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The role of the placenta in feto-neonatal infections

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ABSTRACT

The placenta and membranes may be infected by ascending bacteria from the maternal birth canal or by bacteria, virus and protozoa via haematogenous spread. The maternal and fetal inflammatory reactions, elicited by these microorganisms, are often associated with precise anatomo-pathological findings.

Furthermore, it has been demonstrated a strong relationship between placental inflammation and important perinatal adverse outcomes, including neurologic impairment and chronic lung disease.

For this reason, placenta examination is an important approach for understanding infection and/or inflammation leading to fetal inflammatory response syndrome. For instance, chorioamnionitis caused by ascending infections are characterized mainly by polymorphonuclear leucocytic infiltration of the extraplacental membranes, firstly involving the lower-pole of the amniotic sac, then the intervillous space and later the chorionic plate. In fact, there is an initial "maternal inflammatory response" (MIR) to the infection and leucocytes migrate from the maternal blood stream. Subsequently, the chorionic plate is infiltrated by leucocytes derived from the fetal vessels, and this event characterizes the "fetal inflammatory response" (FIR). The release of proinflammatory cytokines and chemokines within the gestational sac is the leading cause of fetal and neonatal damage.

In conclusion, certain placental reaction patterns may identify and estimate the risk for specific perinatal complications in infants.

The placenta and membranes represent an important barrier that prevents transmission of some microorganisms, but allows others to reach the fetus. They may be infected by a variety of routes; the most frequent include ascending polymicrobial infection from the maternal birth canal in the setting of membrane rupture, that is generally attributed to enterococci, coagulase-positive staphylococci, anaerobic streptococci and *Escherichia coli*. Placental infection can even occur with intact membranes, and this appears to be especially common for *Ureaplasma* species and *Mycoplasma hominis*, found in the lower genital tract of over 70% of women. Infection by *Candida albicans* is uncommon, since the pH of the amniotic fluid inhibits the growth of fungi, while the only virus identified as a possible cause, with a plasmacellular infiltrate, is herpes simplex. Only rarely the infection of amniotic fluid has been attributed to hematogeneous via, as occurs with *Listeria monocytogenes*. Organisms can also reach the placenta through a direct spread from an endometrial infection, which is uncommon as generally the inflammation itself avoids the possibility of a correct implantation. Other rare routes include iatrogenic infection complicating amniocentesis or chorionic villous sampling, anterograde infection from the peritoneum via the fallopian tubes and transmission by spermatozoon [1].

Host defense mechanisms preventing intra-amniotic infection remain poorly elucidated, but specific local host factors likely play an important role. The cervical mucous plug as well as the intact membranes provide a physical barrier to infection of the amniotic fluid and fetus [2].

The presence of infectious agents in the placental membranes engenders a maternal and fetal inflammatory response characterized by the release of proinflammatory and inhibitory cytokines and chemokines within the gestational sac.

The chorion amnion has properties of an immunologically privileged site, since it is designated to protect the allogeneic fetus from rejection by the mother.

When intrauterine inflammation is present, the fetus may be exposed through infected amniotic fluid and/or inflammatory cell transfer from the uteroplacental circulation and subsequently develop a systemic inflammatory response, known as "fetal inflammatory response syndrome" (FIRS) [3].

Upon entry of microorganisms into the placental membranes, both maternal and fetal inflammatory responses are dominated by activation of neutrophils and other components of the innate immune system. On the contrary, the adaptive immune system results to be downregulated; indeed T- and B-lymphocytes and activated macrophages are generally absent [4]. "Acute chorioamnionitis" (ACA) is the pathologic term describing this kind of inflammatory reaction, that generally occurs in the second half of pregnancy. Its prevalence is inversely proportional to gestational age ranging from >50% at viability (23–24 weeks) to 5% at term (>37 weeks) [5].

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The frequency of chorioamnionitis varies markedly by diagnostic criteria, specific risk factors and gestational age. Chorioamnionitis complicates 40–70% of preterm births with premature membrane rupture or spontaneous labor and 1–13% of term births [2].

The association between prolonged rupture of membranes and chorioamnionitis has long been recognized, but in recent years increasing evidence also suggests that ascending genital tract infection may be a cause, rather than a result, of premature rupture of the membranes in preterm gestations. It has been suggested that bacterial infection of the membranes may lead to their premature rupture because of the release of elastases and collagenases from the neutrophil polymorphonuclear leucocytes infiltrating the membranes. Besides, bacteria, by themselves, also diminish the tensile strength and elasticity by the release of proteolytic enzymes.

The relationship between chorioamnionitis and premature onset of labor with intact membranes is more complex. There is considerable evidence that infection is associated with a greatly increased production of cytokines by activated macrophages, including interleukin-1, interleukin-2, tumour necrosis factor, granulocyte colony stimulating factor, interleukin-8 and, most importantly, interleukin-6, that can stimulate prostaglandin synthesis by the amnion and decidua, and inhibit progesterone synthesis, directly eliciting uterine contractility [6,7].

Placenta examination is an important approach for understanding infection and/or inflammation leading to FIRS, providing useful information regarding the aetiology, prognosis and recurrence of pregnancy disorders.

All possible histologic gradations of intensity (grade) and progression of disease (stage) for maternal and fetal inflammatory responses are potentially relevant to clinical outcome. Histologically inflammatory lesions in ascending infections are mainly localized in membranes and chorionic plate while the placental parenchyma inflammation characterizes the haematogenous spread [1].

In ascending infections the main microscopical feature is the presence of polymorphonuclear leucocytic infiltration of the extraplacental membranes: firstly involving the lower-pole of the amniotic sac, then the intervillous space and later the chorionic plate.

Initially the response to the infection is maternal (maternal inflammatory response, MIR) and leucocytes derive from the maternal blood stream, subsequently is fetal (fetal inflammatory response, FIR): leucocytes start to migrate from the fetal vessels towards the chorionic plate (funisitis). Pathognomonic in this sense is the vasculitis limited to the vessel in the chorionic plate which does not extend to the whole placental parenchyma. The prevalence of the FIR increases with both gestational age and severity of the MIR. Moreover, endothelial activation associated with the FIR may promote the formation of chorionic vessel thrombi, which can even embolize to the fetus [4].

In literature many attempts to classify chorioamnionitis have been made. According to Redline et al., maternal and fetal stages were assigned depending on location of polymorphonuclear leukocytes and eventual karyorrhexis of the same, and on absence/presence of necrotizing inflammation. Maternal and fetal grades, instead, were based on maximum polymorphonuclear leukocytes/high-powered field and typology of leucocytes [8].

Fetal exposure to infection may lead to fetal and neonatal death, fetal growth restriction, fetal hypoxia, neonatal sepsis and numerous other postnatal complications.

There is an excess incidence of neonatal asphyxia in those cases of chorioamnionitis associated with delivery before the 35th of gestation, since intra-amniotic infection stresses the fetus, leading to villous oedema, which compresses the fetal villous vessels with resulting diminished fetal oxygenation. Moreover, a mild degree of amniotic fluid infection could predispose the fetus to hypoxia by increasing its metabolic and oxygen demands. In addition, breathing amniotic fluid that contains high quantities of cytokines and prostaglandins could alter fetal pulmonary vasculary resistance and affect fetal and feto-placental hemodynamics. In fact, Kovo et al. demonstrated that intrauterine inflammation, in pregnancies complicated by non-reassuring fetal heart rate patterns during labor, in addition to low cord blood pH, may be also be associated with fetal acidemia, which can sometimes lead to neonatal morbidity and mortality [9].

Overall, chorioamnionitis is associated with up to 40% of cases of early-onset neonatal sepsis, due to the spread of infection to the fetus from the inflamed membranes. The fetus may inhale infected amniotic fluid and develop a congenital pneumonia, while entry of the fluid into the upper respiratory tract can cause meningitis. The fetal skin or eyes can be infected by direct contact with organisms in the fluid, which is probably the aetiological mechanism in a proportion of cases of neonatal pyogenic dermatitis or ophthalmia. Swallowing of the fluid may be responsible for some cases of neonatal gastritis, enteritis or peritonitis. It should be stressed that all these unfortunate complications occur infrequently in chorioamnionitis; on the other hand they rarely occur in its absence [1,6].

Aside from the risk of fetal sepsis, the fetal inflammatory response may induce cerebral white matter injury, intraventricular hemorrhage, and periventricular leukomalacia, which may result in cerebral palsy and other short and long-term neurological deficits. The potential mechanisms of brain injury include cerebral hypoperfusion and ischemia, activation of blood coagulators resulting in capillary thrombosis and necrosis of white matter, and increased permeability of the blood brain barrier, allowing direct passage of microbial products and cytokines into the cerebral tissue.

There have also been a number of claims that chorioamnionits is linked with the development of bronchopulmonary dysplasia, retinopathy of prematurity and impaired renal function [6,10].

At last, different clinical studies have investigated the relationship between ACA and the immune system. De Felice et al. highlighted a reduction of thymus size and a loss of FoxP3 positive lymphocytes in preterm babies after ACA [11]; while Toti et al. suggested a depletion of T-and B-lymphocytes from the spleen [12], that can eventually be related to an ultrasound evidence of pulsation of the fetal splenic vein in women with ACA [13].

In conclusion, improved antenatal screening for chorioamnionitis and identification of effective treatment strategies for preterm infants exposed to intrauterine inflammation will likely provide a better prognosis for infants at risk of multiple organ disease as a result of exposure to inflammation before birth [10].

Conflict of interest

The authors declare no conflict of interest.

References

[1] Fox H, Sebire N. Pathology of the placenta. Infections and inflammatory lesions of the placenta. Saunders Elsevier, 2007;303–34.
[2] Soper DE, Mayhall CG, Dalton HP. Risk factors for intraamniotic infection: a prospective epidemiologic study. Am J Obstet Gynecol 1989;161:562–6.
[3] Blanc WA. Amniotic infection syndrome; pathogenesis, morphology, and significance in circumnatal mortality. Clin Obstet Gynecol 1959;2:705–34.
[4] Redline RW. Inflammatory response in acute chorioamnionitis. Semin Fetal Neonatal Med 2012;17:20–5.
[5] Becroft DM, Thompson JM, Mitchell EA. Placental chorioamnionitis at term: epidemiology and follow-up in childhood. Pediatr Dev Pathol 2010;13:282–90.
[6] Galinsky R, Polglase GR, Hooper SB, Black MJ, Moss TJ. The consequences of chorioamnionitis: preterm birth and effects on development. J Pregnancy 2013;2013:412831.
[7] Holzman C, Lin X, Senagore P, Chung H. Histologic chorioamnionitis and preterm delivery. Am J Epidemiol 2007;166:786–94.

[8] Redline RW, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C; Society for Pediatric Pathology, Perinatal Section, Amniotic Fluid Infection Nosology Committee. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2003;6:435–48.
[9] Kovo M, Schreiber L, Ben-Haroush A, Klien H, Wand S, Golan A, et al. Association of non-reassuring fetal heart rate and fetal acidosis with placental histopathology. Placenta 2011;32:450–3.
[10] Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clin Perinatol 2010;37:339–54.
[11] De Felice C, Toti P, Santopietro R, Stumpo M, Pecciarini L, Bagnoli F. Small thymus in very low birth weight infants born to mothers with subclinical chorioamnionitis. J Pediatr 1999;135:384–6.
[12] Toti P, De Felice C, Occhini R, Schuerfeld K, Stumpo M, Epistolato MC, et al. Spleen depletion in neonatal sepsis and chorioamnionitis. Am J Clin Pathol 2004;122:765–71.
[13] Musilova I, Kacerovsky M, Hornychova H, Kostal M, Jacobsson B. Pulsation of the fetal splenic vein—a potential ultrasound marker of histological chorioamnionitis and funisitis in women with preterm prelabor rupture of membranes. Acta Obstet Gynecol Scand 2012;91:1119–23.