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Erythroblasts in the Vessels of the Placenta – An Independent Factor of Chronic Hypoxic Damage to the Fetus

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Abstract

BACKGROUND: Earlier identification of newborns with sub compensated chronic hypoxic damage based on clinical and laboratory data alone is difficult. Since it is extremely unlikely that chronic hypoxia, superimposed at different times at different stages of the dynamic process of fetal growth and altering the processes of maturation and functioning of its organs and systems, has uniform clinical manifestations in all newborns. Therefore, it is important to search for additional signs of hypoxic damage to the fetus, which will help identify newborns at risk, reduce postnatal complications, and reduce morbidity and mortality.

AIM: The aim is a comparative histological study of the relative number of fetal erythroblasts in the vessels of the placentas from a full-term pregnancy with a low and high risk of fetal hypoxic damage.

MATERIAL AND METHODS: Based on data on the course of pregnancy, the state of health of the mother and the fetus/newborn, as well as histological examination of the placenta, 388 archived placenta tissue samples were selected in two groups: A high-risk group for chronic hypoxic damage to the fetus and a group without clinical and laboratory signs of fetal/newborn hypoxia. The relationship between the number of erythroblasts in the vessels of the placenta and chronic hypoxic damage to the fetus was analyzed.

RESULTS: The high risk of chronic hypoxic fetal damage is higher for placentas with ≥8 fetal erythroblasts in chorionic villi vessels (OR = 3.175; 95% CI = 1.921–5.248, p < 0.001), with maternal vascular malperfusion (OR = 2.798; 95% CI = 1.506–5.164, p = 0.001), and combined (cross) placental lesions (OR = 2.245; 95% CI = 1.246–4.046, p =0.007) with damage of ≥30% of placental tissue.

CONCLUSION: Eight or more fetal erythroblasts in the lumen of the vessels of the placenta are an additional independent factor in chronic hypoxic damage to the fetus. These results are of practical importance for identifying a group of newborns with a high risk of chronic hypoxic damage in the perinatal period and stratification of the risk group in the postnatal period to reduce infant morbidity and mortality.

Introduction

Long-term action of hypoxia in the perinatal period can lead to hypoxic damage to the fetus, a decrease in the adaptive potential of the newborn, an increase in childhood morbidity and mortality, and in the long-term – to an increase in the frequency of cardiological, neurological, and metabolic disorders in the population [1], [2], [3], [4], [5]. Early detection of newborns with compensated chronic hypoxic lesion based on clinical and laboratory data alone is difficult. Since it is extremely unlikely that chronic hypoxia, imposed at different times at different stages of the dynamic process of fetal growth and altering the processes of maturation and functioning of its organs and systems, has the same clinical manifestations in all newborns. Therefore, it is important to search for additional signs of hypoxic damage to the fetus, which will help to identify newborns at risk, reduce postnatal complications, and reduce morbidity and mortality.

Traditional histological examination remains an important part of clinical diagnosis, providing not only the identification of fetal damage and the risk of recurrence of episodes of sub compensation, but also can provide potentially valuable data for epidemiological population studies and preservation of human health throughout life. Intrauterine hypoxia is accompanied by functional and morphological changes in the internal organs of the fetus [4], [6], [7], [8] and the placenta [9], [10], [11]. Histological patterns of chronic hypoxic injury include maternal vascular malperfusion [12], fetal vascular malperfusion [13], and chronic inflammatory damage [14]. These patterns are non-specific, since they are found in some placentas from newborns without clinical and manifestations of asphyxia, and also do not allow differentiating structural changes in the placenta aimed at compensating for reduced oxygenation of vital organs from changes resulting from hypoxia-induced fetal damage.

One of the criteria for prolonged antenatal or intrapartum stress is an increased level of erythroblasts in the blood of a full-term fetus. Some authors believe

that the number of erythroblasts in the vessels of the placenta is not related to the level of erythroblasts in the umbilical cord blood of the fetus and therefore cannot be used for an objective assessment of hypoxic damage [15]. However, scientific studies have established that the identification of erythroblasts in the placenta is a morphological sign of chronic hypoxia, lasting at least several days or weeks [16], but also the number of erythroblasts can increase because of infection, diabetes mellitus, anemia, and Rh-conflict. Qualitative or semi-quantitative criteria are used to assess the phenomenon of fetal erythroblastosis in the placenta [17], [18]. A number of authors suggest calculating the number of erythroblasts in the vessels of the placenta per 100 cells [19], [20], Stanek suggested that finding more than 1 erythroblast/1 field of view at high magnification is a sign of pathology [21].

Thus, the duration of pathological factors, their effect on the fetus, the degree of chronic hypoxic damage to the fetus, and the method of assessing erythroblasts in the vascular lumen remain unclear.

The aim of our study was a comparative histological study of the relative number of fetal erythroblasts in placental vessels from full-term pregnancies with a low and high risk of hypoxic damage to the fetus.

Materials and Methods

Clinical data

A retrospective clinical and morphological study of placentas sent for histological examination was carried out State Municipal Management Organization «Regional Clinic Hospital» and State Municipal Management Organization «Regional perinatal center» city. Karaganda (Kazakhstan) from 2015 to 2020. Clinical data are obtained from medical records in accordance with the requirements of the Ethics Committee. The medical records of women who during this period received medical assistance for childbirth and had a gestational age of more than 37 weeks established by ultrasound fetometry were studied. In all cases, the placentas were sent for histological examination in accordance with the departmental policy, which involves the analysis of placentas of all complicated pregnancies, and additionally, placentas were additionally selected at random from women with uncomplicated pregnancies for research purposes.

The study excluded placentas from pregnancies with moderate-to-severe maternal anemia, diabetes mellitus and gestational diabetes, Rh-conflict, as well as intrauterine growth retardation, antenatal fetal death, multiple pregnancy, fetal malformations, premature detachment of the normally located placenta, and acute inflammatory damage to the placenta.

For all selected cases, data from medical records of newborns were studied. The following information was taken from neonatal records: Apgar scores, cord blood pH, hospitalization in an intensive care unit, need for blood transfusion, need for phototherapy, respiratory distress syndrome, need for mechanical ventilation, necrotizing enterocolitis, intraventricular hemorrhage, hypoxic-ischemic encephalopathy, and convulsions of newborns.

The group of placentas from newborns with a high risk of chronic hypoxic damage was formed on the basis of one or several clinical and laboratory criteria for asphyxia:

1. The pH of the umbilical cord blood is below 7.0 and the excess of bases is ≥12 mml/l;
2. Neonatal hypoxic-ischemic encephalopathy with early onset of moderate and severe degree;
3. Quadriplegia and dyskinesia in newborns. A mandatory requirement in each case was the exclusion of another etiology of damage (birth trauma, idiopathic coagulopathy, infection, premature detachment of the normally located placenta, and large blood loss in the mother in the perinatal period).

In addition, a mandatory histological criterion was used to include previously selected placentas of newborns with asphyxia in the group with chronic hypoxic damage to the fetus, confirming the long-term exposure of meconium as a sign of chronic intrauterine hypoxic stress: Macrophages loaded with meconium in the chorionic plate of the placenta, should add photo for this.

Cases, in which only clinical or laboratory signs of asphyxia were established without histological evidence of prolonged exposure to meconium, were excluded from the study.

Placentas from newborns who did not have the above clinical, laboratory, and histological signs were included in the control group.

Histological examination

Placental excision was carried out in accordance with the standard internal protocol of the pathology department, foreign, and international recommendation [16], [22]. Weighing of placentas was performed without the umbilical cord and amniotic membranes. Placental tissues were fixed in 4% neutral buffered formalin followed by labeling of representative diagnostically significant fragments of the placenta. The material was marked in four paraffin blocks: One block included a roll of amniotic membranes from the edge of the rupture to the edge of the placental disc, a part of the marginal parenchyma of the placenta, and two cross-sections of the umbilical cord taken at a distance of 5 cm one from the fetal and placental ends. Three other paraffin blocks represented representative

areas of the placenta that were used for morphometric analysis.

Histological process and staining with hematoxylin and eosin were performed according to the standard protocol. Macroscopic and histological examination of the placenta was performed in accordance with generally accepted principles Vogel [23]. The histological criteria for assessing the development and maturation of placental villi were the degree of villous branching, stromal differentiation, vascularization, and formation of syncytiocapillary membranes, recommended by Vogel and Benirschke *et al.* which are objective indicators of the developmental characteristics and degree of maturation of the placenta [24], [25], [26].

Morphometric analysis was performed on 10 fields of view in each of three representative areas.

Placental lesions were classified by maternal or fetal origin. Combined placental lesions were considered such as overlapping one or more structural lesions, for example, maternal and fetal malperfusion, chronic non-specific villitis and maternal vascular malperfusion with ≥30% damage to the placental tissue area. For example, a circulatory disorder in the mother describes multiple placental infarcts, fibrin deposits in the interstitial space.

Pathologists with no clinical information about pregnancy and perinatal outcome or previous histopathological diagnosis examined all placentas. For a correct assessment of the correspondence of the histological phenotype to the gestational age, they were given only information about the gestational age. After the histological examination, the results were summarized.

The number of erythroblasts in the placenta was determined by counting in 10 consecutive fields of view in three representative sections of the placenta (at ×40 magnification). Cells with uniformly round, homogeneous basophilic nuclei surrounded by a thin rim of eosinophilic cytoplasm, were considered erythroblasts. Morphometric analysis of histological preparations was carried out using LeicaDM 1000 microscope.

Statistical analysis

Data are presented as n (%) or mean ± standard deviation and analyzed using SPSS 24.0 software. Continuous variables were compared using Student's t-test (with normal distribution of sample data) or non-parametric Mann–Whitney test (with abnormal distribution of sample data). Categorical variables were compared using the Chi-square test. Differences were considered statistically significant at $p < 0.01$ and $p < 0.05$. To determine independent risk factors associated with a high risk of chronic hypoxic damage to the fetus, multinominal logistic regression was used, in which a high risk of chronic hypoxic damage to the fetus was the dependent factor.

Results

During the analyzed period, 388 placentas from pregnancies with a low risk of hypoxic damage to the fetus and a high risk of hypoxic damage to the fetus were examined. State Municipal Management Organization «Regional Clinic Hospital» и State Municipal Management Organization " Regional perinatal center» city. Karaganda (Kazakhstan) from 2015 to 2020. Clinical and morphological characteristics of the formed groups are presented in Table 1.

Table 1: Clinical and morphological characteristics of groups

Characteristic	Control group, n = 194	High risk group chronic hypoxic damage to the fetus, n = 194	P-value
Parity	1.85 ± 1.06	1.92 ± 1.48	0.259
Gestational age (weeks)	39.26 ± 1.74	39.01 ± 1.88	0.117
Mother's age (years)	26.4 ± 5.82	28.79 ± 5.90	0.001*
Under 19-years-old	4 (2.1%)	4 (2.1%)	1.000
Over 40-years-old	9 (4.6%)	11 (5.7%)	0.647
Extragenital pathology			
Preeclampsia	31 (15.9%)	37 (19.1%)	0.424
Chronic arterial hypertension	5 (2.6%)	8 (4.1%)	0.398
Obesity	13 (6.7%)	29 (14.9%)	0.009*
Nicotine addicted	4 (2.1%)	5 (2.6%)	0.736
Vaginal delivery	159 (90.0%)	145 (74.7%)	0.085
Planned cesarean section	35 (18.0%)	49 (25.3%)	0.085
Emergency caesarean section	0 (%)	0 (%)	1.000
Placenta weight. gm	426.36 ± 109.89	446.87 ± 81.29	0.112
Erythroblasts			
1–7 erythroblasts	18 (9.3%)	19 (9.8%)	0.733
8 or more erythroblasts	56 (28.9%)	114 (58.8%)	<0.001*
Histological lesions			
Maternal vascular malperfusion	49 (25.3%)	71 (36.6%)	0.016*
Fetal vascular malperfusion	69 (35.6%)	84 (43.3%)	0.120
Delayed ripening of villi	64 (32.9%)	81 (41.8%)	0.075
Chronic willitis	24 (12.4%)	22 (11.3%)	0.754
Combined damage[v]	49 (25.3%)	73 (37.6%)	0.009*
Damage to the umbilical cord	0 (0%)	0 (0%)	-
Retroplacental hematoma	0 (0%)	0 (0%)	-
Chorioamnionitis	0 (0%)	0 (0%)	-
Meconium-loaded macrophages in the chorionic plate	0 (0%)	194 (100%)	-
Newborn weight, gm.	3835.61 ± 657.4	3769.73 ± 685.6	0.520
Newborn weight<10 percentile	0 (0%)	0 (0%)	-
Neonatal hospitalization (days)	4.43 ± 2.33	12.47 ± 6.76	<0.001*
Admission to the intensive care unit (within the first 6 h after birth)	0 (0%)	24 (12.4%)	-
Apgar at 5 min<7	0 (0%)	49 (25.3%)	-
Cord blood pH below 7.0	0 (0%)	115 (59.3%)	-
Neonatal hypoxic-ischemic encephalopathy with early-onset moderate and severe (Sarnath scale)	0 (0%)	159 (82.0%)	-

Continuous variables are presented as mean ± standard deviation, and categorical variables as numbers (n) (%). [v]More than one type of histological damage in one placenta *Statistically significant differences for $p < 0.05$.

Women in the group with a high risk of fetal hypoxic damage were older than women in the control group (28.79 ± 5.90 vs. 26.4 ± 5.82, [p = 0.001]); however, there were no pregnant women over 40 were identified. In the group with a higher risk of chronic hypoxic damage, obesity was more common in pregnant women (29 [14.9%] vs. 13 [6.7%]) in the control group (p = 0.009). Women in the high-risk group of chronic hypoxic damage to the fetus did not differ from women in the control group in terms of pregnancy parity, gestational age, incidence of preeclampsia, and chronic arterial hypertension.

As expected from the study design, there were no differences in the mode of delivery between the groups, but significant differences in the number of days of neonatal hospitalization were found between the groups with perinatal asphyxia of the newborn and the control group (12.47 ± 6.76 and 3.77 ± 1, 03, respectively, p < 0.001).

In the group with a high risk of chronic hypoxic fetal damage, placentas with more than eight erythroblasts in the chorionic villi lumen were more common (114 [58.8%] vs. 56 [28.9%], [p < 0.001]). However, there were no differences between the groups in the subgroup with 1–7 erythroblasts in the lumen of chorionic villi vessels (p = 0.733) according to Table 1.

In the group with a high risk of chronic hypoxic damage to the fetus, cases with maternal vascular malperfusion and combined injuries were more

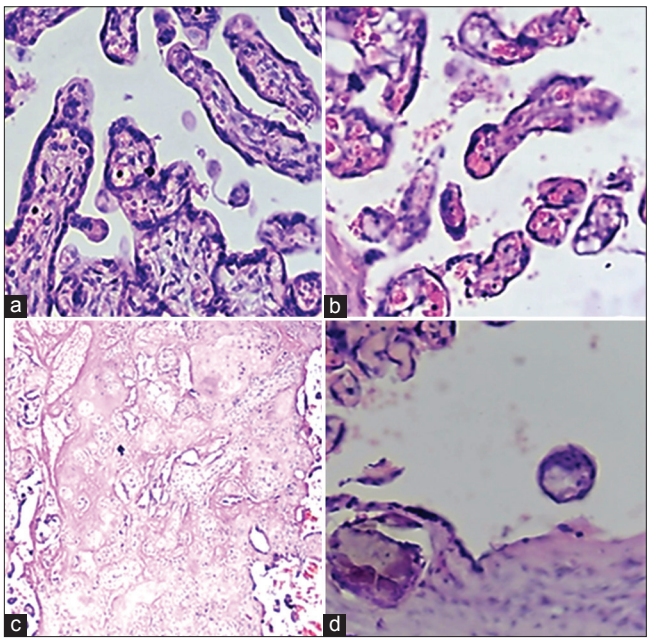

Figure 1: (a and b) Intranatal asphyxia of a newborn (Sarnath grade 3) as a result of chronic prenatal hypoxia. In the vessels of the chorionic villi, fetal erythroblasts are visible with uniformly round, homogeneous basophilic nuclei surrounded by a thin rim of eosinophilic cytoplasm, magnification: ×200. (c and d) Perinatal asphyxia of the newborn because of combined (overgrowth) chronic hypoxic damage to more than 30% of the placental tissue. (c) Organizing placental infarction (maternal vascular malperfusion), magnification: ×100. (d) Occlusive calcified thrombus in the lumen of the placental macrovascular (fetal vascular malperfusion), magnification: ×400

common. At the same time, there were no differences in the frequency of occurrence in the control and experimental groups of such histological findings as fetal vascular malperfusion, delayed maturation of villi, and chronic villitis (Figures 1 and 2; Table 1).

Risk factors for chronic hypoxic fetal injury analyzed by multinominal logistic regression are shown in Figure 3.

Regression analysis showed that the high risk of chronic hypoxic damage to the fetus is higher

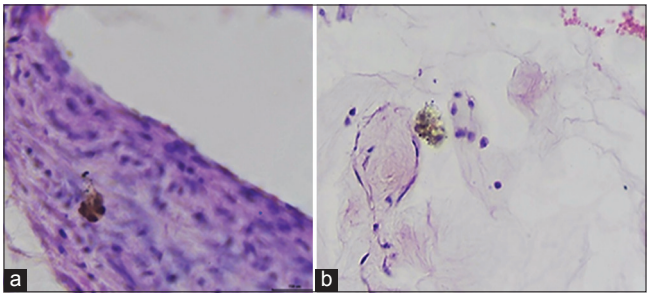

Figure 2: Meconium in microscopic and microscopic examination of the placenta. (a) macrophages in the chorionic plate with multiple granules of meconium in the cytoplasm, stained with hematoxylin and eosin, magnification ×400 and (b) macrophages in vamniotic membranes with multiple meconium granules in the cytoplasm, stained with hematoxylin and eosin, magnification ×400

for placentas with more than eight erythroblasts in the chorionic villi vessels (OR = 3.175; 95% CI = 1.921–5.248, p < 0.001). Maternal vascular malperfusion (OR = 2.798; 95% CI = 1.506–5.164, p = 0.001) and combined injuries (OR = 2.245; 95% CI = 1.246–4.046, p = 0.007) were also associated with an increased risk of chronic fetal hypoxia). In addition, the statistical analysis carried out showed that the number of erythroblasts in the lumen of vessels of more than eight, fetal vascular malperfusion, and combined injuries was independent risk factors for chronic hypoxic damage to the fetus.

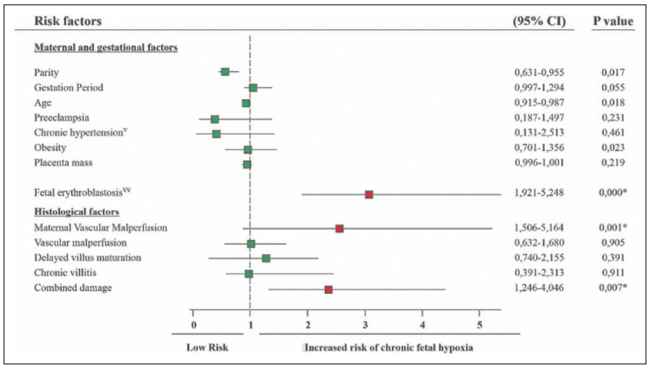

*Figure 3: Risk factors for chronic hypoxic damage to the fetus. v: Chronic arterial hypertension – hypertension diagnosed before pregnancy or before 20 weeks of pregnancy. vv: more than 8 erythroblasts/10 fields of view at ×40 magnification in three representative sections of the placenta. *Statistically significant independent risk factor for chronic fetal hypoxia (p < 0.01)*

Discussion

This study compared the significance of predetermined risk factors for chronic hypoxic damage to the fetus. The results obtained confirm the data of previously published scientific papers that an increase in the number of fetal erythroblasts in the lumen of chorionic villi vessels is a morphological substrate of prolonged chronic hypoxia [12], [13], [16], [17]. In addition, a connection is established with chronic hypoxic damage to the fetus (newborn) and a

diagnostically important number of erythroblasts in the lumen of placental vessels.

Two important results were obtained. First, in the placentas of newborns with a high risk of chronic hypoxic damage, an increase in erythroblasts in the lumen of chorionic villi vessels was more often observed (more than 8 erythroblasts/10 fields of vision at ×40 magnification in three representative sections). These changes confirm the initial hypothesis that the antenatal stress experienced during the perinatal period is an important factor in increasing the number of erythroblasts in the lumen of placental vessels.

For routine histological practice, this means that the detection of eight or more erythroblasts in 10 fields of vision in the vessels of chorionic villi can serve as a sufficient reason for the pathologist to note in conclusion about the pathology of the placenta the opinion about the impact of prolonged chronic hypoxic stress with fetal damage in the perinatal period.

Second, between the group with a high risk of chronic hypoxic damage to the fetus and the control group, there were no differences in the subgroup with the number of 1–7 erythroblasts in the vascular lumen. It is possible that this group is a group of infants who are functionally immature for gestational age with a high risk of clinically unexpected perinatal asphyxia. However, confirmation of this hypothesis for stratification and study of this group requires additional research.

Previously published scientific studies have identified a significant role of fetal vascular malperfusion as an important risk factor for antenatal hypoxic damage to the fetus [13]. In our study, it was found that, along with fetal erythroblastosis, maternal vascular malperfusion and combined placental injuries are independent factors of high risk of chronic hypoxic damage to the fetus. Perhaps, this difference is due to the specific population characteristics of the studied sample with a predominance of preplacental hypoxia due to decidual microangiopathy, since both groups of placentas were obtained from women who had medical indications for delivery in a third-level hospital.

The study has several strengths: First, the large sample size allows a more reliable determination of the relationship between clinical/morphological findings and hypoxic damage to the fetus. Second, the use of a standardized grading system ensures reproducibility of results and allows for more accurate comparisons with the future studies.

Conclusion

The weaknesses of the study include the following: First, the selective nature of the study of the placentas of women with clinical indications for referral to a third-level hospital creates an opportunity for a shift in choice. Second, although the study used standard definitions for various maternal and fetal/newborn medical conditions, some additional details (disease stage, disease duration and severity, treatment, and disease control status) that could potentially affect the development of placental and fetal lesions are not estimated because the sample size was insufficient to carry out such an analysis with sufficient power.

Thus, using a standardized system of histological classification of placental injuries, we have shown a strong relationship between an increased numbers of fetal erythroblasts in the lumen of the chorionic villus vessels (more than 8 erythroblasts/10 visual fields at ×40 magnification in three representative sections) with a high risk of chronic hypoxic damage to the fetus. We also identified a subgroup of placentas with 1–7 erythroblasts (by 10 visual fields with ×40 magnification in three representative placenta sections), potentially stratifying the group of infants functionally immature for gestational age with a high risk of perinatal hypoxia and asphyxia. These results are of practical importance for identifying a group of newborns with a high risk of chronic hypoxic damage in the perinatal period and stratifying the risk group in the postnatal period to reduce infant morbidity and mortality.

Author Contributions

Each author has contributed to the following items (1) concept or design, (2) data collection, (3) data analysis or interpretation, (4) manuscript drafting, and (5) critical revision of important intellectual content.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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