Predictive Study of Serum Matrix Metalloproteinase-8 in Combination with Human Chorionic Gonadotropin in Preterm Amniotic Cavity Infection

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ABSTRACT

The objective of this study was to investigate the predictive value of serum matrix metalloproteinase-8 (MMP-8) combined with human chorionic gonadotropin (hCG) for preterm amniotic cavity infection. The study included ninety patients with preterm labor admitted from June 2021 to October 2022 in the First Affiliated Hospital of Hebei North University, including the premature rupture of membranes group and the intact fetal membranes group. The same number of pregnant women with the same gestational age as in the experimental group were randomly selected as the study subjects in the outpatient clinic. Maternal sera from both groups β-hCG, MMP-8 levels were expressed and compared with those in the group with intra amniotic infection and no intra amniotic infection β- Higher levels of hCG, MMP-8 expression (P<0.05; Placentas from both groups β-hCG, MMP-8 levels were expressed and compared with those in the group with intra amniotic infection and no intra amniotic infection β- Higher levels of hCG, MMP-8 expression were factors associated with the development of preterm intra amniotic infection (P<0.05). It was concluded that in the serum of patients with preterm amniotic cavity infection, MMP-8 β- The values of hCG showed obvious expression by detecting MMP-8 β-hCG expression, which helps to predict the presence of intraamniotic infection, and especially for the prediction of subclinical intraamniotic infection is of high clinical significance. MMP-8 and β- The combined hCG test can provide clinical data support for clinicians to fully judge the prognosis of mother and child and to administer clinical interventions as early as possible, with high diagnostic efficacy.

INTRODUCTION

Premature rupture of membrane (PPROM) occurs in 3% of pregnancies and is the cause of about 25-30% of all premature births and is one of the important causes of perinatal morbidity (Mercer, 2007; Weissmann-Brenner et al., 2009; Blott and Greenough, 1988). One of the most important reasons for the importance of PPROM is its association with the short interval between the time of rupture of the membranes and childbirth, and this issue is of great importance due to the birth of premature babies in PPROM (Mercer, 2007). During the time interval between water sac rupture and childbirth, the possibility of pathogenic microorganisms climbing from vagina to amnion cavity increases and it is believed to play a role in the increase of intrauterine infection (Pasquier et al., 2009; Keyon et al., 2001; Gopalani et al., 2004; Yoon et al., 1999; Lajos et al., 2008).

In some sources, PPROM has been introduced as a pathological process that mostly occurs following inflammation and infection of membranes. In histological studies of membranes after premature rupture of membranes, specific bacterial contamination along the chorioamnion surfaces with brief amnion involvement is indicated. Also, in women, there is a high PPROM incidence of positive culture of amniotic fluid (25-30%) in amniocentesis samples, even when there is no clinical suspicion of chorioamnionitis (Mercer, 2007; Cunningham et al., 2005). Therefore, one of the major risks in PPROM patients is the occurrence of uterine infection, which leads to complications such as chorioamnionitis, postpartum metritis, and perinatal complications such as neonatal sepsis (Mercer, 2007; Yoon et al., 1999).

Premature rupture of the membranes in preterm labour
leaves the amniotic cavity in a state of communication with the outside world and allows amniotic fluid to escape, which in turn leads to amniotic cavity infection in the mother (Zhang et al., 2021). Most amniotic cavity infections are due to the ability of maternal vaginal bacteria to travel retrograde to the amniotic cavity through the amniotic rupture after the fetal membranes have ruptured (Zuo et al., 2021). Most scholars believe that amniotic cavity infection, is one of the main factors leading to a range of complications and sequelae in pregnant women and newborns (Fan et al., 2021).

The early stages of amniotic cavity infection in pregnant women with preterm labour are usually not clearly specific. Therefore, it is difficult to detect amniotic cavity infection earlier and then to intervene in time for the subsequent treatment of the pregnant woman (Fang et al., 2021). Cellular signaling plays an important role in the specific pathogenesis of preterm amniotic cavity infection (Yang and Lei, 2020). In this paper, we chose to analyse β-human chorionic gonadotropin (β-hCG) combined with serum matrix metalloproteinase-8 (MMP-8) expression in mothers with preterm amniotic cavity infection, in order to provide clinical data to support clinicians in predicting the prognosis of mothers and infants and to reduce the occurrence of serious complications through early clinical intervention.

MATERIALS AND METHODS

Study design

Ninety cases of preterm delivery patients from June 2021 to October 2022 in our hospital were collected for the study. The 90 cases were divided into no amniotic infection group and amniotic infection group by age detection of amniotic infection. There were 46 patients in the infected group, age range 24-42 years, with a mean of 29.98±2.28 years, gestational weeks 19-32 weeks, with a mean of 25.29±1.44 weeks, and a history of preterm delivery in 6 patients. There were 44 patients in the infected group, age range 22-40 years, with a mean of 29.98±2.28 years, gestational weeks 19-32 weeks, with a mean of 25.29±1.44 weeks, and a history of preterm delivery in 6 patients. There were 46 patients in the infected group and amniotic infection group by age

The expression of maternal serum β-hCG and MMP-8 levels are higher in the amniotic cavity infection group compared to the group without amniotic cavity infection, with statistical differences (P<0.05). The expressions of placental β-hCG and MMP-8 antibodies were placed in each well, held for 60 min, and then the liquid was removed. The wells were washed 3 times and then blotted dry. All wells were placed in the substrate solution (0.1 mol/L NaHPO₄, 0.05 mol/L citric acid) and 0.1 mL of o-phenylenediamine was added after homogenization. After shading the wells for 20 min, the reaction was terminated. The levels of β-hCG and MMP-8 were analyzed by measuring A450 values with an enzyme marker.

Statistical analyses

SPSS 21.0 software was used for processing. LSD-t test was performed for comparison between groups. The measurement data were described by applying (±s) and the count data were expressed as percent. Correlation analysis was performed by Spearman, while P<0.05 indicated statistical significance.

RESULTS

The expression of maternal serum β-hCG and MMP-8 levels in both groups are shown in Table I. The expression of β-hCG and MMP-8 levels are higher in the amniotic cavity infection group compared to the group without amniotic cavity infection, with statistical differences (P<0.05). The expressions of placental β-hCG and MMP-8 levels in the two groups are shown in Table I. Compared with the group without amniotic cavity infection, the expression of β-hCG and MMP-8 levels are higher in the amniotic cavity infection group.
infection group, with statistical differences (P<0.05).

Table I. Expression analysis of β-hCG and MMP-8 levels in the two groups (±sx).

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum</th>
<th>Placental</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-hCG (μmol/L)</td>
<td>MMP-8 (pg/mL)</td>
</tr>
<tr>
<td>Uninfected</td>
<td>18.04±1.21</td>
<td>19.24±4.23</td>
</tr>
<tr>
<td>Infected</td>
<td>29.25±2.07</td>
<td>31.27±3.51</td>
</tr>
<tr>
<td>t</td>
<td>31.531</td>
<td>14.647</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

As shown in Table II, the diagnostic efficacy of β-hCG and MMP-8 in the diagnosis of intra-amniotic infection in preterm labour was found to be higher in terms of specificity and sensitivity, as well as the Jorden index, while the combination of the two was significantly higher than the diagnostic efficacy of the single index.

Table II. Efficacy of β-hCG and MMP-8 levels expression in the diagnosis of intra-amniotic infection in preterm labour.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Optimal cut-off</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Jorden index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-hCG</td>
<td>6.852</td>
<td>0.751</td>
<td>0.855</td>
<td>0.842</td>
<td>0.829</td>
</tr>
<tr>
<td>MMP-8</td>
<td>4.326</td>
<td>0.594</td>
<td>0.842</td>
<td>0.857</td>
<td>0.846</td>
</tr>
<tr>
<td>Combined test</td>
<td>-</td>
<td>0.854</td>
<td>0.925</td>
<td>0.914</td>
<td>0.843</td>
</tr>
</tbody>
</table>

Table III. Multifactorial logistic regression analysis of intra-amniotic infection in preterm labour.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Beta</th>
<th>SE</th>
<th>Wald P value</th>
<th>OR value 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-hCG</td>
<td>1.626</td>
<td>0.856</td>
<td>5.225 0.001</td>
<td>3.326 1.542-6.621</td>
</tr>
<tr>
<td>MMP-8</td>
<td>1.431</td>
<td>0.18</td>
<td>4.245 0.001</td>
<td>2.586 1.151-5.338</td>
</tr>
</tbody>
</table>

As shown in Table III, the occurrence of intra-amniotic infection in preterm labour was included as the dependent variable and β-hCG and MMP-8 were included as independent variables in a multi-factor logistic regression model analysis. Both β-hCG and MMP-8 were found to be factors in the occurrence of intra-amniotic infection in preterm labour (p < 0.05).

**DISCUSSION**

The mechanism of preterm delivery is a hot topic of research in perinatal medicine, but the etiology leading to preterm delivery has not been comprehensively elucidated (Wang et al., 2020). Relevant studies have shown that preterm labour may be one of the clinical manifestations of most pregnancy complications. The association with infection, a recognized cause of preterm labour, becomes more profound the earlier the gestational week in which preterm labour occurs (Li et al., 2020). Infection may lead to the activation of a variety of pro-inflammatory cytokines, which in turn may result in a disturbance of the immune balance at the maternal-fetal interface, thus causing preterm birth (Chen et al., 2018). With advances in medical technology and the use of various testing techniques and immunology disciplines in obstetrics and gynaecology, the techniques for diagnosing premature rupture of the membranes and intra-amniotic infection have matured (Ma et al., 2020). Among these, maternal blood CRP is widely used in clinical obstetric investigations, but reliance on CRP as a predictor is inadequate. Foreign studies have found that intra-amniotic infection is not significantly associated with CRP level expression, so the search for cytokines with better diagnostic value is significant (Zhou et al., 2020).

It has been demonstrated that inflammatory mediators, such as CRP/PCT, can be elevated in the serum of pregnant women with amniotic cavity infection. MMP-8 is a cellular matrix-degrading enzyme that is stimulated by inflammatory factors that can contribute to the release of MMP-8. High expression of inflammatory factors can impair fetal defences and promote prostaglandin secretion, which in turn can contribute to fetal injury by the immune system and induce preterm labour (Holmström et al., 2019; Gulbiniene et al., 2022). β-hCG is a glycoprotein hormone secreted by placental trophoblast cells during pregnancy. Hormone levels rise significantly when a pregnant woman has damaged fetal membranes or an infection in the amniotic cavity (Liao et al., 2020). In the existing studies, only a single study was conducted for the above infection indicators, which lacked better accuracy.

MMP-8, also known as neutrophil collagenase, is synthesised by bone marrow neutrophils during the maturation phase. It has been found that during normal pregnancy, amniotic fluid does not contain MMP-8, but it is expressed in cervical tissue, where it has a facilitative effect on cervical maturation (Li et al., 2019). The absence of leukocytes, that is, neutrophils, in the amniotic fluid of normal pregnant women means that there is no expression of MMP-8 in the amniotic fluid of normal pregnant women, but the presence of infection in the amniotic cavity, where neutrophils proliferate and secrete large amounts of MMP-8, suggests that MMP-8 could be used as a specific indicator of the level of inflammation in the amniotic cavity (Zhou,
The placenta not only serves as a site of material exchange and nutrient metabolism between the mother and fetus, but also secretes hormones, acts as a pathogen barrier and is an innate immune organ during pregnancy (Choi et al., 2023; Myntti et al., 2017). Studies have shown that intrauterine infections are closely associated with a variety of pregnancy complications, of which placental infections will affect fetal outcome (Pittayapruek et al., 2016). MMP-8, the most important collagenase of type I collagen, is prone to secrete inflammatory factors in large amounts when the uterine cavity is attacked by inflammatory mediators, and high levels of inflammation can activate the neutrophil-secreting MMP-8 pathway, which manifests itself as an overexpression of MMP-8 in the amniotic fluid (Zhang et al., 2020). When MMP-8 breaks down type I collagen in large quantities, the elasticity, tone and strength of the amnion are severely affected, leading to structural weakening of the fetal membranes and premature rupture of the membranes. Premature rupture of the fetal membranes is associated with intra-amniotic infection, creating a vicious cycle that leads to poor pregnancy outcomes (Balciuniene et al., 2021; Chaemsaithong et al., 2018).

**CONCLUSION**

The values of MMP-8 and β-hCG were significantly expressed in the serum of patients with premature amniotic cavity infection. Detection of MMP-8 and β-hCG expression can help to predict the presence of amniotic cavity infection, especially for subclinical amniotic cavity infection. The combination of MMP-8 and β-hCG can provide clinical data to support the clinician’s overall assessment of maternal and infant prognosis and early clinical intervention, with high diagnostic efficacy.

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**IRB approval**

This study was approved by the First Affiliated Hospital of Hebei North University, Zhangjiakou, Hebei075000, China.

**Ethical approval**

The study was carried out in compliance with guidelines issued by ethical review board committee of The First Affiliated Hospital of Hebei North University, Zhangjiakou, Hebei 075000, China. The official letter would be available on fair request to corresponding author.

**Statement of conflict of interest**

The authors have declared no conflict of interest.

**REFERENCES**


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