The significance of amniotic fluid immunological analysis for the prediction of intrauterine infection

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Summary

Intrauterine infection, a dangerous condition for a pregnant woman and her fetus, increases the risk of neonatal death and the incidence of severe diseases like cerebral palsy, chronic lung illnesses and psychomotor disorders. Better prediction of intrauterine infection would support the choice of an appropriate treatment plan during pregnancy and suitable healthcare for the mother and newborn after birth. Herein, we review the immunological analysis of amniotic fluid for prediction of intrauterine infection and survey advances in the field that are bringing us closer to clinical implementation.

Key words: Intrauterine infection; Chorioamnionitis; Preterm birth.

Introduction

Intrauterine infection, also known as chorioamnionitis, is a dangerous condition for the health of a pregnant woman and her fetus. It complicates about 40%-70% of preterm births with premature rupture of membranes (PROM) or spontaneous labor [1]. Intrauterine infection is associated with fetal inflammatory response syndrome, which leads to severe multiorgan (brain, lungs, kidney, heart) injury and a more than 2.4-fold increase in the risk of neonatal death [2]. If intrauterine infection is suspected, it is recommended to discontinue the pregnancy due to the aforementioned health problems. However, preterm newborns are born morphologically and functionally immature. Fetal respiratory function is the last to mature, so there is a higher risk of neonatal respiratory distress syndrome because of immature lungs in preterm birth [3]. For this reason, the management of preterm premature rupture of membranes requires balancing the benefits of pregnancy prolongation and the risk of intrauterine infection.

Diagnosis of chorioamnionitis is based on the Gibbs criteria, introduced more than 40 years ago. Gibbs criteria consist of maternal fever (> 37.8 °C) and at least two of the following criteria: maternal tachycardia (> 100 beats per minute), maternal leukocytosis (white blood cell count), uterine tenderness, fetal tachycardia (> 160 beats per minute) and foul-smelling amniotic fluid [4]. Many studies have indicated that the conventional criteria are limited because of low sensitivity and specificity for detecting chorioamnionitis [5-7] (Table 1).

Imprecise diagnostic criteria have led to a continued search for more specific methods to detect intrauterine infection. Nowadays, more attention is given to how changes of immunological markers in amniotic fluid can predict intrauterine infection since many immune system components that protect the fetus against infection can be found in amniotic fluid.

Immunological Markers in Amniotic Fluid

Cytokines are small proteins, secreted by cells, that regulate intracellular functions [8]. Specific membrane receptors mediate their action and activate intracellular pathways. Cytokines also regulate the immune response to infection helping to preserve pregnancy [9]. However, some inflammatory cytokines are responsible for the development of preterm labor.

Interleukins are the group of cytokines that can predict intra-amniotic infection. There are several interleukins that could be associated with the inflammatory process, but interleukin-1β (IL-1β) seems to be the dominant one for prediction of preterm as well as term labor associated with infectious progression and can be useful for a diagnosis of intra-amniotic infection [10]. Puchner et al. reported that for every increased unit of amniotic fluid IL-1β women were 7.2 times more likely to deliver preterm [11].

Most IL-6 found in amniotic fluid is produced by the amnion and is released in response to infectious stimuli [12, 13]. When compared to non-laboring women, IL-6 is found to be increased in both preterm and term births. A systematic review revealed that elevated mid-trimester amniotic fluid IL-6 levels were associated with spontaneous preterm birth when no prior symptoms manifested [14]. Some studies analyzed IL-6 levels in cases complicated with preterm PROM. Some of these authors state that IL-6 alone cannot significantly predict intra-amniotic inflammation (IAI) in patients with preterm PROM and are only useful in prediction of preterm labor in cases with intact membranes [15].
Clinicians have suggested an amniotic fluid IL-6 cut-off value ≥ 745 pg/mL for the detection of IAI in patients with preterm PROM [16]. Moreover, an amniotic fluid IL-6 cut-off value > 1,000 pg/mL is also useful in the prediction of microbial invasion of the amniotic cavity (MIAC) or histologic chorioamnionitis (HCA) [17] (Table 2).

Tumor necrosis factor-α (TNF-α) is an inflammatory cytokine that plays an important role in the initiation of labor. TNF-α normally is not detected in amniotic fluid during the second and third trimester. This cytokine is important in the pathogenesis of infection-associated preterm labor, while the presence of infection induces the production of this cytokine [18]. TNF-α is also a valuable predictor of chorioamnionitis in cases with preterm PROM [15, 19]. A study by Thomakos et al. found that amniotic fluid TNF-α concentration > 6.3 pg/mL could be a good predictive factor for a positive amniotic fluid culture in mid-trimester pregnancy [20] (Table 2).

Matrix metalloproteases (MMP) are a group of extracellular matrix mediators that can be found in amniotic fluid and are responsible for rupture of membranes. Cytokines are mainly responsible for the control of MMP functions [21]. Elevation of MMP-8 concentrations in the second trimester of pregnancy can strongly predict intra-amniotic inflammation, spontaneous preterm delivery and adverse neonatal outcomes in pregnancies complicated with PPROM [21, 22]. Chaemsaithong et al. in their study of a rapid test of amniotic fluid MMP-8 found that a cut-off value of 10 ng/mL has enough high sensitivity and specificity (85.7% and 72.8%, respectively) for the detection of IAI [23] (Table 2).

Human beta defensins (HBD) are a group of antimicrobial peptides that are synthesized by epithelial cells and neutrophils [24]. Two main defensins are HBD-2 and HBD-3. They act like attractants facilitating the interaction between the acquired and innate immune system [25]. Moreover, HMB2 has antimicrobial activity against Gram-negative bacteria and, to a lesser extent, Gram-positive bacteria [26]. Both main HBD are found in higher concentrations in pregnancies with intra-amniotic infection [27, 28]. Iavazzo et al. investigated HBD-2 in amniotic fluid and their findings demonstrated that HBD-2 was associated with PPROM, but not with preterm labor [29]. The study of Lucovnik et al. demonstrated that elevated levels of amniotic fluid neutrophil defensins (HNP1-3) were associated with histologic chorioamnionitis and can predict infant death or neurological impairment [30]. The study of Espinoza et al. showed that amniotic fluid HNP1-3 levels with a cut-off value of 7.8 ng/mL could be a good predictive factor for MIAC [31] (Table 2).

Soluble Toll-like receptors (sTLRs) are transmembrane receptors that can recognize and respond to microorganisms and also control the activation of an adaptive immune response [32]. These sTLRs can be activated by ligands from many microbes (bacteria, viruses, fungi, parasites). sTLRs-2 is mainly stimulated by lipoproteins and lipopeptides found in the outer membranes of Gram-positive bacteria [33]. Furthermore, sTLRs-2 is a component of amniotic fluid in healthy pregnancies. Its levels increase up to 30 weeks of gestation and decrease thereafter towards term [34]. A study by Kacerovsky et al. investigated sTLRs in amniotic fluid and stated that elevated levels of sTLRs, es-
References


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Conflict of Interest

The authors declare no conflict of interest.
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