Accuracy of C-reactive protein determination in predicting chorioamnionitis and neonatal infection in pregnant women with premature rupture of membranes: a systematic review

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CRD summary
This review assessed the accuracy of C-reactive protein in predicting chorioamnionitis and/or neonatal sepsis in women with pre-term premature rupture of the foetal membranes, and concluded that the available literature did not support its use. These conclusions reflected the limited data available and are likely to be reliable.

Authors’ objectives
To assess the accuracy of C-reactive protein in predicting chorioamnionitis and/or neonatal sepsis in pregnant women with pre-term premature rupture of the foetal membranes.

Searching
MEDLINE and EMBASE were searched from inception to 2007. Search terms were reported. There were no language restrictions. Bibliographies of known reviews and primary articles were screened for additional studies.

Study selection
Diagnostic cohort studies of maternal serum C-reactive protein test (index test), measured in pregnant women with rupture of foetal membranes before 36 completed weeks of gestational age, were eligible for inclusion. The outcome measures (reference standard) were neonatal sepsis defined as a positive blood culture or clinical signs of infection (apnoea, fever, intolerance for feeding, respiratory distress and/or haemodynamic instability) with positive surface cultures; suspicion of clinical chorioamnionitis defined as a temperature of at least 37.5 degrees C, in combination with at least one of uterine tenderness, purulent amniotic fluid, maternal or foetal tachycardia; and histological chorioamnionitis defined as the presence of neutrophil infiltrate in extra-placental membranes. Diagnostic case-control studies, studies considered to have an inappropriate description of the spectrum of patients, and studies without an adequate description of the index test and reference standard, were excluded. Studies were also excluded if data to construct a 2x2 contingency table (numbers of true positive, false negative, false positive and true negative test results) were not extractable.

The C-reactive protein assay method was nephelometry in all but one of the included studies; the remaining study used immunoassay. The diagnostic thresholds used in included studies ranged from >12mg/L to >40mg/L. Gestational age, in included studies, ranged from 20 to 36 6/7 weeks. The interval between the last C-reactive protein determination and delivery varied from 12 to 72 hours; the majority of the studies had C-reactive protein testing at least every 24 hours.

Two reviewers independently assessed studies for inclusion; any disagreements were resolved by consensus or consultation with a third reviewer.

Assessment of study quality
The methodological quality of included studies was assessed based on the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool, with some additional items. Items assessed included: detailed description of the index test (C-reactive protein) and reference test; blinding; missing data; number of patients with index test; and reference test. Items considered by the authors to be clinically relevant were use of antibiotics, timing of the index test, blinding for index and reference test, incidence and details of outcome.

Two reviewers independently assessed methodological quality, using data extraction forms.

Data extraction
Data were extracted for each study to populate 2x2 contingency tables comparing C-reactive protein results with the occurrence of clinical and/or histological chorioamnionitis and/or neonatal morbidity/mortality. These data were used to
calculate sensitivity and specificity values.

Two reviewers independently extracted data, using data extraction forms.

**Methods of synthesis**
Summary receiver operating characteristic (SROC) curves were constructed and pooled estimates of sensitivity and specificity at various cut-off values were calculated using a bivariate meta-regression model. Separate curves were constructed for clinical and for histological chorioamnionitis; no studies fulfilled the inclusion criteria for neonatal sepsis. Although some studies reported several cut-off values for C-reactive protein, each study was used only once in each SROC analysis.

The correlation coefficient (r) was calculated to estimate the strength and shape of the correlation between sensitivity and specificity, and the amount of variance that can be explained due to variation in the diagnostic threshold or cut-off value used.

**Results of the review**
Five diagnostic cohort studies, with a total of 372 evaluable participants, were included in the review. All included studies were prospective studies with consecutive sampling and 'blinding' (details of blinding not reported). Two articles could not be translated and were excluded on this basis.

The reported prevalence of histological chorioamnionitis was 54.6% (124 out of 227 women; range 21 to 63%). The prevalence of clinical chorioamnionitis was 25.8% (85 out of 330 women; range 18 to 50%).

An summary receiver operating characteristic (SROC) was presented for histological chorioamnionitis, but no summary estimates of sensitivity and specificity were reported. The authors stated that significant heterogeneity among studies reporting clinical chorioamnionitis as the reference standard meant that a reliable SROC curve could not be estimated for this outcome.

Reported sensitivities for histological chorioamnionitis (four studies, seven data sets) ranged from 37% at a diagnostic threshold of >40mg/L C-reactive protein to 88% at a diagnostic threshold of >12.5mg/L C-reactive protein. Specificities ranged from 68% at a diagnostic threshold of >20mg/L C-reactive protein to 100% at a diagnostic threshold of >40mg/L C-reactive protein.

Reported sensitivities for clinical chorioamnionitis (four studies, five data sets) ranged from 55% at a diagnostic threshold of >20mg/L C-reactive protein to 100% at a diagnostic threshold of >12.5mg/L C-reactive protein. Specificities ranged from 55% at a diagnostic threshold of >20mg/L C-reactive protein to 98% at a diagnostic threshold of >20mg/L C-reactive protein.

**Authors' conclusions**
C-reactive protein test was moderately predictive of histological chorioamnionitis. The studies of clinical chorioamnionitis were too heterogeneous to pool data. No data were available on C-reactive protein as a predictor of neonatal sepsis. Current literature did not support the use of C-reactive protein in women with pre-term premature rupture of the foetal membranes.

**CRD commentary**
The review addressed a clearly stated research question, defined by appropriate inclusion criteria. No language restrictions were applied to the search strategy, but two articles were excluded because they could not be translated, so relevant data may have been omitted from the review. Measures were taken, throughout the review process, to minimise the potential for error and/or bias.

The methodological quality of included studies was assessed and used, in part, as criteria for inclusion. Appropriate analytical methods were applied, but summary estimates of sensitivity and specificity of C-reactive protein for predicting histological chorioamnionitis, which were referred to in the text, were not reported.
Overall, the authors’ conclusions were appropriate for the limited data available and are likely to be reliable.

Implications of the review for practice and research

**Practice:** The authors stated that, based on existing literature, they are unable to support the use of C-reactive protein as a predictor for chorioamnionitis or neonatal sepsis following pre-term premature rupture of the foetal membranes.

**Research:** The authors stated that further research, preferably in a randomized controlled blinded setting with larger populations, should be conducted to determine the usefulness of C-reactive protein in its prediction of clinical chorioamnionitis and more importantly neonatal sepsis in women with pre-term premature rupture of the foetal membranes.

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