PLACENTAL INVOLVEMENT IN ABNORMAL NEONATAL OUTCOME

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Abstract

The present study looks at the most frequent alterations of the placenta with direct influence upon neonatal outcome and premature birth by treating some aspects like placental adaptation during pregnancy, hemodynamic modifications of the placenta, neonatal morbidity and histopathological alterations with direct impact on preterm birth.

Histopathological alterations of the placenta are a subject that should be known not only by the pathologist but most important by the obstetrician and pediatrician in order to consolidate to reduce the risk of preterm birth and neonatal outcome complications.

In an effort to contribute to this purpose, this article collects and examines some of the aspects found in the literature.

Rezumat

Studiul de fată descrie principalele aspecte histopatologice placentare ce au influentă directă asupra aparitiei unor afectiuni neonatale si asupra nasterii premature. Sunt tratate unele aspecte precum adaptarea placentei în timpul sarcinii, hemodinamica placentară, morbiditatea neonatală si modificările histopatologice cu impact direct asupra nasterii premature.

Modificările histopatologice placentare ar trebui cunoscute atât de pediatru cât si de obstetrician în încercarea de a crea si consolida mecanisme de prevensie care să ducă la reducerea riscului nasterii premature si a complicatilor neonatale.

In efortul de a aduce o mica contributie acestui scop, acest review examinează succint o parte din aspectele tratate în literatura de specialitate.

Cuvinte cheie: placenta, morbiditate neonatala, modificari histopatologice, hemodinamica

Introduction

The survival and development of the human body during pregnancy depends on several factors including the suppression of immunological mechanisms and by creating new ways that would allow the exchange of metabolic substances and will prevent luteolisys [1].

The placenta represents the physical and functional bonding between the maternal organism and the developing fetus. By receiving and processing its metabolic needs, the growth and functionality of the placenta are coordinated to ensure the exchange of nutrients and excretion products between maternal

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and fetal circulatory systems [2]. The placenta is an endocrine organ, with role for synthesis and selective transport of hormones and neurotransmitters. In recent years, findings based on placental lesions described by pathological examination have contributed to a better understanding of some obstetrical pathology such as preeclampsia, fetal growth restriction and preterm birth [3].

Abnormal placental performance may result in severe morbidity or mortality of both mother and fetus. For example, placental insufficiency is a significant health risk trigger for the mother and neonate, evidence suggesting a long-term health connection with the occurrence of cardiovascular disease at adult age [4].

However, the pathological examination of the placenta is rarely requested by the obstetricians and furthermore, when requested, the results of placental examination are reported back only to the Gynecology department, instead of also passing it on to the pediatricians.

Awareness among pediatricians about the benefits of placental findings for neonatal care is limited. Informations on placental lesions can often be helpful towards explaining an abnormal neonatal outcome and might have consequences for treatment.

Placenta examined by the pathologist frequently derives from a preterm birth. Fetal adnexa resulting from a term birth are not sent for examination by routine. The neurologic prognosis cannot be established immediately after birth but long after the majority of the placenta can no longer be examined, loosing important information [5].

This article provides a review that emphasizes the placental roles and adaptation during the pregnancy and highlights the relation between placental lesions described by pathological examination and neonatal mortality and morbidity.

Adaptation of the placenta during pregnancy

As a response to external factors, the placenta adapts its function and architecture to the fetal needs. A great percentage of the nutritive substances from the mother are consumed by the placenta in the growth processes and into the transport function [6].

Among the weight and morphological features, the placenta suffers architectural changes of the chorionic villi as the pregnancy progresses. The coordinated development of the branching of villi it's a necessary condition to the growth and development of the fetus. Before reaching the fetal viability, the fetal vessels branch out inside of the mature intermediate villi, forming 10-16 generations of stem villi.

Once fetal viability is reached, a change is produced, consisting in the forming of a larger number of mature intermediate villi. This type of villi is constituted of a capillary axis without branches in which the longitudinal growth overcomes the one of the actual villi, resulting in terminal villi.

Feto-placental capillaries from the villi are separated from the maternal blood inside the intervillous space only by one thin layer of syncytiotrophoblast. The development of terminal villi is exponentially growing in the second trimester, being characterized by the predominance of angiogenesis without branching [7].

Similar to the umbilical cord vessels, the arteries and the arterioles inside the stem villi are not influenced by the autonomic nervous system, but by the smooth muscle tissue, paracrine interactions of the endothelium and the arterial branching pattern. For example, the first anomaly present in intrauterine growth restriction was the decrease of arterial density in stem villi [8].

Fetal development determines increased placental surface. In the third trimester of pregnancy the growth of terminal villi is accentuated. At term placental surface available for transport reaches 13 m2. This increase is essential in order to assure the nutrient needs of the fast-growing fetus. Practically, is taking place an increase in the placental surface and a decrease in diffusion distance [8,9].

Twin pregnancies are representing a stress factor for the uterine arteries and the placenta, especially the monochorionic ones, a high risk of preterm birth being well known in literature. Unfortunately, there is few data regarding placental histology in twin pregnancies. An increase in

chorioangiogenesys and acceleration of villi maturation in comparison with singleton pregnancies has been found. Chorangiosis represents a histological characteristic defined by an exaggeration in placental angiogenesis, present in post term pregnancies or associated with gestational diabetes. In these cases, the accelerated maturation of villi is not present [6].

Hemodynamic modifications of the placenta

Normal pregnancy involves two major exchanges taking place in the maternal cardiovascular system. First, the uterine blood flow is increased and maternal blood flow towards the placenta is established. In a second step, hemodynamic changes in the maternal circulation are present: blood volume and cardiac debit are increasing rapidly while blood pressure decreases. This apparent paradox is determined by a profound decrease in systemic vascular resistance together with a decrease of blood viscosity due to hemodilution. This adjustment is synergic in promoting an efficient blood supply to the developing fetus [10].

Numerous complications associated to pregnancy, including first and second term miscarriages, IUGR, early onset preeclampsia, preterm birth and preterm rupture of membranes are associated in different degrees with disturbances in the process of transformation of spiral arteries and placental vascular bedding [11-13].

Spiral arteries need to adjust in such manner that increased volume of blood is reaching the intervillous space, but at the same time to maintain adequate pressure. Therefore, spiral arteries conversion is the key in obtaining full term pregnancies [10].

In the absence of pregnancy radial and spiral arteries are high in smooth muscle fibers and have rich autonomic innervation [14,15]. During pregnancy, a series of changes take place according to trimester: in first trimester extra villous trophoblastic cells migrate in the spiral artery lumen and the interstitial trophoblastic cells migrate in the endometrial stroma. During normal pregnancy interstitial trophoblastic cells pass through the internal third of the myometrium and progressively transform in giant cells, lacking motility [16].

Both invasions: endovascular and interstitial are associated with physiological conversion of the spiral arteries even though the molecular mechanisms involved in this process remain uncertain [17,18] . Arteries lose their smooth muscle layer and the elastic lamina and as a result they expand and stop responding to external and internal stimuli. The described process varies in intensity being more accentuated in the central region of the placenta where the trophoblastic invasion is more extensive.

Although this invasion does not take place in the arcuate nor uterine arteries they are expanded during pregnancies, particularly right beneath the implantation site [19,20]. This non trophoblastic expansion is more likely a combined response to hormonal stimuli and nitric oxide, uterine blood flow increasing from approximately 45ml/min in follicular phase to 750ml/min at term [21,22].

In midterm pregnancy the diameter of the arcuate arteries overlaps the one of the uterine arteries, and at term they double their lumen in comparison with the latter.

The purpose of the trophoblastic invasion is the decrease in risk of spontaneous vasoconstriction, assuring an uninterrupted vascularization of the placenta. For the majority of pregnancies an intermittent placental perfusion may have minimal consequences, due to the fact that intervillous blood may assure proper contribution of oxygen and nutrients to the placental tissue until circulation is resumed. Fluctuations in oxygen concentration are an important placental oxidative stress inductor which may lead to significant physiological consequences [23].

The expansion of the distal segment of the spiral arteries decreases flow resistance in these vessels, this process being illustrated by ultrasound measurements. Physiologically, until 22-24 weeks of gestation there will be decreased diastolic flow with the presence of protodiastolic notch. After 24 weeks of gestation the diastolic flow increases, resistivity index decreases (under 0,6 after 26 weeks of gestation) and the protodiastolic notch disappears [23].

Pathological aspects at Doppler examination are represented by the persistency of the protodiastolic notch after 26 weeks of gestation and the increase in the resistivity index. These are significant for impaired trophoblastic invasion associated with decreased compliance of the maternal vessels and decrease in utero-placental circulation.

Alterated placental circulation also influences the umbilical arteries, these modifications (resulting in a decrease of the placental bedding due to thrombosis) are represented by the absence of the telediastolic flow and the presence of reverse flow. The latter underline a more severe alteration in the umbilical circulation and is translated in IUGR and acute fetal distress [23].

Placental lesions and neonatal morbidity

a) Consequences upon the lungs

Pulmonary development and neonatal respiratory issues such as respiratory distress syndrome and bronchopulmonary dysplasia are associated to placental inflammations. Evidences suggest that respiratory distress incidence is reduced in neonates exposed to chorioamnionitis [24,25]. The beneficial effect may be explained by the increase in beta interleukin 1 with role in protein and lipid synthesis in the surfactant in the bronchoalveolar liquid in presence of chorioamnionitis. The latter stimulates the release of cortisol that accelerates pulmonary maturation, resulting in decrease of respiratory distress incidence. Mesenchymal pulmonary tissue is quantitatively reduced, with an increase in gas exchange surface and pulmonary air space. Practically the result is, a lung with better compliance and more surfactant that assures a more efficient gas exchange [26-28].

An ascending uterine infection may also have a negative effect on the new born premature lung, particularly on long term [26]. Chorioamnionitis may increase the risk of bronchopulmonary dysplasia that worseness progressively during the postnatal period, in spite of a good initial respiratory response [29]. Being a multifactorial pathology, difficulties in correlating bronchopulmonary dysplasia to chorioamniotic infection exist [30].

b) Gastrointestinal consequences

Ulcero-necrotic enterocolitis is a pathology that frequently affects a preterm neonate, considered to be of multifactorial etiology.

Numerous studies have shown an association between ulcero-necrotic enterocolitis and placental lesions, particularly obstructive vascular ones (thrombotic vasculopathy, villi congestion, coagulopathy). The presence of ischemia was proposed as an explanation for the etiology of this pathology [31].

c) Preterm retinopathy

Preterm retinopathy is associated with placental lesions, particularly inflammatory ones. These affect preterm neonates and cause chaotic development of retina vessels, leading to scaring and detachment of the retina.

Etiology of the preterm retinopathy is multifactorial but at least a part is due to inflammation mediated by cytokines and growth factors found in the neonate's circulation [32]. The severity of the retinopathy is correlated with an ascending intrauterine infection [33].

d) Cardiac and vascular consequences

Fetal cardiac anomalies are associated with thrombotic fetal vasculopathy most frequent being the septal defects (atrial and ventricular), cardiomegaly and coarctation of the aorta [34].

Fetal thrombotic vasculopathy, refers to recent or remote thrombosis (umbilical vessel, chorion or stem villi) and / or secondary degenerative pathology in fetal vascularization, at distance from the site of thrombosis. May appear as hemorrhage, vasculopathy, endovascular fibrin deposits and fibromuscular hypertrophy [5].

e) Neurological consequences

Regarding the short term neurological prognosis, the majority of the studies insisted on the pathology regarding the white matter: periventricular leukomalacia, intraventricular hemorrhage. Correlations between ascending intrauterine infection and short term neurological prognosis were found, neonatal encephalopathy being associated with fetal thrombotic vasculopathy [31,35].

Histopathological alterations with direct impact on preterm birth

Preterm birth is defined as birth occurring between 20 and 37 weeks of gestation. In WHO reports is mention that in developing countries approximatively 12% of births occur preterm meanwhile in developed countries 9% of babies are born before 37 weeks of gestation [36].

Preterm newborns are susceptible to numerous pathologies correlated with incomplete development of some organs, neurocognitive alterations and ocular pathologies. Beside these consequences preterm birth has also a strong psychological impact on parents and also on society especially economical.

Considering the consequences of preterm birth, risk factors responsible for this pathological complex where widely studied.

The placental factor was included as a risk factor for preterm birth, representing the main cause of early neonatal mortality and morbidity worldwide.

Placental anomalies associated to preterm birth refer to the morphology, implantation and function of the placenta, such as: placenta previa, retroplacental hemorrhage and placental insufficiency [23] Besides this, infectious diseases may induce preterm birth by hyperthermia or by the intrauterine infection that may occur.

a) Histological diagnosis of chorioamnionitis

There are no clinical criteria universally accepted regarding the definition of chorioamnionitis or ascending amniotic infection. The detection of chorioamnionitis is made by following the serum levels of reactive protein C.

The criteria vary depending on examiner and part of the challenge resides in low sensibility of clinical criteria in comparison to the laboratory criteria considered to be gold standard: cultures from the amniotic fluid, PCR of bacteria DNA and histopathological exam of the placenta.

Histology of the placenta has a negative predictive value superior to the other paraclinical criteria. Therefore certainly, in the absence of the chorioamnionitis it may be useful to search other causes of preterm birth [6]

Infections associated to pregnancy that affect the placenta and have ascending progression, are more likely of bacterial etiology. Placental infections due to hematogenous spreading, are more frequently of viral or parasitic etiology. Rarely, an infection following a diagnostic procedure, through direct seeding is possible.

The most frequent etiology is represented by infections originated in the vagina/ cervix and spreaded to the amniotic fluid. The presence of the infectious agent induces an acute inflammatory response primarily the maternal neutrophils being recruited, followed by the fetal ones.

It is estimated that approximately 50-60% of the placentas resulted in premature birth are presenting characteristic findings of amniotic inflammation. In the majority of the cases it is considered that the infection preceded and most probably caused the premature rupture of the membranes.

The presence of fetal inflammatory response, mainly in combination with the extent of the inflammation in one or more arteries are indicator factors of fetal exposure to the infection and possible fetal complications. The old term of funisitis is currently used to describe the presence of neutrophilia in Wharton jelly. The term used for this pathology is fetal vasculitis if two or more arteries are involved and arteritis if only an artery is affected or phlebitis if only the vein is affected [37].

Histological, acute chorioamnionitis can be divided into two components: maternal and fetal

inflammatory response. In the majority of these cases the etiology remains unknown, but sometimes it can be related to maternal hypertension, preterm birth and IUGR [38].

b) Histological diagnosis of reduced uteroplacental perfusion

Reduced uteroplacental perfusion is representing an abnormal exchange of nutrients, due to placental abnormalities, leading to fetal and maternal complications associated with pregnancy. Traditionally, these complications were considered to be preeclampsia and IUGR.

The leading causes of reduced uteroplacental perfusion are not completely understood but is considered that the most important mechanism is abnormal remodelling of uterine spiral arteries. This fact contributes to an abnormal blood flow to the placenta [6]. The altered flow has an overall negative effect on pregnancy, including preterm birth.

Reduced uteroplacental perfusion was defined by histological criteria and by macroscopic examination as:

1) abnormally large or small placentas
2) presence of placental ischemia
3) vasculopathy of decidua arteries
4) the histology of placental villi [39,40].

These characteristics are correlated with the severity and chronicity of reduced uteroplacental perfusion. For example, a trauma can lead to placental abruption with a retroplacental hematoma attached to placenta but with normal weight and architecture of it. The retroplacental surface covered by the hematoma is corelated with the outcome of the pregnancy in these cases .

The presence of a chronic process is associated with changes in the tissue architecture, ischemia and changes in placental dimensions. In complicated cases with reduced uteroplacental perfusion, a reduced uterine surface and small infarct areas can be seen [39].

In preeclampsia, the placenta is not smaller than it should be for gestational age infarction areas do not appear, and the most frequent histological association is the accelerated villi maturation. This aspects appear in IUGR and in preterm births which are not correlated with infection [39-40].

Accelerated villi maturation is a histological representation of adapted placenta to the reduced uteroplacental perfusion. Although is considered to be a subtle modification, sometimes is the only sign in preterm births not associated with infection.

In severe cases of IUGR with early onset of reduced uteroplacental perfusion a pattern called distal mature villi hypoplasia emerges [39].

The moment of installation and the severity of reduced uteroplacental perfusion appears to be correlated with the same physiological mechanism found in preeclampsia, preterm birth and IUGR [39].

These complications can be determined by the same process, variations are due to: parity, diet, race, fetoplacental index [6]. Ultrasound studies have shown that the difference in utero-placental resistivity is closely related to the onset of preterm birth [42].

There are multiple serum proteins associated with reduced uteroplacental perfusion that suggest common molecular path ways [43]. Genetic studies try to identify genes involved in reduced uteroplacental perfusion or associated to a certain infection susceptibility [44].

Conclusions

Although certain associations between neonatal pathology and placental lesions exist, various studies are necessary to confirm the existence of these correlations. Placental histology in preterm births represents a controversial subject in which certain details remain still unknown.

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