EARLY ONSET NEONATAL SEPSIS IN PRETERM PREMATURE RUPTURE OF MEMBRANES

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ABSTRACT

Objective: To determine the frequency of early onset neonatal sepsis in newborn with various duration of preterm premature rupture of membranes (PPROM).

Study Design: Cross sectional study.

Place and Duration of Study: Neonatal Intensive Care Unit Combined Military Hospital, Lahore from November 2009 to November 2010.

Material and Methods: Neonates of singleton pregnancies complicated by preterm premature rupture of the membranes (PPROM) with delivery between 30 and 36 weeks gestation were included in the study. The overall frequency of neonatal sepsis was calculated on clinical and serological basis. Comparison of the frequency of sepsis among groups with varying duration of rupture of membranes was done.

Results: Out of 164 babies, 84 (51.2%) were female and 80 (48.8%) were male. Mean maternal age was 23 years (range: 18-36 years). Mean gestational age was 33 weeks (range: 30-36 weeks). Sepsis was suspected in 41(25%) babies on clinical grounds. C-reactive protein was raised in 36 (22%) neonates. There was statistically insignificant difference between clinical versus serological diagnosis (p=0.515). Frequency of neonatal sepsis was significantly higher in mothers with longer duration of rupture of membrane ($p < 0.001$).

Conclusion: Frequency of neonatal sepsis was observed to be 22%. PPROM is an important risk factor for early onset neonatal sepsis.

Keywords: CRP, Early onset neonatal sepsis, PPROM.

INTRODUCTION

The major cause of neonatal morbidity and mortality is preterm birth. It is divided into three categories; preterm premature rupture of membrane, preterm labor, and early delivery resulting from medical intervention. PPROM is defined as a rupture of the amniotic membranes before 37 weeks of gestation and before the onset of labor[1-2]. PPROM complicates only 3-4.5% of pregnancies but is associated with 40% of preterm deliveries and can result in significant neonatal morbidity and mortality[3]. The three causes of neonatal death associated with PPROM are prematurity, sepsis and pulmonary hypoplasia. Infants born with sepsis have a mortality rate four times higher than those without sepsis[4].

Neonatal sepsis is a clinical syndrome of systemic illness accompanied by bacteremia occurring in the first month of life. Early neonatal sepsis implies that the infection presented at or before first 72 hrs of life. Neonates with sepsis may have nonspecific signs and symptoms including temperature instability, hypotension, poor perfusion with pallor, mottled skin and respiratory distress[5]. The risk for developing neonatal sepsis increases progressively with the time elapsed between rupture of membranes and eventual delivery. A five-fold rise in sepsis is seen when comparing incidences at 24 hours versus 72 hours of premature rupture of membranes. Neonatal screening can be carried out using clinical guidelines as well as selected laboratory investigations. Serum C-reactive protein levels have been shown to be highly sensitive and specific for neonatal sepsis[6-7].

This study aims to observe the frequency of neonatal sepsis in mothers with various durations of premature rupture of membranes, using serum C-reactive protein levels and clinical parameters as indicator of infection. It will also provide an easy screening protocol for neonatal sepsis and allow timely treatment of neonates at risk of developing infections, while at the same time reducing unnecessary

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admissions and antibiotic use in neonates not likely to develop sepsis neonatorum.

MATERIAL AND METHODS

This cross-sectional study was conducted at Combined Military Hospital Lahore from November 2009 to November 2010. Neonates of singleton pregnancies complicated by PPROM with delivery between 30 and 36 weeks of gestation were included in the study. Women with incomplete information, multiple gestations, or a preterm delivery resulting from medical intervention, as well as women who delivered elsewhere were excluded from the study. One hundred and sixty four babies were included through non-probability convenience sampling. In all patients rupture of the membrane was diagnosed by sterile speculum examination. All pregnant women were hospitalized in the Division of Gynecology and Obstetrics, CMH Lahore. All patients were between 30 and 36 of weeks of pregnancy as best estimated by LMP, and confirmed by ultrasonography. C-reactive protein was dispatched in all cases at birth and repeated after 48hrs. For the purpose of this study, C-reactive protein levels of more than 6 IU/L were taken as positive and any one or more of the following signs and symptoms were constituted clinical evidence of sepsis: Unexplained respiratory distress, temperature instability (temperature <35.5°C or >37.5°), unexplained low APGAR without fetal distress, poor perfusion and hypotension. Blood culture was done in all patients with suspected sepsis while urine cultures, CSF and X-ray chest was done in relevant cases. All neonates were admitted in Neonatal Intensive Care Unit. A single course of betamethasone (2 doses of 12 mg 24 hrs apart) was administered to all patients. All patients received antibiotics as per the protocol. Relationship of neonatal sepsis with duration of rupture of membrane was also studied. Duration of rupture of membranes was categorized into three categories as interval between PPROM and delivery of 18-24 hrs, 25-48 hrs and >48 hrs. Data had been analyzed through SPSS version 16. Descriptive statistics were used to describe the results. Chi-square test was applied to study the relationship of neonatal sepsis with duration of rupture of membrane. Comparison of the frequency of sepsis as judged by clinical parameters versus serological markers was also made through chi-square test. A p-value < 0.05 was considered as significant.

RESULTS

Total 164 babies were included in the study. Of these, 84 (51.2%) were female and 80 (48.8%) were male. Mean maternal age was 23 years (Range: 18-36 years). Mean gestational age was 33 weeks (Range: 30-36 Weeks). Average duration of rupture of membrane was 42.1 ± 1.9 hours. Sepsis was suspected in 41 (25%) babies on clinical grounds. Initial C-reactive protein (done within 6hrs of birth) was raised in 8 (4.9%) babies while at 48 hrs C-reactive protein level was raised in 36 (22%) neonates (Table-1). There was statistically insignificant difference between clinical versus serological diagnosis (p=0.515).

Clinical evidence of sepsis showed respiratory distress developed in 25 neonates (15%), unexplained low APGAR without fetal distress in 12 neonates (7%) and poor perfusion and hypotension found in 5 neonates (3%). Blood culture was positive in 24 patients. *E coli* (46%) was the commonest organism followed by *Klebsiella* (25%), *staphylococcus aureus* (25%) and GBS (4%).

Frequency of neonatal sepsis was significantly higher in mothers with longer duration of rupture of membrane (p < 0.001).

DISCUSSION

Preterm premature rupture of membranes (PPROM) affects 5 to 10% of pregnant women and is responsible for around 30% of preterm deliveries. The diagnosis of PPROM is made by obtaining a history of leaking amniotic fluid, clinical assessment, including speculum examination, and laboratory tests such as nitrazine and fern tests. Additionally, both ultrasound evaluation of amniotic fluid volume and assessment of vaginal pH may be helpful in diagnosis of PPROM[8]. The independent relationship with perinatal complications has been illustrated by Arias and Tomich, who have prospectively shown higher rates of severe

neonatal morbidity in pregnancies complicated by PPROM than those caused by idiopathic preterm labor (27% versus 15.1%, $p< 0.02$). PPROM affects 32% to 40% of preterm deliveries, with 60% to 80% of these patients entering spontaneous labor within 48 hours, and the subsequent neonatal sequelae of preterm delivery were ensuing[3-9]. In our study PPROM was documented in 6.5% patients although 5.24% fulfilled the inclusion criteria.

Table-1: Comparison of neonatal sepsis with duration of rupture of membrane.

Duration of rupture of membranes	C-reactive protein at 48 hrs	
	≤ 6 IU	> 6 IU
18-24 hrs	46 (36%)	7 (19%)
25-48 hrs	46 (36%)	6 (17%)
> 48 hrs	36 (28%)	23 (64%)

$p < 0.001$

Sepsis in the newborn is a common disorder affecting 1.1 to 2.7% of all newborns. It is classified into early-onset form (EONS) within the first 72 hours of life and late-onset form (LONS) afterwards. Prematurity predisposes to sepsis: premature infants with a birth weight less than 1000 g (ELBW: extremely low birth weight infants) are particularly at risk with an inverse correlation between gestational age, birth weight, and sepsis[10]. Even late-preterm infants (LPI) have a fourfold higher risk of sepsis than term infants[6,11]. Thus, bacterial infections remain the most common cause for mortality and morbidity in early human life. Clinical symptoms are variable, minimal, and nonspecific[10,12]. In our study sepsis was suspected on clinical grounds in 41 (25%) neonates. Nili and Ansari found suspected cases of sepsis in 33.7%[3]. Signs of infection may be difficult to assess, particularly when the newborn has been partially treated. Sepsis was suspected on clinical grounds in 38% of neonates by Kayange et al[5].

C-reactive protein (CRP) is the most extensively studied acute phase reactant so far and despite the ongoing rise (and fall) of new infection markers it still remains the preferred index for diagnosis of neonatal sepsis in many neonatal intensive care units. The sensitivity of CRP is known to be the lowest during the early stages of infection. For a single CRP determination at the time of first sepsis evaluation the sensitivity and specificity ranges from 22% to 69% and from 90% to 96%, respectively. CD64 seems to have the potential to complement the existing combination of CRP and a cytokine (IL-6 or IL-8) to increase sensitivity up to 100%. Larger trials to define standard measurement protocols and reference values are highly desirable[6]. The combined measurement of a cytokine (IL-6 or IL-8) and CRP is currently considered as the most reliable method with the highest sensitivity and specificity for early diagnosis of both EONS and LONS[13]. IL-6 detects sepsis at an early stage of infection with a maximum of serum levels as early as 1-2 hours after inflammatory reaction has started, potentially even prior to onset of clinical symptoms[14]. The diagnostic window is short, due to the instability of IL-6, resulting in a short half life time of <20 minutes[15]. In contrast, CRP has its optimum sensitivity and specificity during the window of 24–48 hours after onset of symptoms. In our study CRP was raised in 36 (21.95%) newborn babies. CRP positivity was 13%, 11.5% and 38% among newborns born after a latent period of 18-24 hrs, 24-48 hrs and more than 48 hrs respectively. In another study involving premature infants with PROM, 15% had sepsis[16]. The incidence of proven sepsis was 4-6% and in highly suspected and proven sepsis the rate was reported to be 7-11%[7,17]. In another recent study infection occurred in 124 newborns (29%). The odds ratio (OR) of intrauterine infection incidence increased with decreasing gestational age, birth weight and APGAR score, as well as with increasing duration of the time between PROM and birth, called the latency period. Logistic regression showed that IUI was significantly influenced by the latency period (OR=1.37; 95% CI: 1.10-1.71; $p < 0.01$), gestational age (OR=2.29; 95% CI: 1.59-3.30; $p < 0.0001$) and 5-minute

APGAR score (OR=2.50; 95% CI: 1.57-3, 98; $p < 0.001$)[18].

We observed that gram negative organisms were the commonest culprit causing neonatal sepsis. Most common organism isolated was *E coli* followed by *klebsiella*, *Staph aureus* and GBS. Recent data from Pakistan reveals that *S. aureus*, *Klebsiella*, and *E coli* are the common organisms isolated in neonatal units at Karachi and Peshawar, and most of these strains are multidrug resistant[19,20,21]. The findings of our study are similar to those of the National Neonatal Perinatal Database India wherein *Klebsiella* was the predominant pathogen in 29% of cases[21,22]. *S. aureus* has been predominantly isolated in several studies[21,23-24]. Another study from Bangladesh revealed gram negative organisms were responsible for almost 73% of *episodes of neonatal sepsis with E coli* as the most common cause (30%) followed by *Klebsiella spp* (23%)[25-26].

Considering the influence of PPROM on neonatal mortality and morbidity, we found a significant relationship between the length of the interval between the rupture of membranes and delivery on the incidence of neonatal infection, though only in neonates born after PPROM with latency of more than 48 hrs and occurring between 30-33 weeks of gestation. No such correlation was seen among neonates delivered by mothers in whom PPROM had occurred at or after 34 weeks. The authors of the study found no difference in the incidence of infections amongst neonates born up to 48 hrs after PPROM in comparison to newborns delivered more than 48 hrs after PPROM.

CONCLUSION

Frequency of early onset neonatal sepsis was observed to be 22% in our study. The important risk factor which influences the frequency of neonatal infection is length of the interval between PPROM and delivery. CRP is an effective and readily available tool for diagnosis of neonatal sepsis especially in resource constrained set ups. Gram negative organisms are the commonest culprit implicated in early onset neonatal sepsis.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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