УДК 618.36-07: 618.398
https://doi.org/10.17816/JOWD68673-86

FEATURES OF THE PLACENTA STRUCTURE IN POST-TERM PREGNANCY

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For citation: Burkitova AM, Polyakova VO, Bolotskikh VM, Kvetnoy IM. Features of the placenta structure in post-term pregnancy. *Journal of Obstetrics and Women's Diseases.* 2019;68(6):73-86. https://doi.org/10.17816/JOWD68673-86

Received: October 7, 2019 Revised: November 18, 2019 Accepted: December 12, 2019

▪ This review deals with the formation and structure of the placenta in the full-term gestational period and during post-term gestation. The results of various morphological and immunohistochemical studies are analyzed, highlighting changes in the placenta during post-term gestation and the role of expression of immunohistochemical markers, such as CD34, NO synthase, and collagen.

▪ **Keywords:** post-term pregnancy; placenta; placenta "aging"; cotyledon; fibrinoid; immunohistochemistry; CD34; NO synthase; collagen.

ОСОБЕННОСТИ СТРОЕНИЯ ПЛАЦЕНТЫ ПРИ ПЕРЕНОШЕННОЙ БЕРЕМЕННОСТИ

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Для цитирования: Буркитова А.М., Полякова В.О., Болотских В.М., Кветной И.М. Особенности строения плаценты при переношенной беременности // Журнал акушерства и женских болезней. – 2019. – Т. 68. – № 6. – С. 73–86. https://doi.org/10.17816/JOWD68673-86

Поступила: 07.10.2019 Одобрена: 18.11.2019 Принята: 12.12.2019

▪ В обзоре рассмотрены вопросы формирования плаценты, а также особенности ее строения при доношенном сроке беременности и при переношенной беременности. Проанализированы результаты различных морфологических и иммуногистохимических исследований, освещающих изменения в плаценте при переношенной беременности и роль экспрессии иммуногистохимических маркеров, таких как CD34, NO-синтаза, коллаген.

▪ **Ключевые слова:** переношенная беременность; плацента; «старение» плаценты; котиледон; фибриноид; иммуногистохимия; CD34; NO-синтаза; коллаген.

Background

Prolonged pregnancy is of great scientific and practical interest in obstetrics. This problem entails a large number of complications in childbirth and a high perinatal mortality rate. Disorders of the fetus during prolonged pregnancy are associated primarily with changes in the placenta, which have been confirmed by numerous morphological studies.

Concept of Prolonged Pregnancy

In modern obstetrics, "truly post-term pregnancy" and "prolonged (physiologically extended) pregnancy" are known concepts. A truly post-term pregnancy is a pregnancy that lasts more than 42 weeks and necessarily ends with the birth of a child with signs of postmaturity in the presence of characteristic pathological changes in the placenta (e.g., fatty degeneration of the placenta, multiple placental calcifications, and placental infarction).

A prolonged (or physiologically extended) pregnancy is twice as common as truly post-term pregnancy. A prolonged pregnancy is a pregnancy that lasts more than 42 weeks and ends with the birth of a full-term, mature child with no signs of postmaturity but also the presence of pathological changes in the placenta. Thus the final diagnosis of a prolonged pregnancy and delayed delivery is established jointly with a neonatologist only after the birth of a child, depending on the presence of postmaturity signs [1].

Placental Barrier Evolution and Placentation Options

By nature of the structure and the relationship between the chorionic villi and the tissues of the uterine mucosa in mammals, four types of placenta are distinguished. In epitheliochorial placenta (semiplacenta), the chorionic villi enter the recesses (crypts) of the uterine mucosa and come into contact only with its epithelium. Nutrients and oxygen for the developing embryo come from uterine discharge secreted by the uterine glands of the uterine mucosa. During delivery, chorionic villi are pulled out of the crypts, and the mucous membrane is not destroyed. This type of placenta is characteristic of some marsupials (badgers) and placental mammals (pigs, horses, camels, hippopotamuses, dolphins, and whales).

In desmochorial (connective tissue–chorionic) placenta, the chorionic villi penetrate the uterine mucosa, destroy the epithelium, and come into contact with the loose connective tissue of the endometrium, which is located closer to the blood channels. Moreover, the connection with the maternal organism is also not very close, as with epitheliochorial placenta, but the surface of the chorion increases. During delivery, areas without epithelium remain on the mucosal surface, which subsequently regenerate. This type of placenta is found in ruminant artiodactyls (cows and sheep).

In endotheliochorial (vasochorial) placenta, the chorionic villi destroy the epithelium and the loose connective tissue of the uterine mucosa, penetrate into the wall of the mother's vessels, and come into contact with their inner wall, the endothelium. With this type of placenta, the embryo is better provided with nutrients and oxygen, but the size of the placenta is significantly reduced. During delivery, part of the uterine wall tissue is separated from the uterine wall, and minor bleeding occurs. Subsequently, the mucous membrane of the uterus quickly regenerates. This type of placenta is typical in predatory mammals (felines, canines, and martens) and pinnipeds (seals and walruses).

In hemochorial placenta the chorionic villi penetrate through the uterine epithelium, destroy the walls of the blood vessels completely (later, blood lacunae form in their place), and are immersed in the mother's blood. The embryo is fed by osmosis (through the wall of the chorionic villi) from the mother's blood. During delivery, the entire membrane of the uterine mucosa is destroyed, and severe bleeding occurs. The regeneration takes a long time because the defect in the uterine wall is significant. There are two types of hemochorial placenta: villous and labyrinth. In the villous type, chorionic villi branch greatly, which results in a significant increase in their surface area. This type of placenta is typical in primates and humans. In the labyrinth type, contact of the trophoblast with the mother's blood results from branched protrusions of the trophoblast, which merge into a complex labyrinth of channels. This type of placenta is typical for insectivorous mammals (moles and desmans), chiropterans (bats), rodents (rats and beavers), and lagomorphs (rabbits) [2].

Four structures of placenta are distinguished depending on the shape and nature of the chorionic villi distribution. In the diffuse structure, almost the entire surface of the fetal bladder is covered with villi uniformly (diffusely). The chorion is adjacent with its entire surface to the wall of the uterus (in a pig). In the cotyledon structure, chorionic villi are grouped in cotyledons. Between them, there are no villi on the fetal bladder surface (in ruminants). In the belt structure, the chorion with branched villi has the form of a wide belt that covers the fetal bladder (in predators). In the discoidal structure, the site of the villous chorion has the shape of a disk (in baboons, anthropoid apes, and humans).

Thus in the process of evolution, the formation of the placental barrier followed the path of closest contact between the blood of the mother and the fetus. Optimal conditions in this regard

are characteristic of the hemochorial type of the placenta (in primates and rodents), when the blood flow of the mother and fetus is closest and separated only by the epithelium of the fetal capillaries, stroma, and epithelial lining of the villi (E. Govorka). Hemochorial placenta is the most advanced type of placentation that arose in the process of evolution.

Chorion and Placenta Formation

The placenta, being a provisional organ, is formed in the process of embryogenesis and fetal development, plays the role of an intermediary channel between the mother and the fetus throughout the pregnancy, and ceases functioning by the end of labor. The various functions of the placenta are closely related to its structure at different stages of development (implantation, placentation, and fetalization); in each stage, the structure of the organ is improved, depending on the needs of the growing embryo and fetus [2]. The implantation process is characterized by the formation of structures that implement close contact between the maternal and embryonal tissues. Endogenous factors (chromosomal abnormalities, primary hormonal disorders, phenotypic ontogenetic disorders with the development of secondary hormonal insufficiency) play a large role in hampering the implantation process.

In the process of chorion formation, three main periods are distinguished: previllous, villus formation, and cotyledon formation [3]. By the end of the first trimester of gestation, the placentation period of the fetal-placental and uteroplacental blood circulation ends. The cotyledons become the main structural and functional units of the formed placenta; detailed knowledge about the structure and functions of its various departments (central, peripheral, and distal) helps assess morphological changes in the placenta [4]. In the first 12 weeks of gestation, the processes of hyperplasia prevail in the placenta, and its mass increases further as a result of the hyperplasia.

The second trimester of gestation is characterized by growth and differentiation of the fetal bloodstream bed (fetalization of the placenta). During this period, morphofunctional transformations of the placenta are manifested by the convergence of the maternal and fetal blood flows and an increase in the structures involved in the interaction between them and in providing the fetus with oxygen and nutrients. Growth and differentiation of the fetal bloodstream bed are accompanied by an increase in the number of small-diameter terminal chorionic villi. The pinocytic activity of endothelial cells increases, and syncytial nodules form.

During gestation, in the course of maturation of the barrier structural elements, the thickness of these elements decreases markedly, which is associated with the movement of capillaries to the periphery of the villi and into the subcytotrophoblastic zone, with a decrease in the number of cellular elements of the stroma and the appearance of nucleus-free syncytial zones with the formation of syncytiocapillary membranes, which are specialized sites of gas exchange between the mother and the fetus. The emergence of syncytiocapillary membranes, which starts during week 32 of gestation, is a sign of placental maturity.

Placental Structure

The conduit that connects the fetus with the placenta, the umbilical cord (navel cord), normally has two arteries and one vein. Venous blood flows through the arteries from the fetus to the placenta, and arterial blood flows through the vein from the placenta to the fetus. The vessels of the umbilical cord are surrounded by gelatinous connective tissue (Wharton's jelly). In a full-term normal pregnancy, the umbilical cord is 50 to 55 cm long, and its diameter is 1 to 1.5 cm (up to 2 to 2.5 cm in the section nearest the fetus).

After week 12 of gestation, the fetal period of intrauterine development starts; it continues until the end of gestation and is characterized by the further development of the fetus and placenta. Through the placenta, the fetus is supplied with the necessary nutrients and oxygen, and the byproducts are removed [5]. In a normal gestation, the growth of the fetus and its body weight and size are related to thickness and weight of the placenta. Until the 16th week of gestation, placental development is faster than the fetal growth rate. If the embryo

or fetus dies, the growth and development of chorionic villi are inhibited, and the involutional-dystrophic processes in the placenta progress. If the fetus survives, then upon reaching the necessary maturity at the 38th to 40th week of gestation, the formation of new vessels and villi in the placenta is terminated.

The mature placenta is a disk-shaped structure with a diameter of 15 to 20 cm and a thickness of 2.5 to 3.5 cm. Its mass reaches 500 to 600 g. The main structural component of the placenta is the villous tree. There are two surfaces in the placenta: internal (fetal) and external (maternal). The maternal surface of the placenta, which faces the uterine wall, is rough, formed by the structures of the basal part of the decidual membrane [6]. On the fetal surface, which is covered with an aqueous membrane and faces the fetus, there are vessels that diverge radially from the umbilical cord and pass from the place of attachment of the umbilical cord to the edge of the placenta. The structure of the fetal part of the placenta is represented by numerous chorionic villi that are combined into the cotyledons. Each cotyledon is formed by a stem villus with branches containing the vessels from the fetus. In the central part of cotyledon, there is a cavity surrounded by plurality of villi. The mature placenta contains 30 to 50 cotyledons. The cotyledons can be compared to a tree in which the first-order supporting villus represents the trunk, the second- and third-order villi are large and small branches, the intermediate villi are small branches, and the terminal villi represent the leaves. Cotyledons are separated from each other by septa extending from the basal plate.

On the fetal side of the placenta, the intervillous space is formed by the chorionic plate and the villi attached to it, and on the maternal side, it is limited by the basal plate, decidual membrane, and septa extending from it. Most placental villi are freely immersed in the intervillous space and washed with maternal blood. Anchoring villi are fixed to the basal decidual membrane and ensure the placental attachment to the uterine wall [6].

The spiral arteries represent the terminal branches of the uterine and ovarian arteries that feed the pregnant uterus; the mouths of these vessels open into the intervillous space, providing a constant flow of oxygen-rich maternal blood into the intervillous space. Because of the pressure difference, which is higher in the maternal arterial bed than in the intervillous space, oxygenated blood is directed from the mouth of each spiral artery through the cotyledon center to the villi, washes over the villi, reaches the chorionic plate, and returns to the maternal bloodstream through the mouths of veins through dividing septa. At that point, the bloodstream of the mother and the fetus are separated from each other. Thus, the blood of the mother does not mix with that of the fetus.

Placenta in Prolonged Pregnancy

Prolonged pregnancy is a great hazard to the fetus. According to different authors, the frequency of pregnancy prolongation varies from 1.4% to 14%; the average is 8% [7]. In this condition, problems are caused by the aging and resorption of the placenta and by a decrease in the amount of amniotic fluid. The maturity of the fetal organs and systems increases the sensitivity of the central nervous system to oxygen deficiency, which can lead to fetal death even before or with the onset of labor. Among the causes of perinatal mortality, prolonged pregnancy ranks high.

The reasons for prolonged pregnancy are widely covered in the literature. It is believed that postmaturity is influenced by complex neurohumoral factors that disrupt the contractile function of the myometrium and inhibit the timely development of labor [8]. Changes in the placenta can contribute to protracted pregnancy; however, they may instead result from continuation of pregnancy past the due date.

During the period of postmaturity, the placenta weighs 100 to 400 g more than the norm, and the fetal-placental coefficient (ratio of the mass of the placenta to the mass of the fetus) is 0.12 ± 0.01.

The pathogenesis of pregnancy prolongation is largely determined by changes in the placenta [9]. At the end of a full-term pregnancy, involuntarily dystrophic processes develop in the placenta, which are genetically programmed, inasmuch as the duration for intrauterine development of a human is limited. In contrast to all other organs of the female body, the biological feature of the placenta is a short life cycle, determined by the

period of intrauterine growth of the fetus. In this connection, throughout the entire period of intrauterine development of the fetus (280 days), all stages of biological development can be seen in the placenta: growth, maturity, physiological involution, pathological aging, and termination of functioning. In case of a full-term mature fetus ready for extrauterine existence (37 to 40 weeks of gestational age), atrophic, sclerotic, and dystrophic processes develop in the placenta, similar to changes characteristic of physiological aging [10]. The fetal-placental ratio decreases to less than one-seventieth, namely from 9.3 at a term of 8 weeks down to 0.13 at a term of 40 weeks.

By the time the fetus is completely mature (38 to 40 weeks of gestational age), the growth of the placenta is complete, and its functions are increasingly limited. Chorionic basal tissue, fastened along the edge with a fibrinoid substance, do not enable the volume of the placenta to increase, even in the case of a compensatory increase (hyperplasia) of terminal villi.

Involutionary processes at the end of a full-term pregnancy that is then prolonged include circulatory, dystrophic, sclerotic, hypoplastic, and atrophic changes. Circulatory disorders include reduction of fetal-placental circulation; spasm and obliteration of the stem arteries, compensated by opening of arteriovenous anastomoses [11]; and a gradual decrease in the number of functioning capillaries and terminal capillaries. Dystrophic changes are expressed in calcification, which is accumulation of calcium salts in the placental tissue, and a decrease in the total area of villi. The average concentration of calcium in placental tissue is 4 mg/g in the first trimester, 3.65 mg/g in the second trimester, and 10.26 mg/g by week 40. With prolonged pregnancy, the 40-week concentration can increase by three times, but of most importance is that it fully reflects the rate of mineralization of the skeleton of the fetus. Calcification of the placenta is an indicator of the amount of calcium received from the mother's blood into the bloodstream of the chorionic villi. According to the literature, the absence of calcareous deposits in the placenta in a full-term pregnancy indicates either that the pregnancy has unreasonably exceeded term or that the calcium level in the mother's blood is insufficient, and therefore that the bones of the fetus (newborn) are insufficiently mineralized [12].

Sclerotic processes in the vessels of the placenta and placental bed include thickening of the vascular walls, narrowing and obliteration of the lumen, and thrombosis. Hypoplastic and atrophic changes in the chorionic villi (reduction of their diameter, stroma densification, expansion of stromal channels, thinning of the chorion epithelium, and thinning of the placental barrier) are related primarily to the fetal part of the placenta and are physiological indicators of completion of intrauterine development and preparation of the mother, placenta, and fetus for delivery.

The consequence of physiological changes in the placenta (the process of natural involution) is a decrease in intraplacental blood flow in the marginal segments of the placenta to the fetus. Blood circulation in the intervillous space of the placenta is proportionally reduced, which limits the further growth of the fetus [2].

By the time of birth, the uterus reaches the limit of stretching, in combination with a maximum increase in intra-amniotic hydrodynamic pressure. To trigger the contractile activity of the uterus and initiate labor through activity in the amnion, chorion, and decidual membranes of the afterbirth, degenerative changes occur and result in synthesis of prostaglandins of fetal origin (prostaglandin E2) and maternal origin (prostaglandin F2α). However, if for some reason labor does not develop, the physiological involutional-dystrophic processes that have begun in the placenta nonetheless progress steadily, causing aging in accordance with a given genetic program (first, in the fetus side). Their rate can be different, slow, or fast, or they can develop in a parabolic manner [9].

Evolution has provided many mechanisms to protect the fetus and preserve its vital functions. As a rule, the intensity and effectiveness of protective and adaptive mechanisms continue during the 1 or 2 weeks beyond term. If a full-term fetus remains in the uterus—that is, in case of postmaturity—the following protective and adaptive processes are intensified in the placenta, aimed at maintaining the blood supply to the fetus:

– Hyperplasia of terminal villi, accompanied by an increase in the number of functioning capillaries and expansion of postcapillary venules
– Terminal angiomatosis (the formation of vascular glomeruli, indicating an intensive process of neoangiogenesis)
– Chorionic capillary hyperplasia, which temporarily compensates for the decrease in intraplacental blood flow

The severity of these changes depends greatly on the initial state of the placenta. If delivery is delayed along with impaired development of terminal villi because of relative immaturity of the placenta (as a result of the presence of diabetes in the mother or isoimmunization), the development compensatory-adaptive mechanisms can be very limited. If, on the contrary, premature and dissociated maturation of villi occurs (as a result of hypertension or severe gestational toxicosis), then the reserve capacities of the placenta are quickly depleted [9].

The structure of the postmature placenta is heterogeneous. Most often, signs of physiological aging predominate; in other cases, on the contrary, signs of immaturity of its structures are present.

Macroscopically, during prolonged pregnancy, the placenta is thinner, its surface is rather dry, and the boundaries between the lobes are effaced and fuzzy. Meconium staining of the placenta, membranes, and umbilical cord may be observed (a consequence of fetal hypoxia). White infarctions, calcifications, and areas of fatty degeneration are visible on the placenta surface [13].

Microscopic signs of aging include fibrosis of the stroma of large and medium-sized villi; collagenization of the stroma of terminal villi, with syncytial death and deprivation of epithelium in a large number of villi; excessive deposition of fibrin around such villi; thickening of the vessel walls of large and medium-sized villi; perivascular sclerosis; endothelial proliferation, with obliteration of the vascular lumen; increased precipitation of calcium salts, with the deposition of lime in the form of clumps and "dust-like" clusters; and massive fibrinoid fields in the intervillous space.

These changes cannot be considered specific for postmaturity. They are also observed with delivery at term, as well as with various pathologic processes, especially late-stage toxicosis in pregnant women. However, unlike late-stage toxicosis, compensatory-adaptive reactions at the tissue level are not pronounced in the aging placenta. In addition, extensive new infarctions and blood clots in the intervillous space are uncharacteristic in placental aging, but lime deposits that accompany toxicosis are more pronounced in placental aging.

Placenta immaturity in pregnancy prolongation in some cases represents delay in maturation in some cases and dissociated maturation in others. Morphological studies conducted to quantify the degree of maturity and degenerative changes of syncytiotrophoblast [14] showed that the mean proportion of mature syncytium in delayed delivery decreases to 67.7% ± 0.98%, in comparison with normal delivery (82.4% ± 1.62%; $p < 0.001$). Moreover, the mean percentage of sites with preregenerative changes increases to 17.2% ± 1.47% (as opposed to 9.7% ± 1.33% with normal delivery; $p < 0.001$).

The placenta has areas of compensatory capillary hyperplasia along with immaturity phenomena in cases of pregnancy prolongation, in contrast to cases of isoserological incompatibility of mother's and fetus's blood. Compensatory growth of villi with good vascularization, and in some places with capillary hyperplasia, were observed in prolonged pregnancy in cases of live births without signs of asphyxiation. In asphyxiation or perinatal death of the fetus or a newborn, compensatory processes were not apparent, and a delay in vascularization and sclerotic changes in the stroma of the villi were detected. When pregnancy is prolonged for more than 42 weeks, hypovascularization of villi was observed, and a small number of fetus vessels were located mainly centrally [15].

In cases of antenatal death of a fetus after prolonged pregnancy, sclerosis, focal hyalinosis, fibrinoid necrosis and calcification in decidual tissue, and shaggy chorion and fetal membranes are observed. Infiltration with lymphoid and plasmocytic elements is increased in the decidual membrane and smooth chorion. The walls of the vessels of the villi are thickened and sclerosed, with hyalinosis phenomena and sometimes fibrinoid necrosis. The lumen of the vessels is narrowed or obliterated and contains thrombotic masses. Subendothelial and

subepithelial membranes are thickened, deformed and fragmented in places, and the periodic acid–Schiff reaction is markedly positive. In one study, a large number of neutral and depolymerized mucopolysaccharides were found in the sclerosed stroma of villi and the vessel wall, and high-polymer forms were revealed in terminal villi [16].

The syncytiotrophoblast is thinned; there are a lot of "naked" villi and dysfunctional syncytial nodules. In the syncytia, the content of RNA, carboxyl groups, and, to a lesser extent, sulfhydryl groups is reduced. The activity of alkaline phosphatase is increased, and the activity of acid phosphatase is uneven. The activity of sorbitol dehydrogenase, cytochrome oxidase, and nicotinamide adenine dinucleotide is reduced. A study of the content of enzymes in placental tissues showed that the amount of alkaline phosphatase in the placenta was reduced to half the normal level (to 22 ± 1.3 mg per 100 g of tissue, in contrast to the normal level of 53.24 ± 5.7 mg per 100 g of tissue) [16]. The activity of malate and lactate dehydrogenases was high, which indicates an increase in the degree of pathological processes. Stromal sclerosis was noted in the umbilical cord and in the wall of the vessels of the umbilical cord. Calcifications were revealed in connective gelatinous tissue [16].

In prolonged pregnancy, the cytoplasmic membrane of the syncytium has an uneven thickness and is destroyed in places. The endoplasmic reticulum is developed unevenly and contains a small number of ribosomes, which are often in random locations. Mitochondria are rounded, with an unevenly cleared matrix, and cristae are often destroyed. Single lysosomes are present. Large quantities of phagosomes made of granular osmiophilic material with fragments of membrane structures have been found. Nuclear membranes are in some places destroyed, and lumps of chromatin are released into the perinuclear zone. The basal membrane of the trophoblast is thickened, granular-floccose in nature, and devoid of stratification and contains individual lipid inclusions.

In the stroma of the chorionic villi, there are many swollen collagen fibers arranged in different directions. The basement membrane of capillaries has uneven thickness and structureless sites. Endothelial cells are light and contain pinosomes. Mitochondria are few and swollen, with a light matrix, and cristae are poorly expressed. Chromatin is coarse-grained and appears as clumps on the inner surface of the nuclear shell [16].

Changes in the structure of the fetal membranes include diffuse compaction of the connective tissue structures of the amnion and chorion and pronounced hydration. The total thickness of the connective tissue layer between the amnion and the chorion decreases to 30 to 40 μm (50 to 80 μm with timely delivery), which indicates a loss of sinuosity by the connective tissue fibers and reflects pronounced aging of the tissue. In addition, dystrophic changes in the cell cytoplasm and glycogen accumulation are noted [16].

A placenta with pronounced signs of aging has poor compensatory abilities for a prolonged pregnancy. The decrease in the most important functions of the placenta and the frequent emergence of signs of chronic fetal hypoxia in cases of such placentae can be explained by the absence of compensatory reactions.

The question of whether the placenta is subject to aging is still a matter of debate. There are two basic concepts that describe functional and structural changes in the placenta at the end of pregnancy. According to traditional ideas that developed as early as the beginning of the twentieth century, the involutive processes that occur in the placenta during a relatively short period of normal pregnancy reflect its "aging" as an organ. Proponents of this hypothesis believe that as the fetus matures and its own life-support systems develop, the need for trophic, hormonal, gas exchange, immune, and excretory functions of the placenta decreases. In this regard, the corresponding structures undergo physiological reduction, which starts after week 32 but is especially pronounced with a gestational age of more than 42 weeks; such reduction is manifested by a number of atrophic, sclerotic, and dystrophic processes, similar to changes that occur in the physiological aging of other organs. This point of view is based on comparison of clinical, structural, and functional data and does not take into account the differences between temporary changes in this organ and the processes of "aging."

According to another point of view, various structural lesions accumulate in the placenta by the end of pregnancy as a result of pathological changes [1]. The functional activity of the placenta decreases by the end of pregnancy, but this is not an indicator of an aging process. Some researchers have identified signs of additional adaptive maturation in an "aging" placenta. A number of structural changes that occur in the placenta from the third trimester and especially at the end of pregnancy are known as signs of placental "aging." These signs include the placenta mass lag in comparison with fetal growth, a decrease in the functional active surface of the chorion, and a decrease in the size of the intervillous space. The main manifestation of "aging" of the placenta is usually considered to be the accumulation of fibrinoid. Fibrinoid is the most common microscopic finding in examinations of the placenta. Its significance is viewed quite differently by different authors; some pay attention to the possibility of its detection in a. normal placenta, others associate it with placental "aging," and still others explain its appearance as the result of a wide variety of pathological processes.

Currently, two variants of fibrinoid are distinguished: fibrinous-type fibrinoid and matrix-type fibrinoid. The first is considered a product of coagulation of blood of maternal and fetal origin [11]. It is apparently involved in construction of the intervillous space and also protects the damaged trophoblast, playing the role of a transport and immune barrier. Matrix-type fibrinoid is a secretory product of extravillous trophoblast and contains single trophoblastic cells surrounded by the matrix. It is characterized by a positive immunohistochemical reaction with antibodies to oncofetal fibronectin, type IV collagen, and laminin, and it may performs an invasive function.

The results of morphological and histochemical studies of placentae in postmaturity indicate a decrease in activity of redox processes and decreases in the content of glycogen, in functionally active lipids, in RNA, and in neutral glycosaminoglycans.

In dystrophic processes, the transplacental transportation of the proteins of the "pregnancy zone" through damaged cell membranes and microchannels of the placenta is increased, and the level of these proteins is increased in the blood serum and decreased in the placental tissues; the level of thermostable placental alkaline phosphatase, which regulates energy metabolism, decreases, which also leads to the functional insufficiency of the placenta; and the level of trophoblastic (3-globulin and pregnancy-related p2-globulin) decreases, which results in reduction in the production of estrogens and saturation of the mother's body with them. All this confirms the presence of placental insufficiency, which is the leading pathological process in prolonged pregnancy [17].

It has been revealed that maturation and involution of the placenta is controlled by signaling molecules. The genetic development of the fetus and placenta, including invasion, differentiation, growth, and involution of the fetal part of the placenta, depends on oxygen, proteins, extracellular matrix, cytokines, growth factors, prostaglandins, and hormones. An important role in the development and involution of the villus tree is played by factors that regulate the process of vascularization and apoptosis (e.g., endothelial growth factor, factors of neoangiogenesis, and extracellular matrix). With decreases in the processes of angiogenesis and reduction of blood flow, the components of the extracellular matrix are known to be activated. However, in prolonged pregnancy, studies of the placenta at the molecular level are just beginning [13].

Immunohistochemical Markers of Prolonged Pregnancy

In recent years, much attention has been paid to diagnosing prolonged pregnancy by immunohistochemical method. One immunohistochemical marker is CD34, which is a marker for early differentiation of hematopoietic precursor cells and endothelial cells. The inducing role of endothelial adhesion molecules in the process of cytotrophoblastic invasion has been proven [2]. However, aspects of localization of placental insufficiency markers CD34 have not been fully elucidated.

A special form of CD34 was used to study placental preparations from women with physiological full-term pregnancies and to assess

the severity of vascularization in supporting, intermediate, and terminal villi [18]. This marker was observed in the endothelial lining of vessels of all types, mainly in broad arterioles and venules as part of second- and third-order supporting villi and intermediate branches. In the intermediate and terminal branches, 25% to 30% of the villi contained so-called syncytiocapillary membranes. The villi were characterized by converging, and the syncytiotrophoblast was thinned and formed the thinnest sections of the placental barrier, which would ensure maximum diffusion capacity of the placenta at the end of pregnancy. The mean area of expression of CD34 in full-term placentae was 7.8% ± 0.009% [18].

A histochemical study of placental preparations from women with prolonged pregnancy showed that CD34-immunopositive structures were chorionic villi. Narrow lumens were noted in the vessels of second- and third-order supporting villi; that is, obliterative angiopathy developed. In the intermediate and terminal branches, the immunoproliferation of the CD34 marker indicated that there were fewer syncytiocapillary membranes. The mean area of CD34 expression was significantly smaller in placentae from prolonged pregnancies than in full-term placentae (2.3% ± 0.005%; $p < 0.05$) [2].

In a study of endothelial cells, narrow lumens were found in the placental preparations from prolonged pregnancies in the vessels of the supporting and intermediate villi and in the terminal villi in the presence of a sufficient number of narrow capillaries located mainly in the center of the stroma. Syncytiocapillary membranes were not visualized because even capillaries located close to the epithelium were separated from the syncytiotrophoblast by a layer of mesenchymal cells. The mean area of expression of CD34 was significantly less than that in other clinical groups (1.2% ± 0.008%; $p < 0.05$) [1].

In all placental preparations, the expressions of CD34 coincided with those noted in a number of previous studies [2].

An analysis of the microscopic structure of the placenta revealed structural and functional changes in this organ in prolonged and truly post-term pregnancies. In normal pregnancy, the marker allows the visualization of the endothelial lining of vessels of all types, broad arterioles, and venules as part of second- and third-order supporting villi, and intermediate branches. All structural components of the placenta—namely, connective tissue, syncytiotrophoblast, and vessels—are involved in the pathological process. With prolonged pregnancy, obliterative angiopathy develops, and the number of syncytiocapillary membranes decreases. In post-term pregnancy, the gaps in the vessels of the supporting and intermediate villi are narrow; the capillaries in the terminal villi are also narrow and are located mainly in the center of the stroma of the villi. Consequently, in post-term pregnancy, structural and functional changes occur and result in placental insufficiency [19].

In the process of cell differentiation, the expression of CD34 decreases; as mentioned, the area of CD34 expression in women with normal pregnancy significantly exceeds that in women with prolonged and post-term pregnancy. Therefore, the duration and characteristics of the course of pregnancy affect the degree of vascularization of the villous chorion. Immunohistochemical changes in the localization and expression of CD34 as a marker of endothelial dysfunction indicate pronounced pathomorphological abnormalities in the placental complex in cases of prolonged and truly post-term pregnancy [18].

The literature also contains data on the determination of qualitative and quantitative parameters of the expression of nitric oxide synthase in the villous chorion as the main placental vasodilator in women of various age groups. The clinical concept of placental "aging" is based on studies of prolonged pregnancy [20]. To study the phenomenon of the placental "aging," 14 placentas were obtained from women with prolonged pregnancy with fetuses of a gestational age of 42 weeks, the expressions of specific markers in mature and post-term placentae were compared [21]. Expression of prolactin, melatonin, CD34, nitric oxide synthase, CD35, the myeloid cell leukemia 1 (Mc1-1) gene, and p53 was detected in all preparations in post-term pregnancy. All the markers studied were visualized in the same

structures of the villous chorion in placentae from prolonged pregnancies as those from placentae from full-term pregnancies. Statistical analysis of the data did not reveal significant differences in the values of optical density or in the areas of area of all immunohistochemical markers between the placentae from full-term pregnancies and those from prolonged pregnancy.

Thus a quantitative and qualitative analysis of the expression of CD34 and nitric oxide synthase revealed no differences in the degree of expression of these markers in the villous chorion in full-term and prolonged pregnancies, which indicates functional maturity but not "aging" of the placenta. The results obtained expand the idea of morphofunctional changes in the placenta that relate to the age of the pregnant woman, which should be taken into account in obstetric and gynecological practice to increase the effectiveness of therapeutic measures.

As a result of analyses of the influence of a pregnant woman's age on the functional activity of the placenta and of placenta functioning in a prolonged pregnancy, I propose my own hypothesis of placenta "aging" [21]: Placental "aging" is related more to the general condition of the pregnant woman's body than to gestational age; in other words, placental "aging," like any organ in the pregnant woman's body, occurs according to its biological age.

This theory has been confirmed by the numerous morphological findings in pregnant women older than 40 years, mentioned previously, such as increased content of fibrinoid, thinning of the epithelial layer of villi, and a decrease in expression of hormones and biologically active substances as a result of age. The lowest rates of the hormones studied and of biologically active substances have been recorded in women older than 40 years, and the highest were registered in women of younger reproductive age. A decrease in the proliferative activity of the placenta and an increase in cells with programmed cell death also indicate degenerative processes in this organ, progressively increasing with the increase in age of a pregnant woman. Thus the mother's age has a direct effect on the degree of vascularization of the villous chorion [21].

Among local placental vasodilators, endothelial nitric oxide synthase is of greatest importance. Immunohistochemical studies revealed that tests in syncytiotrophoblasts, syncytiocapillary membranes, and endothelium of villi capillaries yielded immunopositive reactions with antibodies to endothelial nitric oxide synthase. Thus age-related processes in the placenta are manifested by a complex of changes that capture all the structural units of the placenta: namely, connective tissue and trophoblast, cell membranes, and the circulatory system. The most important result of the development of age-related changes is insufficient vascularization of the placenta [22].

The authors of another study reported on structural foundations that determine functional changes in placental insufficiency [23]. The main structural collagen that forms the placenta framework is known to be type I collagen. It is expressed in the anchor and basal parts of the villi—namely, in the central part of the villi of the paracentral zones—and it is not expressed in the peripheral zones of the cotyledons.

In the marginal zones, type I collagen is also expressed in the central part of the villi, but to a lesser extent than in the paracentral zone. All this indicates that collagen is insufficiently expressed in the central part of the placenta and its structure in this area is unstable. In areas where the collagen network is not developed, the placental development is disrupted, the rigid collagen structure is poorly developed in the central zone, and it is quite well developed in the villous tree of the paracentral and marginal zones [23].

Type III collagen is distributed quite unevenly in the placenta. In both the paracentral and marginal zones, placental areas were found in which its expression was completely absent. Through quantitative microphotometry, it was demonstrated that the levels of type III collagen in different parts of the placenta can differ by two to four times, which indicates the adaptive variability of the placenta's structure, which is associated with the differential zonation of type III collagen expression. Because type III collagen is characteristic of embryonal and fetal skin and blood vessel walls, its distribution in the placenta is atypical in comparison with the

rest of the mother's body and clinically correlated with the asphyxiation of children during birth. Immunohistochemical studies have shown the influence of types III and IV collagen expression on perinatal outcome, thus revealing tendencies associated with the expression of type III collagen, as well as certain patterns regarding type IV collagen, which is considered the most stable and uniformly distributed in the placenta villi from the central to the marginal zones. Type IV collagen is expressed in the walls of capillaries and blood vessels; therefore, it is traditionally considered the collagen of the vascular bed. This expression occurs not only around the vessel located inside the villi but also in the mesenchymal wall of the villi, which increases the elastic strength of the villi; however, in the absence of types I and III collagen, the mechanical stability of cotyledons is reduced. Expression of type IV collagen is associated with pathogenetic processes in the placenta, which is most clearly seen in the placentae of children with an unfavorable course during early neonatal adaptation. A large amount of this collagen was revealed in the marginal foci of placental involution. If the villus tree is destroyed, type IV collagen is found in fibrin and destroyed villi. Thus type IV collagen is the main component of the destroyed areas of the placenta, which probably enables it to maintain elasticity.

Using monoclonal antibodies to detect types I, III, and IV collagen in the placenta, researchers showed that reduced or abnormal expression of types I and III collagen prevents the creation of a rigid placental framework [23]. Type III collagen demonstrated the maximum topological variability in expression, and its synthesis differed several times in the central, paracentral, and marginal zones of the placental villi. In some parts of the placenta, type III collagen may be absent. In that study, type IV collagen was found in the marginal foci of involuted placentae. Replacing structure-forming collagens of types I and III, type IV collagen plays a role in compensation. The presence of this type of collagen indicates that the compensatory mechanisms of the fetus before delivery are at risk of disruption. All this determines the severity of placental insufficiency, ultimately affecting the outcome of pregnancy for the fetus and newborn [23].

In the course of the literature review, it becomes obvious that the topic of prolonged pregnancy and the placental structure in prolonged pregnancy, as well as the immunohistochemical study of the placenta, have not been not fully studied issue, and the continuation of research is necessary for this urgent issue.

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