นิพนธ์ต้นฉบับ

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

Tul Sittisomwong*
Wannaporn Thungkaniwat* Sompop Limpongsanurak*

Sittisomwong T, Thungkaniwat W, Limpongsanurak S. C-reactive protein as a predictor of chorioamnionitis: a meta-analysis. Chula Med J 1991 Aug; 35(8): 493-498

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 Mediline 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.

Reprint request : Sittisomwong T, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
Received for publication. May 1, 1991.

---

* Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University.

** *Meta-analysis: a new discipline that critically reviews and statistically combines the results of previous reseachs.*
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 difinitive studies are awaited.
A recent review of meta-analysis in the field of public health emphasized its growing importance.

ตุลย์ สิทธิสมวงศ์, วรรณพร ตังคนิวาส, สมภพ ลิ้มพงศานุรักษ์. การพยากรณ์ภาวะอักเสบติดเชื้อในโพรงมดลูก โดยใช้สารปฏิกิริยาต่อโปรตีน ซี: การวิเคราะห์แบบเมตา. จุฬาลงกรณ์เวชสาร 2534 สิงหาคม; 35(8): 493-498

ภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์คลอดในผู้ที่ตั้งครรภ์ไม่ครบกำหนด เป็นภาวะแทรกซ้อนทางสูติศาสตร์ที่พบได้บ่อยประการหนึ่ง การดูแลรักษานั้นเป็นปัญหาสำคัญที่สุด เพราะภาวะนี้จะทำให้มีการเพิ่มปัญหาในทารกทั้งการคลอดก่อนกำหนดและการติดเชื้ออย่างรุนแรง ในขณะนี้ยังไม่มีวิธีการตรวจที่เชื่อถือได้ดีในการวินิจฉัยการติดเชื้อในระยะเริ่มแรก C-reactive protein (CRP) เป็นสารที่สร้างจากตับและจะมีระดับสูงขึ้นในระยะเริ่มแรกของการอักเสบ ได้มีการศึกษาถึงความแม่นยำของการนำระดับ CRP ในเลือดของมารดาใช้เป็นตัวพยากรณ์การเกิดการอักเสบติดเชื้อในโพรงมดลูก ภายหลังภาวะถุงน้ำคร่ำแตก

การศึกษานี้ได้ทำการค้นคว้ารายงานระหว่างปี พ.ศ. 2525 ถึง พ.ศ. 2533 จาก Medline Data Base โดยอาศัยข้อระบุต่าง ๆ ที่กำหนดไว้ล่วงหน้าพบว่ามีจำนวน 5 รายงานที่ตรงตามข้อระบุซึ่งได้นำมาวิเคราะห์รวมกันได้ผลว่าการใช้ CRP ในการพยากรณ์การอักเสบติดเชื้อในโพรงมดลูกที่พิสูจน์โดยผลทางพยาธิวิทยามีความไวร้อยละ 67.7 ความจำเพาะร้อยละ 82.5 positive predictive value ร้อยละ 82.4 negative predictive value ร้อยละ 68.9 จากผลการวิเคราะห์นี้ CRP ในเลือดของมารดา อาจนำมาใช้เป็นเครื่องมือในการคัดกรอง หรือใช้ร่วมกับข้อมูลอื่นทางคลินิกเพื่อวินิจฉัยการอักเสบติดเชื้อในโพรงมดลูกระยะเริ่มแรกได้

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 chorioaminionitis 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.

Ref. No.	First author	No. of patients	CRP cut-off point (mg/dL)	D^+T^+	D^-T^+	D^+T^-	D^-T^-
3	Farb	24	20.0	4	6	1	13
4	Hawrylyshyn	52	12.5	23	1	3	25
6	Ismail	100	20.0	42	7	21	30
7	Fisk	51	20.0	15	4	15	17
Total		**227**	—	**84**	**18**	**40**	**85**

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.

Ref. No.	First author	No. of patients	CRP cut-off point (mg/dL)	D^+T^+	D^-T^+	D^+T^-	D^-T^-
4	Farb	31	20.0	5	6	4	16
5	Romem	51	20.0	6	1	1	43
7	Ismail	100	20.0	15	37	3	45
Total		**182**		**26**	**44**	**8**	**104**

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.

Characteristics	Prediction of chorioamnionitis (%)	
	Histopathologic	Clinical
Sensitivity	67.7	76.5
Specificity	82.5	70.3
Positive predictive value	82.4	37.1
Negative predictive value	68.0	92.9
Incidence of disease	54.6	18.7

Discussions

During expectant management of PPROM, early diagnosis of chorioamnionitis is the greatest concern. When clinical chorioamnionitis occurs, neonatal morbidity and mortality increased.[14] Some have claimed histopathologic diagnosis (inflammation of placenta and membranes).[6,7,25] and amniocentesis with microbiologic study[26] to be related to clinical chorioamnionitis, but others do not agree.[27,28] 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.[29]

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.[6]

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

1. Thomas TG. Premature rupture of membranes. In: Scott JR, Disaia PJ, Hammond CB, (eds.) Danforth's Obsterics and Gynecology. 6th ed., Philadelphia: J.B. Lippincott, 1990: 354
2. Evans MI, Hajj SN, Devoe LD, Angerman NS, Moawad AH. C-reactive protein as a predictor of infectious morbidity with premature rupture of membranes. Am J Obstet Gynecol 1980 Nov 15; 138(6): 648-52
3. Farb HF, Arnesen M, Gesitler P, Knose GE. C-reactive protein with premature rupture of membranes and premature labor. Obstet Gynecol 1983 Jul; 62(1): 49-51
4. Hawrylyshyn P, Bernstein P, Milligan JE, Soldin S, Pollard A, Papsin FR. Premature rupture of membranes: the role of C-reactive protein in the prediction of chorioamnionitis. Am J Obstet Gynecol 1983 Oct 1; 147(3): 280-6
5. Romem Y, Artral R. C-reactive protein as a predictor for chorioamnionitis in cases of premature rupture of the membranes. Am J Obstet Gynecol 1984 Nov 1; 150(5pt1): 546-50
6. Ismail MA, Zinaman MJ, Lowensohn RI, Moaward AH. The significance of C-reactive protein levels in woman with premature rupture of membranes. Am J Obstet Gynecol 1985 Feb 15; 151(4): 541-4
7. Fisk NM, Fysh J. Child AG, Gatenby PA, Jeffery H, Bradfield AH. Is C-reactive protein really useful in preterm premature rupture of membranes. Br J Obstet Gynaecol 1987 Dec; 94(12): 1159-64
8. Vanlente F. The diagnostic utility of C-reactive protein. Human Pathol 1982 Dec; 13(12): 1061-3
9. Bek KM, Neilsen FR, Ovist I, Rasmussen PE, Tobiassen M C-reactive protein (CRP) and pregnancy. An early indicator of chorioamnionitis: a review. Eur J Obstet Gynecol Reprod Biol 1990 Jan; 35(1): 29-33
10. Ohlsson A, Wang E. An analysis of antenatal tests to detect infection in preterm premature of the membranes. Am J Obstet Gynecol 1990 Mar; 162(3): 809-18
11. Verma UL, Hammeed C, Tejani N. Elevated C-reactive protein levels [letter]. Obstet Gynecol 1984 Jun; 63(6): 866-7
12. Ainbender E, Cabatu EE, Guzman DM, Sweet AY. Serum C-reactive protein and problem of newborn infants: J Pediatr 1982 Sep; 101(3): 438-40
13. Salzer HR, Genger H, Muhar U, Lischka A, Schatten C, Polluk A. C-reactive protein:

an early marker for neonatal bacterial infection due to prolonged rupture of amniotic membranes and/or amnionitis. Acta Obstet Gynecol Scand 1987 Apr; 66(4): 365-7

14. Morales WJ, Washington JR, Lazar AJ. The effect of chorioamnionitis on perinatal outcome in preterm gestation. J Perinatol 1987; 7(2): 105-10
15. Potkul RK, Moawad AH, Parto KL. The association of subclinical infection with preterm labor: the role of C-reactive protein. Am J Obstet Gynecol 1985 Nov; 153(6): 642-5
16. Hameed C, Tejani N, Verma UL, Archbald F. Silent chorioamnionitis as a cause of preterm labor refractory to tocolytic therapy. Am J Obstet Gynecol 1984 Aug 1; 149(7): 726-30
17. Camma H, Goossens A, Derde MP, Temmerman M, Foulon, Any JJ. C-reactive protein in preterm labor: association with outcome of tocolysis and placental histology. Br J Obstet Gynaecol 1989 Mar; 96(3): 314-9
18. Gutteberg TJ, Askvik K, Jrgensen T. Serum lactoferrin and C-reactive protein in mother and newborn after preterm rupture of membranes. Acta Obstet Gynecol Scand 1986 Mar; 65(3): 203-5
19. Ernest JM, Swain M, Block SM, Nelsen LH, Hatjis CG, Meris PJ. C-reactive protein: a limited test for managing patients with preterm labor or premature rupture of membranes. Am J Obstet Gynecol 1987 Feb; 156(2): 449-54
20. Teichman AT, Arendt P, Speer CP. Premature rupture of the membranes and amniotic infections: the significance of laboratory tests. Eur J Obstet Gynecol Reprod Biol 1990; 34(3): 217-22
21. el-Mekkawi TM, Abdel Aziz AA, el-Shiemy RE, Abdel Rhaman S, Ofaifo G. C-reactive protein as a predictor of chorioamnionitis with rupture of membranes. J Egypt Public Health Assoc 1985; 60(5-6): 287-99
22. de Souza JJ, Perlman T, Herman AA, Ransome OJ, Kantor RW. C-reactive protein as a predictor of fetal and maternal infective morbidity and fetal mortality. S Afr Med J 1987 Nov; 71(11): 690-2
23. Korman L, Jacobs V, Hodgsen RP, Godfry J, Dunlevy L, Tyler JP, et al. Chorioamnionitis: how useful is the determination of C-reactive protein. Aus NZ J Obstet Gynecol 1988 Jan; 28(1): 45-8
24. Kurki T, Teramo K, Ylikorhala, Paavonen J. C-reactive protein preterm premature rupture of the membranes. Arch Gynecol Obstet 1990 Jan; 24(1): 31-7
25. Hillier SL, Martius J, Krohn M, Kiviat N, Holmes KK, Eschenbach DA. A case-control study of chorioamniotic infection and histologic chorioamnionitis in prematurity. N Engl J Med 1988 Oct 13; 319(15): 972-8
26. Garite TJ, Freeman RK, Linzey EM, Braly P. The use of amniocentesis in patients with premature rupture of membranes. Obstet Gynecol 1979 Aug; 54(2): 226-30
27. Bobitt JR, Hayslip CC, Damato JD. Amniotic fluid infection as determined by transabdominal amniocentesis in patients with intact membranes in premature labor. Am J Obstet Gynecol 1981 Aug 15; 140(8): 947-52
28. Mortimer G, MacDonald DJ, Smeeth A. A pilot study of the frequency and significance of placental villitis. Br J Obstet Gynaecol 1985 Jun; 92(6): 629-33
29. Preterm birth. In: Cunningham FG, MacDonald PC, Gant MF, (eds.) Williams Obstetrics. 18th edl., New Jersey: Prentice- Hall International Incorporation, 1989: 749-51