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Study of Risk factors of Neonatal Sepsis

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Abstract: ***Introduction: Sepsis is the commonest cause of neonatal mortality. Neonatal sepsis is a serious blood bacterial infection in neonate at the age equal to or less than 28 days of life which is manifested by systemic signs and symptom. Sepsis related mortality is largely preventable with prevention of sepsis itself by identifying risk factors of neonatal sepsis, timely recognition, rational antimicrobial therapy and aggressive supportive care. Present study was undertaken to ascertain and study risk factors of neonatal sepsis in tertiary care center. Objectives: To ascertain and study risk factors of neonatal sepsis in tertiary care center. Material & Methods: This prospective observational study was conducted on 372 neonates in NICU of MGM Medical College and Hospital located at Kalamboli. Neonates being admitted to NICU with signs and symptoms of sepsis or presence of predisposing factors for development of sepsis orneonates with suspected sepsis in the NICU were included in study. Result: 372 neonates were included in this study.93.3% of study population had Neonatal risk factors in which Preterm and low birth weight were significant risk factors for sepsis.47.8% of study population had Maternal Risk Factors. The major risk factors were preterm premature rupture of membranes (PPROM) or premature rupture of membranes (PROM) which was present in about 39% of study population.45.7% of study population had fetal risk factors. The major risk factors were fetal tachycardia and bradycardia, suggestive of fetal insufficiency which comprised of 43% of study population. Conclusion: The current study showed maternal, fetal and neonatal risk factors in newborns for neonatal sepsis. Neonatal risk factors have contributed more than maternal and fetal risk factors.***

Keywords: Neonatal sepsis, Risk factors, Antimicrobial sensitivity, Newborn, PROM, LBW, Preterm delivery.

1. Introduction

Sepsis is the commonest cause of neonatal mortality; it is responsible for about 30 - 50% of the total neonatal deaths in developing countries [1, 2]. It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes [3]. Sepsis related mortality is largely preventable with prevention of sepsis itself. This includes timely recognition, rational antimicrobial therapy and aggressive supportive care. India has the highest incidence of clinical sepsis (17, 000/ 1, 00, 000 live births) [4]. The case fatality rate of sepsis among neonates ranges between 25% to 65% in India [5]. Neonatal sepsis arises when pathogenic microorganisms gain entry into the bloodstream causing devastating systemic infection within the first 28 days of life [6, 7]. It is observed that birth asphyxia, prematurity, low birth weight, and other factors such as delivery settings, type of delivery, antenatal care received, newborn mixed feeding, and some cultural practices for cord care are believed to contribute to the incidence of neonatal sepsis across the world causing morbidity and mortality among neonates [8, 9]. Neonatal sepsis (NS) is a serious blood bacterial infection in neonate at the age equal to or less than 28 days of life which is manifested by systemic signs and symptom [10]. The clinical presentation of neonatal sepsis includes: temperature instability, respiratory distress, lethargy, impaired or refusal of feeding, jaundice, absent Moro's reflex, convulsions, bleeding disorder and bulging fontanel [11]. Early identification of these risk factors of neonatal sepsis and early institutional interventions can reduce neonatal mortality and morbidity rates in the country and the world at large. This study aimed at assessing the risk factors of neonatal sepsis in tertiary care center.

2. Literature Survey

Classifications of neonatal sepsis

Neonatal sepsis may be classified according to the time of onset of the disease: early onset (EOS) and late onset (LOS) [12, 13]. Early onset sepsis is mainly due to bacteria acquired before and during delivery, and Late onset sepsis is bacteria acquired after delivery (nosocomial or community sources) [14, 15].

Risk factors of sepsis

Maternal risk factors

Premature rupture of membranes (PROM):

Premature rupture of membrane is one of the most common causes of neonatal sepsis. Once the membranes have been ruptured for >18 hours, the risk of sepsis in the neonate increases approximately 10 - fold over baseline, to a rate of 1% for proven and 2% for suspected sepsis. The risk of proven sepsis with PROM in the preterm infant (PPROM) is increases to 4%–6%. A 5 - minute APGAR score <6 also raises the sepsis risk to 3%–4% [16, 17]

Chorioamnionitis/ Maternal fever:

The problem with chorioamnionitis is one of diagnostic definition in day - to - day clinical practice, with wide variability and interpretation among clinicians. The

generally accepted definition is presence of maternal fever >100.4_F with two or more of the following findings: fetal tachycardia, uterine tenderness, foul vaginal discharge, or maternal leukocytosis. The reported range of neonatal sepsis when chorioamnionitis is present is 3%–20%, with an odds ratio of 6: 42 (2.32–17.8) [18].

Prematurity:
Prematurity and neonatal sepsis increase the risk for premature infants. Preterm infants are more likely to require invasive procedures, such as umbilical catheterization and intubation. Prematurity is associated with infection from cytomegalovirus (CMV), herpes simplex virus (HSV), hepatitis B, toxoplasmosis, Mycobacterium tuberculosis, Campylobacter fetus, and Listeria species. Premature infants have less immunologic ability to resist and combat infection. This leads to infection with common organisms such as coagulase - negative staphylococci an organism usually not associated with severe sepsis [18].

Maternal urinary tract infection (UTI):
As noted, GBS bacteriuria is a risk factor for sepsis. Likewise, UTI of any cause raises the risk of sepsis in the neonate, in part due to raising the risk of prematurity and chorioamnionitis [19].

Multiple birth
In pregnancies complicated by multiple gestation, these physiologic changes may be more pronounced. There are higher levels of progesterone in multiple gestations; therefore, the effects of progesterone may be increased [20]. Additionally, alterations to the immune response are amplified. Women with multiples exhibit an increase shift from T - helper 1 to T - helper 2 immunity as compared to singletons, further decreasing the activation of macrophages, B - cells, and CD8 T cells in this population [21]. This evidence suggests that in multiple gestation physiologic changes are more pronounced and immune response is dampened, both of which may increase the risk of infections in women pregnant with multiples.

Assisted delivery: Use of instrumentation during labor causes an increased risk of susceptibility to infections which are iatrogenic if sterility is not maintained.

Place of delivery: Institutional delivery has comparatively lesser chance in neonates to acquire sepsis due to proper aseptic precautions which are adhered to. Non institutional deliveries (home, travel, public places, etc.) have a higher chance for the neonates to acquire infections.

Fetal risks factors
- **MSL (Meconium stained liqour)** occurs due to fetal asphyxia. Further this may lead to respiratory distress and cause chemical pneumonitis with secondary bacterial infections.
- **Fetal distress** ascertained by the fetal doppler by findings of either fetal heart rate of >160/min (fetal tachycardia) or <110/min (fetal bradycardia). Both the entities are an indication of impending distress or distress to the fetus. The triggering factor can be a maternal infection which further goes on to develop sepsis in the baby.

Neonatal risks factors
The most important risk factor causing sepsis development in the neonatal period is premature birth and low birth weight. Premature babies with low birth weight have a risk of developing sepsis three to ten times higher than full - term babies with normal birth weight. In addition, low levels of transplacental maternal IgG levels in preterm babies are among the risk factors [22]. Fetal distress, low APGAR score, resuscitation of the baby and the multiple pregnancies increase the risk of early - onset sepsis, whereas invasive procedures, such as frequent blood sampling, intubation, mechanical ventilation, catheter/probe insertion, insufficient breastfeeding, long - term parenteral nutrition, low stomach acid and surgical interventions especially increase the risk of late - onset sepsis [23]. Early neonatal sepsis risk factors in developing countries also include inadequate antenatal care, high rate of home birth, unsanitary birth and umbilical cord care practices, and late recognition of conditions that pose a risk of infection in the mother or baby [24].

Other risk factors:
NICU admission, Poor hygiene, Poor cord care, Bottle feeding, Invasive procedure, Superficial infection (pyoderma, umbilical sepsis) Low birth weight (<2500gms) or preterm baby [25, 26]. Febrile illness in the mother within 2 weeks prior to delivery, Foul smelling and/or meconium - stained liquor amnio., Prolonged rupture of membrane (>18 hours), More than 3 vaginal examinations during labor, Prolonged and difficult delivery with instrumentation [27, 28]. Male genders have also been implicated as a risk factor.

3. Materials and Methods

This prospective observational study was conducted in NICU of MGM Hospital and Medical College located at Kalamboli. Institutional ethics committee permission was taken prior to study. Neonates being admitted to NICU with signs and symptoms of sepsis or presence of predisposing factors for development of sepsis orneonates with suspected sepsis in the NICU were included in study. Target sample size taken was 372 by {n= NZP (1 - P) divided by d^2 (N - 1) +Z^2P (1 - P) } where n= sample size with finite population correction, N = Population size, Z= static for 95% level of confidence, P= Expected Proportion, d=Precision (0.05). Informed consent was obtained from parents of each patient before his/her involvement in the study. Neonates were enrolled on the basis of signs and symptoms of clinical sepsis (as per NNF criteria) after thorough clinical examination and proper history taking. The clinical criteria considered (NNF criteria) were – poor feeding, irritability / excessive cry, lethargy poor cry and reflexes, fever, hypothermia, jaundice, vomiting, abdominal distension, tachypnea and grunting, convulsions, diarrhea, pustules, sclerema, cyanosis, bulged fontanelle, DIC/bleeding, poor perfusion / shock, apnea. Congenital anomalies of GI system [e. g. tracheoesophageal fistula, malrotation of the gut], Congenital anomalies of respiratory system [e. g. lobar agenesis], Congenital anomalies of the cardiovascular system [e. g. TGA, complex heart diseases], Inborn errors of metabolism, Congenital anomalies of central nervous system [e. g. microcephaly, anencephaly, other neural tube defects etc.] were excluded. Relevant investigations were sent - CBC, CRP, Blood Culture, PS,

CSF for routine and culture (on high clinical suspicion of meningitis). Neonate was started on empirical antibiotics as per protocol. Each patientwas studied in a methodological manner using a well - designed proforma to find out the risk factors of neonatal sepsis.

4. Results

The current study included 372 neonates being admitted to NICU with signs and symptoms of sepsis or presence of predisposing factors for development of sepsis orneonates with suspected sepsis in the NICU were included in study.

Table 1: Gender distribution amongst study population

Gender	Frequency	Percent
Female	197	53.0
Male	175	47.0
Total	372	100.0

As seen in the above table, there was female predominance amongst study population as compared to males.

Table 2: Gestational Age amongst study population

Gestational Age	Frequency	Percent
Extreme Preterm (<28 weeks)	9	2.4
Early Preterm (28 to < 32 weeks)	96	25.8
Late Preterm (32 to < 37 weeks)	195	52.4
Term (37 to < 42 weeks)	42	11.3
Post Term (>42 weeks)	30	8.1
Total	372	100.0

As seen in the above table, Late Preterm (52.4%) was the most common gestational age amongst study population followed by Early Preterm (25.8%), Term (11.3%) and Post Term (8.1%)

Table 3: Birth Weight (in kg) amongst study population

Birth Weight (in kg)	Frequency	Percent
ELBW (<1000 gm)	9	2.4
VLBW (1000 to 1499 gm)	74	19.9
LBW (1500 to 2499 gm)	145	39.0
NBW (>2500)	144	38.7
Total	372	100.0

As seen in the above table, most of the study population had low birth weight (39%) followed by normal birth weight (25.8%), very low birth weight (19.9%) and extremely low birth weight (2.4%)

Table 4: Inborn/Outborn amongst study population

Inborn/ Outborn	Frequency	Percent
Inborn	295	79.3
Outborn	77	20.7
Total	372	100.0

As seen in the above table, most of the study population were inborn babies (79.3%) followed by outbornbabies (20.7%)

Table 5: Maternal Risk Factors amongst study population

Maternal Risk Factors	Frequency	Percent
No	194	52.2
Yes	178	47.8
Total	372	100.0

As seen in the above table, 47.8% of study population had Maternal RF

Table 6: Fetal Risk Factors amongst study population

Fetal Risk Factors	Frequency	Percent
NO	202	54.3
Yes	170	45.7
Total	372	100.0

As seen in the above table, 45.7% of study population had fetal RF

Table 7: Neonatal Risk Factors amongst study population

Neonatal Risk Factors	Frequency	Percent
No	25	6.7
Yes	347	93.3
Total	372	100.0

As seen in the above table, 93.3% of study population had Neonatal RF.

5. Discussion

Neonatal sepsis, defined by systemic circulatory abnormalities and a variable spectrum of clinical signs, resulting from invasion of the bloodstream by bacteria and other pathogens, as well as from the ineffective host response, in infants up to their first month of life [29]. The risks of neonatal infection and sepsis are inversely proportional to gestational age, thus suggesting that critical components of the immune system reach maturity only in the final weeks of gestation, just before the newborn needs them to successfully manage the transition from microbiological sterility to colonization by a healthy microbiota [30]. Neonatal sepsis has predisposition of: a) differential exposure to specific classes of infectious pathogens; b) the additional impacts of prematurity, low birth weight (LBW) and very low birth weight (VLBW); c) exposure to use of immunomodulatory drugs; and d) risks associated with therapeutic procedures in neonatal intensive care units; e) maternal health factors [31 - 36].

In the present study, there was male predominance amongst proven sepsis as compared to females with a male: female ratio of 1.27: 1. Findings correlate with a study conducted by Verma P et al. who reported that neonatal septicemia was found to be more common in males with male: female ratio was 1.87: 1 [37]. This can be attributed to the fact that the factors regulating the synthesis of gammaglobulin are probably situated on X chromosomes in the male infants.

In the present study, Late Preterm (52.4%) was the most common gestational age amongst study population followed by Early Preterm (25.8%), Term (11.3%), Post Term (8.1%) and Extreme Preterm (2.4%). Most of the study population had low birth weight (39%) followed by normal birth weight (25.8%), very low birth weight (19.9%) and extremely low birth weight (2.4%). These findings correlate well with the study conducted by Shah GS et al., reported that low birth weight, prematurity was present in 48% and 48% respectively [38]. Verma P et al. in their study reported that 60.94% neonates in study group were less than 2.5 kg [39]. Shitaye et al. observed 60% neonates were LBW [40]. Most of the study population were inborn babies (79.3%) followed by outborn babies (20.7%). The incidence of proven sepsis was 23% in the inborn population while 9.1% in the outborn

population. The incidence of probable sepsis was 60% in the inborn population while 70% in the outborn population.

In the present study, 47.8% of study population had Maternal Risk Factors. The major risk factors were preterm premature rupture of membranes (PPROM) or premature rupture of membranes (PROM) which was present in about 39% of study population. Major signs of infection were present in babies who had a PPROM/PROM lasting more than 18 hrs. Risk factor of Maternal infections (fever during 2 weeks before delivery, foul smelling vaginal discharge, CRP positive, clinical chorioamnionitis) was present in 16% of the population. Other factors such as multiple delivery and assisted delivery consisted of 3% and 4% respectively. Verma P et al. in their study reported that out of 239 newborns suspected of sepsis PROM was observed in 146 babies, out of them (38.3%) were proved as sepsis. Other factors predisposing to sepsis were frequent vaginal examination (23.25%), fever in mother (33.33%), and history of foul - smelling liquor (24.72%) [41]. Prior studies have identified maternal risk factors such as age, literacy, socioeconomic status, parity, antenatal care, PPROM, predisposing factors like maternal fever/ foul smelling liquor and mode of delivery [42, 43]. Kumar, et al. observed that maternal risk factors significantly associated with fatal outcome were: inadequate antenatal care, premature rupture of membranes 32%, assisted vaginal delivery 5% [44]. The results correlate with the findings of our study.

In the present study, 45.7% of study population had fetal risk factors. The major risk factors were fetal tachycardia and bradycardia, suggestive of fetal insufficiency and comprised of 43% of the study population. Meconium - stained liquor occurs usually in term fetus under distress where the oxygen transport via placenta is altered leading to hypoxia and gastrointestinal ischemic insult, followed by release of meconium. It was present in 9% of study population.

In the present study, 93.3% of study population had Neonatal risk factors. Preterm and low birth weight were significant risk factors for sepsis. Lower the gestational age and birth weight, higher was the incidence of sepsis in them. Vascular access, central lines, Endotracheal tubes, parenteral nutrition are administered to neonates for treatment, these act as base for growth of organisms. It can act as an additive risk factor for sepsis, or primary source of infection itself. Proper sterile techniques if not adhered to, can cause sepsis pretty swiftly in the neonates. In the extreme preterm, early preterm, extremely low birth weights or low birth weights, these babies being premature, lack developed immunity and proper regulation of the body metabolism. Due to this they are more susceptible to infections and may succumb to it. Bangi and Devi et al., observed that neonatal risk factors significantly associated with higher mortality were gestational age, gender, birth weight, time of onset of symptoms, delay in starting treatment and presence of complications were studied [45].

6. Conclusion

The current study showed maternal, fetal and neonatal risk factors in newborns for neonatal sepsis. Neonatal risk factors have contributed more than maternal and fetal risk factors. Preterm delivery and low birth weight were major neonatal risk factors while prolonged premature rupture of membranes (PPROM) was major maternal risk factor for neonatal sepsis in our study. Encouraging mothers to utilize antenatal services can help to identify the risk factors and possible interventions to minimize the risk of adverse birth outcomes including neonatal sepsis and also improving the healthcare to mothers and babies could be a key factor in reducing neonatal sepsis.

7. Future Scope

A well - designed study with a large sample size with intervention to identify and minimize the risk factors of neonatal sepsis at the earliest could be done.

Conflicts of Interest:
The authors have no conflicts of interest.

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