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## Research Article

# Chorionic Villi with Placental Hypoplasia

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## Abstract

The structure and proliferation of endothelial and muscle cells of the chorionic veins of the underdeveloped placenta were studied. Histological, histochemical, and morphometric studies of the fetal membrane of the placenta of 36 placentas of 280-300 g at 39-40 weeks of pregnancy were carried out in comparison with 15 placentas of 450-500 g. The Ki-67 proliferation marker (Ventana, USA) was studied immunohistochemically with the determination of the proliferation index on the Roche Benchmark XT Ventana (USA) immunohistostainer by counting 1000 nuclei of endothelial cells and myocytes in capillaries, venules, and veins of the stem, intermediate and terminal villi. The outer and inner diameters of the veins were measured. The data were processed using the variation statistics method.

The stem villi are supplied with a vein, artery, and capillaries. Amygdaloid veins are present at the bases, venules are on the surface of the intermediate villi. Capillaries are distinguished in the terminal villi. In hypoplasia, sphincter-like and valve-like structures are formed in the veins. Subendothelial sphincter rings of circularly located myocytes protrude into the lumen. Intimal cushions are obturator longitudinal layers of myocytes. Between the sphincters, the veins are dilated. Valvelike elements with myocytes and collagen fibers are found in small veins. These formations ensure blood distribution in the underdeveloped placenta and a decrease in trophic and oxygen starvation of the fetus. Hypoplasia is accompanied by venodilation with an increase in the external and internal diameters and an increase in the proliferation of cells of the chorionic veins.

## Introduction

The human placenta (P) is a critical structure that performs nutrition and support of the fetus during pregnancy, immunological, endocrine, and barrier functions, removing metabolic waste and xenobiotics [1,2]. The P and the main veins of its fetal surface participate in the delivery of blood enriched with oxygen, energy, and plastic substrate, from the intervillous space to the fetus [3]. Changes in the P revealed during morphological examination help to clarify the causes of complications, as well as to determine the prognosis for the development of the newborn and the course of future pregnancies [4]. Dysfunctional development of the P underlies many pregnancy complications [5], including fetal growth

retardation. Underdevelopment or hypoplasia of the fetus often leads to fetoplacental insufficiency and negatively affects the development of the fetus and its vascular system [6,7].

A few studies are devoted to the anatomical and pathomorphological changes in the veins of the fetal trunk villi in gestosis [8], infections in pregnant women [9,10] and sphincter-like structures of the venous wall [11]. When searching the electronic resources of the Russian National Library and PubMed NCBI for the period from 1990 to 2024, it was found that information on the features of the microscopic organization of the veins of the human chorionic villi is scattered and contradictory; there is no data on the proliferation of cell populations of the venous wall under conditions of hypoplasia P.

## Material and methods of the study

We studied 36 placentas (P) weighing 280300 grams (g) and gestation periods of 39–40 weeks, which corresponds to hypoplasia of the placenta. The comparison group consisted of 15 P of the same gestation period weighing 450–500 g. The age of pregnant women referred for histological examination of the placenta was 26–32 years; 35% of them had an increase in body temperature to 37.5 °C and blood pressure by 10–20 mm Hg. Which was one of the causal factors in the development of hypoplasia of the placenta.

In all the studied cases, delivery took place through the natural birth canal. The material was obtained from maternity hospitals in Yaroslavl, the pathomorphological study was performed at the N.V. Solovyov Municipal Clinical Hospital and approved by the Ethics Committee of the Yaroslavl State Medical University (YSMU) (protocol No. 11 dated October 13, 2023).

Fragments of the fetal and maternal parts of the P in the paracentral and marginal areas were fixed in 10% neutral formalin, Carnoy's fluid, and embedded in paraffin.

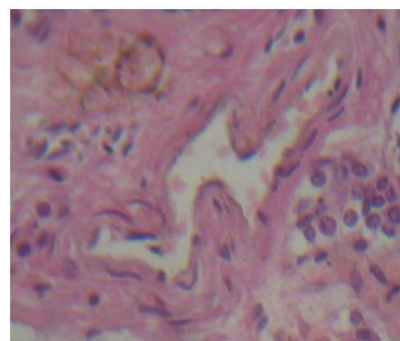
Serial sections of 4–5 µm were stained with hematoxylin and eosin, according to Masson and Hart. Immunohistochemical examination was performed on deparaffinized sections by the indirect immunoperoxidase method with the Ki-67 proliferation marker (Ventana, USA) followed by counterstaining with Mayer's hematoxylin. The number of immunopositive nuclei and determination of the proliferation index was performed on a Roche Benchmark XT Ventana immunohistostainer (USA). In this case, 1000 nuclei of endothelial cells and smooth myocytes (SM) were counted in capillaries, venules, and veins of the stem (SV), intermediate (IV), and terminal villi (TV). The outer and inner diameters of the veins of the chorionic plate were measured using a screw eyepiece micrometer MOV-115x. Quantitative data were processed using the variation statistics method. The significance of differences was judged by the value of the Student's t-criterion ( $p$  - value < 0.01).

## Results

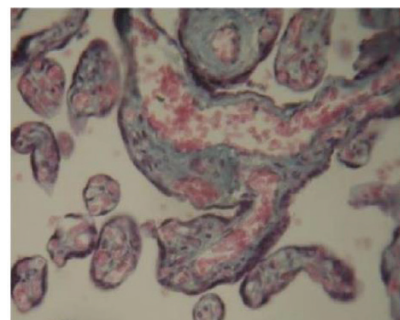
The conducted studies allowed us to establish that the SV is provided with a separate vein, artery, and capillary network of the microcirculatory bed (Figure 1).

At the base of the PV, there are individual veins of the non-muscular type, and venules of the microcirculatory link are determined in the superficial areas (Figure 2). In the TV, there are no venous vessels, only a capillary network is distinguished.

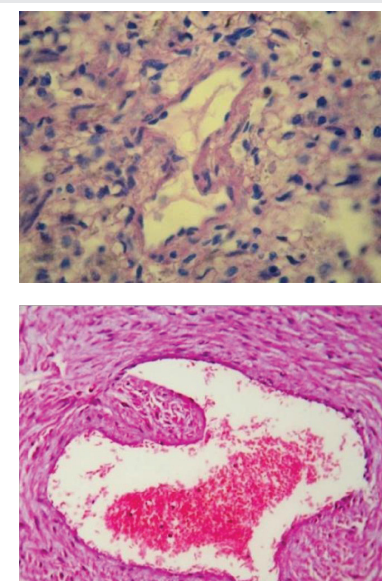
In conditions of hypoplasia of P, changes in small sections of vessels in the form of sphincter-like (SLS) and valve-like structures (VLS) are observed in the venous bed of the chorionic plate. SLS is found in the stem and intermediate villi. It is possible to distinguish two variants of SLS: sphincter rings and intimal cushions. Sphincter rings in some cases belong to the intima, are located under the endothelium, include circularly located GM, and protrude into the lumen of the vein (Figure 3).



**Figure 1:** Vein of the trunk villus. Hematoxylin and eosin staining, increase: objective 90; eyepiece 10 (×900).



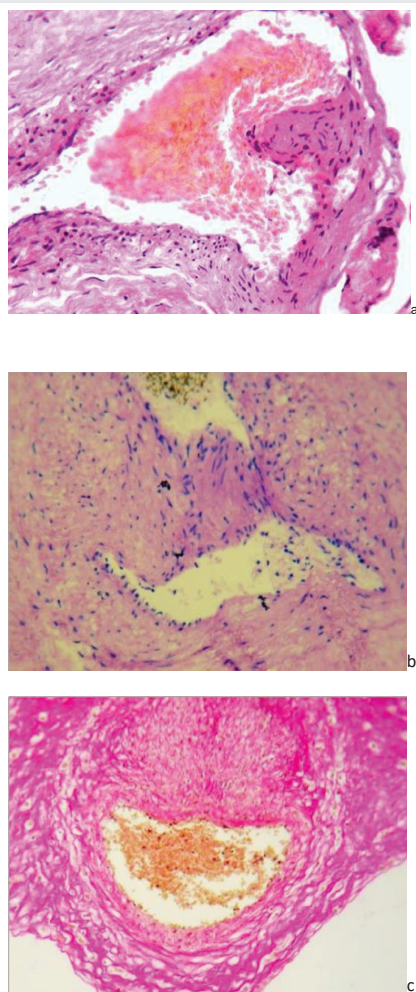
**Figure 2:** Vein and venules of the intermediate villus. Hematoxylin and eosin staining, increase: objective 40; eyepiece 10 (×400).



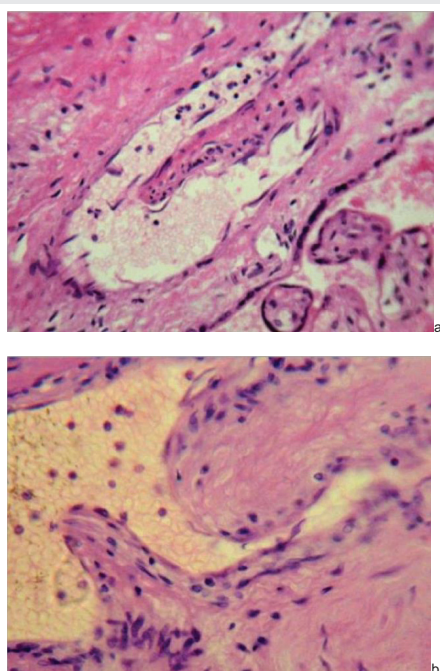
**Figure 3:** Sphincter rings in the veins of the trunk (b) and intermediate villi (a). Hematoxylin and eosin staining, increase: objective 40; eyepiece 10 (b - ×400); increase: objective 60; eyepiece 10 (a - ×600).

Intimal cushions are obturator formations in the form of a cluster of GM located longitudinally directly under the endothelium and protruding into the lumen of the vein. In parallel with this, an expansion of the vein sections located between the sphincters is noted (Figure 4).

The intimal cushions are located in small veins (Figure 5), covered with endothelium, and contain bundles of GM and collagen fibers.



**Figure 4:** Intimal cushions in the veins of the trunk (b, c) and intermediate villi (a), expansion of the vein sections between the sphincters (a, b). Hematoxylin and eosin staining, increase: objective 40; eyepiece 10 ( $\times 400$ ).



**Figure 5:** Valve-like structures in the veins of the trunk (b) and intermediate villi (a). Hematoxylin and eosin staining, increase: objective 40; eyepiece 10 (a -  $\times 400$ ); increase: objective 60; eyepiece 10 (b -  $\times 600$ ).

Morphometric analysis of the veins of the SV and PV of the chorion (Table 1) showed that hypoplasia of the P revealed a significant increase in the external and internal diameter of the veins of the SV and PV.

Proliferative activity of Ki-67 positive nuclei in vascular wall cell populations was detected in chorionic villi (Figure 6, Table 2).

The Ki67 index of immunopositive nuclei in the cell populations of venous vessels and capillaries is higher in the PV chorion. This pattern is also observed in hypoplasia of the PV (Figure 6). The maximum number of Ki-67 immunopositive nuclei was detected in the endothelium of the PV capillaries, the minimum - in the veins of the SV. Hypoplasia of P is accompanied by a reliable increase in the proliferation of the endothelium of the capillaries of the PV and TV. The level of GM proliferation in the veins of the PV exceeds the values of the indicator in the SV by 2.1 times. Under conditions of hypoplasia of P, GM proliferation increases by 1.2 in the PV and 1.3 times in the TV.

## Discussion

The conducted studies have shown that with hypoplasia of the P, there is an expansion of the external and internal diameter of the veins of the SV and PV. Venodilation in the PV with a simultaneous increase in the external and internal diameters is noted in edema, nephropathy, and combined gestosis [2]. It is emphasized that the indicated morphometric changes in the venous vessels of the P reflect the stages of a complex dynamic process aimed at maintaining the balance of the unified biological system "mother - placenta - fetus".

In the venous bed of the hypoplastic P, by the 28<sup>th</sup>-29<sup>th</sup> week of gestation, a complex of regulatory formations is

**Table 1:** Outer and inner diameter of the veins of the human chorionic villi during pregnancy at 39-40 weeks, % ( $\bar{x} \pm s_x$ ).

Group of observations		Outer diameter of veins, $\mu\text{m}$	Internal diameter of veins, $\mu\text{m}$
Stem villi	n	188.2 $\pm$ 1.6	147.7 $\pm$ 2.1
	g	207.7 $\pm$ 2.1*	179.8 $\pm$ 2.4
Intermediate villi	n	43.7 $\pm$ 0.9	37.5 $\pm$ 0.8
	g	56.1 $\pm$ 1.5*	56.7 $\pm$ 1.3*

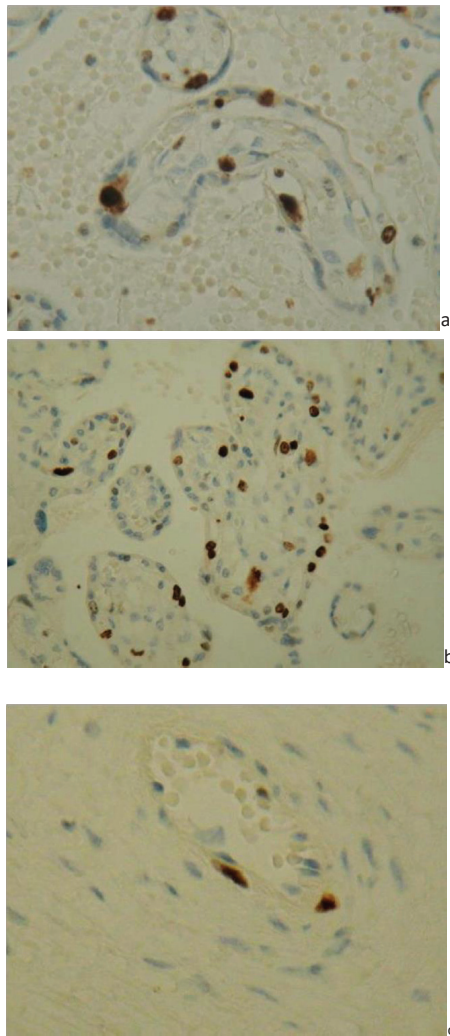
Note: Statistically significant \* at  $p < 0.01$ ; n: Normal pregnancy; g: Placental hypoplasia

**Table 2:** Ki67 index of immunopositive nuclei in cell populations of the vascular wall of human chorionic villi during pregnancy at 39-40 weeks, % ( $\bar{x} \pm s_x$ ).

Group of observations		Endothelial cells			Smooth myocytes	
		Capillaries	Postcapillaries	Veins	Postcapillaries	Veins
Stem villi	n	2.3 $\pm$ 0.3	3.2 $\pm$ 0.5	1.5 $\pm$ 0.3	0.8 $\pm$ 0.2	1.8 $\pm$ 0.3
	g	2.9 $\pm$ 0.4	3.7 $\pm$ 0.4	2.4 $\pm$ 0.3*	1.5 $\pm$ 0.2*	1.9 $\pm$ 0.3
Intermediate villi	n	5.3 $\pm$ 0.7	4.3 $\pm$ 0.4	2.6 $\pm$ 0.4	2.3 $\pm$ 0.3	3.8 $\pm$ 0.4
	g	6.9 $\pm$ 1.1*	5.4 $\pm$ 0.5*	3.5 $\pm$ 0.3*	3.1 $\pm$ 0.4*	4.7 $\pm$ 0.5*
Terminal villi	n	2.8 $\pm$ 0.3	—	—	—	—
	g	3.7 $\pm$ 0.4*	—	—	—	—

Note: Statistically significant \* at  $p < 0.01$ ; n: Normal pregnancy; g: Placental hypoplasia





**Figure 6:** Immunoexpression of the Ki-67 marker by the endothelium and smooth myocytes of capillaries and venules of intermediate (a, b), terminal (a, b), and stem (c) villi of the human chorion during pregnancy at 39-40 weeks complicated by placental hypoplasia. Immunohistochemical reaction with an antibody against Ki67 and counterstaining with Mayer's hematoxylin. Increase: objective 40; eyepiece 7 (b -  $\times 280$ ), objective 60; eyepiece 10 (a, c -  $\times 600$ ).

formed in the form of SPS and KS. SPS is found in the veins of the SV and PV in the form of sphincter rings and intimal cushions. Sphincter rings in some cases belong to the intima, are located under the endothelium, and protrude into the lumen. KS are located in the small veins of the SV and PV, their contractility is limited. KS creates a mechanical obstacle to blood flow, the degree of which is determined by their size [12]. A detailed description of the histological features and a functional assessment of the adaptive structures of the venous wall are presented in previously published monographs [12,13]. It should be noted that these data have not lost their relevance today.

It was shown earlier [14] that in the arterial pool of the fetus and P in hypoplasia, under conditions of a decrease in TV and the lumen of their capillaries, the development of a complex of GM structures of the inner lining of the vessels is stimulated. Regulatory adaptive elements involved in changing the lumen of the arteries are divided into polypoid cushions, sphincters, and GM tunica intima, promoting the rational distribution of

blood flows in the organs of the P, reducing trophic and oxygen starvation of the fetus. It should be noted that valve-like structures did not appear in the arteries of the chorion of the P [14]. Information on sphincter-like structures of the venous wall in modern literature is not numerous [1]. The authors associate these formations with ensuring local regulation of intraorgan circulation.

The conducted studies have shown that hypoplasia of the P is accompanied by an increase in the proliferation of the GM in the veins of the PV and TV. The mechanism of development of SPS and CS in the venous wall is associated with the possibility of phenotypic modification of the GM of the tunica media and their migration to the internal membrane, which is believed to be realized through an immune-mediated reaction [15]. GM in conditions of varicose veins and thrombophlebitis also demonstrates increased proliferative and synthetic capacity [16] and typical changes suggesting a transition from a contractile to a proliferative and synthetic phenotype [17].

Sphincter rings are devices for blocking blood flow. Their main purpose is to retain blood in organs and regulate local blood flow. Intimal cushions are clusters of GM located longitudinally directly under the endothelium and protruding into the lumen of the vessel. When the GM contracts, the cushions thicken and block the lumen of the veins, regulating blood filling and blood flow velocity in the organ or vessel wall [13]. The presence of locking mechanisms in the form of muscle thickenings allows for active blood deposition in certain areas of the peripheral venous bed [12,13]. This regulates blood flow, facilitating the redistribution of blood in connection with the organ's needs at any given moment. The most active redistribution of blood occurs in the peripheral circulation. Considering the large capacity of the venous bed, which significantly exceeds the volume of circulating blood, it should be assumed that the SPS is important in the redistribution of blood. Closing in some places, they retain blood in certain areas; opening in other areas, they ensure its movement in another direction [3,13].

## Conclusion

Analysis of the studied material showed that in the venous bed of the placenta under conditions of hypoplasia, venodilation of the vessels of the stem and intermediate villi is recorded with a simultaneous increase in their external and internal diameters. A complex of regulatory smooth muscle structures of the venous wall is formed. The mechanism of their development is associated with phenotypic modulation of vascular smooth myocytes. These formations contribute to the optimal distribution of blood flows in the territory of the underdeveloped placenta, ensuring the maximum possible reduction in the state of trophic and oxygen starvation of the fetus under conditions of fetoplacental insufficiency.

Dysfunctional development of the placenta underlies many pregnancy complications. Placental hypoplasia often leads to fetoplacental insufficiency and has a negative impact on fetal development and its vascular system. This study provides information that may be useful for understanding the mechanisms of the disease responsible for adverse

pregnancy outcomes, as well as for further assessment of the risk of the disease in adults. Changes in the placenta revealed during morphological examination help to clarify the causes of complications, as well as to determine the prognosis for the development of the newborn and the course of future pregnancies.

At present, much remains unknown regarding the mechanisms underlying the developmental and functional impairment of human fetoplacental vessels, especially in the context of fetal growth retardation. Thus, the study of the morphogenesis of the human placental vascular network under normal and pathological conditions is a promising and relevant direction.

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