C-reactive protein as a predictor of chorioamnionitis: a meta-analysis

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Pre-term premature rupture of membranes (PPROM) is a common problem in obstetrics. The management of patients with PPROM one of the most serious dilemmas in obstetrics since PPROM significantly increases the likelihood of prematurity and serious perinatal infection. Early infection is not reliably predicted nor detected by standard laboratory parameters (white blood cell count differential with differential count, and ESR). C-reactive protein (CRP) is an acute phase reactant, which is produced by the liver. The level of CRP often rises significantly following an inflammatory process.

Articles about the accuracy of CRP as a predictor of chorioamnionitis after PPROM were searched from the computerized Medline Data Base for the period 1982-1990. Available articles were reviewed and five selected articles were analyzed using preset criteria. The result of meta-analysis** showed that the sensitivity, the specificity, the positive predictive value and the negative predictive value of CRP in predicting chorioamnionitis by histopathologic criteria of CRP in predicting chorioamnionitis by pathologic criteria were 67.7%, 82.5%, 82.4% and 68.9%, respectively. The results suggest that CRP may be used as a screening tool or in conjunction with other clinical evidences for the early diagnosis of chorioamnionitis in PPROM.

Key words: C-reactive protein, Chorioamnionitis, Premature, Rupture membranes, Meta-analysis.

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** Meta-analysis: a new discipline that critically reviews and statistically combines the results of previous researches.
The purposes of meta-analysis include the following:
1. to increase statistical power for primary end-points and subgroups;
2. to resolve uncertainty when reports disagree;
3. to improve estimates of effect size; and
4. to answer questions not posed at the start of individual trials.
Meta-analysis has a role to play:
1. when randomized trials have been performed but the results are inconclusive or conflicting;
2. when definitive or large-scale randomized trials are impossible or impractical; and
3. when the results of definitive studies are awaited.
A recent review of meta-analysis in the field of public health emphasized its growing importance.
ควายุน้ำรินนดกอดการเจ็บครบครอคยองในผู้ที่มั่งคั่งไม่ควรกินคนเป็นหวงแพทย์มันทางภูมิศาสตร์ที่พบได้อย่ายาทางหนึ่ง การดูแลรักษาเน้นเป็นย้ำหยุ่นสืบไป เพราะภาวะจะทำให้มีการพั่นพานในการหน้ากระชับรักษาคุณและความการติดเชื้อสู่กระรูปแรก ในขณะนี้ยังไม่มีวิธีการตรวจจับหรือซ้อมได้ในเวลานี้การเจ็บครบครอคยองในระยะแรก C-reactive protein (CRP) เป็นสารที่สร้างจากตับและมุ่งมาที่กลุ่มอาการ เช่นในระยะแรกของการสั่นไหว โดยมีการศึกษาที่ความแม่นยำของการตรวจคัด CRP ในสัดส่วนของการใช้เป็นตัวกระบวนการเจ็บครบครอคยองในระยะแรก อาการดังกล่าวนั้นเร่าน่าจะ

การศึกษาได้ทำการสังเกตการณ์ต่าง ๆ ที่เกิดขึ้นในวันหน้าเวลาน้ำหนัก 5 รายที่ตรวจพบการติดเชื้อได้ก็มีผลปัจจัยต่าง ๆ ที่สามารถทำให้ได้ผลการใช้ CRP ในภาวะกระชับการเจ็บครบครอคยองในระยะแรกที่สูงและน่าจะมีผลทางด้านที่มีความรู้ผลชัดเจน 67.7 ความถี่ของการใช้ positive predictive value 82.5 และ negative predictive value 82.4 ที่ผลการตรวจวัดต่อที่ CRP ในตลอดการเจ็บครบครอคยองมีการใช้ซ้อมเมื่อผลการสั่นไหว หรือได้รับการรักษาได้รับการรักษาดีและได้รับการรักษาดีในระยะแรกๆ ได้
It is generally assumed that intact membranes represent an efficient barrier to ascending infection. About 8%-10% of all pregnancies are complicated by premature rupture of membranes (PROM).\(^1\) PROM in pre-term pregnancy is a leading cause of perinatal morbidity and mortality. Management of pre-term PROM (PPROM) remains a difficult and controversial complication. Expectant management permits significant development of the fetus, but at the same time, chorioamnionitis develops in some cases. Chorioamnionitis can lead to serious sequelae in both mother and infant. Therefore, the diagnosis of this potentially life-threatening complication is important.

The current clinical and laboratory parameters used to detect early chorioamnionitis are non-specific and non-sensitive indicators of chorioamnionitis. C-reactive protein (CRP), an acute-phase reactant to inflammation, was first proposed by Evans et al. (1980)\(^2\) to detect chorioamnionitis in patients with PROM. It appears to be the most sensitive acute-phase protein, rising in the initial stage of inflammation. There have been many reports about the usefulness of CRP as a predictor of subclinical chorioamnionitis in patients with PROM.

The purpose of this meta-analysis is to review critically and analyze articles about CRP as a predictor of chorioamnionitis using pre-set inclusion criteria.

**Methods**

Search strategy: The computerized Medline Data Base was searched for the years 1982-1990 using the following key words: fetal membranes, premature rupture, pre-term, chorioamnionitis, C-reactive protein. Twenty-two articles were identified,\(^3\)-\(^24\) 18 of which were available for review. The criteria for selection of the articles included:

1. Prospective study design.
2. The study population in the articles were pregnant women with PPROM (gestational age being less than 37 weeks). PROM was defined by rupture of membranes before onset of labor and was diagnosed by vaginal pooling of nitrazine-positive fluid in the vagina.
3. The CRP level in maternal serum was measured by a quantitative method.
4. The result of the test was not known by the clinician, so that it did not affect management.
5. Using histopathologic chorioamnionitis and/or clinical chorioamnionitis as the Gold Standard.
6. Enough data should be presented in the article for testing characteristics of test.

Using these criteria, five articles (Journal numbers 3, 4, 5, 6 and 7) were included in this analysis. Journal numbers 8-20 were excluded as listed below.

Journal numbers 21, 22, 23 and 24 were not available for review.

- Review articles Numbers 8, 9, 10
- Letter to editor Number 11
- Study in new born Numbers 12, 13, 14
- Study in pre-term labor Numbers 15, 16, 17
- Using microbiologic study
  - as Gold Standard Number 18
  - as part of clinical diagnosis Number 19

Not enough data for calculation Number 20

**Analysis:** Data from selected articles were used to calculate characteristics of CRP test: with regard to sensitivity, specificity, and positive and negative predictive values. The incidence of chorioamnionitis after PPROM was calculated.

Gold Standard: Histopathologic and clinical chorioamnionitis were used as the Gold Standard and the data were calculated separately.

**Results**

Data from selected articles are shown in Tables 1 and 2. The test characteristics of CRP are shown in Table 3. When histopathologic diagnosis was used as the Gold Standard, the sensitivity, specificity, positive and negative predictive values were 67.7%, 82.5%, 82.4% and 68.0%, respectively. The incidence of histopathologic chorioamnionitis after PPROM was 54.6%. When clinical diagnosis was used as the Gold Standard, the sensitivity, specificity and positive and negative predictive values were 76.5%, 70.3% 37.1% and 92.9%, respectively. The incidence of clinical chorioamnionitis after PPROM was 18.7%.
Table 1. Test characteristics of CRP for prediction of histopathologic chorioamnionitis, with incidence of chorioamnionitis after PPROM.

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>First author</th>
<th>No. of patients</th>
<th>CRP cut-off point (mg/dL)</th>
<th>D⁺T⁺</th>
<th>D⁻T⁺</th>
<th>D⁺T⁻</th>
<th>D⁻T⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Farb</td>
<td>24</td>
<td>20.0</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>Hawrylyshyn</td>
<td>52</td>
<td>12.5</td>
<td>23</td>
<td>1</td>
<td>3</td>
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<tr>
<td>6</td>
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<td>20.0</td>
<td>42</td>
<td>7</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>Fisk</td>
<td>51</td>
<td>20.0</td>
<td>15</td>
<td>4</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>227</strong></td>
<td></td>
<td><strong>84</strong></td>
<td><strong>18</strong></td>
<td><strong>40</strong></td>
<td><strong>85</strong></td>
<td></td>
</tr>
</tbody>
</table>

D⁺ = disease present  
T⁺ = test was positive  
D⁻ = no disease  
T⁻ = test was negative

Table 2. Test characteristics of CRP for the prediction of clinical chorioamnionitis, with incidence of clinical chorioamnionitis after PPROM.

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>First author</th>
<th>No. of patients</th>
<th>CRP cut-off point (mg/dL)</th>
<th>D⁺T⁺</th>
<th>D⁻T⁺</th>
<th>D⁺T⁻</th>
<th>D⁻T⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Farb</td>
<td>31</td>
<td>20.0</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>Romem</td>
<td>51</td>
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<td>1</td>
<td>1</td>
<td>43</td>
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<tr>
<td>7</td>
<td>Ismail</td>
<td>100</td>
<td>20.0</td>
<td>15</td>
<td>37</td>
<td>3</td>
<td>45</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>182</strong></td>
<td></td>
<td><strong>26</strong></td>
<td><strong>44</strong></td>
<td><strong>8</strong></td>
<td><strong>104</strong></td>
<td></td>
</tr>
</tbody>
</table>

D⁺ = disease present  
T⁺ = test was positive  
D⁻ = no disease  
T⁻ = test was negative

Table 3. Test characteristics of CRP for the prediction of histopathologic and clinical chorioamnionitis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Prediction of chorioamnionitis (%)</th>
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<tbody>
<tr>
<td></td>
<td>Histopathologic</td>
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<tr>
<td>Sensitivity</td>
<td>67.7</td>
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<tr>
<td>Specificity</td>
<td>82.5</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>82.4</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>68.0</td>
</tr>
<tr>
<td>Incidence of disease</td>
<td>54.6</td>
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</table>
Discussions

During expectant management of PPROM, early diagnosis of chorioamnionitis is the greatest concern. When clinical chorioamnionitis occurs, neonatal morbidity and mortality increased. Some have claimed histopathologic diagnosis (inflammation of placenta and membranes) and amniocentesis with microbiologic study to be related to clinical chorioamnionitis, but others do not agree. Because amniocentesis for culture and lung maturity testing are invasive procedures and not generally done, in this meta-analysis histopathologic and clinical diagnosis were used as the Gold Standard. Furthermore, histopathologic chorioamnionitis as shown by diffuse inflammation in membranes, especially at the ruptured site, means that infection may be the cause of ruptured membranes.

The incidence of histopathologic chorioamnionitis after PPROM is greater than clinical chorioamnionitis (54.6% : 18.7%) but in this meta-analysis the correlation between them was not evaluated. Ismail believes that histologic chorioamnionitis precedes clinical chorioamnionitis.

Determining the results of test characteristics of CRP in this meta-analysis, CRP can be used as a predictor of chorioamnionitis after PPROM especially using histopathologic diagnosis as the Gold Standard. Low positive predictive value when using clinical diagnosis as the Gold Standard is influenced by the low incidence (18.7%) of clinical chorioamnionitis after PPROM.

To determine positivity of the test, most authors use different cut-off points of CRP. The cut-off point may be calculated from the CRP level of normal pregnant women. Romem (1985) showed that elevated CRP using a day-to-day coefficient of variance of more than 30% of CRP levels between two days is an early diagnostic marker for the detection of chorioamnionitis; however, this has to be confirmed. All selected articles analyzed the accuracy of a single test, but we used a combination of various parameters in clinical practice. Further studies should be carried out early diagnosis of chorioamnionitis using elevated CRP and the usefulness of a combination of CRP with other clinical parameters.

References

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13. Salzer HR, Genger H, Muhar U, Lischka A, Schatten C, Polluk A. C-reactive protein:


