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Activin A Plasma Levels at Birth: An Index of Fetal Hypoxia in Preterm Newborn

PASQUALE FLORIO, SERAFINA PERRONE, STEFANO LUISI, MARIANGELA LONGINI, DONATELLA TANGANELLI, FELICE PETRAGLIA, AND GIUSEPPE BUONOCORE

Department of Pediatrics, Obstetrics and Reproductive Medicine, University of Siena, 53100 Siena, Italy

ABSTRACT

Activin-A is a growth factor involved in cell growth and differentiation, neuronal survival, early embrionic development and erythropoiesis. Hypoxemia is a specific trigger for increasing activin-A in fetal lamb circulation. We tested the hypothesis that fetal hypoxia induces activin-A secretion in preterm newborn infants. Fifty newborn infants with gestational ages ranging from 26 to 36 wk were enrolled in a prospective study performed at the Pediatrics, Obstetrics and Reproductive Medicine Department, University of Siena, Italy. Heparinized blood samples were obtained from the umbilical vein after cord clamping, immediately after delivery. Activin A, hypoxanthine (Hx), xanthine (Xa) plasma levels and absolute nucleated red blood cell (NRBC) count were measured. Activin-A levels ($p < 0.0001$) and NRBC ($p < 0.0001$) were significantly higher in hypoxic than in non hypoxic preterm newborns. Cord activin A levels were significantly related with Hx (τ_a=0.64, τ_b=0.64, $p < 0.0001$) and Xa (τ_a=0.56, τ_b=0.57, $p < 0.0001$) levels, NRBC ((τ_a=-0.45, τ_b=-0.46, $p < 0.0001$) count; pH (τ_a=-0.47, τ_b=-0.48, $p < 0.0001$) and base deficit (τ_a=-0.36, τ_b=0.-0.36, $p = 0.0002$). Preterm newborns with signs of perinatal hypoxia at birth have increased activin-A levels, suggesting that activin-A may reflect indirectly intrauterine hypoxia. **(*Pediatr Res* 54: 696–700, 2003)**

Abbreviations

Hx, hypoxanthine
Xa, xanthine
NRBC, nucleated red blood cell
***τ*,** Kendall's rank correlation coefficient tau

Activin A is a growth factor (βA/βA dimer) mainly produced by the placenta, decidua and fetal membranes and secreted in large amounts in maternal circulation (1–7). Inhibin/activin subunits are expressed in a variety of tissues, including ovary, testis, placenta, adrenal, kidney, brain and pituitary gland. Inhibin A and Activin A have been reported to regulate various physiologic functions, including ACTH and GH secretion, neuronal survival, hypothalamic oxytocin secretion, erythropoiesis, early embryonic development and gonad function (8–11). Activin A concentrations significantly increase in maternal serum with advancing gestation (12), whereas umbilical cord blood serum do not significantly differ from midpregnancy to term gestation (7) and are significantly lower than in maternal serum (6, 7). Disorders of pregnancy due to reduced placental perfusion and various degrees of feto-placental hypoxemia, such as preeclampsia and fetal growth restriction (13) are characterized by increased levels of maternal and umbilical cord activin A (12), and feto-placental and/or maternal isocapnic hypoxemia are specific triggers for an increase in activin A. Indeed, cord blood Activin A levels increase in the sheep after induction of hypoxia, remain elevated throughout hypoxia and return to control values when normal blood flow is restored (14). Activin A subunit mRNA expression is up-regulated during hypoxic ischemia in the adult brain and cerebral hypoxia stimulates Activin A secretion in rat newborns as well as in adult animals (15, 16). No human study to date has determined whether this protein is altered in babies with clinical signs of hypoxia at birth. Perinatal hypoxia set in motion a cascade of biochemical events commencing with a shift from oxidative to anaerobic metabolism, which leads to a rapid rise in the levels of lactic acid and of oxygen free radicals (17). During hypoxia the cutback in oxidative phosphorilation rapidly diminishes reservers of high-energy phopshate. High levels of adenosine and hypoxanthine accumulate in a few minutes (18, 19). The breakdown of hypoxanthine by xanthine oxidase in the presence of oxygen produces a flood of superoxide radicals. Several experimental studies have demonstrated a direct relation between the degree of hypoxia and the severity of oxidative damage due to free radicals production during hypoxia in fetal life (20–22).

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Correspondence: Prof. Giuseppe Buonocore, MD, Department of Pediatrics, Obstetrics and Reproductive Medicine, University of Siena, Policlinico "Le Scotte", V.le Bracci 36, 53100 Siena, Italy; e-mail: buonocore@unisi.it
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We recently demonstrated a hypoxia-induced increase in nucleated red blood cell (NRBC) count at birth and its predictive value for neurodevelopmental outcome (23). We suggested that hypoxia and perinatal distress are the two main factors responsible for increasing NRBC counts by stimulating erythropoietin production.

It has been proposed that activin secretion increases when there is neonatal cerebral hypoxemia (15), giving rise in erythropoietin-induced stimulation of hematopoiesis (24, 25). We tested the hypothesis that activin A plasma levels increase in preterm newborn infants with fetal tissue hypoxia.

MATERIALS AND METHODS

Subjects. Fifty preterm newborn babies with gestational age 26–36 wk (for more details see Table 1), consecutively admitted to the Neonatology Division of Siena, University Hospital, were enrolled in the study. All babies with congenital malformations, inborn errors of metabolism, blood group incompatibility, sepsis, diabetic mothers, multiple gestation, and those not born in the clinic were excluded. Perinatal hypoxia was defined as the presence of at least two of the following conditions: intrapartum distress, as indicated by fetal bradycardia with a heart rate of less than 100 beats per minute, late decelerations, or an absence of heart rate variability; an Apgar score of 6 or less at five minutes; a need for resuscitation for more than one minute with positive-pressure ventilation and oxygen immediately after birth; a pH value of 7.20 or less in umbilical vein (22, 23, 26, 27). Twenty six of the 50 newborns were regarded as hypoxic. Eleven of 26 hypoxic babies were reanalyzed separately to verify whether stricter criteria of hypoxia (pH $<$ 7.10 in umbilical vein, Apgar score $<$ 5 at 5 min) changed our results. Twenty four babies, without signs of perinatal hypoxia were used as control subjects. The degree of hypoxia was ascertained by determination of hypoxanthine (Hx) and xanthine (Xa) concentrations in cord blood. The study was masked throughout. It was approved by the Human Ethics Committee of the Medical Faculty, University of Siena. Informed written parental consent was obtained before enrolment of each infant.

Methods. Heparinized blood samples were obtained from the umbilical vein after cord clamping, immediately after delivery. A complete blood cell count was performed, and total white blood cell count was determined. NRBC count was expressed as the absolute erythroblast count (NRBC/mm^3), obtained by light microscopic examination of May-Grunwald-Giemsa-stained blood smears. Blood gas analysis was measured with a model ABL 505 analyzer (Radiometer, Copenaghen, Denmark) immediately after blood sampling. The blood was centrifuged and analysis of Hx, Xa and activin A was carried out in plasma within 2 h of blood sampling to avoid storage effects. After centrifuging, the plasma and buffy coat were removed. Hx and Xa plasma levels were evaluated by HPLC, using a Varian Vista 5500 high-performance liquid chromatograph equipped with a variable-wavelength UV detector (model 4290, Varian, Palo Alto, CA, U.S.A.) (22). A ready-to-use prepacked column Supelcosil LC-18 column by Supelco (250 $\times$ 4.6 mm internal diameter, 5 μm), with precolumn (20 $\times$ 4.6 mm internal diameter) filled with the same packing (Supelguard, Supelco, St. Louis, MO, U.S.A.) completed the analytical system. The mobile phase gradient used was: time 0 min (A = 100%, B = 0%), time 10 min (A = 90%, B = 10%), time 20 min (A = 80%, B = 20%), time 30 min (A = 100%, B = 0%), with A was 10^{-2} M potassium phosphate buffer at pH 5.5 and B was methanol. The next sample was injected after an interval of 10 min. The flow rate was 1 mL/min and the wavelength 220 nm. The detection limits for Hx and Xa were 0.06 μg/mL and 0.2 μg/mL respectively

Activin A concentrations were measured using specific two-site enzyme immunoassays (Serotec, Oxford, UK), as previously described (28). Briefly, plates were washed and bound

Table 1. *Clinical characteristics of newborns*

Newborns (n)	Hypoxic (n = 26)	Nonhypoxic (n = 24)	p Value
Gestational age (wk)*	30.7 ± 3.9 (27–38)	32.3 ± 3.9 (27–36)	NS
Gender	10 male, 16 female	14 male, 10 female	NS
1-Min Apgar score*	3.5 ± 2.2 (1–7)	7.7 ± 2.5 (3–10)	0.002
5-Min Apgar score*	6.2 ± 1.5 (5–8)	8.9 ± 1.4 (7–10)	<0.0001
Delivery			
Vaginal delivery	19	18	NS
Cesarean section	7	6	NS
Maternal-placental pathology			
Histologic chorioamnionitis	17	12	NS
Abruptio placentae	1	0	
Extensive placental infarction (>5 cm in diameter or multiple lesions >2 cm in diameter)	8	9	NS
Blood gas analysis			
pH*	7.09 ± 0.12 (6.98–7.22)	7.32 ± 0.03 (7.29–7.36)	<0.0001
P_{O_2}*	20.4 ± 10.7 (15.2–39.3)	43.16 ± 8.23 (30–55.8)	0.003
P_{CO_2}*	63.2 ± 17.1 (38.9–83.9)	43.4 ± 8.6 (30.8–56.5)	0.01
Base deficit (mmol/L)*	8.8 ± 4.9 (−16.3–−4.0)	2.5 ± 2.0 (−6.0–+0.6)	<0.0001

Perinatal hypoxia was defined as the presence of at least two of the following conditions: intrapartum distress, as indicated by fetal bradycardia with a heart rate of <100 beats per minute, late decelerations, or an absence of heart rate variability; an Apgar score of ≤6 at 5 min; a need for resuscitation for >1 min with positive-pressure ventilation and oxygen immediately after birth; a pH value of ≤7.20 in umbilical vein.

* Plus-minus values are mean ± SD; 10th and 90th percentile in brackets.

alkaline phosphatase was quantified using a commercially available enzyme immunoassay amplification system (Immuno Select ELISA Amplification System, Dako, Milan, Italy), according to the manifacturer's instructions.

The analytical detection limit of the activin A assay was less than 100 pg/mL; intra-and inter-assay coefficients of variation were 5.0% and 9.0%, respectively. Cross-reactions for each assay with the various inhibin-related proteins were less than 0.5%. Activin A plates were read at 490 nm on an automated ELISA plate reader (Basic Radim Immunoassay Operator, Radim spa, Pomezia, Italy).

Statistical analysis. The data, expressed as means ± SD, median and 10^{th} and 90^{th} percentile, were analyzed for statistically significant differences by Mann-Whitney *U* non parametric test for continuous data and by Fisher's exact test for categorical data. Kendall's rank correlation coefficient was used to asses linkages between variables. Statistical analysis was performed using Stata 8® (Stata Corp.-4905 Lakeway Drive- College Station, TX 77845 USA)

RESULTS

No differences in gestational age and birth weight between hypoxic and non hypoxic babies were found, but newborns with signs of perinatal hypoxia had significantly lower pH (P<0,0001), higher base deficit levels ($p < 0.0001$), higher pCO_2 (P = 0,01) and lower pO_2 levels (P = 0,03) than non hypoxic neonates. (Table 1)

As expected, hypoxic newborns showed significantly higher plasma levels of Hx, Xa and NRBC count than non hypoxic neonates (Table 2).

Activin A levels were significantly higher in hypoxic than non hypoxic newborns (medians, minimum and maximum values: 2.2; 5.4 - 0.5 *versus* 0.5; 1.7 - 0.2 ng/mL, $p < 0.0001$).

There were no difference in clinical characteristics: maternal age, parity, race, gestational age, gender, birth weight, mode of delivery, and placental pathologies the two groups. Similar results, were found in 11 out of 26 hypoxic babies meeting stricter criteria of hypoxia with respect to non hypoxic babies (Table 2)

Cord activin A levels were significantly related with Hx (τ_a=0.64, τ_b=0.64, $p < 0.0001$) and Xa (τ_a=0.56, τ_b=0.57, $p < 0.0001$) levels (Fig. 1A and Fig. 1B), pH (τ_a=-0.47, τ_b=-0.48, $p < 0.0001$) (Fig. 2A) and base deficit (τ_a=-0.36, τ_b=0.-0.36, $p = 0.0002$) (Fig. 2B), and NRBC (τ_a=-0.45, τ_b=-0.46, $p < 0.0001$) (Fig. 3).

DISCUSSION

The present study first refers on activin A and hypoxia in humans: newborns with clinical signs of perinatal hypoxia had higher activin A levels, which were correlated with biochemical features of hypoxia such as higher NRBCs and plasma Hx and Xa levels, as well as lower pH and higher base deficit levels, confirming previous our reported findings (22, 27) and suggesting that hypoxia is a trigger to stimulate activin A secretion. In line with this suggestion is the fact that intrauterine fetal death, a condition due to fetal hypoxia, is characterized by higher activin A levels in amniotic fluid (29), and that the feto-placental and/or maternal isocapnic hypoxemia increase activin A secretion in fetal lamb circulation until the hypoxic stimuli is removed (14).

With respect to the source of this rise of activin A in cord blood of hypoxic neonates, increased expression of activin subunit proteins (30) has been described in placentas of preg-

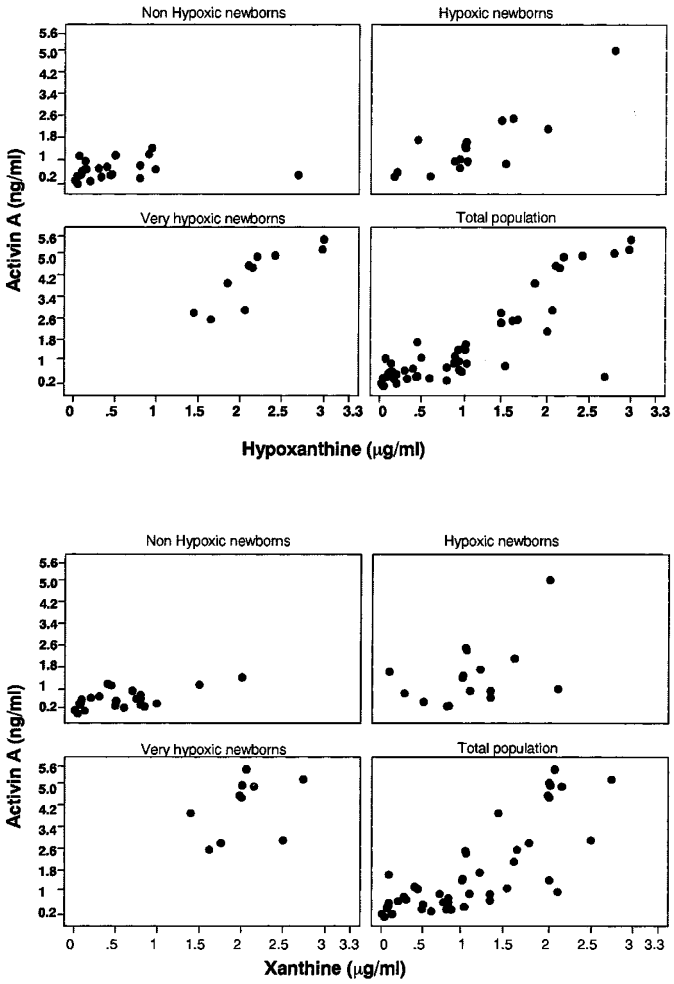

Figure 1. A: Correlations between cord plasma levels of activin A and hypoxanthine. B: Correlations between cord plasma levels of activin A and xanthine.

Table 2. *Cord plasma levels (medians, minimum, and maximum values) of hypoxanthine, xanthine, NRBC, and activin A in nonhypoxic, moderately hypoxic, and very hypoxic babies*

	Nonhypoxic (A)	*p* Value A *vs* B	Moderately hypoxic (B)	*p* Value B *vs* C	Very hypoxic (C)	*p* Value A *vs* C
Hx (μg/mL)	0.2 (0–2.6)	0.0002	1.0 (0.2–2.8)	0.0005	2.1 (1.4–3.0)	<0.0001
Xa (μg/mL)	0.5 (0–2.0)	0.0019	1.0 (0.1–2.1)	0.0004	2.0 (1.4–2.7)	<0.0001
NRBC (× mm^3)	394.5 (0–3,196)	0.0021	2,601.5 (0–9,500)	0.0014	9,045.0 (3,748–10,334)	<0.0001
Activin A (ng/mL)	0.5 (0.1–1.4)	0.0011	1.22 (0.4–5.0)	0.0001	4.5 (2.6–5.5)	<0.0001

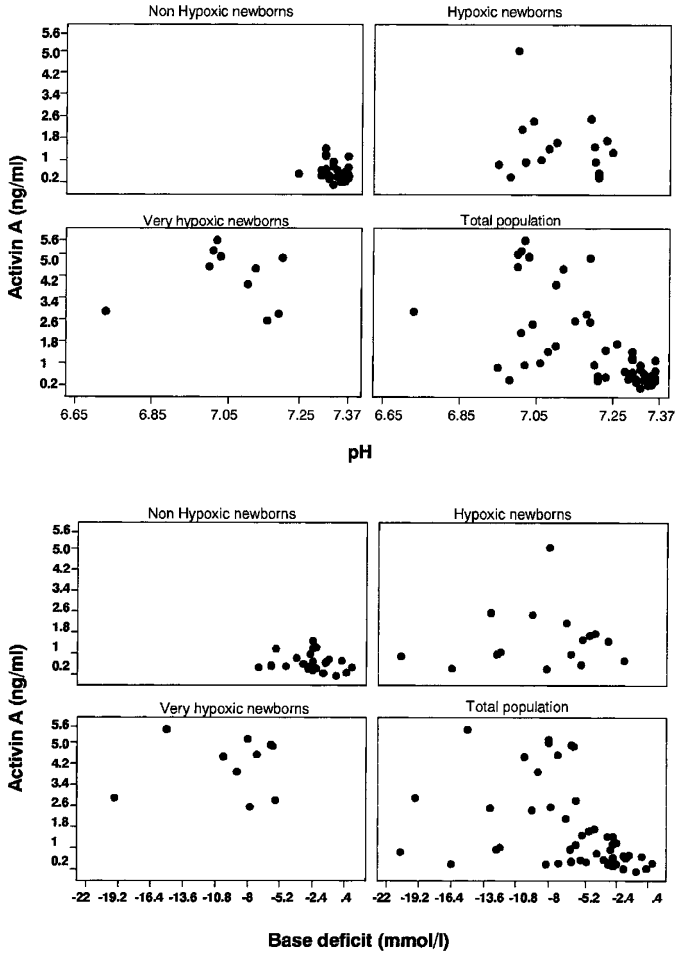

Figure 2. A: Correlations between cord plasma levels of activin A and pH. B: Correlations between cord plasma levels of activin A and base deficit.

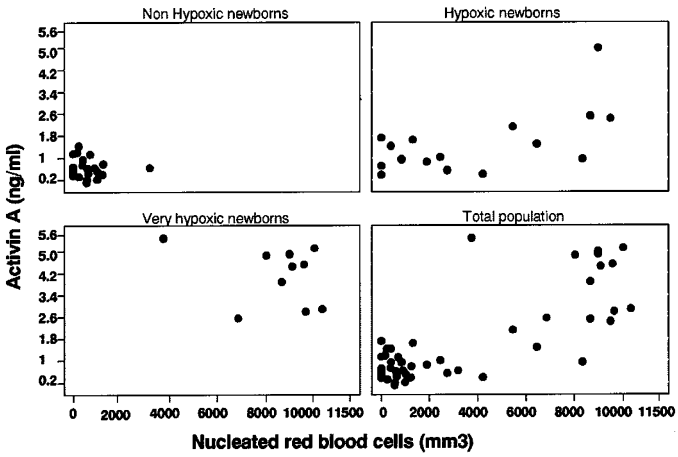

Figure 3. Correlation between cord plasma levels of activin A and NRBC.

nant women with preeclampsia or fetal growth restriction, suggesting that increased levels of activin A in hypoxic newborns may partially be due to increased placental expression and synthesis. However, recent *in vitro* data revealed that hypoxia significantly reduced synthesis and secretion of activin A by the human placenta (31, 32). The data obtained in fetal lambs and our results suggest that the increased levels of activin A in fetal blood arise from the fetus and that a significant relationship exist between this increase and fetal hypoxia

Fetal and neonatal hypoxia is followed by severe changes in erythropoiesis and red cell characteristics (33), through production of erythropoietin (34). Interestingly, activin A augments erythropoietin-induced stimulation of hematopoiesis (24, 25, 35), and directly regulates erythropoiesis (36). The relationship observed between activin A levels and hypoxanthine and xanthine concentrations strongly suggests that hypoxia induces activn A release. The correlation found between activin A and NRBC suggests hypoxia is one of common stimulus for increased erythropoiesis and activin A release. Increased activin A levels in cord blood of hypoxic newborns may also be a further direct trigger to hematopoiesis in the depressed fetus. Since distinct NRBC patterns seem to be related to the timing of fetal neurologic impairment (23, 37–40), the relationship between activin A and NRBC suggests activin A as a possible indicator of fetal injury at birth.

CONCLUSION

In conclusion, intrauterine hypoxia is one of the common factors responsible for increasing activin A levels in fetal circulation. The high correlation of activin A with clinical and biochemical signs of fetal and neonatal hypoxia lead us to suggest that activin A is a possible indicator of intrauterine hypoxia.

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