Original Article

Neonatal sepsis following prolonged rupture of membranes in a tertiary care hospital in Karachi, Pakistan

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Abstract

Introduction: Prolonged rupture of membrane (PROM) is an important risk factor for early onset neonatal sepsis (EONS), which is associated with increased neonatal morbidity and mortality. We reported the incidence and associated risk factors of PROM for culture-proven EONS.

Methodology:The medical records of all neonates born at Aga Khan University, Karachi over a period of five years (2007-2011) with PROM (> 18 hours) were reviewed. Data about maternal and neonatal risk factors for EONS was collected and adjusted logistic regression (AOR) analysis was applied.

Results:Incidence of PROM in this neonatal birth cohort was 27/1,000 live births. A total of 17 (4%) cases with blood-culture proven bacterial sepsis were identified within 72 hours of birth. *Klebsiella pneumonia* (n = 5; 29%) and *Pseudomonas aeruginosa* (n = 4; 24%) were the commonest isolates followed by group B *Streptococcus* (n = 3; 18%) and *Escherichia coli* (n = 2; 12%). Maternal fever (p = <0.001; AOR, 36.6), chorioamnionitis (p < 0.001; AOR, 4.1), PROM > 48 hr. (p < 0.001; AOR, 8.2), neonatal prematurity < 34 weeks (p < 0.001; AOR, 4.1) and low birth weight < 1,500 grams (p 0.001; AOR, 9.8) along with neonatal thrombocytopenia and raised CRP were found to be independent risk factors associated with culture-proven EONS in PROM.

Conclusions: Preventive measures should focus on recognition of these high-risk infants with prompt laboratory screening for sepsis and early institution of empirical antibiotic based on local data. Such approaches would be a safe and cost-effective strategy, especially in developing countries.

Key words: neonatal sepsis; prolonged rupture of membranes; blood culture; prematurity

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Introduction

According to the World Health Organization, approximately four million neonates die annually [1] with a global neonatal mortality rate of 23/1,000 live births [2]. About a million of these deaths are attributable to neonatal infections [3]. The incidence of neonatal sepsis is approximately 1-10/1,000 live births in developed countries, but it was reported as high as three times this number in resource-limited developing countries [4].

Prolonged rupture of membrane (PROM), defined as rupture of membrane lasting more than 18 hours before labor, is found in approximately 8%-10% of all pregnancies [5,6]. PROM is an important risk factor for both early onset neonatal sepsis (EONS) [7,8] and preterm births [9]. Many studies have determined that, besides prematurity being the most common problem, infection was the most serious event and potential complication following PROM [9]. This became even more serious if both were combined [10]. PROM is significant not only in perinatal morbidity and mortality, but also in the long term neonatal complications and sequelae in survived neonates [11]. Improved prenatal care and antenatal antimicrobial treatment of women with a history of PROM had significantly improved neonatal outcome in association with early detection of sepsis and its aggressive management in neonates [12,13].

Some of the risk factors for EONS are generally felt to be more significant than others; however, there is a lack of scientific literature on risk factors of EONS in neonates born with PROM in developing countries. Thus, we conducted this descriptive study to identify the incidence of PROM, bacterial isolates, and risk factors for EONS in neonates born with PROM at a tertiary care hospital in Karachi, Pakistan.

Methodology

Study design and setting

A retrospective chart review of all neonates born with maternal PROM for more than 18 hours at Aga Khan University Hospital (AKUH) in Karachi,

Pakistan over a period of five years (between 2007 and 2011) was performed. AKUH is a 600-bed tertiary health care facility that is accredited by the international arm of the Joint Commission International Accreditation Survey (JCIA).

Patient population and definition

All neonates born with history of PROM (> 18 hour) between 2007 and 2011 were included in the study. Records were retrieved by using a health information management system (international classification of diseases [ICD] 2008; code 761.1) and the internal birth registry, which records all birth and discharge diagnoses. Neonates were excluded if they were born with severe congenital malformation, received empiric antibiotics before sending septic work-up, did not have any laboratory work-up, or were discharged home before 48 hours of life. For the purpose of study, the attending physician's diagnosis of chorioamnionitis based on clinical case definition [14] was accepted and maternal urinary tract infection (UTI) was defined according to the criteria established by the Centers for Disease Control and Prevention National Healthcare Safety Network (CDC/NHSN) Guidelines [15].

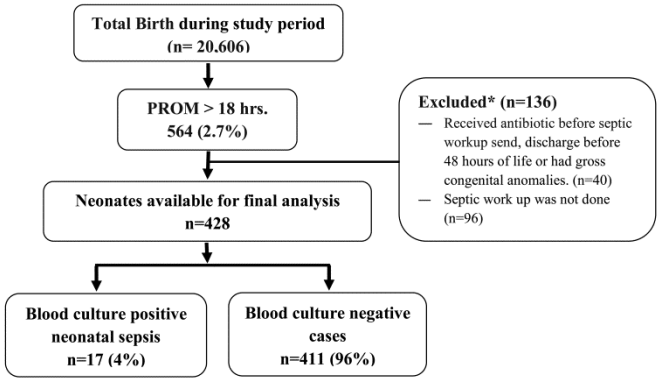
Data collection

Maternal risk factors including fever, UTI, chorioamnionitis, antibiotic use, duration of PROM, and maternal high vaginal swab for GBS positivity were recorded. Neonatal characteristics including gestational age, mode of delivery, birth weight (grams), laboratory investigations (leukocytes count, platelets counts), C-reactive protein, and bacterial pathogens isolated along with antimicrobial susceptibility were recorded.

Statistical analysis

The data was analyzed using SPSS version 20.0. Incidence of PROM (PROM cases divided by annual birth cohort per 1,000 live births) and culture-proven neonatal sepsis in PROM was calculated (positive blood culture divided by neonates with PROM). Results were presented as mean and standard deviation for continuous variables (*i.e.,* maternal age) and frequency and percentage for categorical variables (*i.e.,* duration of PROM, gender, gestational age). PROM-associated risk factors for neonatal sepsis was identified by comparing neonates with positive blood culture and negative blood culture. A p value of 0.05 was considered significant at the univariate level. For the multivariate model, a p value cut-off of 0.001 along with high crude odds ratio were taken into account. Finally, a multiple regression model was applied for all variables in such a way that the variable with the most significant p value was entered first in the final model to calculate the adjusted odds ratio.

Figure1. Flow diagram of the study



**Majority of the patients who were excluded from the study either due to sepsis evaluation not performed and/or were discharged early were asymptomatic and therefore quite unlikely to have EONS. However, these conditions raise the possibility of missed diagnoses of EONS. And if we include these infants in the denominator as blood culture negative cases then the overall incidence of EONS will reduced to 3%.*

Ethical approval

The study was approved by the Ethical Review Board (ERB) of Aga Khan University, Karachi (2190-Ped-ERC-12).

Results

During the study period 20,606 neonates were born; among this cohort, 564 (2.7%) had maternal PROM. A total of 136 neonates (Figure 1) were excluded; therefore, the demographic and clinical data of 428 neonates who had a maternal history of PROM were analyzed.

Mean maternal age of this cohort was 26.5 ± 10 years and the mean duration of maternal PROM was 30 ± 12 hours. Maternal fever (n = 74; 17%), chorioamnionitis (n = 28; 6%), and history of urinary tract infection (n = 22; 5%) were the maternal signs and symptoms at the time of delivery. Most neonates were born at term (n = 307; 72%) and via vaginal delivery (n = 306; 72%). Approximately half had a low birth weight (< 2,500 grams; n = 206; 48%). The mean birth weight was 2,228 ± 685 grams. The maternal and neonatal characteristics of this cohort are summarized in Table 1.

Table 1. Demographic features of study population (n = 428)

Variables		Number (%)
Maternal characteristics		
Age	< 20 yrs.	31 (7)
	20-35 yrs.	313 (73)
	> 35 yrs.	84 (20)
Primigravida		144 (34)
Duration of PROM	18-24 hours	268 (63)
	25-48 hours	125 (29)
	> 48 hours	35 (8)
Received antenatal antibiotics		265 (62)
Positive GBS status		39 (9)
Fever		74 (17)
Chorioamnionitis		28 (7.5)
UTI		22 (5)
Neonatal characteristics		
Mode of delivery	Vaginal delivery	306 (72)
Male		183 (43)
Gestational age	< 34 weeks	38 (9)
	34-37 weeks	83 (19)
	> 37 weeks	307 (72)
Birth weight	< 1,500 grams	62 (14)
	1,500-2,500 grams	144 (34)
	> 2,500 grams	212 (52)
Small for gestational age		139 (10)
	< 34 weeks	10 (2)
	34-37 weeks	34 (8)
	> 37 weeks	95 (22)
Leukocytosis	TLC count (> 26,000/cm)	71 (17)
Thrombocytopenia	< 150,000/cm	83 (19)
	100-150,000/cm	58 (13)
	50-100,000/cm	16 (4)
	< 50,000/cm	9 (2)
Raised C-reactive protein		96 (22)
Required NICU care		78 (18)
Died		15 (4)

Table 2. Spectrum of positive isolates in neonates with PROM

Organism	n = 17
Gram-negative organisms	**12 (71%)**
Klebsiella pneumoniae	5 (29.4)
Pseudomonas aeruginosa	4 (23.5)
Escherichia coli	2 (11.8)
Haemophilus influenza	1 (5.9)
Gram-positive organisms	**5 (29%)**
Group B *streptococcus*	3 (17.6)
Viridans streptococcus	1 (5.9)
Staphylococcus aureus	1 (5.9)

Culture-positive EONS were seen in 17/428 (4%) newborns. The commonest isolates were *Klebsiella pneumonia* (n = 5; 29%), *Pseudomonas aeruginosa* (n = 4; 24%), GBS (n = 3; 18%), and *Escherichia coli* (n = 2; 12%) (Table 2). Culture-proven EONS was ten times more common in preterm than in term neonates [p = < 0.001; crude OR 10 (CI, 3.6-27)]. Logistic regression analysis was performed for the identification of risk factors for culture-positive EONS in maternal PROM and crude and adjusted OR was calculated (Table 3). Maternal fever, chorioamnionitis, PROM > 48 hours, neonatal prematurity (< 34 weeks), and low birth weight (< 1,500 grams) along with neonatal thrombocytopenia and raised CRP were found as independent risk factors associated with culture-positive EONS in maternal PROM. The case fatality rate of this neonatal cohort was 3.5% (n = 15) and was found to be higher in preterm (n = 14; 12%) compared to full term (n = 1; 0.3%) neonates for any cause.

Discussion

Prolonged rupture of membrane (PROM) is an important risk factor for early onset neonatal sepsis (EONS) and preterm births. It continues to be a major cause of mortality and morbidity among neonates worldwide. Our reported incidence of PROM (2.7%) was low compared to the 9.8% incidence found previously in Pakistan [16]. However, the incidence of culture-proven EONS (4%) following PROM was comparable to previously published data (2.6%-8.1%) [17-19]. A much higher EONS incidence rate of 27.9% was reported from Thailand [20], while a study from Bangladesh showed that approximately one-third of all septicemia in neonates was attributable to PROM [21]. These differences are probably due to use of different criteria for diagnosis of neonatal sepsis and/or inclusion of coagulase negative *staphylococcus* and other contaminants.

The pathogens most often implicated in neonatal sepsis in developing countries differ from those seen in developed countries. Group B *Streptococcus* (GBS) is generally rare [22-24] or not seen at all [25], although maternal rectovaginal carriage rates of GBS may be similar to those recorded in developed countries [26]. Gram-negative rods (*i.e.,Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Escherichia coli*)were responsible for the majority of EONS in our study cohort; the same has been reported from various parts of developing countries [27-29].

Prematurity is the most significant cofactor associated with increased perinatal morbidity and mortality [29-31]. Various etiological associations such as infectious, inflammatory, maternal uterine and vascular disease and immunological diseases have been proposed to contribute to prematurity and PROM [32]. The incidence of culture-proven sepsis in combination with prematurity is 4%-6%; in highly suspected sepsis, the rate is 7%-11% [10]. One-fourth of our study cohorts were born prematurely and we observed a fourfold higher risk of EONS among this group compared to term neonates. Neonatal prematurity and low birth weight were also identified as important risk factors for EONS with maternal

Table 3. PROM-associated risk factors for neonatal sepsis

Variables	Total number of neonates (n = 428) No. (%)		P value	Crude OR (CI)	Adjusted OR (CI)
	Positive culture n = 17(%)	**Negative culture n = 411 (%)**			
Maternal characteristics					
No antenatal antibiotics	13 (76)	150 (36)	**0.001**	5.6 (1.8-17.6)	**--**
Duration of PROM (> 48 hours)	7 (41)	28 (7)	**< 0.001**	9.6 (3.3-27.1)	**8.2 (0.7-98.2)**
Maternal fever	15 (88)	59 (14)	**< 0.001**	44.7 (10.0-201.0)	**37.0 (3.4-93.3)**
Chorioamnionitis	12 (71)	16 (4)	**< 0.001**	59.3 (18.6-188.4)	**4.1 (0.6-26.8)**
UTI	3 (18)	19 (5)	**0.05**	4.4 (1.2-17.0)	**--**
Neonatal characteristics					
Gestational age (< 34 weeks)	7 (41)	32 (8)	**< 0.001**	8.3 (3.0-23.3)	**4.1 (0.6-29.8)**
Birth weight (< 1,500 grams)	8 (47)	54 (13)	**0.001**	5.9 (2.2-15.9)	**9.8 (1.5-65.7)**
SGA	9 (53)	130 (32)	**0.066**	2.4 (0.8-7.1)	**--**
Leukocytosis (> 26,000/cm)	7 (41)	64 (16)	**0.003**	6.4 (2.0-21.0)	**--**
Thrombocytopenia (< 150,000/cm)	10 (59)	73 (18)	**< 0.001**	6.6 (2.4-18.0)	**2.6 (0.5-13.0)**
Raised CRP	7 (41)	8 (2)	**< 0.001**	12.8 (4.1-40.4)	**5.0 (1.1-23.5)**

Abbreviations: PROM: prolonged rupture of membrane; UTI: urinary tract infection; SGA: small for gestational age; CRP: C-reactive protein

PROM in our study, as observed elsewhere [31, 32].

The evidence strongly supported the correlation between empiric use of antibiotics in women with PROM and a decrease in the incidence of neonatal sepsis [8,33-35]. Although the risk of neonatal sepsis is reduced, a 5% to 8% risk still remains [10]. However, the decision to start empiric antibiotic in neonates should be based on the presence or absence of certain maternal and neonatal risk factors (*i.e.,* maternal chorioamnionitis, prematurity) and local pathogens and their sensitivity patterns.

It has been reported that the longer the PROM duration, the higher the neonatal sepsis rate [36] and mortality [37] will be. Incidence of documented sepsis in the neonates born of mothers with rupture of membranes < 24 hours is approximately 0.9% and increases to 2.4% and 3.4% when the duration is prolonged to > 24 and > 48 hours, respectively [36]. When signs and symptoms of chorioamnionitis are present, the risk of proven sepsis increases from 3% to 5% [38]. Yield of culture positivity was eight times more in neonates with > 48 hours of maternal PROM at the time of birth. Among the 15 neonatal mortalities, six had maternal PROM of more than 48 hours [6/15; 40%; p = < 0.001; crude OR 13.6 (4-51)].

Maternal GBS colonization and PROM has been considered to be an important risk factor for EONS by some authors. Maternal GBS colonization without clinical manifestations carries a negligible 0.5%-1% risk of EONS; however, this may lead to infection even with light colonization when accompanied by PROM [8,20]. We did not find significant correlation between mothers testing positive for GBS combined with PROM and EONS.

In addition to bacterial blood cultures, various laboratory markers have been used for the early recognition of neonatal sepsis in clinically septic neonates [39]. Out of the various markers of sepsis, high CRP, thrombocytopenia, and leukocytosis were found to be more sensitive markers of neonatal sepsis in our study. We reported a case fatality rate of 3.5%; it is comparable with another similar study that reported a death rate of 4.6% [9]. Almost all neonates were premature (n = 14), as mentioned and reported by other published studies [40].

This is a retrospective chart review; we were not able to assess all the variables and were limited by the completeness of documentation by the treating physician. Most of the possible confounders were dealt with by performing advanced logistic regression analysis; however, because of the constraints of the chart review, not all the confounding variables were addressed. There is variability in the data because of a small number of culture-proven neonatal sepsis in maternal PROM, but the p value and adjusted odds ratio remain highly significant even after adjusted analysis. This was a single-center study and had a limited number of patients, so results should be generalized with caution.

Conclusions

Our data suggest that maternal fever, chorioamnionitis, PROM > 48 hours, as well as prematurity, low birth weight, neonatal thrombocytopenia, and raised CRP are identifiable risk factors for culture-proven EONS in PROM. Therefore, the management strategy for these high-risk neonates in developing countries should focus on identification of risk factors, recognition of clinical conditions with prompt laboratory screening for sepsis, and early institution of empirical antibiotic treatment.

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