Effect of Chorioamnionitis on Neonatal Outcome: A Hospital-Based Study

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Abstract

Objective: The aim of this study was to determine the impact of chorioamnionitis on neonatal outcome.
Methods: This cross-section descriptive study was conducted in the neonatal intensive care unit (NICU) of the Department of Pediatrics, Liaquat National Hospital Karachi from June 1st, 2016 to December 31st, 2016. Neonates (infants < 28 days of age) with maternal risk factors indicative of chorioamnionitis (maternal febrile illness in last trimester, high WBC count in maternal blood, lower abdominal pain or tenderness, and foul-smelling discharge) were included in the study. The neonates with an inborn error of metabolism and congenital anomalies were excluded from this study. The neonates were further categorized by gestational age as a term (gestational age >37 weeks) and preterm (gestational age <37 weeks). The neonatal outcome is classified into binary categories; dead or alive. Data were recorded by the data collectors in the predesigned proforma. The data were entered and analyzed using SPSS version 22.
Results: During the study period, 1200 women delivered a singleton baby, out of which 400 were admitted at NICU. Of 400 infants, a total of 68 neonates of mothers with the indication of chorioamnionitis were enrolled in the study. The mean age of enrolled neonates was 2.55 ± 1.22 days. Out of 68 neonate babies, 33 (48.5%) were males and 35 (51.5%) were females. Only 43 (63%) were delivered, pre-term babies. The morbidities identified were respiratory distress syndrome (33.8%), sepsis (27.9%), intraventricular hemorrhage (10.3%), persistent pulmonary hypertension of newborns (11.8%) and necrotizing enterocolitis (7.4%). A total of 16 (23.5%) neonates died. Out of 16 newborns who died, 32.6% were preterm and 8% were born at term. It was noted that weight, body mass index, fronto-occipital circumference, and gestational age were significant contributors to the mortality.
Conclusion: In conclusion, chorioamnionitis is an important contributor to neonatal mortality and morbidity. The neonates of a mother with indications of chorioamnionitis are at an increased risk of respiratory distress syndrome.
Keywords: Chorioamnionitis, neonatal outcome, mortality, morbidity
IRB: Approved by Research Committee of Liaquat National Hospital; Dated 20th May 2016.
Citation: Sher A, Abbas SK, Tikmani SS, Abro F, Ashraf MJ. Effect of Chorioamnionitis on Neonatal Outcome: A Hospital-Based Study [Online]. Annals ASH KM&DC 2019;24.
(ASH & KMDC 24(3):130;2019)

Introduction

For growth and development of the fetus, the placenta plays a key and critical role. The fundamental role in the development of the normal fetusis during its fetal life[1]. Inflammation and infections of the placenta can lead to a high percentage of occurrence of perinatal mortality and morbidity. Chorioamnionitis is an infection of the placental membranes; characterized by the presence of maternal fever in last trimester of gestation, high WBC count of mother, pain in the lower abdomen or tenderness, foul-smelling discharge and maternal or fetal tachycardia[2-3]. Histopathology of placental lesions shows inflammatory infiltration i.e. lymphocytes, plasma cells,and macrophages. Both membrane and decidua were involved in chronic

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Date of Submission: 5th November 2018
Date of Acceptance: 18th October 2019

chorioamnionitis[4]. Maternal inflammatory cells invasion is a common feature of the lesions. This results in the presence of acute maternal inflammatory infiltrate in the free membrane of gestational sac, chorionic plate or sub-chorionic space. Moreover, the fetal inflammatory response (FIRS) entails acute funisitis that is manifested by an acute inflammatory infiltrate in the umbilical cord or acute vasculitis of the chorionic plate vessels that indicates the progressive severity of the infection[4].

In low-middle-income countries (LMIC), premature rupture of membranes has a strong association with chorioamnionitis, and chorioamnionitis in this setting results in preterm birth with a high mortality rate[5]. Some studies from Africa revealed that malnourished pregnant women are at high risk of developing chorioamnionitis secondary to ascending infections of the urogenital tract[6]. Due to low immunity secondary to malnutrition, African women are vulnerable in developing chorioamnionitis. Undernourished women are more likely to have a low defense mechanism against infections compared to well-nourished women[7]. Therefore in underdeveloped part of the world, the risk of infections is high due to poor antenatal and delivery care and inadequate and low-quality nutrition. In due course, high prevalence of infections especially chorioamnionitis is expected during pregnancy[6-7]. The prevalence of chorioamnionitis was found to be 9.7 / 1000 live births[8]. Studies on placentas showed that amongst term babies (>37 weeks), the prevalence of chorioamnionitis was 3% - 5% and 94% amongst placentas of babies delivered early preterm (21 - 24 weeks)[4].

It has been established that chorioamnionitis has both early and late complications for the delivered neonates. The most serious known risks of neonatal exposure to chorioamnionitis were found to be preterm delivery and early-onset neonatal sepsis and pneumonia[9]. Other identified adverse outcomes include perinatal death, neonatal birth anoxia, intraventricular hemorrhage (IVH), damage to cerebral white matter, and worse of all, serious outcomes including cerebral palsy which is hard to manage, and also other morbidities which can result after preterm birth[10]. The overall outcome of neonatal infections can entirely depend on the organism leading to these morbidities, local versus systematic infection, the time difference between infection onset and initiation of antimicrobial therapy as well as GA of the baby.

Babies born before 37 weeks of gestation and with congenital malformations are the major confounding factors that must be taken under consideration while discussing the prognosis of the sick neonate with parents or caretakers[11]. Recently a study by Pappas et al stated an increase in the probability of impairment of cognitive functions due to neuro development weakening in babies weighing <1500 grams. Neonates that were exposed to CA also showed an increased probability of death[12]. Amongst in infants born at <36 weeks of gestational, CA has been identified as one of the risk factors of developing cerebral palsy[13]. Lee et al reported that CA on histology is major predictor of poor outcome in preterm neonates due to premature rupture of membrane[14].

In mothers of the newborn with CA, the rate of neonatal deaths is variable and found to be 1.40 per 1000 live births (LB) compared to 0.81 per 1000 LB for neonates who were found to be unexposed to CA ; and their odds ratio (OR) is 1.72 (95% CI: 1.20-2.45)[8]. The OR for the neonates who died and had histology presentation of CA in their placenta and had received antibiotics versus those neonates who did not was 0.69 (95% CI = 0.21-2.26)[8]. In another study of infants who were born at 23-32 weeks' of gestational age, besides having histologically confirmed evidence of intrauterine infection and inflammation, the neonatal death rate was 9.9%-11.1%[15].

It was also found that one of the challenges in assessing and evaluating the influence of CA on clinical neonatal outcomes is the difference in diagnostic criteria used in different studies[8-11]. Although interestingly, when calculating for known major morbidity linked with CA, it was not very evident and does not come out to be a self-determining association between CA and death[11].

Various studies have shown the strong association between elevated fetal concentrations of in-

flammatory mediators (i.e. IL-6, IL-1β, and tumor necrosis factor-α (TNF-α) and neonatal sepsis. Multiple studies have proven that early antenatal screening for early detection of CA identification and implementation of effective treatment protocol will possibly provide a better prognosis for neonates born to a mother with a history of CA[10-11]. Similarly, Tita AT et al. in their study stated that clinical CA is estimated to affect 1-4% of pregnancies worldwide in developed countries[16], although data is lacking in these countries, and is expected to be higher than this rate[10-11,17].

The aim of this study is to recognize the established effects of CA on neonates and by early detection and management of CA, it is possible to prevent the risk of mortality and morbidities such as sepsis, respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage. It would also help to lessen the financial and emotional burden on the families. Therefore, it is very crucial to promptly initiate antibiotic therapy to prevent both maternal and fetal complications in casesof clinical CA. Unfortunately, there are studies which have illustrated that even timely introduction of antibiotic therapy has no significant effect on expected morbidities because of which cesarean section to expedite delivery is not indicated worth while in cases of CA unless there are other major obstetric indications to accelerate the process of delivery.

Patients and Methods

This is a cross-sectional study conducted at the Neonatal Intensive Care Unit (NICU) of the Department of Pediatrics, Liaquat National Hospital Karachi. It is a tertiary care hospital with 20 bedded Paediatrics ward, and a NICU with 13 incubators and 4 cots for the neonatal step-down unit. This study was done from June 1st, 2016 to December 31st, 2016.

Term (>37 weeks of gestation) and preterm (<37 weeks of gestation) neonates with maternal risk factors indicative of CA(maternal febrile illness in last trimester, maternal leukocytosis, uterine tenderness, foul-smelling amniotic fluid) were included in the study. Neonates with an inborn error of metabolism (IEM) and congenital anomalies were excluded from the study.

Newborns who fulfilled inclusion criteria were enrolled in the study after written consent taken from the parents of study participants. We used non-probability consecutive sampling technique for sample selection. Data were collected by data collectors (nurses working in the NICU for at least 2 years) on predesigned proforma that included patient case number, gestational age, sex, anthropometric measurements weight (kg), length (cm), fronto-occipital circumference (cm), body mass index (kg/m^2) and length of hospital stay. Additionally, data on morbidity data and mortality were collected. In a two day training by the principal investigator of the study, the data collectors were trained on the questionnaire and taking of anthropometric measurements such as weight, length, and FOC. For standardize anthropometric measurements, measurements taken by the principal investigator were taken as the gold standard.

Respiratory Distress Syndrome (RDS) was defined as the respiratory rate of >60 breaths per minute and signs of respiratory distress (nasal flaring, intercostal and subcostal in-drawing) along with ground glass appearance on the chest X-ray of the baby. Sepsis was clinically defined as the presence of one of the clinical signs (temperature >37.5 or < 35.5^0C, severe chest in-drawing, lethargy, fast breathing, poor feeding with poor sucking, convulsions, and cyanosis) with or without positive blood culture. IVH was defined as sudden pallor, seizure activity with suggestive ultrasound skull findings while PPHN was defined as the presence of fast breathing, respiratory distress, and acidosis, single loud S2 on auscultation or a harsh systolic murmur (secondary to tricuspid regurgitation), cyanosis; poor cardiac function and perfusion. NEC was defined asthe presence of symptoms of poor feeding, bloating, decreased activity, blood in the stool, or vomiting of bile with specific radiologic signs (pneumatosis intestinalis or portal venous air) on X-Ray abdomen.

Taking the prevalence of CA as 17%, confidence interval as 95% and absolute precision of 0.4, the sample size was 400.

Data were entered and analyzed on SPSS version 22.0 for analysis. Continuous variables such as weight, length, FOC, and BMI were presented as means ± SD while discrete variables like sex and binary categories of gestational age (term & preterm) were presented as frequencies and percentages. This distribution of each variable was checked for normality. The students' t-test was used to compare group means of uniformly (normally) distributed continuous variables. The non-parametric test, Mann-Whitney U was used to compare non-uniformly (normally) distributed continuous variables. Pearson's Chi-Squared test was used to compare the categorical variables. Fisher exact test was used when cell count was less than five observations. A 'P-value' <0.05 was considered as significant.

This study was approved by the ethical review committee of Liaquat National Hospital. Informed consent was taken from parents of the neonates mentioning the purpose, risks, benefits,and confidentiality of the study. It was also mentioned that each neonate would be assigned a unique ID and findings of this study will be published in a scientific journal without mentioning the name of the neonate.

Results

During the study period, 1200 neonates were delivered and of them, 400 neonates admitted in the NICU. Out of 400 neonates admitted in NICU, a total of 68 neonates had a history of maternalCA and were enrolled in the study (Fig 1). The mean age of enrolled newborns were 2.55 ± 1.22 days, mean weight 2.24 ± 0.68 kilograms, mean length 47.5 ± 3 centimeters, mean BMI 9.77 ± 2.29 kilogram per meter square, fronto-occipital circumference 33.4 ± 1.51 centimeter and mean gestational age was 34.84 ± 2.29 weeks. Of 68 newborns, 33 (48.5%) were male and 35 (51.5%) were female. Forty-three (63%) were born before 37 weeks of gestation.

Overall, the morbidity factors identified were RDS (33.8%), sepsis (27.9%), IVH (10.3%), PPHN (11.8%) and necrotizing enterocolitis (NEC) (7.4%). Amongst full-term neonates, the morbidity factors were RDS (40%), sepsis (28%) and PPHN (12%). Amongst preterm newborns, the morbidity factors were RDS (30.2%), sepsis (27.9%) and IVH (14%).

A total of 16 (23.5%) neonates died, out of which, 32.6% were preterm and 8% were born at full term. The morbidity factors among neonates who died were RDS (56.3%), PPHN (25%) and IVH (18.8%).

Compared to alive neonates, the anthropometric measurements of neonates who died were; mean weight 1.58 ± 0.41 kilograms (p-value <0.001), mean BMI 7.71 ± 1.81 kilogram per meter square (p-value <0.001), fronto-occipital circumference 32.12 ± 1.45 centimeter (p-value <0.001) and mean gestational age was 32.62 ± 2.3 weeks (p <0.001)-Table 1.

Discussion

This study found a high proportion of neonatal mortality and morbidity amongst babies whose mothers have clinical evidence of CA. Most common morbidity observed are RDS followed by neonatal sepsis, IVH, PPHN, NEC and a three fold increase in the risk of mortality. In a study, it was reported that children of a mother with CA have 35% of morbidity and 6% of neonatal mortality[18].

In this study, we found RDS as major morbidity accounting for 33.8% of cases. Similarly, in a study, it was reported that RDS is a major cause of morbidity contributing to 35%[19]. The essential pathology of RDS is inflammation that results in adaptations of hypertrophy of smooth muscles of pulmonary artery and deposition of collagen leading in microvasculature to fetal pulmonary vascular development[20] leading to an increase in pulmonary vascular resistance and subsequent reduction in pulmonary blood flow in the fetus at 2 and 4 days, respectively. Other studies also found a significant relationship between stages of CA and the development of RDS[21]. Many studies also reported that clinical CA was developed in 1-5% of term pregnancies after ruptured membranes and due to pro-

Table 1. Association of different variables with neonates and outcome

	Mean± SD Term (n=25)	Pre Term (n=43)	P-value	Mean ±SD Death (n=16)	Alive (n=52)	P-value
Weight(kg)	2.88 ± 0.45	1.86 ± 0.48	0.000	1.58 ± 0.41	2.44 ± 0.61	0.000
FOC(cm)	34.84 ± 0.62	32.60 ± 1.23	0.000	32.12 ± 1.45	33.82 ± 1.29	0.000
Length of stay(days)	2.44 ± 0.71	2.62 ± 1.52	0.494	2.56 ± 1.50	2.55 ± 1.22	0.990
Gestational age(weeks)	37.24 ± 0.43	33.44 ± 1.68	0.000	32.62 ± 2.30	35.51 ± 1.82	0.000

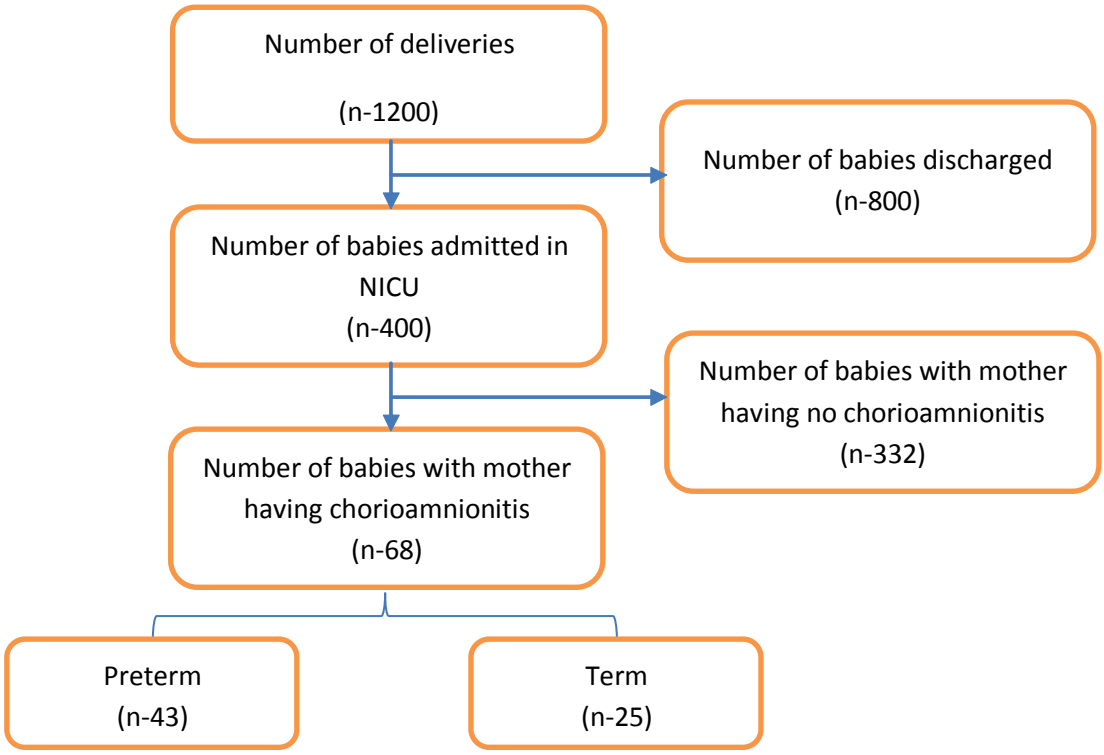

Fig 1. Flow diagram showing the number of deliveries to the final sample

longed labor at the time of term delivery[22]. The possible reasons for RDS could be secondary to intrauterine infections which ultimately would lead to altered lung development along with arrested alveolarization and vascular development[23]. Been et al. demonstrated that babies born to a pregnant women diagnosed with CA have an increased risk of developing RDS and were found to be less receptive to surfactant treatment in comparison to neonates delivered to the mothers identified with no clinical signs of CA[24]. In a systematic review it was concluded that there is an association between fetus of women with chorioamnionitis and development of bronchial asthma in later age. However, there are variations in the literature. Developing chorioamnionitis depends upon time of the infection during pregnancy, age of the child and methods of ascertainment of exposure[25].

This study also found that most of the neonates with the neurological disorder had IVH during their stay in the intensive care unit. There are a few clinical studies that pointed out the relationship between CA and neurological outcomes in newborns (especially preterm) including intraventricular hemor-

rhage, damage to brain white matter which results in a delay in cognition (neuro-developmental delay). Effect of immune system activation as a key finding demonstrated by studies report that intrauterine inflammation is definitely linked with diffuse white matter injury in the brain of preterm neonates and which is mainly due to activation of a systemic inflammatory cascade. Perinatal brain damage is a major cause of developmental delay and devastating lifelong neurological impairments such as mental retardation, cerebral palsy, learning disabilities,and behavioral issues[26]. On average, the cost of the treatment of patients with mental retardation is $51.2 billion and with cerebral palsy, the cost of treatment is $11.5 billion[27].

The relationship between intrauterine inflammation due to CA and neurological injury, particularly cerebral palsy, periventricular leukomalacia, and IVH has been provided by high-quality epidemiologic studies. In preterm deliveries with evidence of exposure to CA in combination with impaired placental perfusion has demonstrated an increase in the risk of poor neurological and neurocognitive outcomes at 2 years of age. Similar observations were made at 8 years of age in children born with evidence of exposure to severe histological CA[26].

Newborns delivered with evidence of CA in mothers are at a very high risk of getting infections in the newborn period. Fetal infection can be caused if pathogens infected the membranes that are the close proximity of the fetus and it has been proven that these pathogens also causing neonatal sepsis within the first week of life. Amongst the common pathogens are Escherichia coli and group B Streptococcus accounting for 27.9% newborn sepsis[28]. Hence, CA exposure to newborns increases the probability of newborn sepsis in first week of life by 1-3%[29]. Compared to the overall risk of newborn sepsis in the first week of life, CA increases the risk by 10 times. CA contributed to higher morbidities in premature newborns especially infections in the first week of life and its complications. A case-control study establishes that the odd of very low birth weight (VLBW) infants exposed to CA is 4.7 (95% CI: 1.4 - 15.9) times higher compared to controls. This relationship is statistically significant (p=0.015). In another comparative study, 39% of newborns with sepsis exposed to histologically proven CA and 24% newborn sepsis without CA (p-0.007)[30].

CA caused by ureaplasmahas been studied extensively and has been linked to congenital pneumonia, prolonged mechanical ventilation, and extensive release of cytokines in the neonatal lungs with subsequent development of broncho pulmonary dysplasia (BPD). However, studies that evaluated the response of antibiotic therapy with erythromycin to reduce the incidence of BPD when the neonatal lungs are colonized or infected with urea plasma have found the use of erythromycin to be a disappointment. More recent studies have found that the results with azithromycin treatment are more promising.

NEC is one of the common complications in the preterm babies but it remains a significant problem for the VLBW infant due to its impending severity and it can also result in both short and long-term complications. Although NEC is believed to have multifactorial etiology, to know the exact mechanism of its development, is not fully understood and its incidence in preterm VLBW deliveries has not changed substantially over time. NEC is supposed to be associated with a particular fetal vascular obstructive lesion, fetal thrombotic vasculopathy, and congested villi. Placental vasculopathy causes uteroplacental insufficiency that leads to circulatory adaptive changes to hypoxia which ultimately results in bowel ischemia that predispose the neonatal gut to develop to NEC1[24]. In this study we found that the frequency of NEC was 5 (7.4%). Of these 5 cases of NEC, 4 (80%) were found to be preterm babies and 1 (20%) term.

Numerous studies have shown elevated pro-inflammatory mediators in amniotic fluid and in infant's serum who was born to the mother with evidence of CA, which has a potential role in the development of PPHN Hagberg at all in his study has emphasized the confounding factors which can be responsible for the consequences of CA in both term and preterm infants[21].

Infants who were discharged were followed after 2 weeks. Among the preterm group, 4 infants were readmitted with clinical signs of sepsis, 2 died, 2 were lost to follow up and 20 stay alive. Among term babies, 20 infants stay alive and four were lost to follow up.

The results of this study should be interpreted keeping in view the limitations of the study since blood culture and sensitivity to exclude the presence of infective organisms was not done. Furthermore, there are chances of incorrect information or re-call bias by participants during follow-up done through telephonic communication. As these are findings of a tertiary care hospital, we recommend large population-based studies to assess the real burden of the CA and its impact.

Conclusion

In conclusion, our study showed that CA is an important risk factor for developing multiple morbidities including RDS and NEC preterm deliveries with expiry rate of 23.5% amongst preterm babies. Pro-inflammation is counter balanced by anti-inflammatory effects of antenatal steroids and antibiotics thus obstetric care is an important factor that may improve the outcome of babies at higher risk.

Conflict of Interest

The authors of the study do not have any conflict of interest with findings of authors of previous studies.

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