INTRA–AMNIONIC INFECTION IN PLACENTAL INSUFFICIENCY AND FETAL RETARDATION

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Fetal retardation is one of the main reasons for perinatal morbidity and mortality. It is a universal reaction, developing in the fetus because of alimentary and oxygen insufficiency, with a decrease in metabolic processes under low placental perfusion.

The placenta is a highly particularized and relatively independent organ that affects the interaction between the fetus and the mother. In physiological conditions the mother-placenta-fetus hemodynamic functional system is well adapted to progressively increasing fetus needs and creates the possibility for the normal development of the fetus under conditions of odiverse environmental changes.

Hemodynamic disorders in the blood circulation of the uteroplacental and fetoplacental as developed against a background of implantation and placentation process derangements, play the main role in the pathogenesis of fetal hypoxia, which leads to a statural-weight value and functional maturing delay of the vital systems and organs of the fetus.

Placental insufficiency normally develops during pregnancy, complicated with the gestosis, miscarriage, extragenital diseases, which present such vascular disorders as essential hypertension and kidney diseases. In addition, this syndrome development occurs in multiple pregnancies, in hemolytic fetus disease and in pathogenic influences, including, stress on the mother and fetus. One of the primary reasons for placental insufficiency is infection. The development of placental insufficiency due to the exposures of the mother to the different factors is a universal reaction. One of the main manifestations of this reaction is disturbance of the main functions of placenta, namely blood circulation.

Intra-amniotic infection occurs when pathogenic organisms damage the fetal membranes, decidua and amniotic fluid. Microorganisms in the amniotic fluid may induce biosynthesis of proinflammatory cytokines, which stimulate the fetal systemic inflammatory response. Until the late 1970s, intact fetal membranes were considered an important barrier to infection of the amniotic fluid and to provide sterile conditions for the growing fetus. Bacterial colonization of the amniotic fluid was presumed to develop only after initiation of labor or rupture of the membranes at or close to term. However, further investigations indicated that this conjecture was erroneous. Amniotic fluid infection was found in 10% of term pregnancies with intact membranes and in 30% of pregnancies with ruptured membranes.

Chorioamnionitis and amniotic fluid infection may be present with or without clinical signs in both mother and fetus. Clinical signs of these conditions could cause an increase in the mother's temperature during either pregnancy or labor, more often with premature membrane rupture. However, we could observe silent (subclinical), intra-amniotic infection with no obvious clinical signs. Clinical cases are observed in 0.5 – 1 % of all pregnancies. In women patients with microbial invasion of the amniotic fluid, only 15 – 55 % exhibit clinical signs of infection. Thus, the mere presence of bacteria in the amniotic fluid is not a sufficient indicator to cause intra-amniotic infection or preterm labor.

Chorionamnionitis is usually revealed after histological examination. Its frequency is about 50 % in preterm labor and 20 % at term. Intra-amniotic infection presents in a morphological examination as an acute diffusive inflammatory process in the extraplacental membranes, chorionic plate of the placenta and umbilical cord. If bacteria are recovered from the amniotic fluid, the condition is defined as amniotic fluid infection. Bacteria could be not found in the amniotic fluid, however.

Amniotic infection is considered one of the main reasons for preterm deliveries, causing one third of such deliveries to occur. At the same time, up to 25 % of women in preterm labor with intact membranes show a positive amniotic fluid culture. The rate of positive amniotic fluid cultures in women without clinical signs of infection varies from 5 to 13 %. Simultaneously, adverse pregnancy outcomes are observed in patients with amniotic fluid infection.

Infection of the amniotic cavity and its contents is a serious complication in pregnancy, affecting both mother and fetus. Maternal consequences are a heightened risk of fever during labor, postpartum endometritis and sepsis. In the case of abdominal delivery these risks are likely to increase.

Microbial contamination of the amniotic cavity highly increases perinatal morbidity and mortality. It has long been known that prematurely born neonates from mothers with amniotic infec-

tion are more likely to have congenital pneumonia, omphalitis, meningi tis, respiratory distress syndrome, low Apgar scores, fetal or neonatal sepsis, with further development of bronchopulmonary dysplasia and necrotizing enterocolitis. High neonatal morbidity is the result of its development under conditions of placental insufficiency, often followed by chronic hypoxia, which may lead to preterm labor and hence to prematurity, immaturity of organs and systems, fetal retardation and, in some cases, destruction of surfactant by aspirated bacteria. Results from several recent reports suggest that long-term consequences of amniotic fluid infection could be severe neurological abnormalities in children, including cerebral palsy, pereventricular leukomalacia and intraventricular hemorrhage. It has been shown that neonates born from women with urogenital infections more often had abnormalities in the coordinating and integration function of central nervous system development with a discernible delay in tonic and reflex reactions. Neonatal nervous system damage could also be caused by maternal mediators of infection, including pro-inflammatory cytokines (interleukin, IL-1, IL-6 and IL-8), tumor necrosis factor (TNF-α) and bacterial endotoxin.

There are three known avenues of bacteria penetration into the fetal bladder: ascension (from the lower genital tract), hematogenous (from the mother) and iatrogenic (the bacterial invasion of the amniotic fluid during invasive diagnostic procedures). In most cases, infection passes to the amnion in an ascendant manner. This will usually occur during labor because of the prolonged rupture of the membranes. However, passage of the bacteria could also occur in women with intact fetal membranes. The source of hematogenous penetration is maternal bacteremia. In this way Listeria mocytogenes, a group of streptococci and Campylobacter, can enter into amniotic fluid. The reasons for iatrogenic bacterial infection are the invasive prenatal diagnostic and treatment procedures (amnio- and chordocentesis, chorion- and placentobiopsy, intrauterine transfusions) and monitoring of the fetus with direct cardiotocography after membrane rupture.

Microbial invasion of the amniotic cavity could induce an inflammatory response by producing pro-inflammatory cytokines (IL-1, IL-6, IL-8 and TNF-α) from placental and decidua tissue, chorion and amnion. The cytokines stimulate prostaglandins production, which increases myometrial contractility, resulting in preterm labor. Most fetuses aspirate the infected amniotic fluid and concurrently the fetus begins to produce pro-inflammatory cytokines. These mediators play an important role in the development of a systemic inflammatory response in the fetus.

The microorganisms that take part in the realization of the intra-amniotic infection are similar to those in other obstetric infections. There are two main groups of bacteria that could be found in two thirds of the women. The first group refers to microorganisms, which are associated with bacterial vaginosis (*Gardnerella vaginalis*, genital micoplasmas and anaerobes); the second group consists of gut-associated aerobic bacteria (*Escherichia coli*, Gram-negative rods and Gram-positive cocci). Anaerobic infection is believed to lead to preterm labor and premature membrane rupture while aerobic infection is one the primary reasons for pyo-septic diseases in mothers, fetuses and neonates. In addition, viruses (e.g., Ciromegalovirus, Parvovirus B19, Herpesvirus) play an important role in the etiology of the intra-amniotic infection. These pathogenic organisms could be the reason for severe fetus affection (such as non-immune hydrops) that could lead to negative perinatal outcomes right up to ante- and postnatal death.

A diagnosis of intra-amniotic infection is difficult to make. The exception is the clinically evident cases in which a pregnant woman has such clinical signs as fever, maternal and fetal tachycardia and prolonged duration of membrane rupture. Most of the cases are subclinical and preterm labor is the only visible sign of the infection.

Concerning pathogenic organisms, bacteriological investigation of the vagina and cervix flora could be used. However, laboratory examination of amniotic fluid is the most specific means of evaluating these organisms. Transabdominal amniocentesis under direct ultrasound guidance allows appropriate samples to be obtained for bacteriological culture, Gram staining, microscopy and biochemical tests. Gram staining is used for uncentrifuged specimens in order to determine the presence of bacteria. The calculation of the polymorphonuclear leukocytes in the investigation of amniotic fluid and bacteriological culture of the amniotic fluid is used for identification of the aerobic and anaerobic bacteria and genital mycoplasmas. Waiting for the identification of the organisms, however, might cause a delay in making proper therapeutic decisions. Until recently, it was possible to verify the fetal pathogenic organism (especially viral) only in fetal blood samples received during chordocentesis. Nowadays, with the advent of polymerase chain reaction (PCR), it is possible to identify the viral, bacterial and parasite genome fragments in the amniotic fluid.

Biochemical analysis of amniotic fluid in patients with suspected intra-amniotic infection is aimed at

obtaining information about infectious markers produced by the maternal host and the fetus or information about metabolites produced by the invading organisms. Maternal markers include proinflammatory cytokines (IL-1α, IL-1*B*, IL-6, IL-8 and TNF) and prostaglandin E2. Elevated levels of these substratums appear in the amniotic fluid one week before preterm labor or histological chorionamnionitis. The strongest predictor of adverse maternal and fetal outcome is IL-6.

Both tests are simple and sensitive markers of intra-amniotic infection. It is also possible to analyze the glucose level and the presence of organic metabolites of pathogenic bacteria in the lower genital tract using liquid chromatography. Inflammatory reaction could be investigated directly in the fetal blood that is collected by chordocentesis. Moreover, blood analyses, analyses of fetal blood gases, pH and concentration of IL-6 in plasma could be done simultaneously.

Thus, intra-amniotic infection is important in the pathogenesis of placental insufficiency, determining adverse perinatal outcomes and high pyo-septic morbidity in pregnant women and puerperas. Modern bacteria verification would help to prescribe timely pathogenetic therapy, which plays a chief role in reducing perinatal morbidity and mortality.

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