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CLINICAL ARTICLE

Clinical and prognostic value of combined measurement of cytokines and vascular cell adhesion molecule-1 in premature rupture of membranes

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ABSTRACT

Objective: To evaluate whether levels of interleukin 6 (IL-6), interleukin 8 (IL-8), and vascular cell adhesion molecule-1 (VCAM-1) in women with premature rupture of membranes (PROM) differ from those in women without PROM. *Methods:* An observational study of full-term primiparous pregnant women with PROM (PROM group) and those undergoing elective cesarean delivery (control group) was performed at a center in Yangzhou, China, between January 2003 and July 2006. IL-6, IL-8, and VCAM-1 levels were measured in maternal blood, cord blood, and amniotic fluid. A pathologic examination of fetal membranes was conducted. *Results:* The IL-6, IL-8, and VCAM-1 levels in maternal serum, amniotic fluid, and cord blood were significantly higher in the PROM group ($n = 58$) than in the control group ($n = 38$; $P < 0.05$ for all comparisons). In the PROM group, the levels increased with duration of membrane rupture ($P < 0.05$ for all). Women with chorioamnionitis had significantly higher levels than women without chorioamnionitis ($P < 0.05$ for all), and women with PROM whose newborns had low Apgar score (≤7) had higher levels than those whose newborns had a higher Apgar score ($P < 0.05$ for all). *Conclusion:* Combined measurements of IL-6, IL-8, and VCAM-1 might help to improve early diagnosis of PROM and chorioamnionitis, and to evaluate the prognosis of newborns.
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1. Introduction

Premature rupture of membranes (PROM) is a common obstetric complication. PROM can not only affect the normal development of the fetus, but can also lead to newborn infection and death. The main cause of PROM is chorioamnionitis induced by infection with bacteria (especially mycoplasma) or viruses, leading to disruption of the fetal membrane structure and rupture of the weakest part of the membranes [1]. After rupture, the inhibitory effect of the amniotic fluid on bacterial growth is weakened and the risk of an ascending infection is increased, with potential consequences including intrauterine infection, asphyxia, premature birth, pneumonia, sepsis, and neonatal death [1,2]. However, most pregnant women with PROM and chorioamnionitis have no clinical symptoms [2], and the complications are difficult to detect during the subclinical stage.

The incidence of PROM in preterm births is 2.5–3.0 times higher than that in full-term births, with one-third of preterm births being attributable to preterm PROM [1–5]. Prematurity is the main cause of neonatal death in newborns without chromosomal abnormality or congenital anomaly [6,7]. It is also related to a broad spectrum of long-term effects in survivors, including neurodevelopmental delay, cerebral palsy, blindness, hearing loss, and chronic lung disease [8,9]. Goldenberg et al. [10] found a premature birth rate of 5%–7% in Europe and of 12%–13% (almost 500 000 premature births per year) in the USA. Other authors [11] have reported a premature birth rate of approximately 9% for Germany—one of the highest rates of premature birth in Europe.

To reduce the incidence of PROM and preterm birth, understanding of the underlying pathophysiological mechanisms needs to improve. Cytokines have an important role in preterm birth. Their release is related to immune status, and abnormal increases or decreases in their concentrations are characteristic of a pathologic pregnancy. The inflammatory cytokines interleukin 6 (IL-6) and interleukin 8 (IL-8) activate neutrophils and immune cells and mediate the adhesion of white blood cells to endothelial cells, and their levels provide an objective measure of the status of intrauterine infection [12–14]. If a pregnancy is accompanied by chorioamnionitis, the body will respond to the bacteria and their metabolic products by secreting IL-6 and IL-8 into the maternal blood, amniotic fluid, and cord blood. The presence of IL-6 and IL-8 in amniotic fluid can lead to disruption of the extracellular matrix of the chorionic–decidual interface owing to elastase release from neutrophils, and can therefore lead to PROM [13,14]. PROM can further aggravate an intrauterine infection and trigger a series of pathophysiologic processes that—combined with chorioamnionitis or prolonged labor—lead to a significant increase in the risk of fetal and newborn infection [15,16].

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PROM can also be triggered after production of vascular cell adhesion molecule-1 (VCAM-1), which is expressed on vascular endothelial cells across the fetal membrane [17]. Various cytokines and inflammatory mediators (IL-6, IL-8, and tumor necrosis factor α [TNF-α]) can stimulate vascular endothelial cells to produce VCAM-1, and binding of VCAM-1 to the antigens V1 and A4 on the surface of white blood cells activates these cells to release elastase and free radicals [17]. Engagement of VCAM-1 enables white blood cells to pass through endothelial cell junctions, cause tissue inflammation, and generate a series of pathophysiological reactions that can lead to PROM [15,17].

The present study was conducted to evaluate whether the levels of IL-6, IL-8, and VCAM-1 in the amniotic fluid, maternal serum, and cord blood of women with PROM are different from those of women without PROM. The findings might improve the early diagnosis of PROM and chorioamnionitis, and help to prevent neonatal infection.

2. Materials and methods

The present observational study was conducted at the School of Clinical Medicine of Yangzhou University, Yangzhou, China, from January 31, 2003, to July 31, 2006 (42 months in total). It included full-term primiparous pregnant women with PROM (PROM group) and pregnant women who underwent elective cesarean delivery (control group). The women in the control group were not matched in any way to the women in the PROM group. Women with maternal disease, obstetric complications, or fetal abnormalities were excluded. Women with pregnancies of less than 24 completed weeks were excluded given the highly variable management options for these individuals. Women with pregnancies of greater than 34 completed weeks were excluded because latent antibiotics are not indicated for this group. The study was approved by the Institutional Review Board of the School of Clinical Medicine of Yangzhou University. All participants provided written informed consent.

Patients were identified using pharmacy records, census lists, and hospital delivery records in an effort to capture all possible preterm PROM diagnoses. The diagnosis of PROM was made according to Zhang [18]. Briefly, five standard tests—medical history, sterile speculum examination, pooling test, nitrazine test, and fern test—were used to diagnose PROM.

Maternal serum, cord blood serum, and amniotic fluid samples were obtained as described previously [18]. Before delivery, 3-mL samples of amniotic fluid and venous blood were collected for testing. The amniotic fluid samples in the PROM group were obtained from the vaginal pool after the rupture of membranes, and the amniotic fluid samples in the control group were collected by amniocentesis. After delivery, 5 mL umbilical cord blood was extracted. All samples were centrifuged at 2500 rpm for 5 minutes, and the supernatant was collected for testing. The samples were stored at −70 °C. All samples were suitable for the analysis.

In addition, 2 cm × 2 cm of the fetal membrane was obtained after delivery, fixed with 10% formaldehyde, and prepared for the examination of chorioamnionitis. Cases of chorioamnionitis were diagnosed as clinical, histological, or both. Clinical chorioamnionitis was defined as documented clinical signs and symptoms suggestive of this disorder. Histological chorioamnionitis was defined, on the basis of previously reported definitions [17], as an acute inflammatory change in any of the tissue samples (amnion, chorion deciduas, umbilical cord, and chorionic plate).

The IL-6, IL-8, and VCAM-1 levels in maternal serum, cord blood serum, and amniotic fluid were measured with double-antibody enzyme-linked immunosorbent assays by Shanghai Senxiong BioTech Industry, Shanghai, China, according to the manufacturer's instructions.

The data were analyzed with SPSS version 19.0 (IBM, Amonk, NY, USA), using the *t* test for comparisons. Several subanalyses were performed, including an analysis by duration of membrane rupture (<16 hours, 16–24 hours, and >24 hours) and an analysis by Apgar score of the newborn (≤7 vs ≥8) among women with PROM, and an analysis by presence of chorioamnionitis in the study population overall. $P < 0.05$ was considered statistically significant.

3. Results

The present study included 58 women in the PROM group and 38 women in the control group. The mean pregnancy duration in the PROM group was 37.8 ± 2.6 weeks and the mean age was 27.6 ± 3.1 years. The mean pregnancy duration in the control group was 38.5 ± 1.6 weeks, with an average age of 26.9 ± 2.4 years.

The levels of IL-6, IL-8, and VCAM-1 in maternal serum, cord blood serum, and amniotic fluid in the control group were significantly lower than those in the PROM group ($P < 0.05$ for all) (Table 1). In the PROM group, the levels increased significantly with an increasing duration of membrane rupture ($P < 0.05$ for all) (Table 2).

In the study population overall, 15 (15.6%) women had chorioamnionitis and 81 (84.4%) women did not. Women with chorioamnionitis had significantly higher levels of IL-6, IL-8, and VCAM-1 in maternal serum, cord blood serum, and amniotic fluid ($P < 0.05$ for all) (Table 3).

In the PROM group, 7 (12.1%) infants had an Apgar score of 7 or less and 51 (87.9%) had an Apgar score of 8 or more. The levels of IL-6, IL-8, and VCAM-1 were significantly higher among those with a lower Apgar score than among those with a higher Apgar score ($P < 0.05$ for all) (Table 4).

4. Discussion

The present study examined the association of clinical outcomes among women with PROM and their newborns with the levels of IL-6, IL-8, and VCAM-1 in maternal serum, cord blood serum, and amniotic fluid. It showed that the IL-6, IL-8, and VCAM-1 levels in maternal serum, amniotic fluid, and cord blood were significantly higher in the PROM group than in the control group. In the PROM group, the levels increased with duration of membrane rupture. Women with chorioamnionitis had significantly higher levels than did women without chorioamnionitis, and women with PROM whose newborns had low Apgar score (7 or less) had higher levels than did those whose newborns had a higher Apgar score. The data indicate that the combined measurement of these markers might be useful for the early diagnoses of PROM and chorioamnionitis, and these variables might also have clinical significance in determining the prognosis of newborns.

It is not possible on the basis of clinical features to predict or identify amniotic cavity infection among women with PROM and to determine whether prophylactic antibiotic therapy is necessary. Previous studies

Table 1
Levels of IL-6, IL-8, and VCAM-1 in maternal serum, cord blood serum, and amniotic fluid of pregnant women.[a]

Marker	PROM group (n = 58)	Control group (n = 38)	*P* value
Maternal serum			
IL-6, ng/L	621.2 ± 127.1	432.8 ± 151.8	0.009
IL-8, ng/L	792.2 ± 273.2	664.9 ± 201.7	0.03
VCAM-1, ng/L	15.8 ± 7.4	11.9 ± 5.5	0.02
Amniotic fluid			
IL-6, ng/L	576.6 ± 162.0	431.2 ± 185.8	0.04
IL-8, ng/L	758.0 ± 315.0	572.4 ± 228.7	0.03
VCAM-1, ng/L	37.1 ± 19.0	28.4 ± 16.4	0.02
Cord blood serum			
IL-6, ng/L	1099.7 ± 295.7	745.1 ± 245.9	0.008
IL-8, ng/L	1808.1 ± 323.0	1447.0 ± 318.9	0.009
VCAM-1, ng/L	10.6 ± 6.1	7.1 ± 4.8	0.007

Abbreviations: IL-6, interleukin 6; IL-8, interleukin 8; VCAM-1, vascular cell adhesion molecule-1; PROM, premature rupture of membranes.
[a] Values are given as mean ± SD unless indicated otherwise.

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