Incidence of Neonatal Infection in Newborn Infants with a Maternal History of Premature Rupture of Membranes (PROM) for 18 Hours or Longer by Using Phramongkutklao Hospital Clinical Practice Guideline (CPG)

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Background: *Phramongkutklao CPG was developed for detecting infants with maternal PROM ≥ 18 hours who had a high risk of infection.*
Objective: *To determine efficacy of the CPG, and risk factors of infection.*
Study design: *Prospective cohort study.*
Material and Method: *Eligible infants were categorized into group I (symptomatic), group II (chorioamnionitis) or group III (asymptomatic). Infants in group I, II and those in group III who had scores ≥ 3 were treated with antibiotics. Infants were followed-up until 28 days of age.*
Results: *104 infants were recruited into the present study. 29 of 104 (27.88%) infants had infection. Risk factors were Apgar scores ≤ 5, PROM > 72 hours, gestational age < 34 weeks, and low birth weight. The success rate of using CPG was 98.08% and antibiotic use was reduced by 53.08%.*
Conclusion: *Phramongkutklao CPG on PROM is safe and cost saving. All risk factors should be included in the guideline.*

Keywords: *Premature rupture of membranes (PROM), Neonatal infection, Clinical practice guideline (CPG)*

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Premature rupture of membranes (PROM) is an important risk factor for infection in neonates. Infection rate increase significantly in infants with a maternal history of PROM > 24 hours (4-15%)[2,3] or chorioamnionitis (9-16%)[2,4]. Although there were recommendations of antenatal antibiotic administration in pregnant women who had PROM ≥18 hours[5], the regimen to prevent neonatal infection postnatally still varied among institutions. Most decisions were made based upon risk factors such as prematurity, maternal chorioamnionitis and antenatal antibiotic administration. Therefore, almost all infants with a maternal history of PROM ≥ 18 hours were treated. These practices led to antibiotic overuses, prolonged hospitalization and increased hospital expenses. To reduce this problem, a Clinical Practice Guideline (CPG) was developed and used at Phramongklao Hospital. The purpose of this CPG was to detect infants at high risk of infection and to minimize the unnecessary antibiotic uses. To evaluate the efficacy of the CPG, the authors performed a cohort study to determine the neonatal infection rate diagnosed by using the CPG. The secondary objectives of the present study were to determine the risk factors of neonatal infection, success rate on preventing re-admission due to infection and the reduction of hospital expenses by using this CPG.

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Material and Method

The authors conducted a prospective cohort study between December 1, 2001 and July 31, 2003 at Phramongkutklao Hospital. All newborn infants with maternal PROM ≥ 18 hours were enrolled. The authors excluded infants who had obvious congenital anomalies, respiratory distress requiring mechanical ventilation and congenital cyanotic heart disease. After obtaining informed consent from parents, all infants were classified into 1 of 3 groups: group I, infants who developed signs and symptoms of infection within 6 hours after birth; group II, infants with maternal chorioamnionitis, and group III, asymptomatic infants without maternal chorioamnionitis. Sepsis work up including complete blood cell count (CBC), blood culture, urine analysis, urine culture, cerebrospinal fluid (CSF) examination and culture were performed in infants of group I and group II. Both groups received ampicillin and gentamicin. Infants of group III were categorized into 1 of 3 subgroups by using a risk score system which was based upon gestational age, sex and 5-minute Apgar scores (Table 1)[4]. Designed score for gestational age < 34 weeks was 2, whereas the scores for gestational age 34-37 weeks, male sex and 5-minute Apgar scores ≤ 5 were 1. Without these factors, the designed score was 0. Total scores were the cumulative scores of gestational age, sex and Apgar scores categories. Infants having total scores of 0 or 1 were observed in hospital for at least 72 hours. Infants having total scores of 2 were observed. CBC and blood culture were also performed in this subgroup. Infants having total scores ≥ 3 were treated with antibiotics after performing sepsis work up. Neonatal infection was classified into probable infection and definite infection. Probable infection was designed for infants having clinical manifestations of sepsis or abnormal complete blood cell count (CBC) with negative cultures. Definite infection was designed for infants having positive blood or urine or cerebrospinal fluid cultures or having pneumonia on chest x-ray. Ampicillin and gentamicin were drugs of choice for all infants having indications for antibiotic use. Duration of treatment depended on result of cultures, infants' history and physicians' decision. Asymptomatic infants having a maternal history of chorioamnionitis or total scores of 3 were treated for 3-5 days. Infants with probable infection were treated for 5-7 days. Infants with definite infection were treated for at least 10 days based upon type of microorganisms, site of infection and physicians' decision. After discharge from hospital, all infants were followed-up until 28 days of age. Infection was classified as definite or probable infection. Definite infection was defined as having symptoms with positive culture of blood, urine, CSF or tracheal aspiration or with evidence of pneumonia on chest X-ray. Probable infection was defined as having symptoms or abonormal CBC without positive cultures. The study protocol was approved by the Ethic Review Committee of the Royal Thai Army Medical Department.

Table 1. Scoring system of risk factors for neonatal infection[4]

Risk factor	Score
Gestational age < 34 weeks	2
Gestational age 34-37 weeks	1
Gestational age > 37 weeks	0
Male infant	1
5-minute Apgar score ≤ 5	1

Incidence of neonatal infection in infants with maternal PROM ≥ 18 hours, and risk factors were determined. The success rate of using the CPG to prevent re-admission due to infection was evaluated.

Since the hospital expense for medical care has not changed across time, the differences of hospital expense between the study period of using CPG and previous practice depended upon the rate of antibiotic use and rate of readmission in infants at risk. Reduction of hospital expenses per year was calculated.

Statistical analysis

Data was analyzed using descriptive statistics. Logistic regression analysis with forward stepwise (likelihood ratio) method was used to identify the association between risk factors and neonatal infection. Data was analyzed at the significant level of 95% confidence interval.

Results

5,182 newborn infants were born alive during the study period. 109 infants had a maternal history of PROM ≥ 18 hours (2.10%). 104 of them were enrolled into the present study (Table 2). Five infants were excluded because of having respiratory distress requiring ventilator support (n = 4) or being deviated from the study protocol (n = 1). Duration of PROM was between 18 and 72 hours in 96 (92.3%) infants.

Table 2. Characteristics of mothers and infants (n = 104)

Characteristics	n	%
Maternal age:		
< 20 years	15	14.42
20-35 years	80	76.92
> 35 years	9	8.65
Duration of PROM:		
18-24 hours	50	48.08
24-72 hours	46	44.23
> 72 hours	8	7.69
Antenatal antibiotics:		
None	30	28.85
Ampicillin	72	69.23
Gentamicin	1	0.96
Amoxycillin	1	0.96
Male infant	53	50.96
Gestational age:		
< 34 weeks	15	14.42
34-37 weeks	29	27.88
> 37 weeks	60	57.69
Birth weight:		
< 1500 grams	1	0.96
1500-2500 grams	29	27.88
> 2500 grams	74	71.15
Mode of delivery:		
Vaginal delivery	79	75.96
Cesarean section	25	24.04
Apgar scores:		
1-minute = 5	8	7.69
5-minute = 5	0	0

Eight mothers (7.7%) had PROM longer than 72 hours. Antenatal antibiotics administration was noted in 74 (71%) cases. There were 53 (51%) male infants. 89 (85.6%) infants were born at a gestational age less than 37 weeks. 30 (28.8%) infants had birth weights less than 2500 grams. Most infants (76%) were born by vaginal delivery. 1 minute Apgar scores were ≤ 5 in 8 (7.7%) infants but none had Apgar scores at 5 minutes ≤ 5. All infants (100%) were followed-up until 28 days of age.

Incidence of neonatal infection

There were 12, 19 and 73 infants in group I, II and III, respectively. Infants in group I developed symptoms within 6 hours after birth and received antibiotic treatment. All infants in group II received antibiotics due to maternal chorioamnionitis but only 12 (63.2%) of them had clinical manifestations of infection. Positive white blood cells in gastric content were noted in 17 infants of group II but only 10 (58.8%) of them developed symptoms of infection. Infants in group III were categoried into subgroups based on a risk scoring system. 58 infants had risk cores of 0 or 1. Thirteen and two infants had risk scores of 2 and 3, respectively. Only 5 of 73 (6.8%) infants in group III had probable infection. Overall neonatal infection was diagnosed in 29 of 104 (27.9%) infants with maternal PROM ≥ 18 hours (Table 3).

Risk factors of neonatal infection

Logistic regression analysis revealed no association of maternal age, antenatal antibiotic administration, sex and mode of delivery to neonatal infection. On the other hand, gestation age < 34 weeks, low birth weight, Apgar score at 1 minute ≤ 5, and duration of PROM > 72 hours were associated with neonatal infection (Table 4).

Success rate of using the CPG

Using the CPG in infants with maternal PROM ≥ 18 hours, all infants were observed in hospital for at least 72 hours. 38 infants (36.5%) were treated with antibiotics. After hospital discharge, 2 infants were re-admitted. One infant from group I was diagnosed as having viral infection at the age of 27 days and received no antibiotic treatment. The other was an infant from group III who had risk scores of 0-1 and received no antibiotics treatment. He was re-admitted at the age of 25 days due to urinary tract infection. Although both infections were less likely to be associated with history of maternal PROM, using the CPG in the present study at least successfully prevented re-admission due to infection in 102 of 104 infants (98.1%).

Hospital expenses

In the past, infants with maternal PROM ≥ 18 hours received antibiotic treatment if they had symptoms of infection; mothers had chorioamnionitis or received antenatal antibiotics. Based on the previous strategy, 81 of 104 (77.9%) infants (12 infants of group I, 19 infants of group II and 50 infants of group III)

Table 3. Incidence of neonatal infection

Group	Number of infants	Symptomatic infants (%)	Definite infection	Probable infection
1	12	12 (100)	3	9
2	19	12 (63.16)	2	10
3	73	5 (6.85)	0	5

Table 4 Factors associated with neonatal infection

Factor	β	Odds ratio	95%CI	p value
Constant	4.148			
Gestational age 34-37 weeks	-3.028	0.048	0.011-0.217	0.000
Gestational age < 34 weeks	-2.444	0.087	0.018-0.426	0.003
1-minute Apgar score ≤ 5	-3.029	0.048	0.005-0.462	0.009

Factors	Relative risk (RR)	95% confidence interval
1-minute Apgar score ≤ 5	3.82	2.43-5.99*
Duration of PROM > 72 hours	3.47	1.56-7.72*
Gestational age < 34 weeks	5.33	2.77-10.25*
Birth weight 1500-2500 grams	3.40	1.84-6.28*
Birth weight < 1500 grams	6.17	3.67-10.35*

* Statistical significance at $p < 0.05$

would receive antibiotic therapy. Therefore the total hospital expense for 81 admissions and 23 observations were 487,425 Baht. In contrast, by using the CPG, only 36 (34.6%) infants were treated after birth and 2 (1.9%) were readmitted after discharge from hospital. The total hospital expense for this current practice was 237,550 Baht (Table 5). Hospital expenses decreased from 487,425 Baht to 237,550 Baht. Therefore, using this CPG reduced antibiotic overuses and saved money 149,925 Baht per year.

Discussion

The incidence of neonatal infection of 27.9% in infants with maternal PROM ≥ 18 hours was higher than previous studies (2.6-8.1%)[2-4] probably due to differences in diagnostic criteria of clinical sepsis in neonates.

St Geme's scoring system[4] in infants with maternal PROM was useful to identify infants at high risk of having infection. The present study confirmed that premature infants[4,6] and low Apgar scores[4], but

Table 5. Hospital expense in infants using CPG (n = 104)

Group	Hospital service	Hospital expense/case (Baht)	Number of infants	Hospital expense(Baht)
Group I	1st admission	5,975	12	71,700
	Readmission	6,125	1	6,125
Group II	1st admission	5,975	19	113,525
	Readmission	6,125	0	0
Group III				
Score 0-1	Observation*	150	56	8,400
	1st admission	5,975	2	11,950
	Readmission	6,125	1	6,125
Score 2	Observation*	150	12	1,800
	1st admission	5,975	1	5,975
	Readmission	6,125	0	-
Score 3	1st admission	5,975	2	11,950
	Readmission	6,125	0	-
Total Hospital expense (Baht)				237,550

* Observation in hospital for 3 days after birth,
Admission after birth to treat infection, Admission after discharge from hospital
Hospital expense included antibiotics, medical equipments, laboratory investigation, nursing care and other medical services

not the male sex, were important risk factors.

One of the criteria to diagnose maternal chorioamnionitis was finding white blood cells more than 5/hpf in infants' gastric content[6]. In the present study only 59% of infants diagnosed as having maternal chorioamnionitis by this criteria developed symptoms of infection. False negative was probably due to contamination of swallowed maternal blood in gastric content[6]. Previous studies also demonstrated low sensitivity and specificity of white blood cells in gastric content in predicting chorioamnionitis. The definite diagnosis of chorioamnionitis should be based on findings of inflammation or infection of placenta[7-9]. Before using these criteria to diagnose chorioamnionitis, furthur studies to compare white blood cells in gastric content with gold standard of placenta examination should be evaluated. However, we suggest that having a large number of white blood cells without red blood cells may be useful in clinical practices since it may represent inflammation of the amniotic fluid.

Concerning the high possibility of negative blood culture in infants, previously all infants whose mothers received antenatal antibiotic therapy were treated with antibiotics. The present study revealed that a history of antenatal antibiotic use or not was not associated with clinical sepsis in neonates. The present result was different from other studies[5,10-12] because the authors didn't analyze types, duration and the number of antibiotic administration. The authors suggest that treating all infants with a maternal history of antibiotic therapy may result in antibiotic overuses. Therefore, the decision to start treatment in these infants should be based on other risk factors. Observation of these infants for at least 72 hours is also important since most infected infants developed symptoms within 24-48 hours of life[3].

In conclusion, the authors demonstrate the incidence of neonatal infection in infants having maternal history of PROM for 18 hours or longer by using Phramongkutklao CPG. The criteria to identify infants at risk should include gestational age < 34 weeks, birth weight < 2500 grams, 1-minute Apgar score ≤ 5 and duration of PROM > 72 hours. All infants having maternal history of PROM for 18 hours or longer should be observed in hospital for at least 72 hours. The Phramongkutklao CPG can prevent overusage of antibiotics and reduce hospital charges. Therefore, the CPG should be implemented in general practice.

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อุบัติการณ์การติดเชื้อในทารกที่มารดามีน้ำเดินก่อนคลอด 18 ชั่วโมง หรือนานกว่าเมื่อใช้แนวทางปฏิบัติของโรงพยาบาลพระมงกุฎเกล้า

วรนาฏ รัตนากร, วิษณุชัย ศรีจริยา, แสงแข ชำนาญวนกิจ, ปรียาพันธ์ แสงอรุณ

***ที่มา**: ภาวะน้ำเดินก่อนคลอดเป็นปัจจัยเสี่ยงต่อการติดเชื้อในทารกแรกเกิด แนวทางปฏิบัติถูกสร้างขึ้นเพื่อครอบคลุมทารกที่มีความเสี่ยงสูงและลดการใช้ยาปฏิชีวนะเกินจำเป็น*

***วัตถุประสงค์**: เพื่อศึกษาผลของการใช้แนวทางปฏิบัติในการดูแลทารกที่มารดามีน้ำเดินก่อนคลอด ณ 18 ชม. และปัจจัยเสี่ยงต่อการติดเชื้อ*

***รูปแบบการวิจัย**: การศึกษาเชิงติดตามไปข้างหน้า*

***วัสดุและวิธีการ**: ทารกที่มารดามีน้ำเดินก่อนคลอด ณ 18 ชม. แบ่งเป็น: กลุ่ม 1 (มีอาการสงสัยภาวะติดเชื้อ); กลุ่ม 2 คือ มารดามีน้ำคร่ำอักเสบ และกลุ่ม 3 คือ ไม่มีอาการและไม่มีน้ำคร่ำอักเสบ ซึ่งจะนำมาให้คะแนนตามปัจจัยเสี่ยง ทารกทุกรายในกลุ่ม 1, 2 และทารกในกลุ่ม 3 ที่มีคะแนนตั้งแต่ 3 ขึ้นไป ได้รับการรักษาด้วยยาปฏิชีวนะ ทารกทุกรายได้รับการติดตามถึงอายุ 28 วัน*

***ผลการศึกษา**: ทารกที่มารดามีน้ำเดินก่อนคลอด ณ 18 ชม. และนำเข้ามาศึกษา104 ราย พบอุบัติการณ์การติดเชื้อ 29 (27.9%) ราย ปัจจัยเสี่ยงต่อการติดเชื้อ ได้แก่ คะแนนแอ๊พการ์ที่ 1 นาที $\leq$ 5, ระยะเวลาน้ำเดิน > 72 ชม., อายุครรภ์ < 34 สัปดาห์ และน้ำหนัก < 2,500 กรัม การใช้แนวทางปฏิบัติสามารถให้การดูแลทารกได้อย่างเหมาะสม 102 ใน 104 ราย คิดเป็นความสำเร็จร้อยละ 98.08 และลดการใช้ยาปฏิชีวนะลงร้อยละ 53.08 เมื่อเปรียบเทียบกับการรักษาในอดีต*

***สรุป**: แนวทางปฏิบัติในการดูแลทารกที่มารดามีน้ำเดินก่อนคลอด ณ 18 ชม. สามารถนำมาใช้ได้อย่างปลอดภัยและประหยัด*