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Comparative Pathomorphological Characteristics of Placental Vessels from Pregnancies with High and Low Risk of Preeclampsia

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Abstract

Relevance: Preeclampsia is a common multisystem specific pregnancy disorder accompanied by remodeling of placental vessels. Vascular structural changes are influenced by both systemic factors and local anomalies, such as umbilical cord pathology. The large variability and inconsistency of histomorphometric changes in placental vessels as markers of placental dysfunction emphasize the need for their further research using standardized methods of morphometric analysis.

The purpose of this work is to evaluate histomorphometric changes in the wall thickness and internal diameter of placental vessels during pregnancy with a different risk of preeclampsia based on screening in the first trimester and umbilical cord pathology.

Methods: A retrospective research included pregnant women grouped by preeclampsia risk (high and low) and additionally stratified by the presence of umbilical cord pathology. The placenta examination and the selection of fragments of placental tissue of the postpartum placenta were carried out in accordance with the consensus recommendations of the Amsterdam Placental Workshop Group. The sections were stained with hematoxylin and eosin and Masson trichrome. Morphometric measurements were performed using ImageJ software (version 1.52). The data were analyzed using the Mann-Whitney U-test with Bonferroni correction.

Results: Systemic and local factors had an impact on vascular remodeling, manifested in changes in wall thickness and diameter of macrovessels. In the low–risk group without umbilical cord pathology, the average vascular wall thickness was 14.4(11.6 - 17.8)μm, and the diameter of the vascular lumen was 124.9(98.4 – 142.6)μm. In placentas with a high risk of preeclampsia without umbilical cord pathology, a significant decrease in the wall thickness of placental vessels was observed to an average of 8.1(6.3 – 8.8)μm, accompanied by a significant expansion of the vascular lumen to 167.7(128.4 – 189.7)μm. The presence of umbilical cord pathology led to thickening of the wall of the proximal vessels 29.1(24.1-37.1)μm with a decrease in the lumen diameter to 93.7(82.7-105-5)μm. The differences between the groups reached statistical significance ($p<0.001$).

Conclusion: This research highlights the combined effect of systemic factors (risk of preeclampsia) and local structural changes (umbilical cord pathology) on the remodeling of placental vessels. A decrease in the wall thickness of the placental vessels, accompanied by an increase in the internal diameter of the vessels, suggests significant structural changes that may be early diagnostic and prognostic markers of a newborn's predisposition to cardiovascular diseases.

Keywords: preeclampsia, chorionic villous vessels; histomorphometry, placenta.

Introduction

Preeclampsia is a serious multisystem condition that affects approximately one in fifteen pregnant women [1]. Preeclampsia is associated with short-term and long-term risks to the mother, including cardiovascular complications, and adverse fetal outcomes such as growth restriction, preterm birth, and perinatal mortality [2–7]. An integrated

approach including risk monitoring, preventive measures and multidisciplinary collaboration is a key solution to reducing the burden of preeclampsia.

One of the important strategies for prevention is to use of low doses of acetylsalicylic acid from the first trimester of pregnancy, which, according to numerous researches, reduces the likelihood of developing preeclampsia in high-risk groups based on screening results [8–10]. Modern first trimester screening programs use a combination of clinical history data biochemical and sonographic indicators to assess the risk of preeclampsia. But despite the success in the development of screening programs, issue of the relationship between the identified risk and histopathological changes in the placenta remains open.

Pathological processes in the «mother-placenta» system, leading to prolonged hemodynamic disorders, may be accompanied by significant remodeling of placental vessels, exacerbating placental dysfunction [11, 12]. Researches of the vessels of the villous tree of the placenta in preeclampsia reveal significant differences in their morphometric parameters compared with physiological pregnancy. However, data on changes in the walls and lumen of blood vessels are contradictory: some authors point to thickening of the walls of blood vessels due to hypertrophy of smooth muscle cells or fibrous processes, others note their thinning and expansion of the diameter of blood vessels, and sometimes do not record significant changes at all [13–17]. The inconsistency of the data indicates the need for further researches of placental vessels in preeclampsia. Changes in the vascular network can act not only as a marker of placental perfusion disorders, but also as an independent factor affecting the outcome of pregnancy. The research of histomorphometric features of placental vessels depending on the risk of preeclampsia and concomitant factors is an important step in understanding the pathogenesis of preeclampsia and individualizing the approach to pregnancy follow-up with stratification of risk groups of women and newborns.

The objective of this paper is to evaluate histomorphometric changes in the wall thickness and internal diameter of placental vessels during pregnancy with a different risk of preeclampsia based on screening in the first trimester and umbilical cord pathology.

Methods

Research design

A retrospective study was performed from January 1, 2022 to January 1, 2024 in the Department of Pathology of the NJSC Karaganda Medical University (Kazakhstan). In the planning stage, the study was analyzed considering the current regulatory and legal acts governing compliance with ethical principles in research involving human subject.

The study was carried out in accordance with the ethical principles of the Declaration of Helsinki [18] and approved by the local bioethics commission of the Karaganda Medical University (09.25.2024). All participants signed a written informed consent, having received full information about this study. All research subjects were guaranteed anonymity.

Prenatal screening of the risk of preeclampsia was conducted in accordance with national standards and clinical protocols of the Republic of Kazakhstan [19, 20]. Screening was performed at gestation from 11 to 13 weeks and 6 days, and risk calculation was carried out using a highly sensitive fluorescent label using automated equipment and software AutoDELFIA, LifeCycle.

Preeclampsia was diagnosed as hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) occurring after 20 weeks of gestation in a previously normotensive woman and accompanied by one or more of the following criteria: proteinuria (more than 300 mg in 24-hour urine or urine protein to creatinine ratio ≥ 0.3 mg/dL), maternal organ dysfunction (including liver, lung, kidney, or central nervous system disease), hematologic abnormalities, or dysfunction of the uteroplacental system [21, 22].

Inclusion criteria are as follows, written informed consent, delivery at a gestation period of more than 33 weeks, prenatal screening performed during pregnancy from 11 to 13 weeks and 6 days, risk factors for preeclampsia in the anamnesis, delivery of the placenta for histological examination.

Exclusion criteria are as follows, chronic arterial hypertension, rhesus-conflict pregnancy, mother's HIV infection, infection with SARS-CoV-2 during pregnancy, age less than 18 years, multiple pregnancies, intrauterine fetal growth restriction, congenital pathologies of the fetus.

The concomitant pathology of the mother included cardiovascular, endocrine, metabolic, autoimmune diseases, as well as chronic kidney diseases.

The umbilical cord pathology was determined by the presence of one or more of the following signs:

- anomalies of umbilical cord attachment: marginal or velamentous attachment;
- abnormal umbilical cord length: excessively long umbilical cord (more than 70 cm) or short umbilical cord (less than 35 cm);
- umbilical cord entanglement around parts of the fetus's body (single and multiple entanglements);
- anomalies in the number of vessels (single umbilical artery);
- true umbilical cord knot.

Four groups were identified as follows,

Group 1 – high risk of preeclampsia with umbilical cord pathology,

Group 2 – high risk of preeclampsia without umbilical cord pathology,

Group 3 – low risk of preeclampsia with umbilical cord pathology,

Group 4 – low risk of preeclampsia without umbilical cord pathology.

Collection of clinical data

Clinical data were collected about patients from the patient medical records using software in an integrated health information system.

At the first prenatal visit, detailed demographic and clinical profiles were recorded for all participants. Key parameters included maternal age, pre-pregnancy body mass index (BMI), obstetric and medical history, gestational age, and blood pressure readings. For participants receiving prophylactic acetylsalicylic acid, data on the dosage and duration of therapy were collected from subsequent prenatal visits. In addition, information on pregnancy complications, gestational age at delivery, in particular, Apgar scores at 1 and 5 minutes postpartum were extracted from medical records.

The medical data were anonymized by coding each subject using a unique identifier.

Clinical data of women, and characteristics of the course of pregnancy of women in the study groups, including information on anthropometric indicators, medical history and concomitant diseases are presented in Table 1.

Table 1 Clinical characteristics of pregnancy, maternal and fetal/newborn outcomes

Parameters		Risk of preeclampsia high n = 21	low n = 6 3	p-value
Mother's age, years	Me (Q1-Q3)	38 (35-40)	30 (26-34.5)	**0 .0001**
Gestation period according to ultrasound, weeks	Me (Q1-Q3)	35 (34-36)	35 (34-36)	-
Parity , n (%)	primiparous	15 (71.4)	18 (28.6)	**0.002**
	multiparous	6 (28.6)	45 (71.4)	
Body mass index , n (%)	underweight	1 (4.8)	7 (11.1)	
	normal weight	5 (23.8)	45 (71.4)	
	overweight	7 (33.3)	7 (11.1)	
	obesity	8 (38.1)	4 (6.4)	
Chronic diseases 1 , n (%)	Yes	5 (23.8)	9 (14.3)	0.311
	No	16 (76.2)	54 (85.7)	
Bad habits , n (%)	Yes	1 (4.8)	1 (1.6)	0.409
	No	20 (95.2)	62 (98.4)	
FGR , n (%)	Yes	-	-	-
	No	21 (100.0)	63 (100.0)	
Macrosomia , n (%)	Yes	-	2 (3.2)	0.409
	No	21 (100.0)	61 (96.8)	
Antenatal fetal death , n (%)	Yes	-	-	-
	No	21 (100.0)	63 (100.0)	
Child's gender , n (%)	female	10 (47.6)	31 (49.2)	0.900
	male	11 (52.4)	32 (50.8)	
Apgar score (1 min)	Me (Q1-Q3)	7 (7-8)	8 (7-9)	0.087
Apgar score (5 min)	Me (Q1-Q3)	8 (8-9)	9 (8-9)	0.122
Placenta weight (g)	Me (Q1-Q3)	344 (313-408)	389 (345-427.5)	**0.033**
Pathology of the umbilical cord	Yes	8 (38 . 1)	19 (30.2)	0.286
	No	13 (61.9)	44 (69.8)	
Taking aspirin	Yes	20 (95.2)	-	**0 .0001**
	No	1 (4.8)	63 (100.0)	
Preeclampsia	Yes	2 (9.5)	3 (4.8)	0.425
	No	19 (90.5)	60 (95.2)	

1 – diabetes type 1 or 2, obesity grade 2-3 , kidney disease or autoimmune diseases.
p <0.05- value indicating statistically significant differences between groups , calculated using the chi - square test , Fisher's exact test or Mann-Whitney U test, Student's t-test, depending on the data

Selection of placental tissues

Placental tissue collection was carried out in accordance with the internal policy of the organization, national and international recommendations [23].

Each placenta was transported for histological examination after the birth. If immediate analysis was possible, the sample was promptly transferred to the laboratory for excision. If immediate analysis was not possible, placentas were stored at 4°C in a refrigerator. Stored placentas were transported to the laboratory under controlled temperature conditions until the 48-hour storage period had expired. All stages, including collection, storage, transport, and laboratory processing were carefully documented to ensure transparency, compliance with safety standards, and adherence to protocol.

Histological examination of the placenta

Placental tissue samples were fixed for 24 hours in 10% formalin at 4°C, then subjected to standard processing, including dehydration in increasing concentrations of alcohols and embedding in paraffin. Sections of 3–4 μm thickness

were deparaffinized and stained for histological examination. Histological sections were stained in Mayer's hematoxylin, then washed with water and stained with eosin according to a standard protocol.

To visualize and identify collagen fibers in the vessel wall, Masson trichrome staining was used with a commercial kit (Bio-Optica, Italy). Collagen fibers were stained dark blue and blue, contrasting with other tissue components, muscle fibers were stained red, and cell nuclei were stained black and dark brown.

Histomorphometric analysis

Histomorphometric analysis of placental vessels was conducted according to the methodology described in a previously published work [24]. Histological identification of chorionic villi was carried out by the following this work [25].

Criteria for excluding sections:

- lack of vessel lumen;
- poorly distinguishable boundaries of the vessel walls;
- obliquely cut arteries (the ratio of perpendicular diameters is more than 1.3).

Histomorphometric examination of 20 arterioles was performed in each zone.

Digital images of histological sections were acquired using an EX30 microscope in ImageJ software. All equipment was calibrated to convert pixel size to micrometers before analysis. All measurements were performed manually by one trained, highly qualified investigator who was blinded to pregnancy outcomes, patient medical history, and placental risk group classification. The measured values were entered into a Microsoft Excel data spreadsheet for subsequent analysis.

Morphometric measurements were performed manually in software after calibration. For each vessel was measured:

- inner and outer diameters;
- the thickness of the placental arterioles, calculated as half the difference between the outer and inner vessel diameter.

Each measurement was taken in four standardized directions corresponding to 3, 6, 9, and 12 o'clock on a standard clock face. The values obtained in each direction were recorded and the arithmetic average of these measurements was calculated to obtain the wall thickness value for each vessel.

All morphometric measurements were performed manually by a single researcher who did not have access to information about pregnancy outcomes, the clinical history of patients, or the group to which each of the placentas belonged (high or low risk group).

Statistical analysis

Data analysis and visualization were performed using IBM SPSS Statistics v.22 program (StatSoft, Inc., USA).

At the preliminary data analysis stage, the normality of distribution of quantitative variables was assessed using the Shapiro-Wilk test. The Levene test was utilized to test the uniformity of the variances. For quantitative traits with normal distribution, the mean and standard deviation were calculated. The sets of quantitative indicators, with a different distribution from the normal one, were presented as a median (Me) and first and third quartiles (Q1-Q3). Nominal data is presented in the form of absolute values and percentages. To compare the distribution frequencies by qualitative characteristics between groups, the statistical chi-square criterion with the Yates correction or the exact Fisher criterion was used. To compare groups with data without pattern of normal distribution, we used the Mann-Whitney U-test. To reduce the risk of type I errors in multiple comparisons, we use the Bonferroni correction. In the case of normal data distribution, comparisons between groups were made using Student's t-test.

Results

Socio-demographic characteristics medical history data of women, clinical characteristics of pregnancies and newborns of high and low risk groups of preeclampsia are presented in Table 1.

The table data show that in the group of women with a high risk of preeclampsia, the age of women was higher (Me 38 years vs. 30 years, p = 0.0001), and the incidence of obesity was higher (38.1% vs. 6.4%). Also, a woman with a high risk of preeclampsia showed a decrease in placental mass (Me 344 g vs. 389 g, p = 0.033). Chronic diseases were more common in women at high risk of preeclampsia, but the differences did not reach statistical significance.

Analysis of the wall thickness of the placenta vessels

The results of measurements of the arterioles the placenta of the research groups are presented in Table 2 and Figure 1.

In the group with a high risk of preeclampsia and umbilical cord pathology, for proximal arterioles the median wall thickness was 29.1 (24.1 – 37.1)μm, the standard deviation is 11.4μm, the minimum value is 12.4μm, the maximum value is 47.2μm. For distal arterioles, the median wall thickness was 7.8(6.4 – 8.1) μm, the standard deviation was 3.4μm, the minimum value was 4.9μm, the maximum was 12.9μm.

In the group with a high risk of preeclampsia without umbilical cord pathology, for proximal arterioles the median wall thickness was 8.7(6.1–9.2)μm, the standard deviation was 11.0μm, the minimum value was 3.1μm, the maximum value was 43.1μm. For distal arterioles, the median wall thickness was 8.1(6.3 – 8.8)μm, the standard deviation was 1.7μm, the minimum value was 5.2μm, the maximum was 11.3μm.

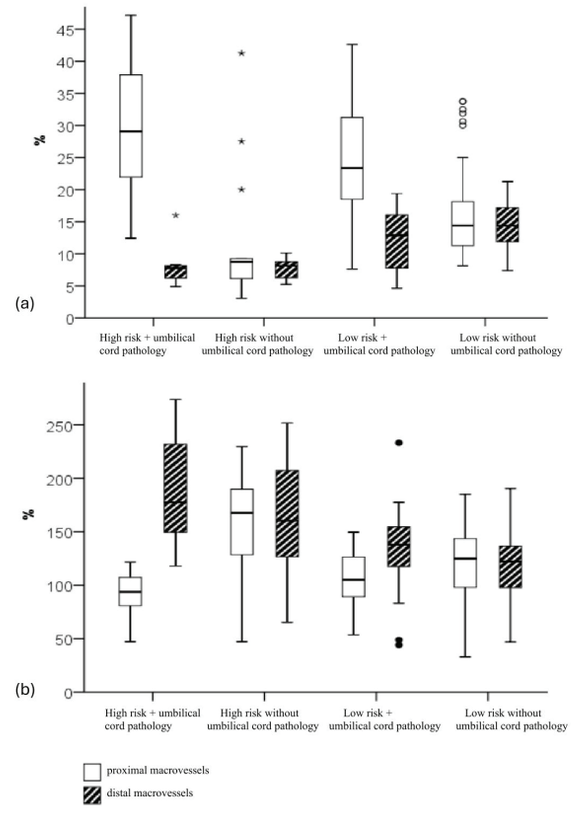

Figure 1 – Wall thickness and diameter of proximal and distal placental arterioles a. thickness of the walls of placental macrovessels, μm b. lumen diameter, μm

Table 2 Morphometric measurements of proximal and distal vessels in placentas with different risks of preeclampsia and umbilical cord pathology

Parameters, μm		Group 1 High risk + umbilical cord pathology n = 8	Group 2 High risk without umbilical cord pathology n = 1 3	Group 3 Low risk + umbilical cord pathology n = 19	Group 4 Low risk without umbilical cord pathology n = 44	Groups with differences	p-value
Proximal macrovessels							
wall thickness	Median	29.1	8.7	23.4	14.4	1 and 2, 1 and 4, 2 and 3, 3 and 4	0.0025 , 0.00 36 , 0.00 45 , 0.0 028
	25–75%	24.1 – 37.1	6.1 – 9.2	18.5 – 31.3	11.6 – 17.8		
internal diameter	Median	93.7	167.7	105.2	124.9	1 and 2, 2 and 3, 2 and 4,	<0 .001, 0.0016 , 0.0047
	25–75%	82.7 – 105.5	128.4 – 189.7	89.2 – 126.4	98.4 – 142.6		
Distal macrovessels							
wall thickness	Median	7.8	8.1	12.9	14.4	1 and 4, 2 and 4	0.00 4, 0.007
	25–75%	6.4 – 8.1	6.3 – 8.8	7.8 – 16.1	11.9 – 17.0		
internal diameter	Median	177.7	160.4	137.9	122.0	1 and 4, 2 and 4	0.0 04 , 0.00 47
	25–75%	152.7 – 230.0	126.6 – 207.3	117.5 – 154.7	98.2 – 136.0		

In the group with a low risk of preeclampsia and umbilical cord pathology, for proximal arterioles the median wall thickness was 23.4 (18.5 – 31.3)μm, the standard deviation is 9.6μm, the minimum value is 7.6μm, the maximum value is 42.6μm. For distal arterioles, the median wall thickness was 12.9(7.8 – 16.1) μm, the standard deviation was 5.0μm, the minimum value was 4.6μm, the maximum was 25.3μm.

In the group with a low risk of preeclampsia and umbilical cord pathology, the wall thickness of the proximal arterioles was 14.4 (11.6 – 17.8)μm, the standard deviation was 7.5μm, the minimum value was 8.1μm, the maximum value was 33.8μm. For distal arterioles, the median wall thickness was 14.4(11.9 – 17.0)μm, the standard deviation was 3.7μm, the minimum value was 7.4μm, the maximum was 25.4μm.

Analysis of the lumen diameter of placental vessels

In the group with a high risk of preeclampsia and umbilical cord pathology, the diameter of the proximal arterioles was 93.7(82.7 – 105.5)μm, the standard deviation was 27 μm, the minimum value was 47.2μm, the maximum value was 121.6μm. For distal arterioles, the median diameter of the vessels was 177.7(152.7 – 230.0)μm, the standard deviation was 53 μm, the minimum value was 117.9μm, the maximum was 273.7μm.

In the group with a high risk of preeclampsia without umbilical cord pathology, the diameter of the proximal arterioles was 167.7(128.4 – 189.7)μm, the standard deviation was 57.3μm, the minimum value was 47.1μm, the maximum value was 229.6μm. For distal arterioles, the median diameter was 160.4(126.6 – 207.3)μm, the standard deviation was 57.3μm, the minimum value was 65.3μm, the maximum was 251.7μm.

In the group with a low risk of preeclampsia and umbilical cord pathology, the median diameter of the proximal arterioles was 105.2(89.2 – 126.4)μm, the standard deviation was 22.6μm, the minimum value was 53.6μm, the maximum value was 149.5μm. For distal arterioles, the median diameter was 137.9(117.5 – 154.7)μm, the standard deviation was 43.7μm, the minimum value was 44 μm, the maximum was 233.2μm.

In the group with a low risk of preeclampsia and umbilical cord pathology, the diameter of the proximal arterioles was 124.9(98.4 – 142.6)μm, the standard deviation was 27.5μm, the minimum value was 33 μm, the maximum value was 185 μm. For distal arterioles, the median wall thickness was 122.0(98.2 – 136.0)μm, the standard deviation was 32 μm, the minimum value was 46.9μm, the maximum was 190.4μm (Table 2).

Discussion

The present research presents a histomorphometric analysis of the placental vascular network with a different risk of preeclampsia based on the results of screening in the first trimester and the presence/absence of umbilical cord pathologies.

The obtained data show significant differences in the histomorphometric parameters of placental vessels between the study groups. In the high-risk group of preeclampsia without umbilical cord pathology, there was a significant thinning of the arteriolar wall of the proximal placenta with dilation of their lumen compared with low-risk groups ($p<0.001$). These changes may indicate compensatory vascular dilation aimed at maintaining placental perfusion. However, a decrease in vascular wall thickness indicates progressive structural changes that reduce the ability to adapt, accompanied by impaired vascular tone and elasticity. We believe that the observed diffuse dilation of blood vessels in combination with thinning of their walls indicates a violation of the normal process of vascular remodeling in which a decrease in the thickness of the muscular layer of blood vessels and dilation of their lumen may be the result of underdevelopment of the vascular wall in early pregnancy. This is confirmed by the systemic nature of the lesion, affecting both the proximal and distal parts of the placental vascular network. The results obtained are consistent with our previously published results [24].

In the high-risk group with umbilical cord pathology, signs of proximal fibromuscular sclerosis were observed, accompanied by vascular obliteration and compensatory dilation of distal vessels. Such changes indicate a prolonged exposure to a pathological factor, leading to a progressive loss of vascular adaptation. The revealed signs of ectatic macroangiopathy and proximal sclerosis expand the understanding of the systemic nature of damage to the placental vasculature in preeclampsia. Umbilical cord pathology associated with proximal fibromuscular sclerosis may act as an additional risk factor for vascular remodeling of the placenta. This confirms the hypothesis about the effects of systemic and local factors that enhance vascular dysfunction.

We believe that these structural changes reflect long-term and repeated exposure to a pathological factor that leads to disruption of the vascular remodeling process. This in turn causes obliteration of proximal vessels, limiting blood flow and compensatory dilation of distal vessels in order to maintain perfusion. However, such a compensatory mechanism may be insufficient to ensure blood flow, contributing to the development of placental hypoperfusion, chronic tissue ischemia and their dysfunction. These changes highlight the importance of studying the relationship between pathological vascular remodeling and ischemic processes in the placenta, as well as the impact on maternal and fetal health outcomes.

On the other hand, the observed structural changes in the placenta suggest similar pathological processes in the fetal vascular system. The morphological and functional relationship between the vessels of the placenta and the fetus indicates the likelihood of the fetus developing a predisposition to vascular pathologies, such as hypertension and cardiovascular diseases in the postnatal period.

The data of this research confirm that pathological remodeling of placental vessels is a systemic process that can be detected even in women without obvious clinical symptoms of preeclampsia, but with a high risk of preeclampsia. This makes it possible to consider a high risk during screening, even without subsequent clinical manifestation, as a possible indicator of ischemic processes in the placenta due to progressive vascular remodeling. However, this assumption requires further research.

Limitations of the research include fluctuations in data, which may be due to a small number of cases in subgroups, the single-center nature of the research, as well as the lack of long-term follow-up to assess the impact of identified structural changes in placental vessels on the health of the newborn and mother in the long term. Conducting multicenter researches with an increased sample will increase the representativeness and validity of the results. Further research in this area will contribute to the development of a personalized approach in obstetrics and pediatrics, clarifying the prognostic significance of the identified placental macrovascular changes and their integration into clinical practice for the prevention of long-term adverse effects for both mother and child.

Conclusion

Significant differences in placental macrovascular remodeling were found in women at high risk of preeclampsia, including thinning of the vascular wall and dilation of the vascular lumen with thinning of the muscular layer in the vascular wall. These changes indicate a disruption of normal vascular remodeling processes, leading to a decrease in the adaptive potential of the placenta, limitation of its ability to respond to physiological and pathological changes, and an increase in vascular resistance. These changes may present the different temporal and spatial pattern of the action of pathological factors that limit the adaptive capabilities of blood vessels. These results emphasize the need for further research to clarify the mechanisms of development of pathological remodeling of placental vessels and their impact on the health of mother and child, which may contribute to the development of personalized approaches to the treatment of pregnancy complications.

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References

1. Chang K-J, Seow K-M, Chen K-H. Preeclampsia: Recent Advances in Predicting, Preventing, and Managing the Maternal and Fetal Life-Threatening Condition. *International Journal of Environmental Research and Public Health*. 2023; 20(4): 2994. https://doi.org/10.3390/ijerph20042994
2. Kermack AJ, Van Rijn BB, Houghton FD, Calder PC, Cameron IT, Macklon NS. The 'Developmental Origins' Hypothesis: relevance to the obstetrician and gynecologist. *J Dev Orig Health Dis.* 2015; 6(5): 415–424. https://doi.org/10.1017/S2040174415001324
3. Katsi V, Kanellopoulou T, Makris T, Nihoyannopoulos P, Nomikou E, Tousoulis D. Aspirin vs Heparin for the Prevention of Preeclampsia. *Current Hypertension Reports.* 2016; 18(7): 57. https://doi.org/10.1007/s11906-016-0664-3
4. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet*. 2016; 387 (10022): 999–1011. https://doi.org/10.1016/S0140-736(15)00070-7
5. Chappell LC, Cluver CA, Kingdom J, Tong S. Pre-eclampsia. *Lancet*. 2021; 398(10297): 341–354. https://doi.org/10.1016/S0140-6736(20)32335-7
6. deMartelly VA, Dreixler J, Tung A, Mueller A, Heimberger S, Fazal AA, Naseem H, Lang R, Kruse E, Yamat M, Granger JP, Bakrania BA, Rodriguez-Kovacs J, Rana S, Shahul S. Long-Term Postpartum Cardiac Function and Its Association With Preeclampsia. *J Am Heart Assoc.* 2021; 10(5): e018526. https://doi.org/10.1161/JAHA.120.018526.
7. Brandt Y, Ghossein-Doha C, Gerretsen SC, Spaanderman MEA, Kooi ME. Noninvasive Cardiac Imaging in Formerly Preeclamptic Women for Early Detection of Subclinical Myocardial Abnormalities: A 2022 Update. *Biomolecules*. 2022; 12(3): 415. https://doi.org/10.3390/biom12030415.

8. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, Matallana CP, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Meiri H, Gizurarson S, Maclagan K, Nicolaides KH. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *N Engl J Med.* 2017; 377(7): 613–622. https://doi.org/10.1056/NEJMoa1704559
9. Côté ML, Demuth B, Ghesquière L, Bujold E. Aspirin before the 11 th week of pregnancy to prevent pre-eclampsia. *Int J Reprod Biomed.* 2024; 22(8): 679–680. https://doi.org/10.18502/ijrm.v22i8.17245
10. Huang J, Chen X, Xing H, Chen L, Xie Z, He S, Wang X, Li Y, Cui H, Chen J. Aspirin and heparin for the prevention of pre-eclampsia: protocol for a systematic review and network meta-analysis. BMJ Open. 2019; 9(2): e026920. *Published* 2019 Feb 24. https://doi.org/10.1136/bmjopen-2018-026920
11. Dash PR, Whitley GS, Ayling LJ, Johnstone AP, Cartwright JE. Trophoblast apoptosis is inhibited by hepatocyte growth factor through the Akt and beta-catenin mediated up-regulation of inducible nitric oxide synthase. *Cell Signal.* 2005; 17(5): 571–580. https://doi.org/10.1016/j.cellsig.2004.09.015.
12. Gill JS, Salafia CM, Grebenkov D, Vvedensky DD. Modeling oxygen transport in human placental terminal villi. *J Theor Biol.* 2011 Dec 21;291:33-41. https://doi.org/10.1016/j.jtbi.2011.09.008.
13. Salih MM, Ali LE, Eed EM, Siniyeh AA. Histomorphometric study of placental blood vessels of chorion and chorionic villi vascular area among women with preeclampsia. *Placenta*. 2022 Jun 24; 124: 44–47. https://doi.org/10.1016/j.placenta.2022.05.011.
14. Akhlaq M, Nagi AH, Yousaf AW. Placental morphology in pre-eclampsia and eclampsia and the likely role of NK cells. Indian J Pathol Microbiol. 2012; 55(1): 17–21. https://doi.org/10.4103/0377-4929.94848.
15. Wilhelm D, Mansmann U, Neudeck H, Matejevic D, Vetter K, Graf R. Increase of segments of elastic-type blood vessel walls in fetal placental stem villi during pre-eclampsia at term. *Anatomy and embryology.* 1999; 200(6): 597–605. https://doi.org/10.1007/s004290050307.
16. Shen X, Wang C, Yue X, Wang Q, Xie L, Huang Z, Huang X, Li J, Xu Y, Chen L, Lye S, Wei Y, Wang Z. Preeclampsia associated changes in volume density of fetoplacental vessels in Chinese women and mouse model of preeclampsia. *Placenta*. 2022; 121: 116–125. https://doi.org/10.1016/j.placenta.2022.03.002.
17. Baran Ö, Tuncer M, Nergiz Y, Akkuş M, Erdemoğlu M, Büyükbayram H. An increase of elastic tissue fibers in blood vessel walls of placental stem villi and differences in the thickness of blood vessel walls in third trimester pre-eclampsia pregnancies. *Open Medicine.* 2010 Apr 1;5(2):227-34. https://doi.org/10.2478/s11536-009-0025-6
18. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013; 310(20) :2191–2194. https://doi.org/10.1001/jama.2013.281053
19. Statement of the Minister of Healthcare of the Republic of Kazakhstan "On approval of the Standard for organizing prenatal ultrasound screening in the Republic of Kazakhstan" dated June 21, 2022 No. RK MH-54.
20. The clinical protocol "Antenatal care" was approved by the joint commission on the quality of medical services of the Ministry of Healthcare of the Republic of Kazakhstan on July 28, 2023.
21. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G, Ishaku S. Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension*. 2018; 72(1): 24–43. https://doi.org/10.1161/hypertensionaha.117.10803
22. The clinical protocol "Hypertensive conditions during pregnancy" was approved by the joint commission on the quality of medical services of the Ministry of Healthcare of the Republic of Kazakhstan on March 17, 2023.
23. Khong TY, Mooney EE, Ariel I, Balmus NC, Boyd TK, Brundler MA, Derricott H, Evans MJ, Faye-Petersen OM, Gillan JE, Heazell AE, Heller DS, Jacques SM, Keating S, Kelehan P, Maes A, McKay EM, Morgan TK, Nikkels PG, Parks WT, Redline RW, Scheimberg I, Schoots MH, Sebire NJ, Timmer A, Turowski G, van der Voorn JP, van Lijnschoten I, Gordijn SJ. Sampling and definitions of placental lesions: Amsterdam placental Workshop group consensus statement. *Arch Pathol Lab Med.* 2016; 140: 698–713. https://doi.org/10.5858/arpa.2015-0225-cc.
24. Makhambetova K, Kamyshanskiy Y, Ponamareva O, Amirbekova Z, Oshakhtiyeva N, Kunanbaeva S. Placental Macrovascular Pattern from Pregnancies with Maternal Hypertensive and Fetal Growth Capacity Complications. *Pathophysiology*. 2024; 31(4): 699–708. https://doi.org/10.3390/pathophysiology31040050
25. Vogel M. Pathologie der Plazenta: Spätschwangerschaft und fetoplazentare Einheit. In: Kloppel G, Kreipe H, Remmele W, editors. Pathologie. Heidelberg: *Springer-Verlag;* 2013: 519–539.