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Vascular Malperfusion – As a Morphological Pattern of Preeclampsia

L. M. Stabayeva[1]*, I. Mukhammad[1], Maida Tussupbekova[1], Olga Kostyleva[1], Raihan Nygyzbaeva[1], G. N. Imanbayeva[1], Yasminur Turdybekova[2], Aynura Zhumakayeva[3], Dinar Kalieva[4], Yevgeniy Kotov[1], Aigul Mergentay[5], Ainur Meldebekova[6]

[1]Department of Pathology, Karaganda Medical University, Karaganda, Republic of Kazakhstan; [2]Department of Obstetrics, Gynecology and Perinatology, Karaganda Medical University, Karaganda, Republic of Kazakhstan; [3]Department of Oncology and Radiation Diagnostics, Karaganda Medical University, Karaganda, Republic of Kazakhstan; [4]Department of Surgical Diseases, Karaganda Medical University, Karaganda, Republic of Kazakhstan; [5]Department of Public Health, Karaganda State Medical University, Karaganda, Republic of Kazakhstan; [6]Department of Internal Medicine, Karaganda Medical University, Karaganda, Republic of Kazakhstan

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***Correspondence:** Leila Stabayeva, Department of Pathology, Karaganda Medical University, 40 Gogol Street, Karaganda City, 100008, Republic of Kazakhstan. E-mail: Stabaeva@qmu.kz
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Abstract

BACKGROUND: The system "mother-placenta-fetus" is in a complex functional balance and dysfunction of any of the components can compromise others. The placenta plays an important role in the development of preeclampsia, since preeclampsia can occur in the absence of a fetus, but in the presence of a trophoblast. In this regard, the study of morphological placental patterns in preeclampsia can give an idea of preeclampsia as a pathology in general, as well as its relationship with hypoxic damage to the fetus.

AIM: The aim of the study was to study the identification of morphological patterns of placental lesions associated with preeclampsia.

MATERIALS AND METHODS: A retrospective and morphological study of 355 placentas sent for histological examination in the period from 2015 to 2020 was carried out. During the analyzed period, 184 placentas from pregnancies with an established diagnosis of preeclampsia and 171 placentas from pregnancies with a physiological course were studied.

RESULTS: It has been established that preeclampsia is associated with a smaller mass, size and height of the placenta. As morphological patterns associated with preeclampsia, such histological signs of maternal vascular malperfusion, such as infarcts and arterial atherosclerosis, were identified.

CONCLUSIONS: The heterogeneity of clinical and histological signs associated with both the physiological and pathological course of pregnancy reflects the different gestational age of the onset of the disease and the stage of development of the adaptive capabilities of the placenta. Identification of morphological patterns associated with hypoxic damage to the fetus allows us to identify a group of newborns with a high risk of chronic hypoxic damage in the perinatal period and to stratify the risk group in the postnatal period to reduce infant morbidity and mortality.

Introduction

Preeclampsia is one of the major hypertensive disorders of pregnancy, characterized by a high degree of heterogeneity both in clinical signs and in the severity of the disease and its outcomes. Pregnancies complicated by preeclampsia are often accompanied by maternal complications such as eclampsia, pulmonary edema, and liver rupture [1], [2], [3], [4]. Some researchers believe that preeclampsia is also a significant factor in cardiovascular complications in pregnant women [5], [6], [7], [8]. Preeclampsia has severe consequences for the fetus. In the studies of Hansen A. found that infants born to mothers with preeclampsia have a significantly higher chance of developing bronchopulmonary pulmonary dysplasia [9], [10], [11].

It follows from the above that preeclampsia leaves a permanent defect in the systemic and pulmonary circulation of the blood of the offspring, which, under stress, can lead to cardiovascular diseases in adulthood. An important role in the pathogenesis of preeclampsia is also played by the maternal syndrome, characterized by a generalized systemic inflammatory response involving the maternal endothelium through the production of proinflammatory cytokines and antiangiogenic factors [12], [13], [14], [15], [16], [17], [18]. Recent review articles describe the main role of antiangiogenic factors in the pathogenesis of preeclampsia [19], [20], [21], [22]. Maternal endothelial dysfunction may cause maternal disease and may subsequently lead to clinical manifestations [23], [24], [25], [26]. Thus, preeclampsia is a clinically and laboratory-defined pathological condition in which various etiological processes are hidden, remain insufficiently studied, and have a multifaceted genesis of development.

Table 1: Clinical characteristics of mother and fetus, perinatal outcomes

Characteristics	Preeclampsia (n = 184) (%)	Physiological pregnancy (n = 171) (%)	p-value
1	2	3	4
Mother characteristics			
Parity	2.85 ± 1.58	2.51 ± 1.71	0.002*
Mother's age, years	27.55 ± 6.76	25.54 ± 4.40	0.007*
Under 19 years old	14 (7.6)	2 (1.2)	0.014*
Over 40 years old	16 (8.7)	4 (2.3)	0.010*
Extragenital pathology			
Preeclampsia	184 (100)	0 (0)	-
Chronic arterial hypertension	0 (0)	0 (0)	-
Gestational diabetes mellitus	0 (0)	0 (0)	-
Obesity	29 (15.8)	15 (8.8)	0.046*
Nicotine use during pregnancy	13 (7.1)	6 (3.5)	0.322
Drinking alcohol during pregnancy	1 (0.6)	0 (0)	0.627
Racial identity			
Caucasoid	43 (23.4)	41 (24.0)	0.849
Mongoloid	141 (76.6)	130 (76.0)	0.894
Fetal characteristics and perinatal outcomes			
Gestation period (weeks)	39.28 ± 1.92	39.44 ± 1.71	0.153
Vaginal labor	93 (50.6)	142 (83.0)	<0.001*
Planned cesarean section	35 (19.0)	29 (17.0)	0.789
Emergency caesarean section	56 (30.4)	0 (0)	<0.001*
Newborn weight at birth, gm	3092.83 ± 635.7	3402.87 ± 553.7	<0.001*
Newborn weight<10 percentile	19 (10.3)	4 (2.2)	0.002*
Antenatal fetal death	0 (0)	0 (0)	-
Neonatal hospitalization (days)	6.46 ± 4.62	4.83 ± 2.01	<0.001*
Apgar at 5 minutes<7	94 (51.1)	0 (0)	<0.001*
Umbilical cord blood pH below 7.0	45 (24.5)	24 (14.0)	0.041*
Neonatal hypoxic-ischemic encephalopathy with early onset of moderate and severe degree (according to the Sarnat scale)	21 (11.4)	0 (0)	0.009*

Continuous variables are presented as mean ± standard deviation and categorical variables as number (n) (%). *Statistically significant differences for p<0.05.

Materials and Methods

A retrospective and morphological study of placentas sent for histological examination from two large clinics from 2015 to 2020 was carried out. In accordance with the purpose of the work, the studied material was divided into two groups: Group I (n = 171) – placentas from pregnancies with a physiological course; Group II (n = 184) – placentas from preeclampsia pregnancies. Placentas from pregnancies with moderate and severe maternal anemia, diabetes and gestational mellitus, and Rh incompatibility, as well as intrauterine growth retardation, antenatal fetal death, multiple pregnancies, fetal malformations, premature detachment of normally located placenta, and acute inflammatory diseases were excluded from the study placental injury.

Data are presented as n (%) or mean ± standard deviation. Continuous variables were compared using Student's t-test (with a normal distribution of sample data) or non-parametric Mann–Whitney test (with non-normal distribution of sample data). Categorical variables were compared using a Chi-square test. Differences were considered statistically significant at $p < 0.05$.

Clinical characteristics of the mother, fetus, and perinatal outcomes in each of the formed groups are presented in Table 1.

Women in the preeclampsia group did not differ from women in the normal pregnancy group in terms of nicotine and alcohol use during pregnancy, incidence of chronic hypertension and gestational diabetes, and race.

Comparative characteristics of the results of a macroscopic examination of placentas from pregnancies with an established diagnosis of preeclampsia and placentas with a physiological course of pregnancy are presented in Table 2.

There were no statistically significant differences in the length ($p = 0.052$) and width ($p = 0.148$) of the placental disc in the studied groups of placentas from pregnancies with preeclampsia and physiological pregnancy. In addition, the placentas of the studied groups did not differ in shape and placental shape index ($p = 0.900$).

Morphological characteristics of the umbilical cord, revealed during macroscopic examination, are presented in Table 3 and Figure 1.

There were no differences between the preeclamptic and normal pregnancy groups for cord characteristics such as cord insertion, eccentric, distance to the placental margin from the cord insertion, marginal, and sheath insertion.

Table 2: Characteristics of the placenta revealed by macroscopic examination

Characteristics	Preeclampsia (n = 184) (%)	Physiological pregnancy (n = 171) (%)	p-value
Placenta weight without umbilical cord and amniotic membranes, gm	379.0 ± 78.9	439.0 ± 53.1	0.000*
Fetoplacental index	7.3 (3.5–11.7)	5.8 (5.1–9.9)	0.000*
Placental disc length, cm	20.2 ± 4.9	21.2 ± 4.3	0.052
Placental disc width, cm	17.6 ± 3.7	18.3 ± 4.1	0.148
Placenta height, cm	1.6 ± 0.9	2.0 ± 1.0	0.000*
Placenta shape			
Rounded	51 (27.7)	59 (24.0)	0.422
Oval	81 (44.0)	59 (41.5)	0.635
Other	52 (28.3)	59 (34.5)	0.205
Placenta shape index**	0.373 ± 0.336	0.362 ± 0.313	0.900

Continuous variables are presented as mean ± standard deviation, mean, range, and categorical variables as number (n) (%). *Statistically significant differences for p<0.05. **(Placental disc length, cm)/(Placental disc width, cm)$^{-1}$.

Table 3: Characteristics of the umbilical cord in macroscopic examination

Characteristics	Preeclampsia (n = 184) (%)	Physiological pregnancy (n = 171) (%)	p-value
Attaching the umbilical cord			
Central	59 (32.1)	60 (35.1)	0.547
Eccentric	95 (51.6)	87 (50.9)	0.887
Marginal	23 (12.5)	19 (11.1)	0.686
Enveloped	7 (3.8)	5 (2.9)	0.647
Distance to the edge of the placenta from the insertion of the umbilical cord	4.59 ± 2.01	4.88 ± 1.91	0.136
Eccentric attachment index			
Number of umbilical cord vessels			
Three vessels	184 (100)	171 (100)	-
Two vessels	-	-	-
The tortuosity of the umbilical cord			
Severe	71 (38.6)	47 (27.5)	0.027*
Moderate	89 (48.4)	84 (49.1)	0.887
Weak	24 (13.0)	40 (23.4)	0.011*
Direction of crimp			
Left	134 (72.8)	127 (74.3)	0.759
Right	50 (27.2)	44 (25.7)	0.759
Umbilical cord length			
Normal (<70 cm)	169 (91.8)	160 (93.6)	0.535
Long (from 70 to 95 cm)	12 (6.5)	9 (5.3)	0.616
Very long (>95 cm)	3 (1.6)	2 (1.2)	0.713
Umbilical cord nodes			
True cord knot	1 (0.5)	1 (0.6)	0.959
1 or more false nodes	67 (36.4)	56 (32.7)	0.469
Thin umbilical cord (less than 0.8 cm)	19 (10.3)	4 (2.2)	0.002*
Umbilical cord entanglement	11 (6.0)	0 (0)	0.001*
The presence of pronounced narrowing of the umbilical cord	2 (1.1)	1 (0.6)	0.606
Combined damage	141 (76.6)	67 (45.0)	0.000*

Continuous variables are presented as mean ± standard deviation, mean, range, and categorical variables as number (n) (%). *Statistically significant differences for p<0.05.

In addition, there were no differences between the groups of placentas with preeclampsia and physiological pregnancy in the direction of the umbilical cord tortuosity, the length of the umbilical cord, and the presence of true and false nodes.

Thus, in the study sample, placentas from pregnancies with an established diagnosis of preeclampsia weighed less and were lower in height than placentas from physiological pregnancies. In the group of placentas from pregnancy with preeclampsia, combined injuries of the umbilical cord were statistically significantly more common, including more than one of the structural features of the umbilical cord, different from the norm.

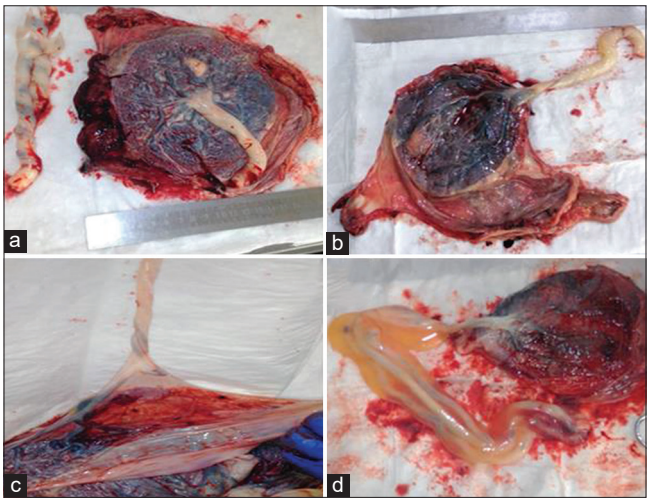

Figure 1: Characteristics of the umbilical cord on macroscopic examination of the placenta in a study in study groups of placentas from preeclamptic and physiologic pregnancies. (a) central attachment of the umbilical cord; (b) marginal attachment of the umbilical cord; (c) sheath attachment of the umbilical cord; and (d) pronounced edema of the umbilical cord Wharton's jelly (signs of acute hypoxia).

Histopathological patterns associated with preplacental blood malperfusion (maternal vascular malperfusion) in the study groups of placentas are presented in Table 4 and Figures 2 and 3.

The results of our study revealed that in the group of placentas from pregnancy with preeclampsia, heart attacks were more common than in the group with physiological pregnancy. There were no differences in the number of placentas with infarcts occupying <30% between the groups.

It was found that in the group with preeclampsia more often than in the group with physiological pregnancy, there were placentas with dissociated impaired maturation of chorionic villi with a predominance of mature forms of chorionic villi.

In the group of placentas from pregnancy with preeclampsia, more often than in the group with physiological pregnancy, placentas with chorangiosis, as well as hemorrhages in the stroma of the chorionic villi, were more common. There were no differences between the groups in such histological features as massive fibrin deposits in the intervillous space (p = 0.103) and laminar necrosis (p = 0.279) (Table 5).

Thus, the results indicate that the histological features associated with maternal vascular malperfusion are more common in the preeclamptic group (Figure 2), which confirms the results of previously published studies.

It should be emphasized that the histological conclusion of maternal vascular malperfusion is not based on any single placental findings observed macro or microscopically, but rather is a composite of findings including primary changes in the maternal decidual vasculature and/or secondary changes in the placental villous parenchyma. In the study population, morphological signs of maternal vascular malperfusion, different from the group with physiological pregnancy,

Table 4: Histopathological patterns associated with maternal vascular malperfusion

Characteristic	Preeclampsia (n = 184) (%)	Physiological preeclampsia (n = 171) (%)	p-value
Infarction			
In ischemic stage	16 (8.7)	5 (2.9)	0.021*
In necrotic stage	26 (14.1)	9 (5.3)	0.003*
Organization stage	34 (18.5)	11 (6.4)	0.001*
The volume of infarction			
≤5%	26 (14.1)	24 (14.0)	0.979
From 6% to 30%	15 (8.2)	11 (6.4)	0.535
≥ 30%	36 (19.6)	0 (0.0)	0.000*
Maturation disorders			
Dissociated development of chorionic villi with a predominance of mature forms of chorionic villi	32 (17.4)	6 (3.5)	0.000*
Dissociated development of chorionic villi with focal persistence of immature forms of chorionic villi	50 (27.2)	44 (25.7)	0.759
Vascular damage			
Acute atherosis of arterioles of the basal membrane	39 (21.2)	11 (6.4)	0.000*
Fibrinoid vascular necrosis	46 (25.0)	17 (9.9)	0.000*
Hypertrophy of the muscle layer of the decidual arterioles	51 (27.7)	12 (7.0)	0.000*
Decidual vascular thrombosis	27 (14.7)	4 (2.3)	0.000*
Persistence of extra villous trophoblast	16 (8.7)	14 (8.2)	0.864
Combined damage (more than one damage)	79 (42.9)	21 (12.3)	0.000*

Continuous variables are presented as mean ± standard deviation, mean, range, and categorical variables as number (n) (%). *Statistically significant differences for p<0.05.

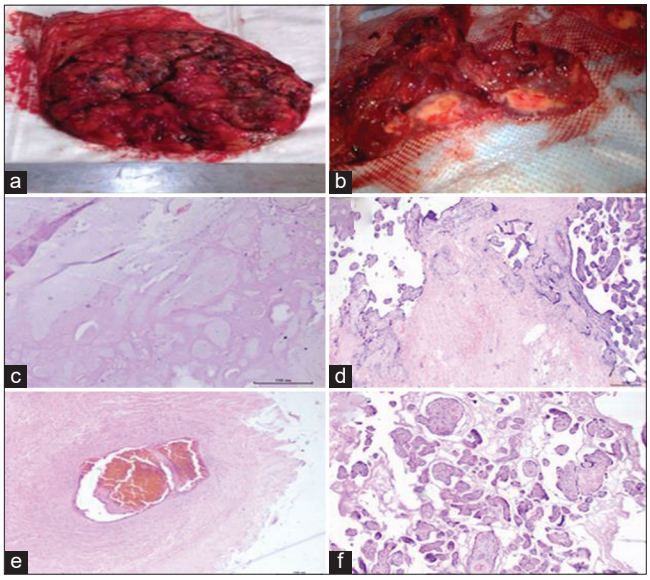

Figure 2: Macroscopic and histological signs of maternal vascular malperfusion in the study groups of placentas (a and b) placenta from pregnancy 37 weeks + 4 days, multiple placental infarcts. (c) Placenta from pregnancy 39 weeks + 2 days, preeclampsia, placental infarction. Staining hematoxylin and eosin, magnification ×100. (d and f) Placenta from pregnancy 37 weeks + 6 days, physiological pregnancy, fibrin deposits in the intervillous space. Staining hematoxylin and eosin, magnification ×100. (e) Placenta from pregnancy 37 weeks, preeclampsia, fibrinoid necrosis of the vessel wall. Staining hematoxylin and eosin, magnification ×100

were infarcts (occupying more than 30% of the volume of the placenta parenchyma), dissociated impaired maturation of chorionic villi with a predominance of mature forms of chorionic villi, atherosclerosis of the arteries of the basal plate, fibrinoid necrosis of the vessels, hypertrophy of the muscle layer of decidual arterioles, and thrombosis of decidual vessels.

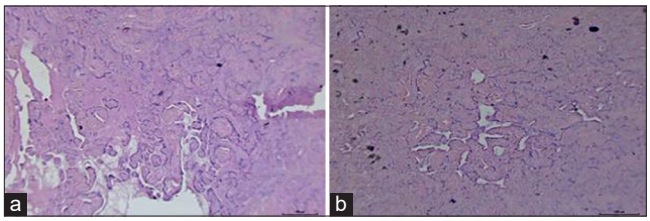

Figure 3: Other histological patterns of combined hypoxic injury to the placenta. (a) fibrinoid deposits in the intervillous space during slowing down of maternal blood flow. Staining: hematoxylin and eosin, magnification: ×100. (b) Acute hypoxic damage in chronic hypoxia with clustering of chorionic villi against the background of a hypoxic pattern. Staining: hematoxylin and eosin, magnification: ×100

Table 5: Other histological features of chronic hypoxic injury

Characteristic	Preeclampsia (n = 184)	Physiological pregnancy (n = 171)	p-value
Chorangiosis			
Predominantly Type 1	79 (42.9)	24 (14.0)	0.000*
Predominantly Type 2	56 (30.4)	18 (10.5)	0.000*
Type 1 and Type 2	25 (13.6)	19 (11.1)	0.480
Hemorrhages in the stroma of the villi	21 (11.4)	4 (2.3)	0.001*
Massive fibrin deposits in the intervillous space	9 (4.9)	3 (1.8)	0.103
Laminar necrosis	15 (8.2)	9 (5.3)	0.279

Microscopic signs of fetal vascular malperfusion in the group of placentas with an established diagnosis of preeclampsia and the group of placentas with physiological pregnancy are presented in Table 6.

In the group of placentas from pregnancy with preeclampsia, occlusive thrombi were more common than in the group with physiological pregnancy in the lumen of large vessels of the chorionic villi and chorionic plate, as well as combined lesions, including more than one injury. In addition, obliterating angiopathy was more common in the group with preeclampsia.

Between the two groups of placentas, there were no differences in such signs of fetal vascular malperfusion as foci of avascular villi and foci of villi with stromal-vascular karyorrhexis, areas of the placenta with severe vascular ectasia. In both groups, there were no differences in the number of placentas with a pronounced delay in the maturation of the chorionic villi (Figure 4).

Thus, the obtained results indicate that most of the histological signs associated with fetal vascular malperfusion occur with the same frequency in both study groups (Figure 4).

In the study population, morphological signs of fetal vascular malperfusion, different from the group with physiological pregnancy, were obliterating angiopathy and occlusive thrombi.

Table 6: Microscopic signs of fetal vascular malperfusion

Characteristic	Preeclampsia (n = 184)	Physiological pregnancy (n = 171)	p-value
Delayed maturation in villi	29 (15.8)	26 (15.2)	0.885
Fibrosis of the stroma of villi			
Focal	14 (7.6)	21 (12.3)	0.141
Diffuse	7 (3.8)	9 (5.3)	0.508
Thrombus			
Occlusive	16 (8.7)	4 (2.3)	0.010*
Recanalized	17 (9.2)	19 (11.1)	0.560
Focal	15 (8.2)	9 (5.3)	0.279
Diffuse	3 (1.6)	1 (0.6)	0.351
Intramural fibrin deposits	23 (12.5)	19 (11.1)	0.686
Obliterating angiopathy	29 (15.8)	14 (8.2)	0.029*
A vascular villi			
Small foci of a vascular villi (2-4)	11 (6.0)	9 (5.3)	0.771
Medium foci of avascular villi (5–10)	15 (8.2)	11 (6.4)	0.535
Large lesions of a vascular villi (>10)	4 (2.2)	1 (0.6)	0.205
Stromal vascular karyorrhexis of villi			
Small foci of villi with stromal-vascular karyorrhexis (2–4)	6 (3.3)	8 (4.7)	0.881
Middle foci of villi with stromal-vascular karyorrhexis (5–10)	24 (13.0)	14 (8.2)	0.140
Large lesions of villi with stromal-vascular karyorrhexis (>10)	3 (1.6)	1 (0.6)	0.351
Combined damage (more than one damage)	39 (21.2)	16 (9.4)	0.002*

Continuous variables are presented as mean ± standard deviation, mean, range, and categorical variables as number (n) (%). *Statistically significant differences for *P*<0.05.

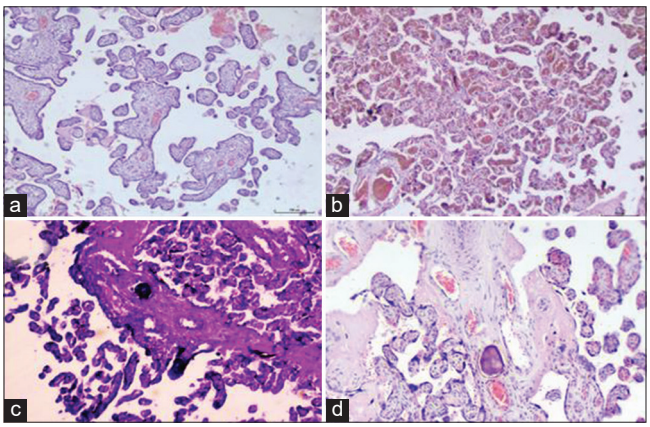

Figure 4: Histological patterns of fetal vascular malperfusion. (a) placenta from pregnancy 39 weeks + 1 day, preeclampsia, delayed maturation of chorionic villi. Staining: hematoxylin and eosin, magnification: ×100. (b) placenta from pregnancy 37 weeks + 6 days, preeclampsia, homogeneity of the morphological pattern, chorangiosis Type 1 and Type 2, focal increase in syncytial nodes, decrease in the extracellular matrix of chorionic villi, increase in Hofbauer cells and cytotrophoblast of the villi. Staining: hematoxylin and eosin, magnification: ×100. (c) Placenta from pregnancy 37 weeks + 1 day, preeclampsia, obturating calcified thrombus in the lumen of the macro vessel of the placenta. Staining: hematoxylin and eosin, magnification: ×100. (d) Placenta from pregnancy 38 weeks + 3 days, preeclampsia, maternal nicotine dependence, calcifications and fibrinoid deposits in the intervillous space. Staining: hematoxylin and eosin, magnification: ×200

During the study, it was found that the morphological patterns of the placenta in preeclampsia are characterized by heterogeneity. In this regard, placentas from pregnancies with preeclampsia, depending on the risk of chronic hypoxic damage to the fetus, were further divided into two subgroups (with a high risk of chronic hypoxic damage to the fetus and a low risk of chronic hypoxic damage to the fetus). Based on the analysis of the results obtained, we can formulate the following.

Conclusion

1. It has been established that preeclampsia is associated with a smaller mass, size, and height of the placenta, but an increased fetoplacental index and umbilical cord tortuosity other than normal, as well as combined cord injuries, including more than one of the structural features of the umbilical cord, different from the norm, compared with placentas from physiological pregnancy.
2. The morphological picture associated with preeclampsia is the following histological signs of circulatory disorders in the mother: infarcts (occupying more than 30% of the volume of placental parenchyma), dissociated maturation of chorionic villi with a predominance of mature forms of chorionic villi, atherosclerosis of basal plate arteries, fibrinoid necrosis of vessels, hypertrophy of the muscular layer of decidual arterioles, and thrombosis of decidual vessels. Most of the histological signs associated with fetal vascular malperfusion occurred with the same frequency in both study groups.

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