PREVALENCE OF EARLY ONSET NEONATAL SEPSIS IN TERM PROLONGED RUPTURE OF MEMBRANE, ASSOCIATED FACTORS AND MANAGEMENT PRACTICE IN TIKUR ANBESSA SPEECIALIZED HOSPITAL AND GANDHI MEMORIAL HOSPITAL, ADDIS ABABA, ETHIOPIA INSTITUTION BASED PROSPECTIVE CRROSSECTIONAL STUDY

A RESEARCH THESIS TO BE SUBMITTED TO ADDIS ABABA UNIVERSITY,COLLEGE OF HEALTH SCIENCES; PEDIATRICS AND CHILD HEALTH DEPARTMENT IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE SPECIALTY CERTIFICATE PROGRAM IN PEDIATRICS AND CHILD HEALTH

BY: MANDEFRO SECHIW (PEDIATRICS AND CHILD HEALTH YEAR III RESIDENT

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ADDIS ABABA, ETHIOPIA

ADDIS ABABA UNIVERSITY COLLEGE OF HEALTH SCIENCES SCHOOL OF MEDICINE DEPARTMENT OF PEDIATRICS AND CHILD HEALTH

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Advisors:

1. **Dr. Asrat Demtse Pediatrician , consultant neonatologist)**

Declaration form

This is to certify that the thesis prepared by Dr Mandefro Sechiw, entitled Prevalence of early onset neonatal sepsis in term prolonged rupture of membrane, associated factors and management practice in Tikur Anbessa Specialized and Ghandi Memorial Hospitals, Addis Ababa, Ethiopia, February,2024 and submitted in partial fulfillment of the requirements of speciality complies with the regulations of the university and meets the accepted standards with respect to originality and quality. This thesis has not been presented for a degree in any other university, and that all sources of materials used for the thesis have been acknowledged

THE ASSURANCE OF PRINCIPAL INVESTIGATORS

I, the undersigned, affirm that the work included in this postgraduate degree thesis is original to me, that it hasn't been submitted for credit toward a degree at any other university, and that I have properly cited all academic sources.

1.Name of the student: _____Signature_____ Date. ____

APPROVAL OF THE ADVISORS

This thesis has been submitted with my approval as university advisor.

Name of the first advisor: _____Signature _____ Date. _____

APPROVAL OF EXAMINER

Name: _____

Signature _____ Date. _____

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Acknowledgment

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Acronym

PROM……Prolonged rupture of membrane

EONS……Early onset neonatal sepsis

WHO……..World health organization

TASH ……..Tikur Anbessa specialized hospital

GDM/DM ……Gestational diabetes mellitus

APH ……..Antepartum hemorrhage

NICU ……Neonatal intensive care unit

IRB …….Institutions review board

AMR …….antimicrobial resistance

HAI……hospital acquired infection

Y-NHH…….....Yale New Heaven Hospital

SIRS ……..Systemic inflammatory response syndrome

GA……Gestational age

HTN……..Hypertension

APGAR ……(**A**-activity,**P**-pulse,**G**-grimace,**A-**apperarance,**R**-respiration)

CRP……..C- reactive protein

SPSS …….. Statistical Package for Social Sciences

AGA……..Appropriate for gestational age

SGA……..small for gestational age

LGA……Large for gestational age

MAS……meconium aspiration syndrome

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Abstract

Background: Generally newborn babies are at higher risk of infection because of their weak immune systems related to their age. According to the World Health Organization, approximately four million neonates die annually with a global neonatal mortality rate of 23/1,000 live births . About a million of these deaths are attributable to neonatal infection. Prolonged rupture of membrane is one of the risk factors for EONS and it is more common in term pregnancy. However there was no study in Ethiopia about its association of EONS in term neonates.

Objective: The overall aim of this study was to determine the prevalence of EONS in term prolonged rupture of membrane and associated factors at TASH and Gandhi memorial hospital

Methods: Institutional based prospective cross sectional study was conducted among 319 selected newborns who were evaluated at TASH and Gandhi memorial hospital from August 1st 2023 to January 30th 2024 .Data was collected from patient history, physical examination, laboratory results and from chart review through a structured questionnaire. Data was compiled and analyzed using software Statistical package for social science (SPSS) version 26. Descriptive statistics were performed using frequency, mean and standard deviation. Bivariable and multivariable binary logistic regression were done to identify risk factors of EONS .Adjusted odds ratio with 95% confidence interval at a p-value<0.05 was declared as statistically significant.

Result: About 278/ 319 (87%) of the mother were between the age of 20 to 35 years. Around 2/3 (76%) of mothers gave birth vaginally and in about 67 (21%) of cases C/S was done. Labor was spontaneous in about 88%. Most mothers 292(91.5%) delivered at hospital. Duration of labor was less than 20 hours in about 89% of cases. Most of the mothers (93%) took antibiotics for more than 04 hours before delivery. More than ½(58.6%) of newborns were male and 97% had normal birth weight. The prevalence of EONS was 32/319(10%). Tachypnea was the most common (87.5%) sign of sepsis. Around 2/3 (78%) of cases developed clinical manifestation with in the first 24 hours of life. Maternal fever (p value < 0.05 AOR, 73). Newborns with duration of ROM <24 hours was 87 %(0.13(0.02, 0.80) less septic as compared to duration of ROM more than 72 hours.

Conclusion: Maternal fever, prolonged duration of rupture of membrane and no maternal antibiotics administration was associated with early onset sepsis.so proper advice about rupture of membrane during ANC follow up and early prophylactic antibiotics admirations recommended.

Key words: neonatal sepsis, prolonged rupture of membrane, associated factors, Addis Ababa

1. INTRPDUCTIONS

1.1 Back ground of the study

A secondary infection-related systemic inflammatory response syndrome (SIRS) is neonatal sepsis. The presence of two or more of the following symptoms: fever or hypothermia, tachycardia, tachypnea or hyperventilation, and an unusually high or low white blood cell count, are indicative of systemic inflammatory response syndrome. ((1), (2)

Due to their weakened immune systems and age, newborns are more susceptible to illness. Most illnesses in neonates are brought on by bacteria, while others are brought on by viruses (3), (2). Bacteria are present in a mother's birth canal, particularly if she is actively infected. The fluid in the birth canal may be swallowed or inhaled by the baby during birthing, potentially causing bacteria or viruses to enter his bloodstream and lungs. Newborn infections can spread quickly, therefore prompt identification and treatment are crucial for the best possible result (3). A clinical state of bacteremia with systemic signs and symptoms of infection during the first four weeks of life is known as neonatal sepsis (3)

One of the main causes of death and morbidity is neonatal infection. Neonates with bacterial sepsis and meningitis frequently have a close relationship; meningitis is associated with 30% of instances of early-onset sepsis and 75% of cases of late-onset sepsis (3). Considering the high mortality rates, there must be a high index of suspicion for neonatal sepsis

Neonatal sepsis is classified based on the infant's postnatal age at the beginning of the illness. Different subspecialties have slightly different definitions, but most clinicians define early-onset sepsis as something that happens at or before 72 hours of life, and late-onset sepsis as something that happens at more than 72 hours to 7 days ((1), (3), (2)). Infection is defined as an infection that is confirmed by positive culture results for blood and cerebrospinal fluid taken from infants aged ≤72 hours plus at least five days of antibiotic therapy (4).

In cases of early-onset sepsis, newborns contract the illness through vertical transmission, which can occur from either ascending amniotic fluid infection or bacterial flora acquired from the mother's anogenital tract during vaginal birth (1).

The bacteria associated with maternal anogenital colonization are those pyogenic pathogens most commonly responsible for early-onset sepsis: group Streptococci (GBS) and Gram-negative enteric bacilli. GBS affects most of the time term (73%) and *E coli* affects preterm (81 %) (4).

Bacteremia in newborns might present physically normal and without any symptoms.(3). Therefore, laboratory testing is crucial to the diagnosing process. It is imperative to obtain a blood culture from a newborn suspected of having sepsis right away. Drawing at least 1 milliliter of blood is advised because a smaller fraction may not be able to identify low-level bacteremia. (1), (5). Urine cultures are usually not recommended for evaluation of EOS but should be considered for evaluation of LOS (6). Any infant who exhibits clinical signs that point to central nervous system involvement or who has a positive blood culture should have a lumbar puncture with investigation of the cerebrospinal fluid (CSF) and culture. Peripheral white blood cell (WBC) count with differential is often used in the evaluation of sepsis. Six to twelve hours after delivery, it is recommended to order a WBC with differential, as counts collected later are more likely to be abnormal and signal an inflammatory response than counts obtained at birth. ((1), (7)). Studies have shown leukopenia and a high percentage of immature to total white blood cells were associated with early-onset sepsis. Late-onset sepsis has been associated with both high and low WBC, high absolute neutrophil count, and high percentage of immature to total white blood cells (7).

C-reactive protein (CRP): Sepsis and other inflammatory diseases are associated with elevated CRP levels. Elevated CRP can also result from a number of non-infectious inflammatory diseases, such as intraventricular hemorrhage, meconium aspiration, neonatal hypoxia, fetal discomfort, and maternal fever (8). Neonatal sepsis cannot be diagnosed with a single CRP result due to its insufficient sensitivity and specificity (9). Sepsis appeared highly improbable based on two CRP values of less than 10 mg/L that were collected 8 to 48 hours apart (10).

After rupture of membranes for longer than twenty-four hours, the risk of newborn infection is roughly one percent. There is a 3–5% increase in risk when chorioamnionitis manifests clinically (11) . Less than 1% of pregnant women with intact membranes at term will have organisms grown from amniotic fluid (12). If the amniotic cavity's integrity is damaged by prenatal operations (such as cerclage installation or amniocentesis), the rate may be greater.

There are two categories of factors that raise the risk of infection: those that are related to the baby after birth and those that occur during the intrapartum period. Maternal GBS colonization, fever, chorioamnionitis, prolonged membrane rupture (>18 hours), and

insufficient intrapartum antibiotic therapy prior to birth are intrapartum factors that raise the risk of infection (3).The risk of infection in the infant is inversely proportional to degree of prematurity and lower birth weight (13).
Both nonspecific symptoms and focal indicators of infection can be present in neonates with bacterial sepsis (2).

General: fever, fluctuating temperatures, "Not doing well," inadequate nutrition, and edema respiratory system: retractions, tachypnea, dyspnea, and apnea grunting, flaring, and cyanosis Renal-system:-Oliguria
Cardiovascular system: Bradycardia, hypotension, pallor, mottling, chilly, clammy skin, and tachycardia
Central nervous system: hyperreflexia, hypotonia, tremors, seizures, irritability, lethargy, aberrant newborn reflex, irregular breathing, full fontanel, high-pitched cry Hematological system: thrombocytopenia, anemia, splenomegaly, and jaundice Metabolic: hypo- and hyperglycemia are common conditions.

Globally, the incidence of PROM varies, with estimates from the World Health Organization putting it at 8% to as high as 19% in nations like China (14). Regardless of the length of labor, the risk of newborn sepsis rises linearly with the duration of membrane rupture during the first 36 hours (15).In Ethiopia, the combined prevalence of early rupture of the membranes in pregnant women was 9.2% (16). Premature rupture of the membrane was substantially correlated with the following factors: no prenatal care visit; history of premature rupture of the membrane; abortion history; abnormal vaginal discharge; and urinary tract infection (16).

When it occurs more than eighteen hours before delivery, it is referred to as prolonged rupture of the membranes (PROM 17). The therapy of asymptomatic newborns is challenging in the lack of early, sensitive, and specific diagnostic tools (18).

newborn sepsis is a leading cause of newborn death and a critical global health issue, particularly in low- and middle-income countries (LMICs), which account for 99% of all neonatal deaths worldwide (19)..

The World Health Organization estimates that the newborn death rate worldwide is 23 per 1,000 live births, or over four million babies that pass away each year(13). Neonatal infections are thought to be the cause of almost a million of these deaths [13]. In wealthy

countries, the incidence of neonatal sepsis is between 1–10/1,000 live births; but, in underdeveloped countries with limited resources, the frequency has been recorded to reach up to three times that amount.

PROM SCORE (3)

	High risk factors	Scores
1	Gestational age < 34 weeks	2
2	Gestational age 34-37 weeks	1
3	Maternal clinical amnionitis Maternal temperature >38oC Sustained fetal tachycardia >160bpm Presence of PMN or bacteria in stained Sediment of amniotic fluid or infants' gastric fluid	1
4	5th minutes APGAR score < 6	1
5	Active labor >/= 20 hrs during PROM.	1

Scores		**Recommended Management**
I	0 – 1	Observation only
II	2	Microbial culture of gastric aspirate, umbilical cord blood, urine followed by observation.
III	>/= 3	As above plus examination and culture of spinal fluid followed by antibiotic therapy.

1.2 Statement of the problem

Each year, infections in the neonate cause more than 550 000 fatalities. Preventive measures, early diagnosis, prompt care seeking, administration of the proper antibiotics, and follow-up can prevent the majority of these deaths. More than half of all deaths in neonates and children under five in 2015 were caused by infectious illnesses, particularly in sub-Saharan Africa and southern Asia. The most common of them were pneumonia (920 000 deaths annually), diarrhea (526 000 deaths annually), newborn sepsis (401 000 deaths annually), and malaria (306 000 deaths annually)(20). Globally, antibiotic resistance is the greatest cause of mortality, with a greater burden in settings with little resources. Antibiotic courses are commonly administered to term babies whose mothers experienced prolonged rupture of membranes (PROM) in low- and middle-income nations. Given the increased rates of antibiotic resistance and the possible negative effects of antibiotic exposure in neonates, rational antibiotic use is essential. Nonetheless, it might be fatal to ignore sepsis patients (21). In 2019, bacterial antimicrobial resistance (AMR) was linked to 4.95 million fatalities (22).When resources are scarce, it may not always be able to manage sepsis effectively, and sepsis care is further compromised by the global rise in antimicrobial resistance (AMR) (22).

1.3 Significant of the study

Among term babies born after PROM utilizing the simplified care method with few or no antibiotics in the first week of life, there was an incidence of potential sepsis of 7.5% in a resource-limited nation with high rates of bacterial sepsis and newborn mortality. By following this procedure, antibiotic exposure was decreased in nearly 90% of newborns, potentially preventing numerous problems (21). Numerous research on neonatal sepsis and associated factors have been conducted in Ethiopia; however, despite the fact that many newborns with this issue are evaluated in neonatal intensive care units, there is little information on the correlation between PROM and early onset neonatal sepsis in term neonates. The findings from this study, which will evaluate the prevalence, could serve as a future baseline. One of the main factors contributing to neonatal death and morbidity is antimicrobial resistance (AMR). The objectives of this research are to determine the causes of sepsis, provide early antibiotic administration, increase knowledge of risk factors, and prevent the overuse of antibiotics.

2 Literature review

A prospective study was carried out at the GSL Medical College and Hospital in Rajahmundry, India, between December 2013 and November 2014. Included in the study were all newborns born to mothers who had a history of protracted rupture of the membranes lasting more than eighteen hours. That study determined that 14.5% of cases were EONS. Sepsis affects newborns with low birth weights (66%) more frequently than babies with normal birth weights (34%), and preterm neonates (61.5%) more frequently than term neonates (38.5%). Additionally, the most prevalent isolate was Staphylococcus aureus (45.45%), followed by CONS (27.27%) (23)

At Aga Khan University Hospital (AKUH) in Karachi, all neonates born with maternal PROM for more than 18 hours throughout a five-year period (2007–2011) had their retrospective charts reviewed once again. In this sample of neonates, the incidence of PROM was 27 per 1,000 live births. Within 72 hours of birth, 17 (4%) cases of bacterial sepsis with blood-culture confirmation were found. The most frequent isolates were group B Streptococcus (n = 3; 18%), Escherichia coli (n = 2; 12%), and Klebsiella pneumonia (n = 5; 29%) and Pseudomonas aeruginosa (n = 4; 24%). PROM > 48 hours ($p < 0.001$; AOR, 8.2), born prematurely < 34 weeks ($p < 0.001$; AOR, 4.1), maternal fever ($p = <0.001$; AOR, 36.6), and chorioamnionitis ($p < 0.001$; 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 (24)

In Jordan, a retrospective analysis was carried out on neonates admitted with PROM who were older than 34 weeks. There were 176 neonates in total. The group B streptococcus (GBS) status of each mother was unknown. 74.4% of them had no symptoms. 23 newborns (13%) had sepsis with no culture, while nine infants (5%) had positive cultures. The proportion of sepsis-affected babies falling into the "ill appearing" category was substantially greater (12.5% vs. 0.0%, P value < 0.0) (18)..

The meta-analysis included a fixed effects model, and the results are shown as mean difference (MD) for continuous variables, relative risk (RR), risk difference (RD), and number necessary to treat (NNT) (if appropriate) for categorical data. 95% confidence intervals (CI) are displayed with every outcome. Included in this study are the results of two

studies totaling 838 women. The use of antibiotics significantly decreased the infectious morbidity in mothers (chorioamnionitis or endometritis): RR 0.43 (95% CI 0.23, 0.82), RD -4% (95% CI -7%, -1%), NNT 25 (95% CI 14 -100). No statistically significant changes were seen with regard to newborn morbidity outcomes (14)

A retrospective study was conducted of the records of infants who had positive blood cultures taken during their stay as inpatients in the NICU at Y-NHH between 1989 and 2003. All results were compared with 60 years of historical data. Additionally, records of infants who were 30 days or older, had positive blood cultures, and were admitted to Y-NHH outside of the NICU were examined. 862 organisms in all were found in 755 sepsis events involving 647 infants.Compared to the preceding 10-year research period, the percentage of cases of late-onset sepsis increased while the percentage of instances of early-onset sepsis dropped. Sepsis attributable to Escherichia coli and group B streptococcus decreased overall. There were no sepsis incidents from S pyogenes or Streptococcus pneumoniae, which were frequent in the survey's early years. Between 1928 and 2003, the death rate from sepsis dropped steadily from 87% to 3%.

A case-control research conducted from 1993 to 2007 at 14 hospitals in California and Massachusetts on infants born at or before 34 weeks gestation. Within 72 hours, the case subjects' bacterial infection was verified by culture. Below 100.5°F, the risk of infection showed a linear association with the highest intrapartum mother temperature; above that, the risk grew quickly. The length of the membrane breach showed a consistently rising correlation with the probability of infection. A higher risk was linked to both post-term and late-preterm deliveries. In the era of group B streptococcus prophylaxis, the risk of maternal group B streptococcus colonization is reduced. Reduced risk was linked to any intrapartum antibiotic administered more than four hours before to birth (13).

A systematic literature review that examined hospital systems, surveillance systems, and other sources was part of another study that comprised 471 million individual records or isolates and 7585 study-location-years. This study estimated that 4•95 million fatalities (3•62–6•57) will be associated to bacterial AMR in 2019, of which 1•27 million (95% UI 0•911–1•71) would be directly attributable to bacterial AMR.At the geographic level, Australasia has the lowest death rate from resistance (6.5) per 100 000, whereas western sub-Saharan Africa has the greatest death rate (20.9–35.3) per 100 000.The top six infections linked to resistance-related deaths (Escherichia coli, followed by Staphylococcus aureus,

Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa) were responsible for 929 000 (660 000-1 270 000) deaths attributable to AMR and 3·57 million (2·62-4·78) deaths associated with AMR in 2019 (22).

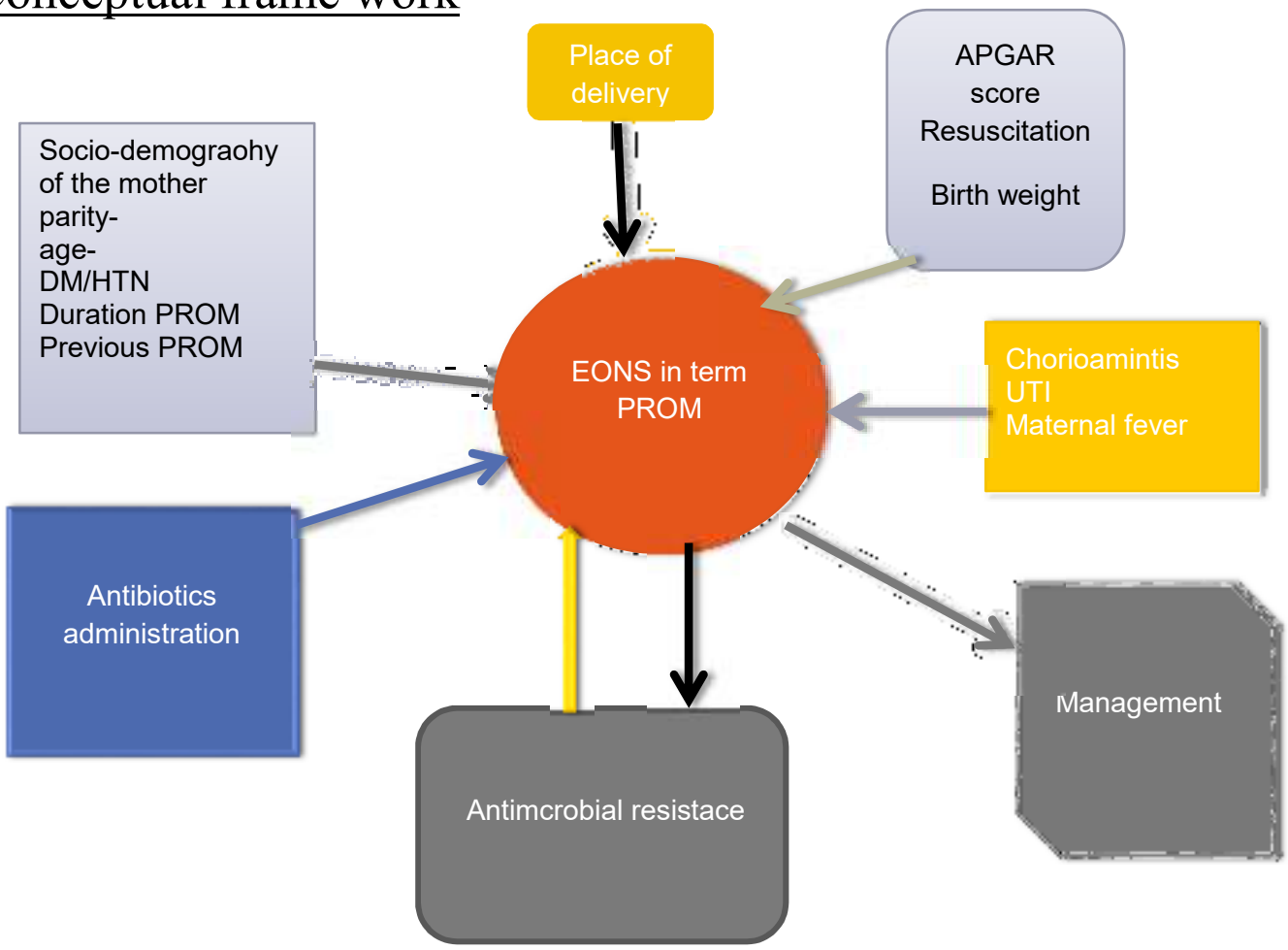
A prospective research on quality improvement was conducted in Papua New Guinea in 2019. Within seven days, ten of the 133 newborns (7.5%; 95% CI 4.4% to 13.2%) had sepsis. 4.5% was the EONS rate. Out of the ten, five were in the group that did not receive antibiotics, and five were in the group that received stat doses of antibiotics (OR for sepsis if given a stat dose of antibiotics 0.54; 95% CI 0.15 to 2.0, p=0.34). By following this procedure, antibiotic exposure was decreased in nearly 90% of newborns, potentially preventing numerous problems (21)..

A registry study included 113,568 singleton infants that occurred at term after a labor trial; elective cesarean births were not included. It was discovered that the interval between membrane rupture and delivery was associated with the probability of a neonatal sepsis diagnosis. Neonatal sepsis rates varied from 0.3% at the time of membrane rupture to delivery, 0.5% from 6 to 18 hours, 0.8% from 18 to 24 hours, and 1.1% after 24 hours. Up to 36 hours after the membrane rupture, the probability of newborn sepsis rose independently and almost linearly, with an odds ratio of 1.29 for every additional 6 hours of rupture. Additionally, there was an increase in risk with male newborn gender, primiparity, gestational age, and birth weight. Labor duration was not an independent risk factors.

As part of the Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS) initiative, mothers and their newborns were enrolled in a prospective observational cohort research that covered 12 clinical sites from Bangladesh, Ethiopia, India, Pakistan, Nigeria, Rwanda, and South Africa .Between November 12, 2015, and February 1, 2018, a total of 29 483 mothers and 30 557 infants were enrolled. Incidence of clinically suspected sepsis was 166•0 (95% CI 97•69–234•24) per 1000 livebirths, laboratory-confirmed sepsis was 46•9 (19•04–74•79) per 1000 livebirths, and all-cause mortality was 0•83 (0•37–2•00) per 1000 neonate days. Maternal hypertension, previous hospitalization of the mother within a year, average or higher monthly household income, ward size (>11 beds), ward type (neonatal), living in a rural area, preterm birth, perinatal asphyxia, and multiple births were associated with an increased risk of clinically suspected sepsis, laboratory-confirmed sepsis, and all-cause mortality. 881 [72•5%] of the 1215 cases of sepsis with laboratory confirmation happened in the first three days of life (25).

Another study conducted in Ethiopia comprised 10,495 study participants in a comprehensive systematic review and meta-analysis of eighteen studies, with a reported range of newborn sepsis from 17% to 78%. Neonatal sepsis had a pooled prevalence of 45% (95% CI: 35, 55; I2 = 99.3%, p < 0.01). The prevalence of early-onset newborn sepsis was shown to be 75.4% (95% CI: 68.3, 82.6). The study area's subgroup analysis, or by region, showed that the Amhara region had the greatest rate of newborn sepsis (64.4%), while Southern Nations, Nationality, and People had the lowest rate (28%; 95% CI: 16, 40) (26).

Conceptual frame work



3 Objective

3.1. General objective

- To determine the prevalence of early onset neonatal sepsis in term newborns with prolonged rupture of membrane at TASH and Gandhi memorial hospital from August 1 to January 30, 2024

3.2 Specific objectives

- To determine the prevalence of early onset neonatal sepsis in Term Prolonged rupture of membrane
- To identify associated factors that affects the occurrence of EONS in Term Prolonged rupture of membrane
- To assess the management practice of neonate born with Term PROM

4. Methods and materials

4.1. Study design

Institutional based cross sectional study design with prospective data collection

4.2. Source population

All term newborns evaluated at Neonatal ICU in Tikur Anbessa specialized and Gandhi memorial hospital from August 1, 2023 to January 30,2024

4.3. Study population

Neonate born to PROM mother at term from August 1, 2023 to January 30, 2024

4.4. Study area

Tikur Anbessa specialized hospital which is the biggest and oldest hospital in the capital city, Addis Ababa, Ethiopia. The hospital is administered by Addis Ababa University and is the largest and oldest teaching hospital among all in Ethiopia providing teaching for about 300 medical students and 350 residents each year. TASH provides diagnosis and treatment for approximately 400,000 patients each year. Gandhi memorial hospital is one of the oldest public hospitals in Addis Ababa giving service mainly maternal and neonatal health. Provides care for more than 4,000 newborns per year.

4.5. Study period

From August 1st 2030 to January 30, 2024

4.6. Sample size determination and sampling technique

4.6. 1. Sample size determination

- ✓ Based on single population proportion formula . Since the prevalence of EONS in term PROM not known p will be 50%.$n = \frac{z^2 p(1-p)}{e^2}$,n = the required sample size p = proportion of EONS with PROM = 50%
- ✓ $Z_{\alpha\backslash 2}$ = the critical value at 95% confidence level = 1.96 e = precision (margin of error) = 5% $n = 384$
- ✓ Estimated number of term newborns during the study period is 1500, with the correction formula $\_Nc = \frac{\text{no}}{1+\frac{\text{no}-1}{\text{N}}}$ where no is calculated sample size and N = total number of term newborn. Nc = 304
- ✓ Adding 5% no responder final sample size is 319

4.6.2. Sampling technique

Neonates born at term with prolonged rupture of membrane at Tikur Anbessa hospital and Ghandi memorial hospital were identified during the study period. Those who full fill the inclusion criteria were selected by convenience sampling method. 219 cases were selected from Gandhi and 100 cases were selected from TASH.

4.7. Selection criteria

4.7.1. Inclusion criteria

Prolonged rupture of membrane more than 18 hours

Gestational age (GA) ≥ 37 weeks to 42 weeks

The first 72 hours of age

4.7.2. Exclusion criteria

Preterm less than 37 weeks

Who have severe congenital anomalies

After 72 hours of age

Maternal chorioamnionitis

4.8. Study Variable

4.8.1. Dependent Variable

Early onset neonatal sepsis

4.8.2 Independent Variable

Socio-demographic Characteristics:

Age, parity, place of residence

Maternal DM/HTN, APH

PROM: duration of PROM ,presence of labor

Mode of delivery

Maternal fever

Place of delivery

5th minute APGAR score and Resuscitation

Antibiotics administration

Birth weight

Duration of labor

4.9. Operational Definition

PROM - rupture of membrane more than or equal to 18hrs

EONS-sign and symptoms of sepsis with the first 72 hours of delivery

Sepsis –SIRS Plus isolated or suspected infection

SIRS- The presence of two or more of the following criteria (one of which must be abnormal temperature or leukocyte count) defines SIRS (27):

Temperatures of >38.5°C or <36°C (axillary temperature >38°C or 35.5°C) can be recorded using a rectal, bladder, oral, or central probe that measures core temperature.

Bradycardia, which is defined as a mean heart rate <10th percentile for age in children under one year old, or tachycardia, which is defined as a mean heart rate more than two standard deviations above normal for age

Acute pulmonary process requiring mechanical ventilation or a mean respiratory rate greater than two standard deviations above the norm

Total WBC<5,000 or >20,000 with granulocytes >70%, or a leukocyte count that is high or low relative to age, or more than 10% immature neutrophils (3).

Probable sepsis/culture negative - Sometimes a pathogen may not be isolated in culture, but the neonate still exhibits clinical signs and symptoms that raise suspicions of sepsis, such as persistently elevated C-reactive protein, persistent respiratory, cardiopulmonary, or neurological symptoms that cannot be attributed to other illnesses, or laboratory abnormalities that point to sepsis (cerebrospinal fluid pleocytosis, persistently elevated C-reactive protein)

Culture proven sepsis – When a pathogenic microorganism is isolated.

Sepsis unlikely – infants exhibiting minor and/or sporadic symptoms (such as a fever on its own or other symptoms that go away shortly) who do not exhibit sepsis and who have negative cultures after 36 to 48 hours.

Chorioaminitis- In 2015, a National Institute of Child Health and Human Development Workshop expert panel recommended use of the term "triple I" to address the heterogeneity of this disorder

Maternal fever: At any given time, a recorded fever is defined as a mother's oral temperature measuring ≥39.0°C (38.5 axillary). Repeat the measurement in 30 minutes if the oral

temperature ranges from 38.0°C (axillary 37.5°C) to 38.9°C (38.5 axillary 38.5°C); if the repeat reading stays at least axillary 37.5 0°C, it is considered a documented fever**.**

Suspected triple I- Maternal fever without a clear source plus any of the following:

1. Baseline fetal tachycardia (greater than 160 beats per min for 10 min or longer, excluding accelerations, decelerations, and periods of marked variability)
2. Maternal white blood cell count greater than 15,000 per mm^3 in the absence of corticosteroids
3. Definite purulent fluid from the cervical os

Confirmed triple I- All of the above plus objective laboratory findings of infection, such as:

1. Positive amniotic fluid Gram stain for bacteria, low amniotic fluid glucose (≤14 mg/dL), high amniotic fluid white cell count in the absence of a bloody tap (>30 cells/mm^3), or positive amniotic fluid culture results, or
2. Histopathologic evidence of infection or inflammation or both in the placenta, fetal membranes, or the umbilical cord vessels (funisitis)

4.10. Data collection tool and Procedure.

The primary investigator chose the study cases and then gathered the data. A structured checklist that included the mother's and the newborn's sociodemographic data as well as clinical symptoms, test results, and management was employed. Information was coded and saved.

4.11. Data Quality control and management

To guarantee the data's quality, Five percent of the sample was assessed using the structured checklists. Prior to beginning data collecting, issues found during the pre-test were fixed. Every question was correctly coded, and the primary investigator provided ongoing oversight throughout the pre-test and data collecting periods. Every day that data was being collected, the collected data was examined for consistency and completeness.

4.12. Data analysis and interpretation

The collected data was coded and checked for completeness and entered to SPSS version 26.0 for analysis. Descriptive statistics like frequency, mean and median were used to describe the data. Binary logistic regression method was fitted to identify factors associated with early onset neonatal sepsis among term PROM. Binary logistic regression analysis was used to examine the impact of independent variables on the outcome variable. Using the enter technique, multivariable logistic regression was performed on all variables with p values less

than 0.2 in the bivariable logistic regression. To verify the model's assumptions, the Hosmer-Lemeshow goodness of fit test was employed. The adjusted odds ratio (AOR) with a 95% level of significance was used to establish the direction and strength of the link. In the multivariable regression, variables with a p-value of less than 0.05 were considered to be significant risk factors for early onset neonatal sepsis.

4.13. Ethical consideration

Ethical clearance was obtained from the pediatrics and child health Department's Research and Publications committee and Addis Ababa public health research and emergency directorate. Then an official letter of support and a copy of ethical clearance was submitted to neonatal intensive care unit at TASH and Gandhi. Confidentiality was maintained at all levels of the study

4.14. Dissemination of results

The finding of the study will be submitted to AAU, school of medicine and health science, department of pediatrics and child health and Ghandi memorial hospitals in Addis Ababa, Ethiopia, Addis Ababa Public Health Research and Emergency Directorate and other concerned bodies. The results of the research will also be published in national or international scientific journals.

5. Result

5.1. Socio-demography and clinical characteristics of the of the of the mothers

Study was done on 319 participants from August 1 to January 30, 2024 in TASH and Ghandi memorial hospital. About 278/ 319 (87%) were between the age of 20 to 35 years and 22/319(6.9%) were above 35 years. More than half of them (55%) were multigravida and 42.9% were primigravida. Parity of the mother was almost similar with gravidity. All of the mothers were from Urban (Addis Ababa and around Addis) and all had ANC follow up. PICT was positive in 6 /319 (1.6%) of the mother and VDRL was reactive in only one cases. HBSAG was reactive in 3/319(0.9%)cases. Around 7/319(2.2%) of the participants had hypertension and GDM was found in 4/319(1.3%).2 cases had APH.(table 1)

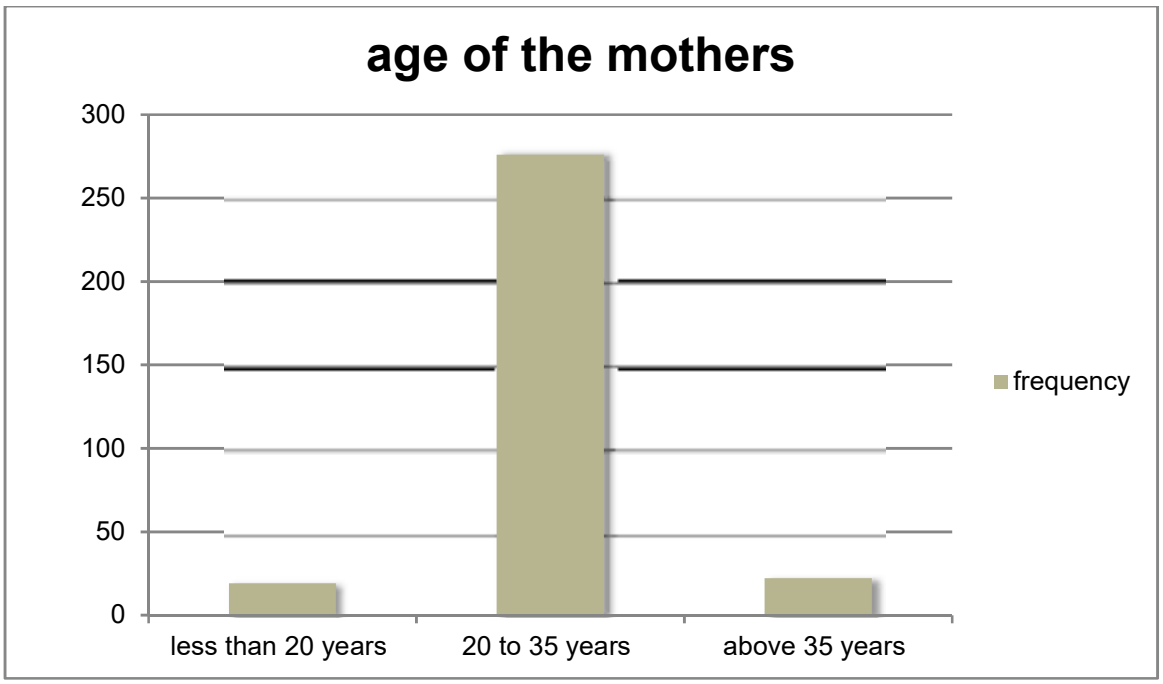


Figure 2: Distribution of mothers based on age in term prolonged rupture of membrane

Table 2: socio- demography of the mothers

Variables	Categories	Frequency	Percent
Age of the mother	Less than 20 years	19	6
	20 to 35 years	276	87.6
	Above 35 years	22	6.9
Gravidty	One	137	42
	2 to 5	176	55
	>=5	6	2
Parity	One	150	47
	2 to 5	163	51
	>=5	6	2
PICT	Positive	5	1.6
	Negative	314	98.3
VDRL	Reactive	1	0.3
	Non reactive	318	99.7
HBSAG	Reactive	3	0.9
	Non reactive	316	99.1
ANC	Yes	100	100
	no	0	0
Residency	Urban	100	100
	rural	0	0
Comorbidities	No	303	95
	hypertension	4	2.2
	GDM/DM	3	0.9
	APH	2	0.6
	Others	3	0.9

5.2 Labor and delivery

Around 2/3 (76%) of mothers gave birth vaginally and in about 67 (21%) of cases C/S was done, NRFHP being the most common indication. Instrument was applied in 10 cases. Labor was induced in about 12% and spontaneous in 88%.Most mothers 292(91.5%) delivered at hospital and only one delivery was at home the remaining 26(8%) deliveries were at health center. Duration of labor was less than 20 hours in about 89% of cases.

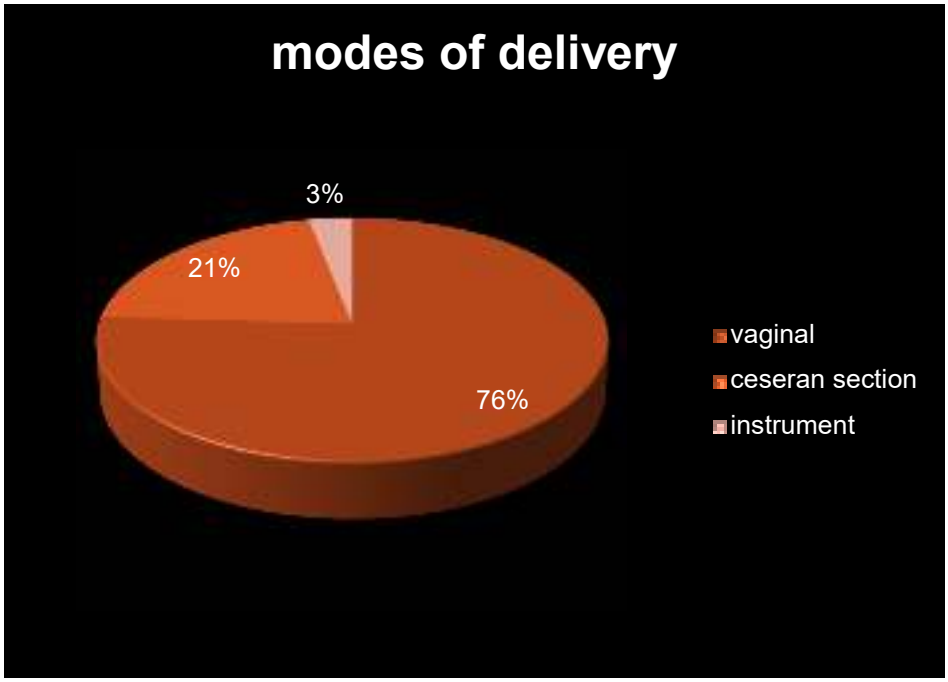


Figure 3: distribution by mode of delivery

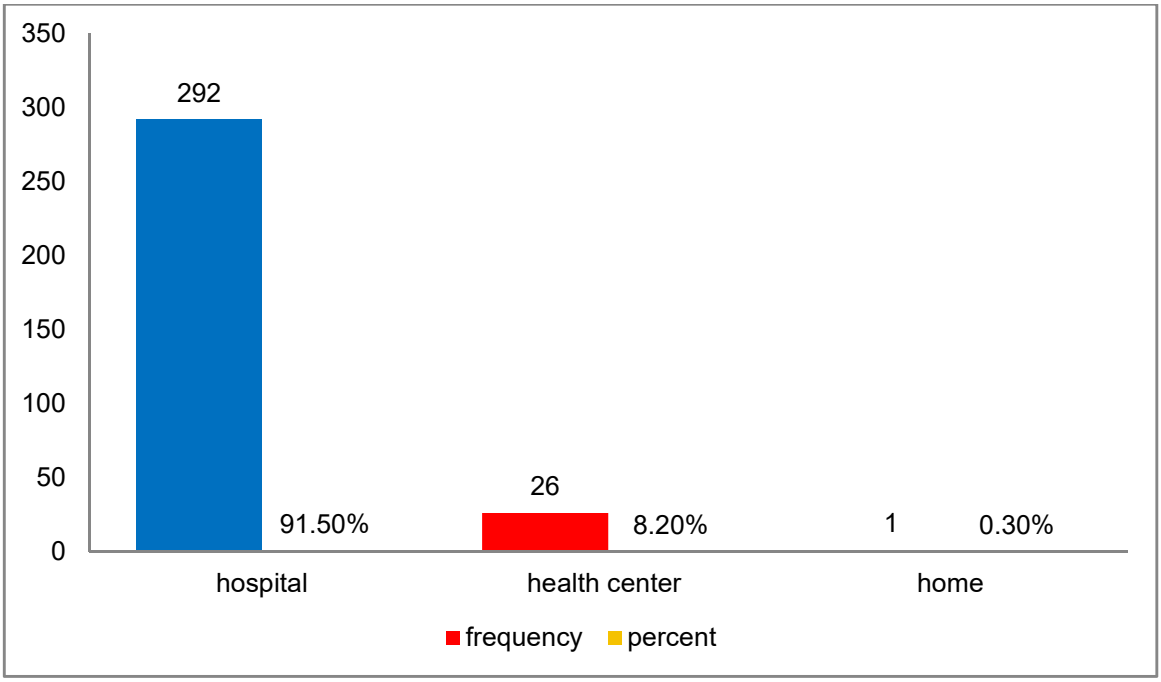


Figure 4: distribution by place of delivery

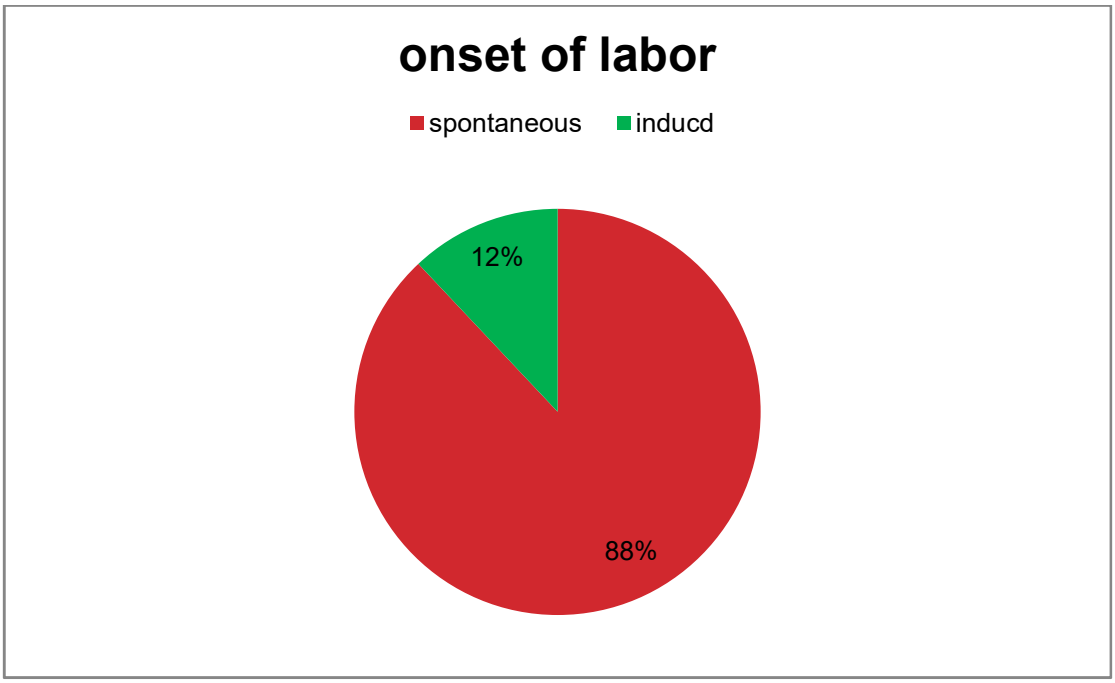


Figure 5: distribution by onset of labor

5.3. Neonatal characteristics

More than half (58.6%) of the newborns were male. Most of them (97.6%) had normal birth weight. Around 4 (1.3%) and 3(0.9%) were macrosomia and low birth weight respectively. Most of newborns (97.6%) were AGA. APGAR score was low in 2(0.6%) cases for them resuscitation was done. The was no meconium exposure in about 307(96%) of cases and there was 8(2.5%) and 4(1.3%) grade 2 and 3 meconium respectively .(table 1.1)

Table 3: Demography of neonates in term prolonged rupture of membrane TASH and Gandhi

Variables	Categories	Frequency	Percent
Sex of the neonate	Male	187	58.6
	Female	132	41.4
Weight	Normal	312	97.6
	Macrosomia	4	1.3
	Low	3	0.9
	AGA	312	97.6
	SGA	3	0.9
	LGA	4	1.3
APGAR	Normal	317	99.4
	Low	2	0.6
Resuscitation	No	317	99.4
	Yes	2	0.6
Meconium	No	307	96
	Yes 12		4

5.4. Prevalence of sepsis and clinico laboratory characteristics

Clinical manifestations consistent with early onset neonatal sepsis were documented and the neonates having these signs of sepsis considered as positive outcome. Among 319 neonates 32 (10%) of them had signs of sepsis. More than 2/3 of cases (78%) developed sign of sepsis with in the first 24 hours. Around 15 % of them become symptomatic with 24 to 48 hours and the remaining (7%) at 3rd day of life. Respiratory system was affected more. The most common sign being tachypnea (87.9%) followed by tachycardia (57.6%)**.**Around 17/32 (51.5%) of cases had hypothermia and 02 neonates had fever. Nearly one third (27.3%) had depressed neonatal reflex mainly sucking. (Figure 7)

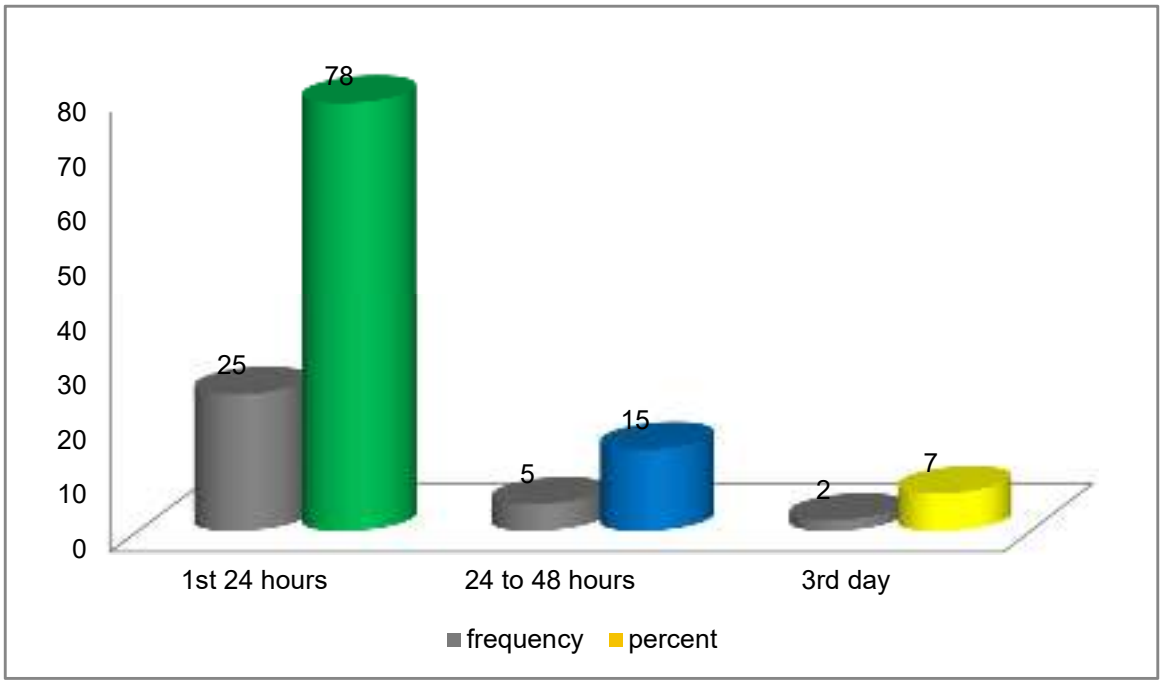


Figure 6: onset of clinical manifestation of sepsis

Complete blood count and C- reactive protein was done for all cases. CBC was normal in 18/32 (56%) of symptomatic neonates. around ¼ of cases had leukocytosis WBC count > 20,000/micro and 12.5 % had neutrophil > 70 % and 2 cases had WBC count < 5,000/micro. C- reactive protein was positive in more than half 22/32 (68%) of cases and negative in 30 %. blood culture was done for only 39/319(12%) and for 21 (65%) of symptomatic cases and there was no growth within 72 hours . CSF analysis was done only for 3 cases with the result of high cell count in one case and normal in others.(table 4)

Table 4: Complete blood count and CRP of newborns with prolonged term PPROM at TASH and Gandhi memorial hospital, 2024

Laboratory		Sepsis (n=32)	No sepsis (n=287)
CBC	Normal	18(5.6%)	275(86%)
	WBC > 20, 000/microL	8(2.5%)	10(3%)
	WBC < 5,000/micro	2(0.6%)	00
	N> 70%	4(1.3%)	1(0.3%)
CRP	Positive	22 (6.8%)	9(2.8%)
	Negative	10(3 %)	277 (87%)

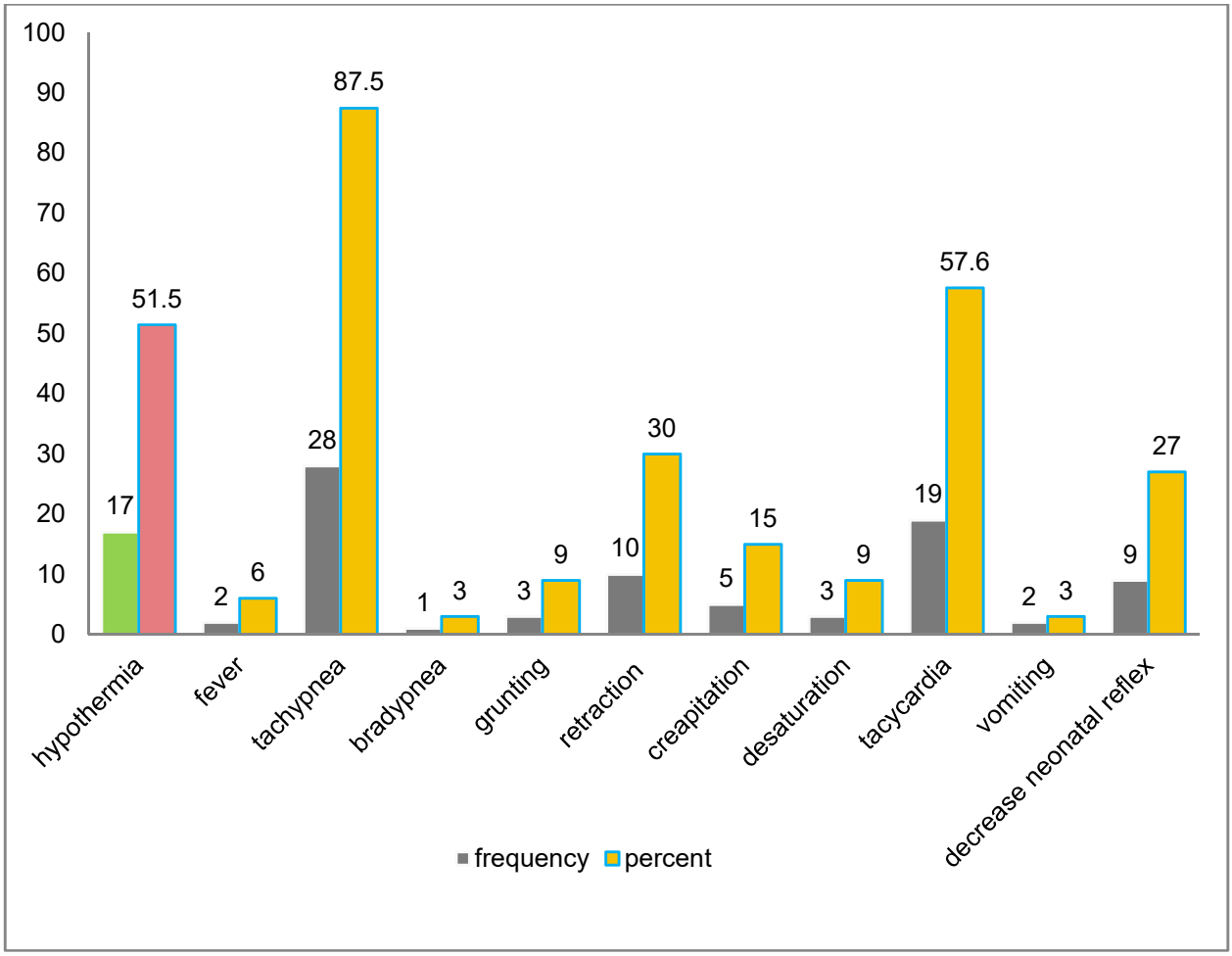


Figure 7: clinical manifestation of early onset neonatal sepsis

Other diagnosis

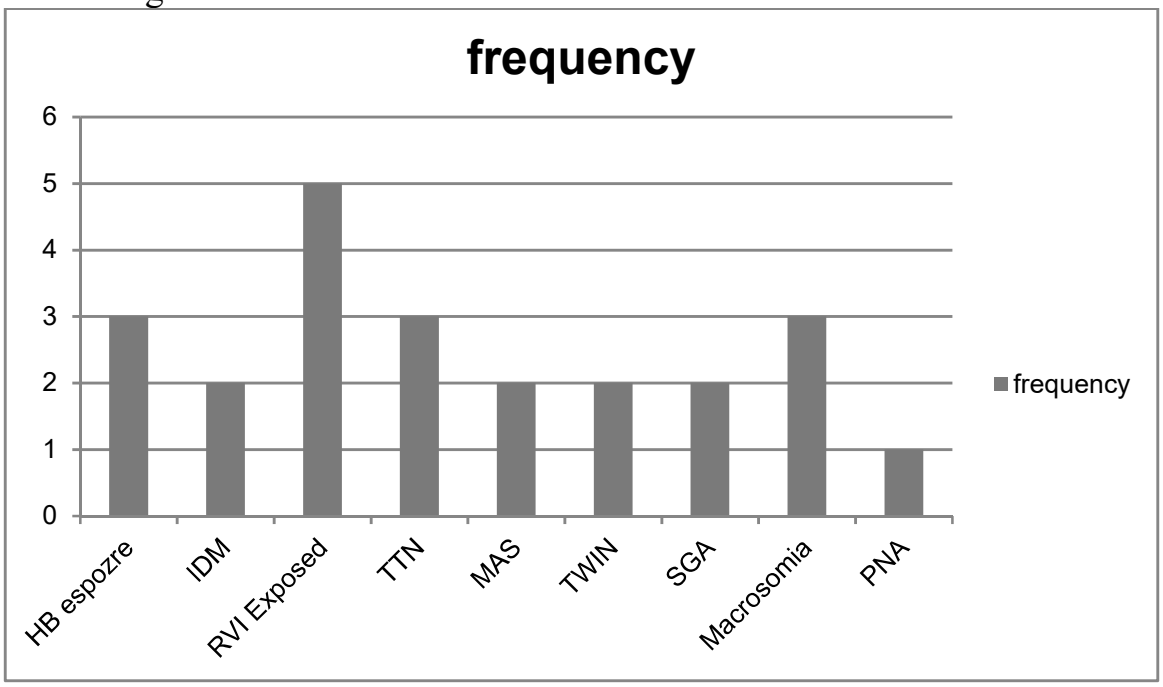


Figure 8; other diagnosis

5.5. Factors associated with early onset neonatal sepsis

In order to identify the risk factors for early onset neonatal sepsis, bivariable and multivariable binary logistic regression was done. All variables were tested by bivariable binary logistic regression analysis and variable with a p-value of < 0.2 were entered into the multivariable logistic regression. Gravidity, parity, onset of labor, duration of labor, duration of rupture of membrane, maternal antibiotics ,maternal fever, meconium exposure, APGAR score and resuscitation had p value ,< 0.2 in bivariable regression model .Duration of ROM, maternal antibiotics admiration , maternal fever were significantly associated with early onset neonatal sepsis in multivariate binary logistic regression.

Table 5 : frequency of factors associated with early onset neonatal sepsis

Variables		Frequency	Percentage
Duration of ROM	18 to 24 hours	132	41.4
	25 to 36 hours	134	42
	37 to 48 hours	38	11.9
	49 to 72 hours	5	1.6
	More than72 hours	10	3.1
Maternal antibiotics	no	17	5.3
	Less than 4 hours before delivery	7	2.2
	More than 4 hours before delivery	295	92.5
Maternal fever	Yes	5	1.6
	no	314	98.4

ROM = Rupture of membrane

In about 132/319(41%) of mothers the duration of ROM was between 18 to 24 hours. almost similar number of cases (42%) had duration of rupture of membrane between 25 to 36 hours .around 3% of mothers had ROM for more than 3 days. most of the mothers (92.5%) were given IV antibiotics for more than 4 hours before delivery commonly ampicillin and sometimes ceftriaxone before delivery. Around 17(5 %) of the mothers with prolonged rupture of membrane were not given antibiotics totally and 7 cases were given for less than 4 hours before delivery. Five out of 319/1.6% mothers had recorded fever. The odds of developing sepsis in mothers with no antibiotics administration is 16 as compared with mothers given antibiotics for more than 4 hours before delivery.

Table 5: Bivariable and multivariable binary logistic regression analysis for risk factors of early onset neonatal sepsis among neonates born after prolonged rupture of membrane after 37 weeks of gestational age in TASH and Gandhi memorial hospital Addis Ababa ,Ethiopia 2024

Variables	Categories	Sepsis (n=32)	No sepsis (n=287)	COR(95% CI)	AOR (95% CI)
Gravidty	One	17(5.3%)	120(37.6%)	1.00	
	2 to 5	15(4.7%)	161(50.5%)	0.65(0.316,1.3)	
	Above 5	0(0%)	6(1.9%)		
Parity	One	19(6%)	131(41%)	1.00	
	2 to 5	13(4%)	158(49.5)	0.59(0.24,1.21)	
	Above 5	0(0)	6(1.9)		
Duration of labor	<20 hours	26(8%)	258(80%)	0.48(0.18,1.2)	
	>= 20 hours	6(1.9%	29(9%)	1	
Duration ROM	18 to 24 hours	11(3.4%)	120(37.6%)	0.12(0.034 ,0.37)	0.045(0.012,0.17)*
	25 to 36 hours	11(3.4%)	123(38.6%)	0.105(0.035,0.34)	0.05(0.014,0.2)*
	37 to 48 hours	3(0.9%)	36(11%)	0.09(0.03,0.46)	0.05(0.009, 0.23)*
	>49 hours	7(2.2%)	8(2.5%)	1	1
Maternal fever	Yes	4(1.3%)	1(0.3%)	1.00	73(7.1,937)*
	No	28(8.8%)	286(89.6%)	0.24(0.03,0.277)	1.00
Maternal antibiotics	No	7(2.2%)	10(3.1%)	9.13(3.155,26.04	16.6(4.9,56)*
	< 4 hours	4(1.2%)	3(0.9%)	17.39(3.6,82)	34.19(6.3132)*
	>4 hours	21(6.6%)	274(86%)	1.00	1.00
Onset of labor	Spontaneous	3(0.9%)	256(80%)	1.096(0.92,1.3)	
	Induced	6(1.9%)	26(8%)	0.57(0.2,1.27)	
Meconium	No	29(9%)	278(87%)	0.3(0.121,3.2)	
	GII	2(0.6%)	6(1.9%)	1.00(0.6,1.7)	
	GIII	1(0.3%)	3(0.9%)	1.00	

***= p value < 0.05**

5.6 Management

Antibiotics was not started for 276/319(86.5%) and started (mainly ampicillin and gentamycin) in 43/319 (13.5%). Antibiotics started for 11 cases who had no clinical manifestation of sepsis based on positive CRP.CRP was repeated after 24 hours of the initial determination and antibiotics was discontinued for those who had negative CRP and with normal evaluation but continued for 05 to 07 days for those who had clinical manifestation of sepsis irrespective of CRP and for those who had positive repeated CRP irrespective of other signs of sepsis. Other cases managed accordingly, HAART, HB IG, and vaccine.

6. Discussion

One of the main causes of infant death, neonatal sepsis is a serious global health concern, particularly in low- and middle-income countries (LMICs), which account for 99% of all neonatal deaths worldwide (19). In low- and middle-income nations, reported rates of newborn sepsis following PROM vary greatly depending on the clinical case definition, population, environmental and health service circumstances, and treatment strategy.

The study was done on 319 selected newborns with prolonged rupture of membrane at term gestational age at TASH and Gandhi memorial hospital, hospital based prospective crossectional study. Within this research, 10% of newborns had early-onset sepsis, with a 95% confidence interval of 6.7% to 13.3%. CL).

However the result of this study is higher than the previous studies done in papa New Guinea 2018 and Pakistan 2013. In Papa New Guinea the prevalence of sepsis within 7 days was 7.5 % which is almost similar with this study but when sub grouped in to EONS only 4.5% (21) . The difference might be from selection criteria in which they didn't include the newborns with clinical evidence of sepsis at birth, low sample size which was 170 in that study but we included symptomatic cases at birth. The prevalence of EONS in Pakistan was 4%. The result of our study may be exaggerated as compared to this study because they used only blood culture confirmed sepsis. In contrary the prevalence in this study was low as compared to other studies in Jordan and India ((18), (23). Sepsis prevalence in Jordan was 23 percent. The approach, sample size, and inclusion criteria could all be to blame for the discrepancy. They performed blood cultures on all cases, including premature newborns, but we didn't. The risk factor for EONS is prematurity alone, and consequences from preterm can be hard to

distinguish from sepsis, particularly when sepsis is culture-negative. Preterm and term neonates were included in the 14.5% prevalence in India.

Clinical manifestations consistent with early onset neonatal sepsis were documented and the neonates having these signs of sepsis considered as positive outcome. More than 2/3 of cases (78%) developed sign of sepsis with in the first 24 hours. Around 15 % of them become symptomatic with 24 to 48 hours and the remaining (7%) at 3rd day of life. As we compared from the previous study done in Papa New Guniea, the number of cases with in the first 24 hours was higher in our study 78%vs 10% (21). They didn't include symptomatic newborns at birth.

Respiratory system was affected more. Pneumonia is common in early onset neonatal sepsis. This result was supported by study (23) where respiratory distress was the most common sign of sepsis (54.5%)

Maternal fever, duration of rupture of membrane and maternal antibiotics administration were associated with early onset neonatal sepsis with p- value of < 0.05. The presence of maternal fever is significantly associated with early onset neonatal sepsis. This finding is supported by different studies ((4), (21), (18), (23), (24)).The odds of developing sepsis among newborns whose mother had fever is 73(7.1_756) as compared to newborns whose mother didn't have fever . Duration of ROM between 18 to 24 hours had 87% lower risk of developing sepsis as compared to ROM > 72 hours , AOR = 0.13(0.02,0.80).

7. Limitation of the study

Incomplete documentation about some maternal characteristics like fever and time of antibiotics administration for the mother. The main limitation of this study was inability to do blood culture for all cases especially at Gandhi memorial hospital where there was no blood culture media. There was also narrow literature to compare with.

8. Conclusion

Maternal fever, prolonged duration of rupture of membrane and no maternal antibiotics administration was significantly associated with early onset sepsis. Respiratory system was commonly affected followed by tachycardia and temperature instability. Proper advice about rupture of membrane during ANC follows up and early prophylactic antibiotics admirations recommended

9. Recommendation

Based on the result we found from this study our recommendation is to have strict follow up of maternal fever and clear documentation for obstetrics side with proper advice about signs of rupture of membrane and other danger signs during ANC follow up. For NICU units to have blood culture media and to give some trainings on how to take blood sample for culture. And also to keep neonates with PROM more than 48 hours and maternal fever for at least 72 hours with follow up .For minister of health, Addis Ababa health office and TASH to prepare simplified protocol on how to manage and follow term new born after prolonged rupture of membrane.

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ANNEN-I

1. Sociodemography of the mother	1. Age ____ 2. Gravida ___ 3. Parity ____
2. Residency	1. Urban 2. Rural
3. ANC follow up	1. yes 2 no
4. Base line investigations	a. PICT _____ b. VDRL_____ c. HBSAG___

5. Comorbid conditions	1. GDM/DM 2. Hypertension 3. APH	Other_____
6. Mode of delivery	1. Vaginal 2. C/S(indication _____) 3. Instrumentation(indication _____)	
7. Place of delivery	1. home 2. health center 3. Hospital	
8. Onset of labor	1. Spontaneous 2. induced	
2. Duration of labor	A. less than 20 hors B. more than 20 hours	
3. Rupture of membrane	A. 18 to 24 hours B. 24 hours to 36 hours C. 36 hors to 48 hours D. 48 hours to 72 hours E. > 72 hours	
4. Maternal antibiotics administration	A. no B. Yes 1. less than 4 hours of delivery 2. more than 4 hours of delivery	
5. Maternal fever	A. Yes B No	
6. Clinical chorioaminitis	A. yes B no	
7. Meconium exposure	A. yes (Grade_____ B. No	
8. Birth weight	A. normal birth wt___gm B. Macrosomia_____gm C. low birth weight ___ gm	1. AGA 2. SGA 3. LGA
9. Sex	A. Male B. female	
10. APGAR score at 1st and 5th minute	A. normal B low	
11. Resuscitation done	A. Yes B. No	
12. Clinical manifestations	**A. Asymptomatic** **B. IF Symptomatic specify based on involved systems**	
13. Temperature	A. hypothermia __ B. hyperthermia___ c. normal__	

14 Respiratory system	A. Tachypnea ___ B. Bradypnea__ C. Apnea D. Grunting E. Retraction F. Crepitation G. low oxygen saturation H. Normal
15 Cardiovascular system	A. Tachycardia__ B. Bradypnea__ C. Delayed capillary refill__ D. D cold extremities E. Other _____ F. Normal
16 Gastrointestinal system	A. vomiting B. diarrhea C. abdominal distention D. jaundice E. other_____ F. normal
17 Hematology	
18 Renal	
19 Central nervous system	A. abnormal body movement B. decrease mentation C. bulged fontanel D. depressed neonatal refle E. high pitched cry F. Other _____ G. Normal
20 Others	
21 Onset of clinical manifestation	1. 1st 24 hrs 2. 24 to 48 hrs 3. 48 to 72 hrs
22 Laboratory abnormalities	
22.1 Complete blood count	A. White blood cell count ____ B. Neutrophil percentage/ ANC ___ C. Platlate count ___ D. not done

22.2 CRP	A. Negative B. Positive
22.3CSF Analysis	
22.4 Blood culture	A. Negative B. Has growth (specify type of bacteria and susceptibility_____) C. Not done
23 Management	A. Antibiotics not started B. Antibiotics started (specify type of antibiotics and duration_____
24 What are the additional Dx ?	