Nucleated red blood cell counts in growth-restricted neonates with absent or reversed-end-diastolic umbilical artery velocity

R. Axt-Fliedner, H. J. Hendrik, W. Schmidt

Department of Obstetrics and Gynecology, University of the Saarland, Homburg/Saar (Germany)

Summary

Objective: To determine the effect of increasing circulatory impairment in fetuses on the neonatal nucleated red blood cell count.
Methods: Seventy-seven fetuses with suspected intrauterine growth restriction (abdominal circumference < 5th percentile), subsequent birth weight < 10th percentile for gestational age and abnormal umbilical artery Doppler flow velocity were enrolled in the study. Fetuses were assigned to the following groups on the basis of the last Doppler examination before delivery: group 1, umbilical artery S/D ratio > 2 SD above the gestational age mean, group 2, absent end-diastolic velocity in the umbilical artery, group 3, reversed end-diastolic velocity in the umbilical artery. Neonatal nucleated red blood cells were obtained from the umbilical artery within 1 min after delivery with follow-up examinations until the nucleated red blood cell count was < 5/100 white blood cells. Perinatal and neonatal data were recorded from the charts.
Results: Significantly higher nucleated red blood cell counts [median 144, range 9-964] with lowest birth weights [mean 932 g, range 530 g-2060 g] were detected in group 3 and in group 2 [median 65, range 2-720; mean 1049 g, range 630 g-2110 g] compared to group 1 [median 22, range 2-201; mean 1565 g, range 860 g-2780 g, p< 0.001, respectively]. The persistence of nucleated red blood cells in the neonatal circulation was prolonged in group 3 [median 5.2, range 1-13 days] compared to group 2 [median 3.9, range 1-8] and group 1 [median 1, range 0-2]. Neonates in group 3 also had decreased platelet counts, hematocrit and hemoglobin values. Cord blood gases showed a significant decrease of arterial and venous pH values in groups 2 and 3 which was accompagnied by a significant decrease in base excess values. Four neonatal deaths, three of them in the reversed-end-diastolic velocity and one in the absent end-diastolic velocity group, occurred.
Stepwise regression demonstrated that absent or reversed end-diastolic flow velocities, birth weight, gestational age and arterial base excess contribute significantly to the elevation of the nucleated red blood cell counts.
Conclusions: Increased nucleated red blood cell counts at birth and their longer persistance in the neonatal circulation are associated with antenatal abnormal umbilical artery Doppler studies in growth restricted fetuses. The nucleated red blood cell count might therefore become an additional valuable tool in the diagnosis of growth restricted fetuses who are metabolically compromised.

Key words: Nucleated red blood cells; Doppler Flow; Fetus; Growth restriction.

Introduction

There is increasing evidence, that hypoxic-ischemic injury of the newborn might not be related to labor, but may have occurred during pregnancy. Only in about 10%-20% of cerebral palsy cases do clinical or biochemical parameters of severe fetal asphyxia occur. Therefore, the assessment of additional markers of antenatal, intrauterine hypoxemia is a relevant task and has important medico-legal aspects [1-4].

Surveillance of fetuses at risk and detection of circulatory deterioration is a domain of Doppler ultrasonography. There is evidence that abnormal umbilical artery Doppler values are associated with adverse perinatal outcome [5-9]. Growth restricted fetuses with absent or reversed-end-diastolic velocity in the umbilical artery are believed to be at significantly high risk for intrauterine hypoxemia and acidemia with subsequent neurologic sequelae and further adverse outcome [8a, b, 9].

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Recently, elevated numbers of nucleated red blood cells have been reported to be associated with intrauterine hypoxemia and subsequent neurological impariment [10, 11]. There have been few reports dealing with the relationship of abnormal fetal arterial and venous Doppler studies and elevated nucleated red blood cells at birth [12a, b, 13, 14a, b].

The purpose of this study was to determine whether the extent of circulatory impairment is related to an increase of neonatal nucleated red blood cell counts at birth.

Material and methods

A total of 77 fetuses with suspected fetal growth restriction (abdominal circumference < 5th percentile for gestational age), with a complete nucleated red blood cell count and with a Doppler examination of the fetoplacental unit within five days (mean 3.6 days) before delivery were enrolled in this prospective study. The patients were recruited from a population of pregnant women who were referred to our ultrasound department for evaluation of fetal well-being in case of suspected fetal growth retardation, oligohydramnios, maternal hypertension, preeclampsia or pathologic fetal heart rate patterns. Multiple pregnancies, chorioamnionitis, maternal renal disease, maternal diabetes, maternal cardiovascular pathology other than hypertension and fetuses with chromosomal or structural anomalies were excluded from evaluation.

Doppler examinations were performed in the second and third trimester with an Acuson 128 XP/10 (Mountain View, California, USA) or with Siemens-Sonoline-Elegra (Erlangen, Germany) ultrasound equipment. A 3.5-MHz or 5 MHz curved-array transducer with a high-pass filter of 100 Hz was used. The Doppler examination was performed with the patient lying in a semi-recumbent position.

Doppler waveforms were obtained from a free-floating central part of the umbilical artery in the absence of body movements, fetal breathing or cardiac arrhythmia with the sample volume covering the whole vessel. The middle cerebral artery was visualized at about 1 cm of its origin in the circle of Willis in an axial view. Care was taken to minimize fetal head compression, because this is known to influence the flow velocity waveforms of the middle cerebral arteries. For every vessel examined five consecutive waveforms of similar quality were accepted for analysis. The ratio of mean peak systolic (S) over diastolic (D) velocity (S/D ratio) was determined. Abnormal umbilical Doppler results were those > 2 SD above the mean for gestational age of our local reference ranges [15]. Fetal brain sparing was supposed when the S/D ratio was < 2 SD below the mean of our local reference ranges for the middle cerebral artery.

Within the first 60 seconds after delivery a blood sample was drawn from the umbilical artery and vein by needle aspiration into a tube containing ethylenediaminetetra-acetic acid. NRBC count was assessed from the umbilical artery sample. Two blood smears of each sample stained with Wright's stain were prepared, and the number of NRBCs per 100 WBCs was assessed by light microscopy by two trained observers who were blinded for the study groups [14a, b]. Complete follow-up blood cell counts were conducted during the first days of life.

According to the Doppler findings fetuses were allocated to three groups (Table 1). Group 1 had umbilical artery S/D ratios > 2 SD above the mean (n = 41), group 2 (n = 24) had absent end diastolic velocities in the umbilical artery and group 3 (n = 12) had reversed end-diastolic velocities in the umbilical artery.

The estimated time of delivery was assessed by last menstrual data and a vaginal ultrasound measurement of the crown-rump length within the first 12 weeks after the last menstruation. SGA was defined as a fetal abdominal circumference < 5th percentile for gestational age of our reference ranges [16]. According to Davey and McGillivray previously normotensive women with diastolic blood pressure ≥ 140/90 mmHg measured on two occasions six hours apart after 20 weeks of gestation

Table 1. — *Doppler results and nonstress test in the different study groups.*

	Umbilical artery	Centralization	Non-reactive nonstress test
Group 1 (n = 41)	> 2 SD/mean	0	13 [32]
Group 2 (n = 24)	AEDV	15 [71]	20 [83] ‡
Group 3 (n = 12)	REDV	11 [92] †	11 [92] †

Abnormal: > 2SD above the locally used reference ranges [14], † p < 0.01 compared with group 1, ‡ p < 0.05 compared with group 1, centralization: S/D ratio < 2 SD/mean in the middle cerebral artery.

and with proteinuria of at least 1+ on protein stick testing or a proteinuria > 0.3g/24h were considered preeclamptic [17]. Histologic chorioamnionitis was diagnosed by the presence of acute inflammatory cell infiltration of both layers of the membranes. Prematurity was defined as delivery before 37 completed weeks of gestation. Outcome measures included nucleated red blood cell counts, birth weight, gestational age at delivery, mode of delivery (vaginal delivery, cesarean section because of clinical signs of fetal distress; e.g., abnormal fetal heart rate patterns and meconium stained amniotic fluid, umbilical acidosis), arterial and venous cord gases, Apgar scores, admission to the neonatal intensive care unit and length of stay in the neonatal intensive care unit as well as neonatal data.

The results were analyzed with the SPSS statistical software (SPSS Inc., Chicago, IL, USA). Distribution of nucleated red blood cells was non-normal. Neonatal nucleated red blood cell counts are presented as median and range, otherwise mean ± SD was used. Statistical analysis included the Mann-Whitney U-Test, Student's t-test, χ^2 analysis of variance and stepwise regression analysis. The Bonferroni correction for multiple testing was used. A p-value < 0.05 was considered to indicate a significant difference.

Results

Forty-one fetuses (53%) had a S/D ratio > 2 SD with positive end-diastolic velocity in the umbilical artery without brain sparing. Those fetuses were allocated to group 1. Thirty-six fetuses (47%) presented with absent- or reversed-end-diastolic velocities in the umbilical artery. Among those fetuses 26 (34%) showed evidence of brain-sparing in the middle cerebral artery. Table 1 shows the three study groups with respect to the Doppler findings. A non-reactive nonstress test was seen more frequently in groups 3 and 2 than in group 1 (Table 1).

Table 2 summarizes the obstetrical data of the study groups. Gestational age at delivery as well as birth weights were progressively lower among the study groups with higher numbers of neonates < 3rd percentile for gestational age in group 3 and 2 than in group 1. In contrast, fetuses in group 3 and group 2 were more likely to be delivered by cesarean section for fetal distress. The incidence of preeclampsia increased among study groups. The lowest Apgar scores were found in group 3 compared to group 2 and group 1. Cord gas values were lower in group 3 compared to group 2 and group 1 with significant different values of arterial pH and arterial base excess. In addition most fetuses with arterial pH values < 7.20 and arterial base excess values < –8 mmol/l were found in group 3. Not unexpectedly, the placental weight decreased among study groups (Table 2).

The neonatal data are given in Table 3. Fetuses in group 3 and 2 were admitted more frequently and stayed longer at the neonatal intensive care unit. Three cases of intracerebral hemorrhage were found in group 3. No necrotizing enterocolitis was observed. Four neonatal deaths occurred, one in group 2 and three in group 3. The neonatal deaths were cause by multiorgan failure in three cases, in one case severe respiratory distress syndrome occurred. The four neonates had 964, 720, 273 and 203 nucleated red blood cells/100 white blood cells at birth

Table 2. — *Delivery outcomes.*

	Group 1 n = 41	Group 2 n = 24	Group 3 n = 12
Gestational age at delivery (wks)	33.1 [±3.7]	31.0 [±2.8] *	29.3 [±3.1]
No. < 37 wks	32 [54.2]	22 [91.7] † *	12 [100] *
Cesarean section for fetal distress	17 [41.5]	22 [91.6] *	11 [91.6] *
Preeclampsia	19 [46.3]	12 [50.0]	9 [75.0]
Birth weight (g)	1565 [±693]	1049 [±362] *	932 [±393] *
<5th	19 [46.3]	19 [79.2] *	9 [75] †
<10th	22 [53.7]	5 [20.8]	3 [25]
Apgar score < 7 at 5 min	3 [7.3]	3 [12.5]	2 [16.6]
Cord gases			
Arterial pH	7.27 [±0.06]	7.24 [±0.07] ‡	7.21 [±0.05] †,
Venous pH	7.30 [±0.08]	7.26 [±0.06] ‡	7.25 [±0.06] †
Arterial pO_2	19.6 [±3.3]	16.4 [±4.0] ‡	15.7 [±4.2] ‡
Arterial pCO_2	51.1 [±3.9]	50.3 [±7.3]	48.4 [±12.3]
Arterial bicarbonate	22.0 [±2.1]	20.8 [±3.6]	19.6 [±2.3]
Arterial base excess	-3.6 [±3.4]	-5.6 [±4.6] (p=0.05)	-7.1 [±4.1] †, §
Arterial pH < 7.20	4 [9.8]	4 [16.7]	3 [25]
Arterial base excess < -8	4 [9.8]	6 [25.0]	5 [41.7] †, ¶
Placental weight (gm)	273 [±56.5]	258 [±50.9] ‡	228 [138.1] †, ¶

Data are presented as numbers with percentage of groups in parentheses or as mean ± SD, * $p < 0.001$ compared with group 1, † $p< 0.01$ compared with group 1, ‡ $p < 0.05$ compared with group 1, § $p < 0.01$ compared with group 2, ¶ $p < 0.05$ compared with group 2.

Table 3. — *Perinatal outcomes.*

	Group 1 n = 41	Group 2 n = 24	Group 3 n = 12
Neonatal intensive care unit admission	35 [85.4]	24 [100] †	12 [100] †
Neonatal intensive care unit length of stay (days)	59.3 [±25.5]	75.1 [±33.8]	95.7 [±33.6] †, ¶
Duration of mechanical ventilation (days)	1.8 [±3.4]	5.8 [±5.4] †	7.8 [4.7] *, ¶
Intraventricular hemorrhage	0	0	3 [25.0] ¶
Necrotizing enterocolitis	0	0	0
Respiratory distress syndrome	1 [2.4]	12 [50.0] ‡	8 [66.6] †
Neonatal death	0	1 [4.2]	3 [25.0]

Data are presented as numbers with percentage of groups in parentheses or as mean ± SD, * $p < 0.001$ compared with group 1, † $p < 0.01$ compared with group 1, ‡ $p < 0.05$ compared with group 1, § $p < 0.01$ compared with group 2, ¶ $p < 0.05$ compared with group 2.

with persistence of > 5 nucleated red blood cells/100 white blood cells after three days of life (Table 3).

Detailed data of the neonatal blood cell count is given in Table 4. The nucleated red blood cell count increased progressively among groups with presence of higher numbers of nucleated red blood cell counts for a longer period in group 3. In addition, we observed lower platelet counts and lower hematocrit values in group 3 compared to group 2 and group 1 (Table 4). A stepwise multiple regression was performed with birth weight, gestational age, and presence of end-diastolic velocity as the independent variables and nucleated red blood cell count as the dependent variable. This analysis revealed that absent and reversed end-diastolic velocity in the umbilical artery ($R^2 = 0.29$, $p < 0.01$), arterial base excess ($R^2 = 0.24$, $p < 0.05$), birth weight and gestational age ($R^2 = 0.34$, $p < 0.01$, each) were significant independent determinants of the nucleated red blood cell count at birth. In addition, absent or reversed end-diastolic velocity was the strongest determinant of persistence of nucleated red blood cell count ($R^2 = 0.27$, $p < 0.01$). Reversed end-diastolic velocity in the umbilical artery showed the strongest correlation with high counts of nucleated red blood cells ($r = 0.42$, $p < 0.001$) compared with the arterial pH value ($r = -0.22$, $p < 0.05$) the arterial base excess value ($r = -0.32$, $p < 0.01$), the arterial pO_2 level ($r = -0.30$, $p < 0.05$) and the arterial pCO_2 level ($r = -0.28$, $p = 0.06$).

Discussion

The data presented in our study demonstrate that in fetuses with intrauterine growth restriction severe circulatory impairment is associated with elevated nucleated red blood cell counts and longer persistence of higher nucleated red blood cell counts in the peripheral blood at birth. The elevation of nucleated red blood cell precursors

Table 4. — *Neonatal blood cell count.*

	Group 1 n = 41	Group 2 n = 24	Group 3 n = 12
Nucleated red blood cell count per 100 white blood cells	22 [2-201]	65 [2-720] *	144 [9-964] *, §
Days until nucleated red blood cells < 5/100 white blood cells	1 [0-2]	3.9 [1-8] *	5.2 [1-13] *, ¶
Hemoglobin (mg/dl)	16.2 [12.3-23.5]	16.0 [12.7-22.6]	14.8 [10.7-17.9]
Hematocrit (%)	51.0 [36.7-54.1]	47.2 [36.1-64.1]	46.2 [32.2-55.0] ¶
White blood cell count (x1000)	9.2 [4.0-14.9]	8.9 [3.8-36.9]	7.3 [2.5-16.1]
Platelet count (x1000)	243 [172-358]	166 [79-284] ‡	114 [69-333] †

Data are presented as median with range in parentheses, * $p < 0.001$ compared with group 1, † $p < 0.01$ compared with group 1, ‡ $p < 0.05$ compared with group 1, § $p < 0.01$ compared with group 2, ¶ $p < 0.05$ compared with group 2.

might help in determining severe metabolic compromise in growth retarded fetuses more accurately than with cord gas values alone. These findings are in keeping with data from animal studies and from prenatal studies dealing with fetal plasma erythropoietin concentrations obtained by cordocentesis from severe growth restricted fetuses [18-20].

Nucleated red blood cells are immature erythrocytes and are frequently seen in variable numbers in the blood of newborns. Generally up to eight nucleated red blood cells are found in the circulating blood of healthy term newborns. Their presence was already noted by Anderson in 1941 [21]. Fetal erythropoiesis is mainly driven by the hypoxia-erythropoietin-nucleated red blood cell precursor axis, and increased nucleated red blood cells in the peripheral blood are supposed to reflect increased erythropoiesis in the fetal liver or a premature release of these percursors from the bone marrow [22, 23]. Evidence for hypoxia-induced extramedullary erythropoiesis was reported by Naeye, who showed persisting hepatic erythropoiesis in infants with chronic neonatal hypoxemia [24].

Our obstetrical data confirm the well-known fact of decreased birth weight and gestational age at delivery in case of severe uteroplacental insufficiency. One caveat of our study was that the mean gestational age in the absent- and reversed-end-diastolic group was significantly lower than in the group with present end-diastolic velocity. However previous data from our and other groups underline, that observed differences in nucleated red blood cell counts among study groups can not be explained by different gestational ages alone [12, 14a, b]. Not unexpectedly, nonreactive nonstress tests occurred more often among fetuses with absent- or reversed-end-diastolic Doppler flow velocity. This was followed by a higher number of cesarean sections performed for fetal distress in groups 2 and 3.

Like others we found differences in cord gas analyses of fetuses with absent and reversed-end-diastolic umbilical artery velocity compared to fetuses with present end-diastolic velocity reflecting an impaired maternal-fetal gas exchange [12a, b, 13, 19]. Arterial and venous pH decreased progressively. We also noted significantly lower arterial base excess values in groups 2 and 3. As other groups we found decreased arterial pO_2 levels in fetuses with absent or reversed-end-diastolic velocity but no significant increase in pCO_2 levels [12a, 18, 19]. However, Snijders and co-workers found a stronger association in the degree of increase in fetal plasma erythropoietin with the degree of erythroblastosis than with acidemia or pO_2 level [18]. They concluded therefore, that the erythroblast count may provide a better measure of tissue oxygenation rather than the blood pH or the pO_2 level. In addition, in our study the decrease in arterial bicarbonate levels in fetuses with absent or reversed end-diastoloc velocity failed to reach statistical significance. Another caveat of our study concerning cord blood gases is that some of the patient data were collected after labor, whereas other patients underwent a cesarean section prior to the onset of labor.

Nucleated red blood cell counts were significantly higher in fetuses with absent or reversed-end-diastolic velocity and persistence of elevated nucleated red blood cell counts was most prominent in fetuses of the latter group. Interestingly in fetuses with the highest nucleated red blood cell counts we found lower hematocrit and hemoglobin levels than in the other two groups, which appears to be in contrast to an increased hematopoiesis in response to chronic intrauterine hypoxemia. This finding is in line with results of previous studies [12a, 13, 19]. We also found a significant reduction of platelet counts in those fetuses with absent or reversed-end-diastolic umbilical artery velocity. A possible explanation for this could be that in growth-restricted fetuses, hypoxemia could directly depress megakaryocyte proliferation or result in dysfunctional erythropoiesis [25-27]. In addition, fetal bone marrow could preferentially produce erythropoietic precursors with subsequent thrombocytopenia [27]. Furthermore increased intraplacental thrombotic events could lead to increased platelet consumption in growth retarded fetuses [28].

In conclusion we have shown a relation between elevated neonatal nucleated red blood cell counts and their longer persistence in the neonatal blood with the severity of umbilical artery Doppler flow abnormality in growth-restricted fetuses. Perinatal data were worse in those fetuses with reversed-end-diastolic velocity in the umbilical artery. The finding that reversed-end-diastolic velocities in growth retarded fetuses were more strongly associated with high nucleated red blood cell counts than with a marked decrease in arterial pO_2 levels or increase in pCO_2 levels supports a possible valuable role for nucleated red blood cell counts in the assessment of metabolic compromise in growth-restricted fetuses.

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Address reprint requests to:
R. AXT-FLIEDNER, M.D.
Dept. Ob./Gyn. Division of Prenatal Medicine
University of Lubeck
Ratzeburger Allee 160
23538 Lübeck (Germany)