84/59	143	NS
Gestational age (wk)	328	30 (26/31)	86	35 (33/36)	99	39 (38/41)	143	<0.001
Birth weight (kg)	328	1.3 (0.7/1.7)	86	2.3 (1.7/3.0)	99	3.4 (2.7/4.0)	143	<0.001
Small for gestational age (<P10)	328	15 (17)	86	27 (27)	99	17 (12)	143	<0.05
Delivery vaginal/abdominal	328	10/76 (12/88)	86	28/71 (28/71)	99	57/86 (40/60)	144	<0.01
At birth								
pH arterial	309	7.33 (7.2/7.4)	80	7.30 (7.2/7.4)	94	7.30 (7.2/7.4)	135	<0.01
Base deficiency (mmol/l) arterial	241	−4.0 (−0.8/−8.6)	25	−2.4 (−0.5/−8.5)	87	−3.2 (−0.6/−7.3)	129	NS
Apgar 5 min	328	7 (3/9)	86	9 (7/10)	99	9 (9/10)	143	<0.001
Apgar 10 min	328	8 (6/9)	86	9 (8/10)	99	9 (9/10)	143	<0.001
Postnatal course until 2–3 d								
Endotracheal ventilation	328	33 (38)	86	1 (1)	99	0 (0)	143	<0.001
Any positive pressure support	328	65 (76)	86	16 (16)	99	0 (0)	143	<0.001
Early-onset sepsis proven	328	5 (6)	86	2 (2)	99	0 (0)	143	<0.01
Patent ductus arteriosus treated	243	27 (31)	86	2 (2)	99	0 (0)	58	<0.001
Intraventricular hemorrhage, >I	136	7 (8)	86	0 (0)	50	0 (0)	0	NS
Postnatal course until discharge								
Necrotizing enterocolitis, >IIa	328	1 (1)	86	0 (0)	99	0 (0)	143	NS
Retinopathy of prematurity, >I	84	3 (3)	84	0 (0)	0	0 (0)	0	—
Moderate/severe BPD	328	6 (7)	86	0 (0)	99	0 (0)	143	<0.001
Death	328	8 (9)	86	1 (1)	99	0 (0)	143	<0.001
MR-proADM (nmol/l)								
At birth, venous cord blood	270	1.4 (0.9/2.2)	74	1.1 (0.8/1.8)	82	1.0 (1.0/1.4)	114	<0.001
At 2–3 d of life	183	1.4 (0.9/2.3)	57	0.9 (0.4/1.4)	47	0.9 (0.7/1.0)	79	<0.001

Characteristics were compared using Mann–Whitney *U* test or Fisher's exact test as appropriate. *P* > 0.05 was considered nonsignificant.

BMI, body mass index; BPD, bronchopulmonary dysplasia, oxygen at 36 wk postmenstrual age; CRP, C-reactive protein; CTG, cardiotocogram; GA, gestational age; *M*, median; m/f, male/female; MR-proADM, midregional proadrenomedullin; NS, not significant; *P*, percentile; PPRM, prolonged premature rupture of membranes.

MR-proADM Concentrations in Paired Arterial and Venous Umbilical Cord Plasma Samples

Paired umbilical cord arterial and venous plasma MR-proADM concentrations were closely related ($R_s = 0.825$, $P < 0.001$, $n = 108$; **Figure 1**). Overall, MR-proADM concentrations were slightly higher in venous, as compared with arterial samples (mean (M) = 1.03 vs. 1.01 nmol/l, $P < 0.05$). In 76 (70.4%) of 108 pairs, MR-proADM concentrations were higher in venous than arterial samples, whereas in the remaining 32 (29.6%) cases umbilical arterial MR-proADM exceeded venous MR-proADM. No differences in clinical parameters were found when comparing the two groups.

Relationship Between GA and MR-proADM Plasma Concentrations at Birth and at 2–3 d

Birth weight (BW) and GA at birth were inversely related to MR-proADM concentrations in venous umbilical cord plasma ($R_s = -0.421$, $R_s = -0.403$, respectively, both $P < 0.001$, $n = 270$; **Figure 2a**) and to MR-proADM concentrations in plasma from 2–3 d of life ($R_s = -0.530$, $R_s = -0.541$, respectively, both $P < 0.001$, $n = 183$; **Figure 2b**).

Paired plasma MR-proADM concentrations at birth and 2–3 d of life were directly correlated ($R_s = 0.367$, $P < 0.001$, $n = 125$). MR-proADM concentrations decreased in term (GA 37–41 wk) and moderately preterm infants (GA 32–36 wk) but not in very preterm infants (GA 24–31 wk), as shown in **Figure 3**.

Impact of Labor on Cord Blood MR-proADM Plasma Concentrations

Term infants born by elective cesarean section ($n = 55$) had significantly lower MR-proADM concentrations in cord blood than infants born by vaginal delivery ($n = 41$) or secondary cesarean section (after the onset of labor, $n = 18$; $M = 0.93$ vs. 1.15 and 1.18 nmol/l, respectively, $P < 0.001$). In preterm infants, there was no impact of delivery mode on MR-proADM concentrations.

Figure 1. Scatter plots of paired arterial and venous umbilical cord plasma MR-proADM concentrations at birth. Spearman's rank order correlation coefficient (R_s) = 0.848, $P < 0.001$, $n = 108$. MR-proADM, midregional proadrenomedullin.

Arterial umbilical cord blood pH did not correlate with MR-proADM concentrations at birth among all infants ($n = 270$) or infants stratified by GA. Arterial umbilical cord blood base deficit, however, was inversely related to MR-proADM concentrations at birth in the total cohort ($R_s = -0.414$, $P < 0.001$, $n = 196$) and subsets defined by GA (term ($n = 103$): $R_s = -0.514$, $P < 0.001$; moderate preterm: ($n = 70$) $R_s = -0.326$, $P < 0.01$; very preterm: ($n = 23$) $R_s = -0.414$, $P < 0.05$). Five- and 10-min Apgar scores were related to MR-proADM concentrations in cord blood for preterm infants only ($n = 74$; $R_s = -0.412$, $P < 0.001$ and $R_s = -0.266$, $P < 0.5$, respectively).

Increased MR-proADM Plasma Concentrations at Birth and With Perinatal Infection

Variables associated with perinatal infection (maternal C-reactive protein and leukocyte count immediately before the onset of parturition, intrapartum fever $\geq 38^\circ\text{C}$, histological signs of chorioamnionitis, and bloodstream-proven EOS) were each significantly related to MR-proADM plasma concentrations in venous umbilical cord blood at birth: the continuous

Figure 2. Relationships between birth weight and MR-proADM concentrations at (a) birth in venous umbilical cord blood ($R_s = -0.421$, $P < 0.001$, $n = 270$) or at (b) 2–3 d of life ($R_s = -0.531$, $P < 0.001$, $n = 183$). MR-proADM, midregional proadrenomedullin.

Figure 3. MR-proADM concentrations in paired samples of venous umbilical cord blood at birth (gray boxes) and at 2–3 d (white boxes) of life in infants with gestational age <32 wk ($n = 45$), 32–36 wk ($n = 30$), or 37–41 wk ($n = 50$). MR-proADM concentrations are presented as box (interquartile range) and whisker (5–95% range) plots. Levels of significance between various groups were calculated by Mann–Whitney U test as indicated (** $P < 0.001$). MR-proADM, midregional proadrenomedullin.

maternal parameters C-reactive protein and leukocyte count correlated directly with MR-proADM at birth, $R_s = 0.258$ ($n = 162$) and 0.270 ($n = 197$), respectively (both $P < 0.001$). In the total group of infants with venous umbilical cord blood samples at birth ($n = 270$), MR-proADM concentrations at birth were significantly elevated in the presence of any of the following variables: clinical chorioamnionitis ($M = 1.60$ nmol/l, range 0.8–2.59, $n = 23$) vs. $M = 1.09$ nmol/l, range 0.3–3.42, $n = 247$, $P < 0.001$); histologic chorioamnionitis ($M = 1.74$ nmol/l, range 0.93–2.59, $n = 15$ vs. $M = 1.18$ nmol/l, range 0.62–3.42, $n = 128$, $P < 0.001$); blood-stream proven EOS ($M = 1.57$ nmol/l, range 1.17–1.72, $n = 5$ vs. $M = 1.11$ nmol/l, range 0.3–3.42, $n = 265$, $P < 0.001$). Similar results were obtained when analyzing only preterm infants with venous umbilical cord blood samples at birth ($n = 156$), as shown in **Figure 4**.

As amnion infection is a leading cause of preterm delivery, and prematurity was inversely related to MR-proADM concentrations, we performed a stepwise multiple regression analysis, including GA at delivery, arterial umbilical cord blood pH, arterial umbilical cord blood base excess, and clinical chorioamnionitis. Clinical chorioamnionitis ($P < 0.001$) and umbilical cord blood base excess ($P < 0.001$) retained a significant impact on MR-proADM cord blood concentrations but not GA at delivery or umbilical cord blood pH.

MR-proADM Plasma Concentrations at 2–3 d

Each of the various infant variables recorded during the post-natal course was strongly related to prematurity (**Table 1**). Even within the group of extremely premature infants, all of the variables studied were significantly related to GA and BW. However, within the group of extremely premature infants,

Figure 4. MR-proADM concentrations at birth were higher in preterm infants when chorioamnionitis or EOS was noted. Of 156 preterm infants with venous umbilical cord blood samples at birth, neither clinical nor histologic chorioamnionitis nor EOS was recorded in 127 subjects (Control). Clinical chorioamnionitis was present in 22 of 156 preterms (Clinical, in 12 subjects chorioamnionitis was verified by histologic examination). Histo M was found in 8 of 156 preterms, whereas Histo FM was found in 7 of 156 preterms. Bloodstream-proven EOS was diagnosed in 5 of 156 preterm infants. MR-proADM concentrations are presented as box (interquartile range) and whisker (5–95% range) plots. Levels of significance between groups were calculated by Mann–Whitney U test as indicated (* $P < 0.05$; ** $P < 0.01$). EOS, early-onset sepsis; Histo FM, histologic chorioamnionitis with both maternal and fetal reaction; Histo M, histologic chorioamnionitis with only maternal reaction; MR-proADM, midregional proadrenomedullin.

MR-proADM concentrations at 2–3 d did not correlate with GA ($R_s = -0.047$, $P = 0.731$) or BW ($R_s = -0.076$, $P = 0.473$) but were significantly ($P < 0.01$) higher in infants receiving any positive pressure respiratory support (endotracheal ventilation: $M = 1.5$ (range 0.74–3.8) nmol/l, $n = 25$; noninvasive respiratory support (nasal or pharyngeal continuous positive airway pressure: $M = 1.28$ (range 0.74–2.6) nmol/l, $n = 21$) as compared with those without any positive pressure support ($M = 1.01$ (range 0.72–1.86) nmol/l, $n = 11$). The other variables had no influence on MR-proADM concentrations at 2–3 d.

Clinical chorioamnionitis was associated with MR-proADM concentrations at 2–3 d ($P = 0.03$), applying a stepwise regression model together with GA at delivery ($P = 0.168$). A further stepwise regression model was applied to test histologic chorioamnionitis and GA at delivery as potential influencing markers on MR-proADM concentrations at 2–3 d of life. The regression analyses revealed a significant impact of both histologic chorioamnionitis ($P = 0.033$) and GA at delivery ($P < 0.001$) on MR-proADM levels at 2–3 d of life.

DISCUSSION

This prospective cross-sectional study presents data concerning the concentrations of plasma MR-proADM in preterm and term infants at birth and at 2–3 d of life. This is the first study of its kind to present such data. The major findings are as follows: (i) MR-proADM plasma concentrations are closely

related in paired arterial and venous umbilical cord samples at birth. (ii) The more preterm an infant is at birth, the higher MR-proADM plasma concentrations are at birth and 2–3 d. (iii) Irrespective of GA and BW, MR-proADM plasma concentrations are increased at birth in infants of mothers with clinical or histologic chorioamnionitis and signs of antenatal cardiovascular compromise (base deficit). (iv) At 2–3 d of life, respiratory support is associated with higher MR-proADM plasma concentrations.

The concept of replacing the cumbersome measurement of bioactive and rapidly cleared peptides by measurement of their stable, nonfunctional, and cognate peptides derived from a common precursor has greatly increased our capacity for both diagnosis and prognosis. This improvement in assay technology has implemented MR-proADM measurements in several large clinical trials in adult medicine (20,21).

Although many studies have been conducted on plasma concentrations of bioactive ADM in preterm and term newborns (7–10,17–18,22), just one analysis has been published thus far on MR-proADM in healthy term newborns. This analysis described values for MR-proADM in venous umbilical cord plasma (19). Term infants born without risk factors for vertically transmitted infections had slightly lower MR-proADM values ($M = 0.84$, range = 0.55–1.38 nmol/l) than infants with these risk factors but without signs of sepsis ($M = \sim 0.88$, range = 0.11–2.54 nmol/l). These values are very similar to our data on healthy term newborns and clearly above the circulating plasma MR-proADM concentrations published for healthy adults ($M = 0.33$, range = 0.10–0.64 nmol/l; ref. 12).

Moreover, our data unequivocally show that the more preterm an infant was born, the higher MR-proADM plasma concentrations were at birth and at 2–3 d (Figure 3). This inverse relation of MR-proADM concentrations at birth and at 2–3 d of life to GA as well as BW denotes an involvement for ADM in development, specifically the development of the cardiovascular system. ADM is a major endogenous vasodilator (2) and blood pressure and prematurity are related in a linear fashion, i.e., the lower the GA at birth, the lower the blood pressure during the first days of life (23). An increasing body of literature has led to the present attitude of permissive hypotension in the extremely low-birth-weight infant when signs of good perfusion are present (24). We speculate that high levels of ADM in preterm infants result in low systemic vascular resistance and hence low blood pressure. With the drop in ADM, blood pressure increases during the first days unless there is diastolic run-off through a patent ductus arteriosus.

Our finding of an association of respiratory support with higher MR-proADM plasma concentrations at 2–3 d is supported by the data of Kamata *et al.*, as they demonstrated elevated levels of plasma ADM in umbilical cord blood at birth and at 3 and 6 d of life in infants with persistent pulmonary hypertension neonatorum (25). This supports the notion that circulating ADM plays a role in regulating pulmonary vascular tone (26) and may be involved in lung differentiation and maturation (27).

Bacterial endotoxins and inflammatory cytokines induce the expression of ADM (28,29), and both the secretion of ADM and MR-proADM are increased during sepsis in adults (30,31) and neonates (32). These data are in line with our findings of elevated MR-proADM concentrations in cord blood at birth in infants with EOS and/or chorioamnionitis. Arterial hypotension is a common finding in sepsis and may be caused in part by elevated ADM, which, together with the ADM-binding protein, also has anti-inflammatory properties (33).

Base deficit in umbilical cord blood is a marker of chronic fetal stress and indicates increased anaerobic glycolysis, which is caused by systemic fetal hypoxia or regional hypoxia when microcirculation is impaired, e.g., in inflammation. Placental ADM mRNA and protein, as well as secreted ADM, have been shown to be increased in response to hypoxia in experimental settings (34–36). This supports our finding that chronic fetal stress is related to elevated MR-proADM plasma concentrations at birth. In contrast, arterial umbilical cord blood pH is a marker of acute birth stress and vaginal delivery. As compared with elective abdominal delivery, vaginal delivery elicits a dramatic surge in stress hormones in term and preterm infants as shown earlier (37,38). MR-proADM concentrations at birth did not show any association with arterial umbilical cord blood pH, and only in term infants were MR-proADM concentrations at birth slightly increased in infants born vaginally as compared with infants born by elective caesarean section ($M = 1.15$ vs. 0.93 nmol/l, respectively, $P < 0.001$).

In contrast to previous studies employing bioactive ADM in cord blood (8), MR-proADM concentrations were not altered in our study cohort when preeclampsia was present. It has been reported that values of bioactive ADM measured 6 h after birth were elevated in preterm infants developing intraventricular hemorrhage (17). Within our cohort of very preterm infants (GA 24–31 wk, $n = 90$), eight infants developed intraventricular hemorrhage of different grades. Neither MR-proADM concentrations in cord blood at birth nor at 2–3 d were significantly increased in these infants.

An important limitation of this exploratory study is the small number of infants with serious morbidities, including intraventricular hemorrhage and bloodstream proven EOS. Whether or not MR-proADM may offer clinically helpful pieces of information in sick preterm infants warrants differentially designed studies focusing on this question.

In conclusion, MR-proADM concentrations at birth are associated with immaturity and inflammation. The elevated MR-proADM concentrations may be causally linked to reduced systemic vascular resistance observed in these two conditions.

METHODS

Between March 2009 and December 2010, a total of 328 infants born at the University Hospitals of Basel and Zürich were enrolled in this prospective, cross-sectional study after obtaining informed written consent from the parents. The study was approved by the institutional review boards of the University Hospital of Basel and Zürich (Ethikkommission beider Basel, EKBB 07/09, Kantonale Ethikkommission Zürich, KEK 08/09).

Blood samples were drawn from 270 umbilical veins at the time of delivery, with an additional 108 paired samples from the umbilical artery and an additional 125 paired blood samples from postnatal day 2–3. Additional blood samples were taken at postnatal day 2–3 from 58 infants. After collecting blood in EDTA tubes, samples were stored at 4°C until centrifugation, performed within <8 h. Plasma was transferred into a new EDTA tube and subsequently frozen at –28°C. MR-proADM (nmol/l) was measured in a single batch with BRAHMS KRYPTOR automated immunofluorescent assay (BRAHMS Biomarkers; Thermo Fisher Scientific, Hennigsdorf, Germany) (39).

Details of the pregnancy, delivery, and the infants' birth were collected from the charts. Placentas were histologically examined for signs of chorioamnionitis (maternal and fetal reaction) and altered placental perfusion capacity by the local pathologists (Rosmarie Caduff, Institute of Pathology, University Hospital Zurich; Elisabeth Bruder, Institute of Pathology, University Hospital Basel). When the various pathomorphological findings, including impaired maternal blood flow through the intervillous space (infarcts) or impaired fetal blood flow through the cord and allantoic vessels or chorionic villi (fetal thrombotic vasculopathy) were considered significant, decreased placental perfusion capacity was diagnosed (40). Prolonged premature rupture of the membranes was defined as rupture of membranes more than 18 hours before labor and before 37 wk gestation. Data concerning the infants' health after birth were recorded by the staff on the maternity or neonatology wards. Clinical data were recorded as described previously (41) based on the standardized definitions of the Swiss Neonatal Network. Both invasive (endotracheal ventilation) and noninvasive (nasal or pharyngeal continuous positive airway pressure) ventilation was counted as positive pressure support. Management of patent ductus arteriosus, including diagnosis and treatment, was performed as previously published (42). Clinical chorioamnionitis was diagnosed in women who had three or more of the following signs: leukocytes >20,000/μl, C-reactive protein >40 mg/dl, temperature >38°C, maternal tachycardia >100 bpm, and fetal tachycardia >160 bpm.

A stepwise multiple regression was applied to assess the impact of GA at delivery, arterial umbilical cord blood pH, arterial umbilical cord blood base excess, and clinical chorioamnionitis on plasma MR-proADM alterations in venous umbilical cord blood whereas GA at delivery, clinical chorioamnionitis and histologic chorioamnionitis were investigated as variables affecting infant MR-proADM levels at 2–3 d of life.

Data were analyzed employing IBM SPSS Statistics 19.0 (SPSS, Chicago, IL) in a strictly nonparametric fashion (Mann–Whitney *U*, Kruskal–Wallis, and Fisher's exact tests). All continuous variables are reported as *M* (range). *R*_s values were calculated to characterize the relationships between continuous variables. A *P*-value < 0.05 was considered to be significant.

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