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The inflammatory milieu of amniotic fluid in acute-chorioamnionitis decreases with increasing gestational age

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ABSTRACT

Introduction: The inflammatory milieu decreases in the placenta and amniotic fluid (AF) with gestational age (GA). However, there is no information about whether the inflammatory milieu of AF in the setting of the same placental inflammatory condition decreases with GA. We hypothesized that the inflammatory milieu of AF in acute chorioamnionitis would decrease with increasing GA.

Methods: The inflammatory milieu of AF was examined in 617 singleton preterm pregnancies (<36 weeks) delivered within 5 days of amniocentesis. Study population was divided into GA at delivery ≤30 weeks (n = 148), 30–34 weeks (n = 226), and 34–36 weeks (n = 226). Acute-chorioamnionitis was classified according to the severity (i.e., mild, total grade 1; moderate, total grade 2; and severe, total grade 3–6) or involved compartment (i.e., chorionic plate, amnion and chorio-decidua). The inflammatory milieu of AF was determined by matrix metalloproteinase-8 (MMP-8) concentration.

Results: 1) AF MMP-8 concentrations decreased in patients with acute-chorioamnionitis ($P < 0.001$), but not inflammation-free placenta, with increasing GA; 2) AF MMP-8 concentrations were less intense at higher GA in patients with moderate and severe (each-for $P < 0.005$), but not mild, acute-chorioamnionitis; 3) AF MMP-8 concentrations decreased in the context of the same involved compartment (i.e., chorionic plate inflammation, amnionitis, or chorio-deciduitis) of acute-chorioamnionitis (each-for $P < 0.001$) with increasing GA; 4) Moreover, there was a significant inverse relationship between GA and AF MMP-8 concentrations in patients with acute-chorioamnionitis ($r = -0.453$, $P < 0.0000001$), but not inflammation-free placenta ($r = -0.071$, $P = 0.170$).

Discussion: AF MMP-8 concentrations in acute-chorioamnionitis distinctly decrease throughout preterm-gestation. This finding suggests that the inflammatory milieu of AF decrease in acute-chorioamnionitis with GA.

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1. Introduction

Acute-chorioamnionitis is more frequent in pregnant women with lower gestational age (GA) at delivery [1–3]. Moreover, previous studies demonstrated the lower GA, the higher frequency of intra-amniotic infection and inflammation in patients with preterm labor and intact membranes (PTL) [4] and preterm premature rupture of membranes (preterm-PROM) [5]. However, we have not found any studies examining whether the intensity of AF inflammation changes throughout gestation even when controlling for the placental inflammatory condition.

Placental function changes with GA [6,7]. Of note, the inflammatory milieu of placenta and AF decreases throughout normal pregnancy as in the following [8–13]. Firstly, oxidative stress significantly decreases and anti-oxidant level progressively increases in the placenta of normal pregnancies with GA [8] and in the AF of patients with preterm-PROM regardless of intra-amniotic infection and acute-chorioamnionitis throughout the preterm period [9]. Oxidative stress induces chemokine expression and oxidative phospholipid leading to pro-inflammatory cytokine response [14], and anti-oxidant suppresses pro-inflammatory cytokine response to lipopolysaccharide (LPS) in both the placenta and AF of rats [15] and in the human fetal membranes [16]. Secondly, apoptosis increases in the extra-placental membranes and placenta of human pregnancies with increasing GA [10,11]. This finding is also identified in normal pregnancies with the use of in vivo ^{31}P-MR spectroscopy [12]. Moreover, apoptosis-inducer such

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as TNF-related apoptosis-inducing ligand (TRAIL) increases in AF from mid-pregnancy to term of normal pregnancy [13]. In general, apoptosis actually blocks the production of pro-inflammatory cytokines and induce the production of anti-inflammatory factors [17,18]. Therefore, given that the inflammatory milieu of placenta and AF decreases throughout normal pregnancy [8–13], it is plausible that the inflammatory milieu of AF decreases with increasing GA even when pregnant women have the same placental inflammatory condition. We hypothesized that AF matrix metallo proteinase-8 (MMP-8) concentrations, as a measure of the inflammatory milieu of AF, in acute-chorioamnionitis would decrease with increasing GA. The objective of current study is to examine this issue.

2. Methods

2.1. Study design

Study population consisted of 617 singleton preterm-pregnancies who delivered before 36 weeks and within 5 days of amniocentesis at the Seoul National University Hospital between January 1993 and December 2007. This criterion of amniocentesis-to-delivery interval was used to preserve a meaningful temporal relationship between the results of AF and the pathologic findings of placenta obtained at birth. AF MMP-8 concentrations, as a measure of the inflammatory milieu of AF, were compared according to GA at delivery in patients with the same severity (i.e., mild, moderate and severe) and involved compartment (i.e., chorionic plate inflammation, amnionitis and chorio-deciduitis) of acute-chorioamnionitis. Study population was divided into 3 groups according to GA at delivery: 1) GA at delivery $\leq$ 30 weeks ($n = 148$); 2) 30 weeks < GA at delivery $\leq$ 34 weeks ($n = 226$); and 3) 34 weeks < GA at delivery < 36 weeks ($n = 243$). At our institution, amniocentesis for the retrieval of AF was routinely offered to all patients who were admitted with the diagnosis of PTL and preterm-PROM for the identification of intra-amniotic infection or inflammation, and was also performed to assess fetal lung maturity in patients with maternal–fetal indication such as preeclampsia. Moreover, we routinely recommended and performed placental pathologic examination in all preterm pregnancies. Written informed consent was obtained from all patients. The Institutional Review Board of Seoul National University Hospital approved the collection and use of these samples and information for research purposes. The Seoul National University has a Federal Wide Assurance with the Office for Human Research Protections (OHRP) of the Department of Health and Human Services of the United States. The Institutional Review Board of Seoul National University Hospital specifically approved this study.

2.2. Acute-chorioamnionitis and funisitis

Placental tissue samples obtained for pathologic evaluation included chorio-amniotic membrane roll (chorio-decidua and amnion), chorionic plate, and umbilical cord. These samples were fixed in 10% neutral buffered formalin and embedded in paraffin. Sections of prepared tissue blocks were stained with hematoxylin and eosin. Pathologists were masked to the clinical information. Acute-chorioamnionitis was defined in the presence of acute inflammatory changes on examination of chorio-amniotic membrane roll and chorionic plate of the placenta, and the presence of acute inflammation in chorio-decidua, amnion and chorionic plate was classified as grade 1 or 2 according to the previously published criteria [19] as in the following; 1) amnion, grade 1: at least 1 focus of >5 neutrophils, and grade 2: diffuse neutrophilic infiltration; 2) chorion-decidua, grade 1: at least 1 focus of >5 neutrophils, and grade 2: diffuse neutrophilic infiltration; and 3) chorionic plate, grade 1: >1 focus of at least 10 neutrophilic collections or diffuse inflammation in subchorionic fibrin, and grade 2: diffuse and dense inflammation, neutrophilic infiltration into connective tissue of placental plate, or placental vasculitis. Total grade was used to determine the severity of acute-chorioamnionitis from 1 to 6 according to the criteria previously reported [19]. Acute-chorio amnionitis was divided into mild acute-chorioamnionitis when the total histologic grade was 1, moderate acute-chorioamnionitis when the total histologic grade was 2, and severe acute-chorio amnionitis when the total histologic grade was equal or higher than 3. Funisitis was diagnosed in the presence of neutrophil infiltration into the umbilical vessel walls or Wharton's jelly, and classified as grade 1 or 2 according to the previously published criteria [19] as in the following; 1) grade 1: neutrophilic infiltration confined to umbilical vessel walls, and 2) grade 2: extension of neutrophilic infiltration into Wharton's jelly. Funisitis was classified separately from acute-chorioamnionitis, as it is a fetal rather than maternal inflammatory response.

2.3. AF study

AF was cultured for aerobic and anaerobic bacteria and for genital mycoplasmas (Ureaplasma urealyticum and Mycoplasma hominis) for the evaluation of intra-amniotic infection according to the methods previously described [20]. Positive AF culture was defined in the presence of aerobic or anaerobic bacteria, or genital mycoplasmas. The remaining fluid was centrifuged and stored in polypropylene tubes at −70 °C. The inflammatory milieu of AF was determined by MMP-8 concentration. Among study population ($n = 617$), 592 patients were included in the analysis of AF MMP-8 concentration, because the test of AF MMP-8 concentration was not performed in 25 patients due to the limited amount of the remaining fluid. MMP-8 concentration in stored AF was measured with a commercially available enzyme-linked immunosorbent assay (Amersham Pharmacia Biotech, Inc, Little Chalfont, Bucks, UK). The sensitivity of the test was <0.3 ng/ml. Both intra- and inter-assay coefficients of variation were <10%. Details about this assay and its performance were previously described [21].

2.4. Statistical analysis

Kruskal–Wallis test was used for the comparisons of continuous variables, and post-hoc tests were performed by Dunn's multiple comparison test. Comparisons of proportions were performed with Pearson's chi-square test. The linear by linear association was used as the test for trend. Spearman's rank correlation test was used for the identification of the relationship between AF MMP-8 concentrations and GA at delivery. Statistical significance was defined as $P < 0.05$.

3. Results

Table 1 compared the clinical characteristics and pregnancy outcomes according to GA at delivery. Lower GA at delivery was associated with a higher rate of positive AF culture, acute-chorioamnionitis, and inflammation in each compartment (i.e., funisitis, chorionic plate inflammation, amnionitis and chorio-deciduitis) (each for $P < 0.005$; by both Pearson's chi-square test and linear-by-linear association) (Table 1). Moreover, there was a significant difference in the frequency of moderate and severe (each for $P < 0.05$), but not mild, acute-chorioamnionitis according to GA at delivery (Table 1). However, we did not find a significant difference in the total grade of severe acute-chorioamnionitis between each group according to GA at delivery (Table 1, $P > 0.05$). Of

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