Amniotic fluid biomarkers in the diagnosis of intra-amniotic infection in preterm singleton pregnancies

-Association with microbial invasion of the amniotic cavity and histologic chorioamnionitis

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Abstract

Chorioamnionitis, the main single cause of preterm delivery, which occurs in 10 to 13% of deliveries annually worldwide, can be subdivided into clinical and subclinical forms. The latter is more common and includes intra-amniotic infection (IAI), inflammation, and histologic chorioamnionitis (HCA). Diagnosing subclinical chorioamnionitis is necessary for optimal timing of delivery. Amniotic fluid (AF) biomarkers allow gathering of information on the inflammatory status of the uterine cavity.

The aim of the study was to evaluate AF biomarkers in the diagnosis of intra-amniotic infection.

The study was conducted at the University Hospital of Helsinki, Finland, Department of Obstetrics and Gynecology, between March 2012 and October 2015. The study population comprised 155 cases with a suspicion of IAI or preterm prelabor rupture of the membranes (PPROM) and 46 controls. Amniocentesis was performed in 105 cases between 22+0 and 36+5 weeks of gestation and in 46 controls. AF was obtained vaginally from 53 cases. In such AF samples, AF-lactate dehydrogenase (AF-LD) and AF-Glucose concentrations were determined. Determination in amniocentesis samples was of AF-LD, AF-Glucose, AF-matrix metalloproteinase (MMP)-8, AF-cathelicidin, AF-MMP-9, AF-myeloperoxidase, AF-interleukin-6, AF-neutrophil elastase (HNE), AF-elafin, AF-MMP-2, AF- tissue inhibitor of matrix metalloproteinases -1 (TIMP-1), AF-MMP-8/TIMP-1 molar ratio, and AF-C-reactive protein (CRP) levels. AF-MMP-8 measurement was by an immunoenzymometric assay, AF-LD and AF-Glucose by immunochemiluminometric assays, and others by commercial ELISA. Microbiological analyses were based on molecular microbiology and culture techniques. An experienced pathologist performed placental histopathologic examination. Data on pregnancies came from the hospital database.

The most optimal cut-off value based on the ROC-curve for AF-LD in vaginally obtained AF against HCA was 1029 IU/L with a sensitivity of 65% and specificity of 69%. In such samples, glucose concentrations did not differ between women with or without HCA. In amniocentesis samples, AF-LD and AF-Glucose correlated with HCA and MIAC, and the most optimal cut-off values for both end-points were a respective 429 IU/L and 0.7 mmol/L. When AF-LD and AF-Gluc concentrations were adjusted by gestational age at amniocentesis, the association disappeared. The concomitant use of AF-LD and AF-Glucose provided no additional value. AF-MMP-8, AF-cathelicidin, AF-MMP-9, AF-MPO, AF-IL-6, AF-Elafin, AF-HNE, and AF-TIMP-1 were associated with MIAC, but AF-MMP-2 and AF-CRP were not. The results were similar also when adjusted by gestational age at amniocentesis. Neutrophil-produced biomarkers were associated with IAI. MIAC occurred equally often in pregnancies with PPROM and with intact membranes. Infection and inflammation were more common at lower gestational ages.

In conclusion, the accuracies of AF-LD and AF-Glucose were quite poor, meaning that better biomarkers for IAI diagnostics are essential. None of the other biomarkers studied out-performed others, and larger studies are needed to confirm and further extend our results. However, IAI seemed to be associated with neutrophil activation. The usefulness of each biomarker for clinical purposes depends more on local circumstances, laboratory method availability, and the clinicians´ familiarity with each biomarker than on exact differences in accuracy.