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Prolonged Rupture of Membranes, Neonatal Outcomes and Management Guidelines

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Abstract

Background: Prolonged rupture of membranes (PROM) is a risk factor for early-onset neonatal sepsis (EOS). In the absence of early specific and sensitive diagnostic tools, management of asymptomatic infants is difficult. This study was conducted to investigate clinical outcomes of newborns born to mothers with PROM.

Methods: A retrospective study of neonates ≥ 34 weeks admitted due to PROM was conducted. Medical charts were reviewed. Neonates were classified into three categories based on their status at birth: ill appearing, well, and equivocal. Sepsis risk calculator was retrospectively applied.

Results: A total of 176 neonates were included. All mothers had unknown group B streptococcus (GBS) status. Of them, 74.4% were asymptomatic. Nine infants (5%) had positive cultures, and 23 infants (13%) had culture-negative sepsis. The newborns with sepsis fit into the "ill appearing" category with a significantly higher proportion (12.5% vs. 0.0%, P value < 0.0).

Conclusions: Reliable early diagnostic tools for neonatal sepsis are lacking. Adopting a protocol that utilizes multiple methods and follow-up for the clinical condition of these infants are the key factors to avoid missing neonates with true sepsis and decreasing the use of antibiotics in those without infection.

Keywords: Prolonged rupture of membranes; Sepsis; Neonate; Group B streptococcus; Guidelines

Introduction

Amniotic membranes are protective to the fetus, with anti-inflammatory, anti-bacterial, and anti-viral properties [1]. Prolonged rupture of membranes (PROM) is considered when the duration is more than 18 h prior to delivery [2]. The incidence of PROM worldwide is variable, ranging from 8% as recorded by the World Health Organization [3] to around 19% in countries such as China [4]. The association between neonatal sepsis and the duration of membrane rupture was first reported in 1963 [5] in a study which showed a higher rate of newborns with either clinical or proved sepsis to mothers with ruptured membranes of more than 6 h. Many subsequent studies have linked PROM to neonatal sepsis [6-8]. In contrast, others have dismissed the relation between PROM and neonatal sepsis [9].

In the absence of early specific and sensitive diagnostic tools for neonatal sepsis, management of infants born to mothers with PROM proves to be a dilemma, especially for asymptomatic neonates at birth [10]. Tools such as the Kaiser Permanente early-onset neonatal sepsis (EOS) calculator [11] help physicians calculate the risk of EOS in neonates at 34 weeks' gestational age and older. It has multiple predictors, including the highest maternal temperature reached, maternal group B streptococcus (GBS) status, and antibiotics taken within the intrapartum period. It can be useful in determining which neonates should take antibiotics and which should be under routine care or close observation. However, some are skeptic about the predictability of the calculator, with reports of up to 75% missed cases of not administering antibiotics to neonates with positive blood cultures when relying on the EOS calculator [12].

The predictability of laboratory investigations such as complete blood count (CBC) and C-reactive protein (CRP) is low especially at the onset of illness, or initially in asymptomatic newborns. Their use to rule out sepsis should depend on serial measurements [13].

Therefore, this diagnostic challenge might justify the practice of admitting all neonates born to mothers with PROM and administering empirical broad-spectrum antibiotics. This is where the problem lies, as many of these asymptomatic neonates do not have sepsis, and yet take empirical antibiotics for an extended period of time. This practice drastically increases the load on neonatal units, and exposes the newborn infants to hospital-acquired infections and medication side effects [14].

In our institution, this issue is further complicated by the lack of antenatal GBS screening as most of our neonates are born to mothers with unknown GBS status. Our current practice is to admit all newborn infants born after PROM to the

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neonatal intensive care unit (NICU) and initiate antibiotics regardless of their symptoms.

The aim of this study is to review the outcome of newborns to mothers with PROM and unknown GBS status and identify significant risk factors that indicate the need for antibiotic administration. We also aim to develop a protocol for management of newborns with PROM.

Materials and Methods

This is a retrospective study conducted at Jordan University Hospital NICU. The main objective is to evaluate the clinical outcomes of newborns exposed to PROM and their incidence of EOS. In addition, we evaluated the diagnostic utility of the EOS calculator, abnormal laboratory tests, and clinical signs in correctly identifying EOS in neonates born to mothers with PROM.

This study was approved by The University of Jordan Deanship of Scientific Research and by Jordan University Hospital Institutional Review Board (IRB). This study was conducted in compliance with the ethical standards of Jordan University Hospital on human subjects as well as with the Helsinki Declaration.

All admitted neonates born to mothers with PROM between January 2011 and December 2015 were included. They were identified from the hospital data base. Their medical charts were reviewed for demographic and clinical data. Laboratory investigations including blood culture results were also documented. Only neonates who were 34 weeks' gestational age were included in the analysis.

Our unit's protocol is to admit all newborns born to mothers with PROM into the NICU. Blood culture should be obtained at birth and empirical treatment with ampicillin and amikacin should be initiated.

Regarding blood investigations, CBC is usually done within the first 12 h in all infants. However, the practice regarding CRP is variable. While it was checked for most infants at 48 h to guide response to treatment, initial CRP at 6 - 12 h of age was not performed for all of them.

Sepsis was defined as the presence of clinical signs and symptoms consistent with sepsis with or without positive blood culture. Culture-negative sepsis was defined as treatment with antibiotics for ≥ 7 days in neonates with negative blood cultures [15].

Abnormal white blood count was defined as a count above 25×10^9/L (leukocytosis) or below 5.0×10^9/L (leukopenia). Thrombocytopenia was defined as a count below 150×10^9/L, and CRP was considered negative if < 5 mg/dL.

Investigators reviewed the neonates' charts and collected data for retrospective entry into the EOS calculator to determine a base-line risk of EOS at birth. These data included gestational age, duration of maternal membrane rupture, maternal colonization GBS, if the mother received intrapartum antibiotic therapy. If the mother is afebrile, maternal highest temperature was assumed to be 37.0 °C.

Next, investigators classified each neonate as "well, equivocal, or ill" using the clinical signs described on the Kaiser Permanente website; (https://neonatalsepsiscalculator.kaiserpermanente.org). Newborns with symptoms of mild to moderate respiratory distress were classified as equivocal although they were treated with nasal continuous positive airway pressure (CPAP) and should be considered as "ill" according to the above mentioned sepsis calculator. The reason for this is that all newborns with such presentation are managed by nasal CPAP in our unit. Each neonate's EOS risk was determined using the EOS calculator, with the "incidence of EOS" variable set at the highest incidence provided by the calculator (4/1,000 live births) as neonatal sepsis is still a significant morbidity in Jordan. This way, the generated recommendation will carry the lowest threshold for antibiotic treatment and will guarantee a safer approach. We compared culture-proven and culture-negative septic neonates with those whose sepsis was ruled out in regards to presentation, laboratory results, and the sepsis risk calculator recommendation.

Table 1. Demographic Characteristics of Neonates ≥ 34 Weeks' Gestational Age Admitted due to Prolonged Rupture of Membranes

Character	Distribution
Gestational age (mean ± SD)	36 ± 1.7
Birth weight (mean ± SD)	2,767 ± 777
Small for age (number/%)	9/5
Male gender (number/%)	126/71.66
Cesarean section delivery (number/%)	81/46.0
Apgar scores (mean)	
First min	7
Fifth min	9

Statistical analysis

Frequencies were compared using Chi-square test. Comparisons between groups' means were performed using the *t*-test. Statistical significance was set at $P < 0.05$.

Results

One hundred seventy-six neonates with PROM at 34 weeks' gestational age and above were included. Mean gestational age is 36 ± 1.7 weeks. Mean birth weight is 2,767 ± 777 g. Most of them were of male gender (71.66%) (Table 1). Duration of membrane rupture was mostly < 2 days (57.3%), and all mothers had unknown GBS status (Table 2).

Of them, 74.4% were completely asymptomatic at birth. Nine infants (5%) had positive cultures, and 23 infants (13%) had culture negative sepsis (Table 3). The newborns with sepsis fit into the "ill appearing" category with a significantly higher proportion (12.5% vs. 0.0%, P value = 0.000), and had higher rates of antibiotics prior to delivery (40.6% vs. 23.6%,

Table 2. Infection Risk Factors in Neonates ≥ 34 Weeks' Gestational Age Admitted due to Prolonged Rupture of Membranes

Characteristic	Number (frequency)
PROM	
PROM < 2 days	101 (57.3)
PROM 2 - 6 days	36 (20.5)
PROM > 7 days	39 (22.2)
Maternal UTI	26 (14.8)
Unknown GBS status	176 (100)
Maternal chorioamnionitis	2 (1.1)
Peripartum maternal fever	9 (5.0)

PROM: prolonged rupture of membranes; UTI: urinary tract infection; GBS: group B streptococcus.

P value = 0.049), higher rates of positive CRP at 48 h, and a longer hospital stay (10 ± 3 days vs. 4 ± 2 days, P value = 0.000) (Table 4).

Table 3. Clinical Characteristics and Outcomes of Neonates ≥ 34 Weeks' Gestational Age Admitted due to Prolonged Rupture of Membranes

Characteristic	Number (frequency)
Status at birth	
Well	131 (74.4)
Ill	4 (2.3)
Equivocal	45 (25.6)
WBC > 25,000	7 (4.0)
WBC < 5,000	2 (1.1)
Thrombocytopenia	11 (6.3)
CRP baseline positive	11/56 (19.6)
CRP positive at 48 h	40/147 (27.2)
Blood culture positive	9 (5.1)
Length of hospital stay (average ± SD)	5 ± 3
Mortality	1 (0.57)

WBC: white blood cell; CRP: C-reactive protein.

Discussion

Management of asymptomatic newborns with PROM is puzzling. The American Academy of Pediatrics proposed guidelines for their management that depend on several factors [16, 17]. Most importantly was clinical status; any critically ill newborn should be given empirical antibiotics. As for asymptomatic neonates, management depends on gestational age and other risk factors, mainly GBS, intrapartum antibiotic coverage, and laboratory tests results.

GBS is the leading causative agent of EOS worldwide [18]. In the USA, the Centers for Disease Control and Prevention (CDC) recommends a universal screening for GBS in pregnant women around the 35th week of gestation [19], and studies in the UK reported a decline in GBS infection rates when following a screening protocol [20]. However, there is a peculiar lack of GBS screening efforts in Jordan despite significant carriage rate among pregnant women [21]. In our study, the GBS status of all the mothers (100%) was unknown, which was a major additive risk factor for neonatal sepsis in our cohort.

Of the 176 newborns ≥ 34 weeks' gestation who were included, 32 (18%) had sepsis, and nine of them (5%) had culture proven sepsis. This rate of sepsis is slightly higher than previously reported rates [15, 22]. The higher rate in our cohort might be exaggerated due to our definition of sepsis where neonates with positive CRP at 48 h were considered septic. For the sake of this study, we did not consider any positive blood culture as contamination as all the organisms found in our blood cultures were previously reported as neonatal sepsis causative agents. Furthermore, since we are planning to draft a protocol for management of these infants, considering all abnormal results as causative agents will help reach a safer protocol. The lack of GBS intrapartum chemoprophylaxis is a major factor for higher rates of EOS. Other factors like intrapartum obstetric practice variation, such as not restricting manual examination frequency, although not investigated in this study, might provide explanation for the higher rate of EOS.

When a neonate shows symptoms at birth, empirical antibiotics are indicated. The difficulty arises when these infants are asymptomatic. In this situation laboratory investigation should be used to guide decisions, mainly CBC and CRP values. The utility of CBC in predicting those with sepsis has been investigated and proven unreliable [23]. In our cohort none of the infants with sepsis has leukocytosis, and there was no difference between infants with sepsis and normal newborns regarding leukopenia (3% vs. 1.4%, P value = 0.492). Using CRP is not very helpful at the onset of illness [24]. Serial CRP readings have more value [13] which helps in the follow-up of infants at risk who did not receive empirical antibiotics. In those who received antibiotic therapy, CRP is useful in monitoring treatment response [25, 26]. In neonates who had CRP done at 6 - 12 h of age, there was no significant difference between those with sepsis and normal newborns (28.6% vs. 21.2%, P value = 0.656). However, at 48 h there was a significant difference between the two groups (43.8% vs. 27.54%, P value = 0.008). This significance is subject to selection bias since rising CRP at 48 h is part of the criteria to define neonates with sepsis, as this difference illustrates the importance of serial CRP measurements.

The other tool that can be utilized in decision making for asymptomatic newborns is the sepsis risk calculator. It is considered a helpful tool for prediction of sepsis in neonates with infection risk factors [14]; however it is not completely reliable in predicting sepsis in normal newborns and has been shown to miss neonates with true sepsis [12, 22]. Applying sepsis calculator retrospectively has some limitations, relying on the medical charts, and assuming maternal temperature [22], but in this case where drafting a protocol is the aim, it is an acceptable method. The most important step when using the calculator tool is determining the general condition of the newborn. "Well" and "ill" conditions are simple to decide. The "equivocal" condition is tricky and might not be a univer-

Table 4. Comparison of Neonatal Characteristics and Outcomes Between Normal Newborns and Those With Sepsis

Characteristics	Newborns with sepsis (n = 32)	Normal newborns (n = 144)	P value
Well	19 (59.3)	100 (69.4)	0.270
Ill	4 (12.5)	0 (0.0)	0.000
Equivocal	9 (28.1)	36 (25)	0.713
Sepsis calculator recommendation			
Empirical antibiotics recommended	13 (40.6)	31 (21.5)	0.240
Strongly recommended antibiotics	1 (3.1)	2 (1.4)	0.492
Blood culture recommended	1 (3.1)	11 (7.6)	0.359
Vital signs every 4 h	3 (9.4)	25 (17.4)	0.263
Routine care recommended	16 (50.0)	75 (52.1)	0.831
Gestational age (average)	36 ± 1.7	36 ± 1.7	1.0
SGA	3	6	0.226
Male gender		81	
Cesarean section	16	65	0.617
Apgar score (first/fifth min)	8/9	8/9	
Urinary tract infection	6	20	0.483
Fever	2	7	0.746
Chorioamnionitis	1	1	0.240
Any antibiotic before delivery	13 (40.6)	34 (23.6)	0.049
PROM ≤ 2 days	20	81	0.517
PROM 2 - 6 days	3	22	0.386
PROM ≥ 7	8	31	0.668
WBC > 25,000	0	7	0.669
WBC < 5,000	1 (3)	2 (1.4)	0.492
Platelets < 150	5	11	0.115
CRP baseline positive	2/7 (28.6)	11/52 (21.2)	0.656
CRP positive at 48 h	14/26 (43.8)	38/138 (27.54)	0.008
Blood culture positive	9	0	0.000
Length of hospital stay (average ± SD)	10 ± 3	4 ± 2	0.000
Mortality	0	1	0.240

SGA: small for gestational age; PROM: prolonged rupture of membranes; WBC: white blood cell; CRP: C-reactive protein.

sally applied definition in all units. According to the calculator tool, the need for CPAP outside the delivery room automatically puts the newborn in the "ill appearing" category. On the other hand, the persistence of tachypnea and other respiratory distress symptoms beyond 4 h of age puts the newborn in the "equivocal" group. We believe this is confusing and contradicting. For a newborn who has prolonged respiratory transition, or respiratory distress signs persisting beyond the delivery room, our unit protocol indicates CPAP as treatment. The sepsis calculator tool placed the symptoms in one category and the therapy in a different one. Therefore, we suggest that since CPAP is the most widely used therapy for respiratory distress, neonates on CPAP therapy for mild to moderate respiratory distress who are hemodynamically stable and are improving should not be classified as "ill". In this study all our newborns with mild to moderate respiratory distress at birth were considered "equivocal".

In this study, most infants (67.6%) were classified "well" at birth. There was no significant difference in the "well" or the "equivocal" categories between the group with sepsis and the normal newborns (59.3% vs. 69.4%, P value = 0.27 for the "well" group, and 28.1% vs. 25.0%, P value = 0.713 for the equivocal group). However when it comes to the "ill" category, none of the normal newborns were classified as "ill" (12.5% vs.0.0%, P value = 0.000). This emphasizes the importance of the clinical status and stresses the importance of starting immediate antibiotics in newborns who are ill at birth.

Applying sepsis calculator in our cohort could have saved 77% of the neonates' unnecessary antibiotic treatment. However, the sepsis calculator recommendation could have missed 50% of our newborns with sepsis in whom the recommendation was routine care. Previous studies have shown similar

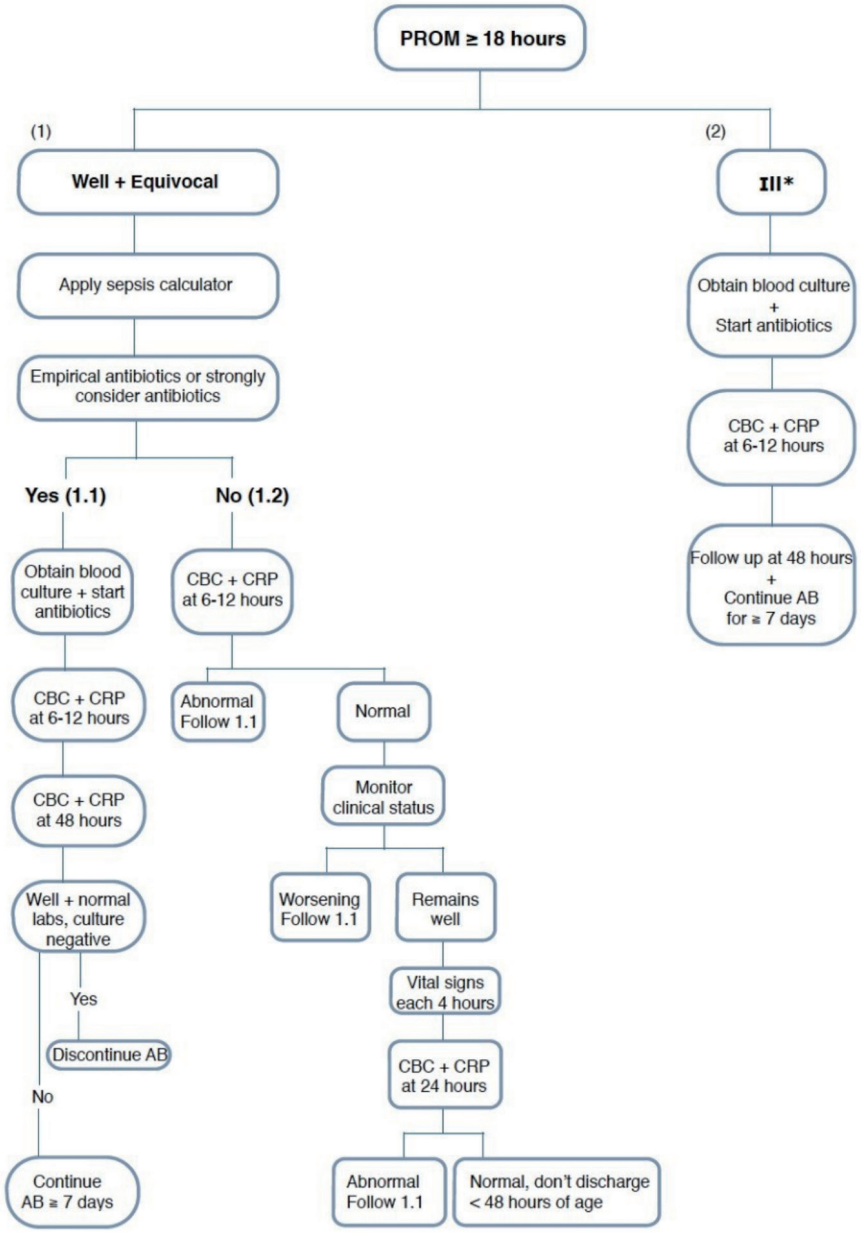

Figure 1. Suggested protocol of management of neonates born to mothers with prolonged rupture of membranes.

findings but to a lesser extent [15]. Sepsis calculator should be used with other diagnostic methods in order not to miss newborns with sepsis. Close monitoring of newborns with sepsis risk factors should be implemented regardless of their clinical status at birth or sepsis calculator recommendation. The follow-up strategy should combine clinical status and laboratory serial investigation.

There was no significant difference between the two groups regarding other maternal risk factors like the presence of urinary tract infection, maternal fever, or chorioamnionitis. However, the use of any antibiotics prior to delivery was significantly higher in the newborns with sepsis (40.6% vs. 23.6%, P value = 0.049). With the lack of GBS prophylaxis guidelines in our hospital, most of the included ladies received broad spectrum antibiotics for maternal illness shortly before birth, so they were considered non-protective when calculating sepsis risk factors [19]. The higher rate of antibiotics prior to delivery in those with sepsis might signify serious maternal illness that increased the risk of these newborns to sepsis.

It is clear that there is no single reliable tool in our setting that can be applied to predict which neonate is going to have sepsis. Applying multiple diagnostic methods, adopting strict follow-up strategy for those who do not receive antibiotics and keeping low threshold for antimicrobial treatment are

very important especially at the beginning of changing current practice to insure a high safety profile of the newly adopted protocol.

Based on the current study and previously published guidelines [16, 17], our suggested protocol will depend on many factors for decision making regarding antimicrobial therapy in neonates with PROM that include clinical status, sepsis calculator recommendations, and laboratory investigations. Therapy will be started for ill newborns and when the sepsis calculator recommends starting antibiotics. For newborns who were not given antimicrobial therapy, at any time when their clinical status deteriorates or their laboratory investigations become abnormal, they will be switched immediately to the treatment group (Fig. 1).

This study among others is important to improve the practice of neonatology. Ensuring the transition in practice must be done safely as generating new recommended protocols is nation/setting specific. Our study has many limitations, with the main limitation being its retrospective nature. A prospective study is planned to investigate the usefulness of the suggested protocol.

Reliable early diagnostic tools for neonatal sepsis are lacking. Adopting a unit-specific protocol that utilizes multiple methods and applying strict follow-up for the clinical condition of these infants are the key factors to avoid missing neonates with true sepsis and decreasing the use of antibiotics in those without infection.

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Conflict of Interest

The authors have no conflict of interest to declare.

Informed Consent

This is a retrospective chart review study. Informed consent is not applicable.

Author Contributions

MA contributed to the idea, design, analysis, and writing of the manuscript. AA and RE contributed to data gathering, analysis, drafting manuscript, and approving final manuscript. SA contributed to analysis, drafting manuscript, and approving final manuscript. EB contributed to data acquisition and approving final manuscript.

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