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Intrauterine Infection Predictors among Preterm Premature Rupture of Membrane Patients

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ABSTRACT

Introduction: The preterm premature rupture of membrane (PPROM) complicates pregnancy for 1 to 2% of all women and it is associated with 30 to 40% of preterm birth. It is difficult to determine whether infection as the cause or consequence of preterm delivery. Therefore, this study aimed to review several markers to predict intrauterine infection for good management among PPROM patients.

Methods: The author searched in PubMed, Cochrane, and Ovid using searching strategy "MeSH". There were 25, 20, and 2 articles found in PubMed, Cochrane, and Ovid; respectively which finally ended to 8 cohort or case control studies and 2 systematic reviews. Critical appraisal was based on validity, importance, and applicability (VIA).

Results: In maternal parameters, sensitivity of temperature, heart rate, leucocyte count, and CRP were low without regarding the infection. Besides, biophysical profile score and fetal heart activity were insensitive to predict intrauterine infection. Fetal marker such as leucocyte and neutrophil count was increased in intrauterine infection; however, it was not specific. Positive amniotic fluid Gram stain revealed a high sensitivity (80%) in prediction of intrauterine infection with aerobic or anaerobic organism. Procalcitonin should be considered as weak predictor for intrauterine infection (low sensitivity). Essential markers for predicting intrauterine infection non-invasively were IL-6 and TNF-α.

Conclusion: Amniotic fluid IL-6 and TNF-α are strong predictors for fetal inflammatory response syndrome (FIRS) and/or histological funisitis.

Key words: Intrauterine infection, Preterm premature rupture of membrane, Marker

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INTRODUCTION

The preterm premature rupture of membrane (PPROM) complicates pregnancy for 1 to 2% of all women and it is associated with 30 to 40% of preterm birth. It is also associated with maternal and perinatal morbidity and mortality due to intrauterine infection [1,2]. In USA, at least 40% of preterm births were associated with intrauterine infection [3]. Actually, it is difficult to determine whether infection as the cause or consequence of preterm delivery; however, intrauterine infection or inflammation leads to fetal inflammatory response syndrome (FIRS) and histological chorioamnionitis (HCA) [4]. The need to diagnose intrauterine infection is essential to determine the optimal time of delivery in PPROM patients as it requires balancing between potential benefits of pregnancy prolongation and risk of intrauterine infection which impacts to perinatal morbidity and mortality [5]. Therefore, a lot of studies were conducted to predict the intrauterine infection in PPROM patients.

Clinical assessments such as maternal temperature, fetal activity, and fetal heart rate (FHR) pattern were attempted to predict the intrauterine infection. Meanwhile, other studies tried to predict intrauterine infection through amniotic gram stain, leucocyte count [6], C-reactive protein as acute phase protein produced in liver during infection [7], procalcitonin [8], IL-6, IL-8, and TNF-α [5,9]. Therefore, this study aimed to review several markers to predict intrauterine infection for good management among PPROM patients.

METHODS

In order to answer the question above, we did a searching on PubMed through keywords, namely "Fetal Membranes, Premature Rupture" [Mesh] AND intrauterine infection OR fetal inflammatory response syndrome OR chorioamnionitis AND prediction. Apart from that, we also searched on the Cochrane database by using MeSH descriptor: [Fetal Membranes, Premature Rupture] AND intrauterine infection or fetal inflammatory response syndrome OR chorioamnionitis AND prediction. In Ovid,

the searching strategy was preterm premature rupture of membrane AND intrauterine infection OR fetal inflammatory response syndrome OR chorioamnionitis AND prediction. Due to the limitation of systematic review or meta-analysis article as the highest level in the evidence-based medicine, we accepted all studies related to the topic. Finally, there were 25, 20, and 2 articles found in PubMed, Cochrane, and Ovid; respectively. Of 47 articles found, 14 articles were appropriate with the aim of study; then, 2 articles were written in Polish, 2 articles had duplicated. Therefore, there were 10 articles consisted of 8 cohort or case control studies and 2 systematic reviews.

Critical appraisal was based on validity, importance, and applicability (VIA) in studies written by Carroll et al. [6], Andrezj et al. [8], Carroll et al. [10], Kunze et al. [5], Carroll et al. [11], Giuseppe et al. [9], Carroll et al. [12], Carroll et al [7]. Another systematic review was written by Trochez-Martinez et al. [13], Rafli et al. [14].

Figure 1 showed the process of study identification and selection.

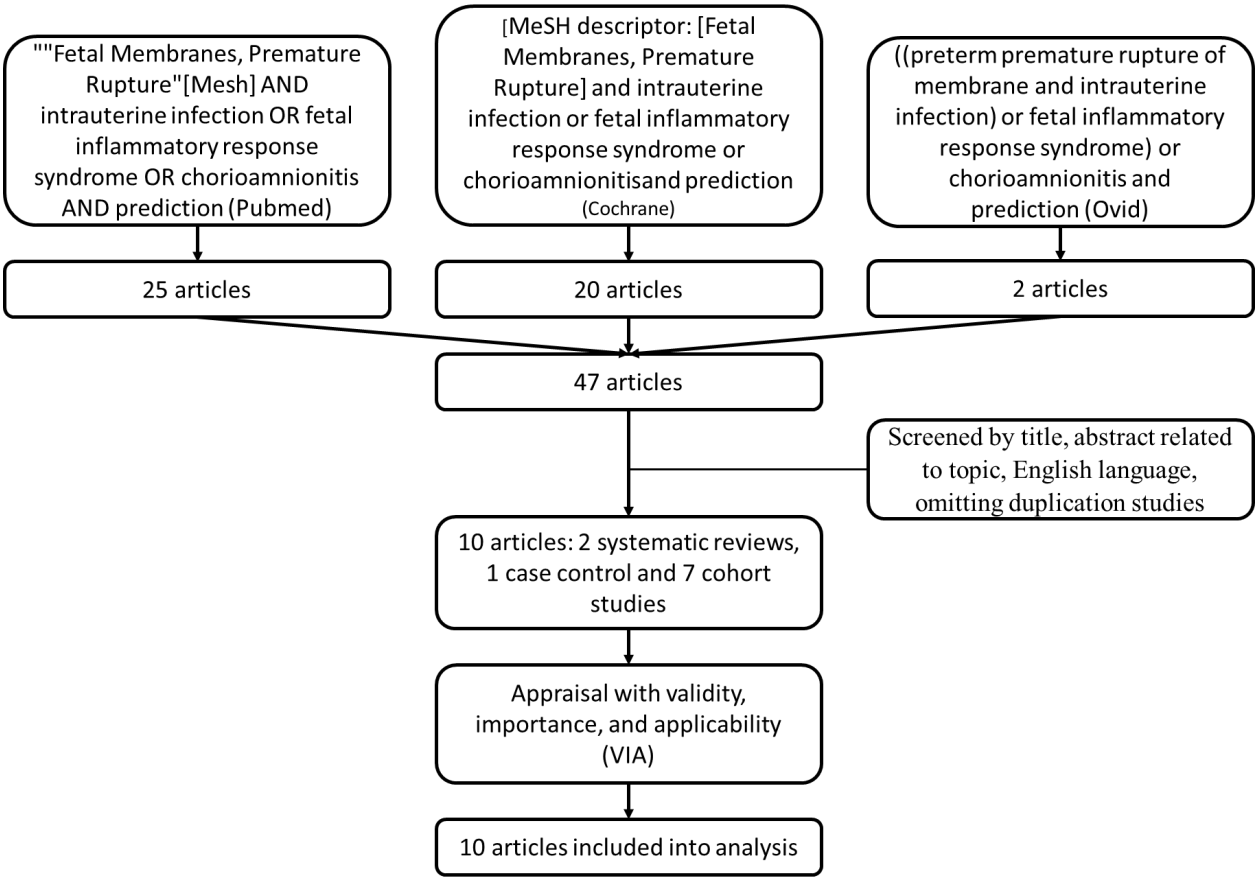

Figure 1: Flowchart of selecting articles using in review

RESULTS

Of 10 studies appraised, all studies in appropriate with VIA criteria based on critical appraisal of diagnostic study and systematic review by Centre for Evidence-Based Medicine, University of Oxford, 2010. Systematic reviews showed Patients-Intervention-Comparison-Outcome (PICO) and inclusion criteria were in line to the aim of this study. Unfortunately, both systematic reviews assessing the accuracy of CRP in predicting chorioamnionitis and/or neonatal sepsis in PPROM women were heterogeneity among studies. Meanwhile, other included studies attempted to find the most accurate marker to predict intrauterine infection. Table 1 and Table 2 showed the result of appraisal between systematic reviews and diagnostic studies.

Table 1: Appraisal result of systematic review

Study	Validity					Importance
	PICO	Relevant studies	Criteria for inclusion appropriate	Included studies valid	Similar among studies	Results

Trochez-Martinez et al. [13]	Determine the diagnostic accuracy of CRP in the detection of chorioamnionitis in women with PPROM.	MEDLINE (1966–2006), EMBASE (1974–2006), PubMed and the Cochrane Library (2005)	Full manuscripts of studies evaluating the performance of CRP for the diagnosis of chorioamnionitis following PPROM	The methodological quality of the studies was assessed using recognised methods and checklists	Not similar among studies	Asymmetric SROC AUC=0.8317 SE (AUC)=0.0413 Q* index=0.7642 SE (Q*)=0.0380
Rafli et al. [14]	Assess whether CRP accurately predicts chorioamnionitis and/or neonatal sepsis in women with PPROM	Electronic search in Medline (1951–2007) and Embase (1974–2007) databases	All studies evaluating the use of CRP in pregnant women with rupture of fetal membranes before 36 completed weeks of gestational age had maternal serum CRP tested	The data extracted were placed on data extraction forms using the QUADAS - tool	Not similar among studies	Figure 2, Figure 3 [14]

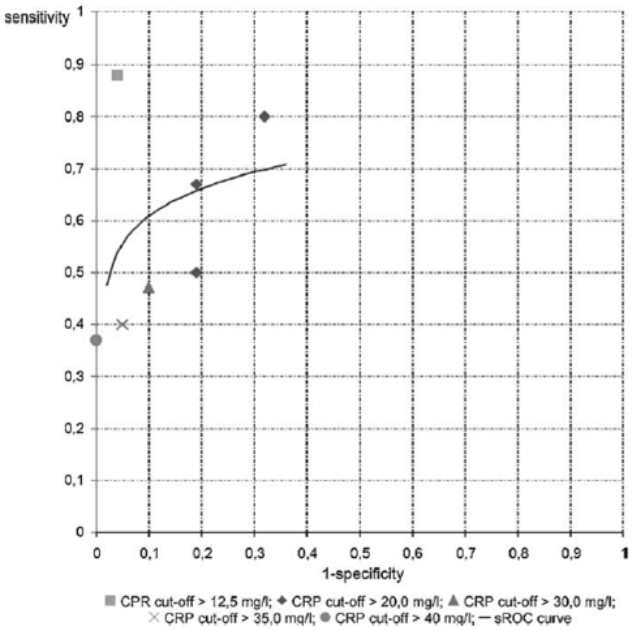

Figure 2: sROC curve for CRP and histological chorioamnionitis (■) CPR cutoff>12.5 mg/l; (◆) CRP cut-off>20.0 mg/l; (▲) CRP cut-off>30.0 mg/l; (×) CRP cut-off>35.0 mg/l; (●) CRP cut-off>40 mg/l; (-) sROC curve

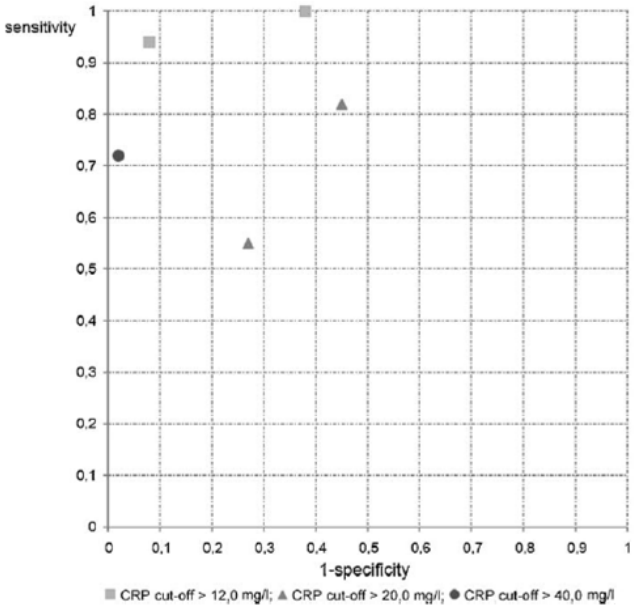

Figure 3: sROC curve for CRP and clinical chorioamnionitis (■) CRP cut-off>12.0 mg/l; (▲) CRP cut-off>20.0 mg/l; (●) CRP cut-off>40.0 mg/l

Table 2: Appraisal result of diagnostic studies

Study	Validity			Importance	Applicability
	Diagnostic test evaluated representative patients	Reference standard applied	Independent, blind comparison between index test and "gold standard"	Test characteristics presented	The methods can be permitted replication
Carroll et al. [6], Cohort studies	Yes (Women with PPROM)	Yes	Yes	Gram stain to aerobic and aerobic culture of amniotic fluid Sensitivity: 80% Specificity: 97% PPV: 86% NPV: 95% Gram stain to fetal bacteremia Sensitivity: 50%	Yes

				Specificity: 88%				
				PPV: 43%				
				NPV: 91%				
				The median leucocyte count in the positive amniotic fluid culture (median 50/mm^3) was significantly higher than in negative culture (p<0.01)				
Andrzej et al. [8], Case control	Yes (Women with PPROM between 24 and 34 weeks (case) and PROM greater 36 weeks (control))	Yes	Yes	PCT ≥ 2.2 ng/mL for congenital infection				Yes
				Sensitivity: 18%				
				Specificity 52%				
				PPV: 17%				
				NPV: 53%				
				Likelihood ratio: 0.36				
				PCT ≥ 2.2 ng/mL for histological chorioamnionitis				
				Sensitivity: 25%				
				Specificity: 50%				
				PPV: 17%				
				NPV: 63%				
				Likelihood ratio: 0.50				
Carroll et al. [10], Prospective cohort	Yes (Women with PPROM)	Yes	Yes	Amniotic fluid culture				Yes
				Low BPP				
				Sensitivity	0.36	PPV	0.5	
				Specificity	0.78	NPV	0.67	
				Fetal tachycardia				
				Sensitivity	0.14	PPV	0.67	
				Specificity	0.96	NPV	0.65	
				Reduced FHR variation				
				Sensitivity	0.29	PPV	0.53	
				Specificity	0.85	NPV	0.66	
				Nonreactive NST				
				Sensitivity	0.39	PPV	0.28	
				Specificity	0.37	NPV	0.5	
				Reduced AFI				
				Sensitivity	0.82	PPV	0.39	
				Specificity	0.22	NPV	0.67	
				Fetal blood culture				
				Low BPP				
				Sensitivity	0.5	PPV	0.26	
				Specificity	0.73	NPV	0.89	
				Fetal tachycardia				
				Sensitivity	0.29	PPV	0.67	

				Specificity	0.97	NPV	0.88	
				Reduced FHR variation				
				Sensitivity	0.36	PPV	0.31	
				Specificity	0.85	NPV	0.88	
				Nonreactive NST				
				Sensitivity	0.5	PPV	0.14	
				Specificity	0.41	NPV	0.82	
				Reduced AFI				
				Sensitivity	1	PPV	0.44	
				Specificity	0.76	NPV	1	
Kunze et al. [5], Cohort studies	Yes (Patients with PPROM (23 0/7 to 33 1/7 weeks))	Yes	Yes	FIRS (from amniotic fluid)				Yes
				IL-6 cut off was 1000 pg/mL (IMMULITE): AUC>0.84; (Quickline): AUC>0.88				
				TNF-α cut off was 200 pg/ml (IMMULITE): AUC>0.84; 300 pg/mL (Quickline): AUC>0.92				
Carroll et al. [11], Cohort studies	Yes (Patients with PPROM)	Yes	Yes	Fetal bacteremia				Yes
				The mean leucocyte and neutrophil counts in all three groups were significantly higher than normal. The leucocyte and neutrophil counts were above the 95th percentile of the normal range in 58% (22 cases) and 66% (25 cases), respectively, of the 38 cases with positive fetal blood and/or amniotic fluid cultures and in only 15% (8 cases) and 13% (7 cases), respectively, of the 53 with no infection.				
Giuseppe et al. [9], Cohort studies	Yes (Patients with PPROM (24-32 weeks of gestation))	Yes	Yes	IL-6 for detection of microbial invasion of the amniotic cavity				Yes
				IL-6>10 ng/mL in the amniotic fluid				
				Sensitivity: 80.9%				
				Specificity: 76.8%				
				PPV: 64.1%				
				NPV: 88.7%				
				IL 6>200 pg/mL in cervical secretion				
				Sensitivity: 78.5%				
				Specificity: 73.1%				
				PPV: 60.0%				
				NPV: 86.9%				
Carroll et al. [12], Cohort studies	Yes (Patients with PPROM)	Yes	Yes	Positive amniotic fluid culture				Yes
				Sensitivity: 77%				

				Specificity: 44% PPV: 44% NPV: 77% Likelihood ratio of positive: 1.43 Likelihood ratio of negative: 0.53 Positive fetal blood culture Sensitivity: 40% Specificity: 76% PPV: 23% NPV: 87% Likelihood ratio of positive: 1.64 Likelihood ratio of negative: 0.79	
Carroll et al. [7], Cohort studies	Yes (Patients with PPROM)	Yes	Yes	Intrauterine infection was associated with increased maternal temperature, leucocyte count, and CRP levels	Yes

DISCUSSION

We found from the studies, especially from Carroll et al. [7], that maternal clinical symptoms such as temperature, heart rate, leucocyte count, and CRP have a low sensitivity and specificity to predict an intrauterine infection. This is not very surprising since many reports said that the most common etiology of intrauterine infection is *U. urealyticum* and *M. hominis*, which are less likely to produce clinical symptoms than other bacterial infections. The fact that intrauterine infection hardly develops a clinical symptom made these parameters have a low role to predict intrauterine infection. However, some studies demonstrated that majority of PPROM with positive amniotic fluid or fetal blood culture showed subclinical infection which was related with neonatal sepsis. Therefore, they stated that observation of maternal parameters was essential without proof of intrauterine infection [7].

Fetal well-being is also a factor that is considered as a predictor of intrauterine infection. Several studies [10,15,16] attempted to predict intrauterine infection with this factor. Unfortunately, both studies showed that fetal well-being has a low sensitivity that also explained by the pathogen (Mycoplasma species) is less likely producing clinical sign of chorioamnionitis both in mother and fetus. In the other hand, abnormal fetal heart rate can also be caused by impaired fetal oxygenation. Abnormal fetal blood gases also showed no association with intrauterine infection in the study. This implies that fetal well-being have a little predictive value.

Several simple fetal markers such as leucocyte and CRP also showed a little role to predict intrauterine infection. Both markers were not specific since they both elevated even though negative fetal blood and amniotic fluid culture [11]. Gram stain also failed to show a good ability to predict the intrauterine infection because its low sensitivity and a culture from lower genital tract could not be a reliable predictor of intrauterine infection because the culture was similar with normal pregnancy [16-18].

The role of CRP in predicting intrauterine infection is also debatable. In systematic review by Trochez-Martinez et al. [13] stated that most studies revealed that CRP as predicting of histological chorioamnionitis had sensitivities of 50-80% with a false-positive rate of 10-30%. Only Fisk et al. [19] in this systematic review concluded that there was an association between elevated of CRP level and histological chorioamnionitis; however, there was often overlapping between infected and non-infected PPROM cases. They concluded that there was still lack of evidence to use CRP as an early diagnostic test of chorioamnionitis following PPROM. The use of CRP in histological chorioamnionitis is debatable because in very premature pregnancy, a patient would be managed conservatively until the first sign of infection. Another infection parameter, procalcitonin (PCT), also showed a weak ability to predict intrauterine infection with a sensitivity and specificity of 18% and 52% to predict congenital neonatal infection and sensitivity of 25% and specificity of 50% to predict histological chorioamnionitis.

Romero et al. [20] stated that IL-6 concentration in amniotic fluid had better predictor for intraamniotic infection than amniotic fluid Gram stain and white blood cell count. This study is supported by the findings of Giuseppe et al. [9] that showed increased level of IL-6 in amniotic fluid confirmed the intrauterine infection with the cut off 200 pg/mL (sensitivity of 78.5%; specificity of 73.1%; relative risk of 4.6 times for intraamniotic infection). It could be taken from cervical secretion to

reduce the invasive procedure using amniocentesis [21,22].

Several years later, Kunze et al. [5] established IL-6 and TNF-α in vaginal secretion from amniotic fluid were strong predictors for fetal inflammatory response syndrome (FIRS) and/or histological funisitis. Another issue was how to obtain the sample. Kunze et al. [5] used commercially available garlic press to squeeze vaginal secretion out of sanitary pads to reduce contamination. They determined a cut off value of 1000 pg/mL for amniotic fluid IL-6; meanwhile the cut off value for TNF-α was 300 pg/mL in Quickline POC test and 200 pg/mL in the IMMULITE.

Based on review above, the author summarized that clinical symptoms of maternal and fetal could not accurately predict intrauterine infection. Some markers such as IL-6 and TNF-α showed some role to predict intrauterine infection. Further studies should be conducted to determine the cut-off value of these two parameters.

CONCLUSION

Amniotic fluid IL-6 and TNF-α have a good ability to predict intrauterine infection in PPROM.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests.

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