ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES

SCHOOL OF NURSING AND MIDWIFERY, DEPARTMENT OF NURSING

NECROTIZING ENTEROCOLITIS AND ASSOCIATED FACTORS AMONG ENTERAL FED PRETERM AND LOW BIRTH WEIGHT NEONATES ADMITTED IN SELECTED PUBLIC HOSPITALS, ADDIS ABABA, ETHIOPIA, 2020.

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Contents

List of figure

List of table

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List of Abbreviations

AAU: Addis Ababa University

AREDFV: Absent or reversed end diastolic flow velocity

ELBW: Extremely Low Birth Weight

EMDHS: Ethiopian Mini Demographic Health Survey

EPTF: Exclusive Preterm Formula

ETEF: Early Total Enteral Feeding

HM: Human Milk

LBW: Low Birth Weight

LOS: Late Onset Sepsis

MOM: Mother Own Milk

NEC: Necrotizing Enterocolitis

NICU: Neonatal Intensive Care Unit

NPO: Nothing by Mouth

PDA: Patent Ductus Arteriosus

RCT: Randomized Control Trial

RDS: Respiratory Distress Syndrome

ROP: Retinopathy of Prematurity

TPN: Total Parenteral Nutrition

VLBW: Very Low Birth Weight

ELBW: Extremely Low Birth Weight

ABSTRACT

BACKGROUND: NEC is the most common multifactorial and devastating gastrointestinal emergency, and primarily affects premature infants particularly in those born at, <32 weeks' gestation and/or <1,500gm birth weight in neonatal intensive care units worldwide. **Objective:** To assess prevalence and factors associate with NEC among enteral feed preterm and low birth weight neonates admitted in NICU in selected public hospitals of Addis Ababa, Ethiopia, 2020. **Methods:** Institutional based cross-sectional study was conducted from March 25 to May 10, 2020 among preterm neonates admitted from January 1, 2019 to January 1, 2020 on 350 samples in Addis Ababa, Ethiopia. A simple random sampling technique was used to select sampling units and study participants' medical card. Data was collected using structured format data collection tool by 4 trained BSc nurses. Data was entered to Epi-data 4.6 and exported to SPSS V 26 for analysis. Bivariate and multivariate logistics regression was used to analyze the association between dependent and independent variables and P-value <0.05 at 95% CI was declared statistically significant. Finally, text and tables was used for data presentation.

Result: The overall prevalence of NEC was 89 (25.4%) of infant found developed NEC. The majority of neonates who developed NEC were 10.6% of them are 28+1 to 32 weeks, and those who were 32+1 to 34, 34+1 to 36+6 and <=28 weeks of gestational age accounts 10.2%, 2.6% and 2% respectively. Likewise, most 11.7% of them are VLBW (1000 to 1499gm) and the rest 8.3% are 1500 to 2499g and less than 1000gm birth weight neonate's accounts 5.4%. From January 2019 to January 2020, we reviewed 89 neonates with NEC. Forty-nine of the infants recovered from NEC (14.0%) and 40 (11.4%) infants deaths were attributed to NEC. **Conclusion:** Out of 350 preterm and low birth weight neonates, 89 (25.4%) of neonates developed NEC. From the 89 infants with NEC 49(14.0%) of them were improved and 40 (11.4%) of infant was died. Gestational age, low APGAR score, birth weight, chorioamnionitis, hypertension, prolonged labor, neonates colonized by pathogenic bacteria/ having early or late onset infection and use of CPAP ventilation were observed as significantly predicting factor associated with the diagnosis of NEC in the study area.

Key words: Prematurity, Necrotizing Enterocolitis, Low birth weight, Enteral feeding, NICU.

CHAPTER 1 INTRODUCTION

1.1 **Background**

Necrotizing enterocolitis (NEC) is an acute inflammatory disease occurring in the newborn's intestines which is the most common multifactorial and devastating gastrointestinal emergency, and mainly affects 90% of premature infants specially in those born at, <32 weeks' gestation and <1,500gm birth weight in neonatal intensive care units worldwide. The pathogenesis of NEC in the premature condition remains incompletely explained. In most case; prematurity, hypoxia-ischemia, bacterial colonization of the gut, and formula feeding are well recognized risk factors (1, 2).

NEC is one of the leading causes of morbidity and mortality in preterm infants with incidence ranges between 3% and 28%, with an average of approximately 6% to 10% in infants born weighing less than 1500 grams, with mortality rates of 20–30% and approaching 50% in infants who require surgery. Both incidence and case fatality rates of NEC highly increase among the smallest and most premature infants, and intrauterine growth restriction confers a higher risk of disease than that of a normally grown preterm infant (1, 2).

As number of prematurity increases, feeding strategy becomes a major clinical challenge, Very low birth weight and very preterm infants are not often able to be directly breast fed and prolonged parenteral nutrition and sepsis will predispose them to necrotizing enterocolitis (3).

Morbidity and mortality of NEC is 10-30% and 30-50% among very preterm (< 32 weeks) or very low birth weight (VLBW: < 1500 grams) and extremely low birth weight (ELBW: <1000 grams) infants respectively and extremely preterm (< 28 weeks) infants are at highest risk and there has not been a significant change in the past 20 years (4, 5).

Evidence exists that feeding with artificial formula rather than human milk increases the risk of developing NEC. Other differences in enteral feeding regimens, such as the timing of first feed and the amount daily volume increments. Because of gastrointestinal hormone, secretion and motility are stimulated by enteral milk, enteral fasting during the early neonatal period could diminish the functional adaptation of the immature gastrointestinal tract and may contribute to inter-unit variation in the incidence of NEC (6-8).

The favorable time for introducing enteral feeding to a premature and VLBW infant is controversial. Trophic feeding is the practice of feeding very low birth weight premature neonates early to stimulate development of their immature gastrointestinal tract, enhance gut motility and thereby decrease risk of NEC. Thus, improve growth, decrease need for parenteral nutrition leading to fewer episodes of sepsis and a shortened hospital stay. Once started and tolerated, trophic feedings are increased gradually in medically stable infants and parenteral nutrition is decreased (9).

Although the fear of precipitating NEC remains widespread, randomized controlled trials have repeatedly failed to show any relationship between feeding practices and the occurrence of NEC. Premature infants, mainly weighing <1500gm are not able to coordinate breathing, sucking and swallowing by which they requires tube feeding. Intestinal tract readiness for feeding may decide by the presence of active bowel sounds, passage of meconium, and absence of abdominal distention, and bilious gastric aspirate. For those medically stable infant's enteral feeding can be started as early as day one using a small amount of trophic feed (approximately 10 ml/kg/day) to stimulate gastrointestinal tract and prevent mucosal atrophy which is escalated by 10-20ml/kg/day as the baby tolerates initial feed volume. Clinical studies across the world have consistently demonstrated that infants who are fed soon and are escalated according to a feeding plan achieve full enteral feeds earlier than their counterpart (10).

Opposing advances in neonatal care and suggestive clinical and basic science examination, the etiology, associated factors and mechanisms leading to clinically apparent NEC are unclear, although various causal factors have been proposed (1, 2), specific treatment strategies are lacking, and morbidity and mortality from this disease remain high. NEC develops principally in premature and forecasting which babies will develop the disease and settle the diagnosis before fulminant disease has occurred has been difficult.

1.2 Statement of the problem

Every year, an estimated 15 million infants are born preterm (before 37 completed weeks of gestation), and this number is increasing (11, 12). Preterm infants are susceptible to many complications, including respiratory distress syndrome, chronic lung disease, compromised immune systems, cardio- vascular disorders and intestinal injury (NEC) (13).

In 2017, 2·5 million newborn deaths occurred globally, accounting for 47% of deaths in children younger than 5 years. Slightly more than a third of these deaths resulted from preterm related causes like NEC, RDS (35%), intra-partum complications (mainly intra partum hypoxia) (23%), and sepsis including meningitis (15%) account for three quarters of all neonatal deaths (14).

In Ethiopia, neonatal death rate did not decrease as that of post-neonatal and child mortality. There has been slower progress in reducing neonatal mortality; which is 39 deaths per 1000 live-births in 2005 VS 29 deaths per 1000 live births in 2016 EDHS, but has remained stable since the 2016 EDHS and 30 deaths per 1000 live births in the 2019 EMDHS (15). Prematurity -related complications have contributed to about 30% of neonatal deaths in Ethiopia which are primarily predispose for the development of necrotizing enterocolitis (16).

In a study conducted at Addis Ababa public hospital preterm prevalence accounts 16.15%, among this 32.3% and 12.2% of them are very preterm and extremely preterm respectively; two thirds of deaths were attributable to prematurity (34%). Mortality was inversely associated with gestational age and birth weight with the death of 52.5% among very preterm (<= 32wks of GA), 83·0% preterm infants who weighed less than 1000 g, and 47·6%) of infants who weighed between 1000gm to less than 1500gm (17-20).

NEC develops mainly in premature neonates exposure to metabolic substrate in the context of immature intestinal immunity, microbial dysbiosis and mucosal ischemia. Worldwide studies result showed that the incidence of NEC varies among US centers and across continents, but ranges between 3% and 28%, with an average of approximately 6% to 10% in infants born weighing less than 1500 grams, with mortality rates of 20–30% and approaching 50% in infants who require surgery. Both incidence and case fatality rates of NEC increase with decreasing

birth weight and gestational age, the incidence increases dramatically in the smallest and most premature infants, and intrauterine growth restriction confers a higher risk of disease than that of a normally grown preterm infant (1, 2).

According to hospital based studies prevalence of Necrotizing enterocolitis was estimated as 4% and mortality rate is higher among lower gestational age group infants with an associated death accounts of 22.2% in 28–31 weeks, 55.6% in 32–34 week, and 22.2% in 35 to <36 weeks. But these prevalence estimation may not able to identify the exact magnitude of NEC since the study aimed at total premature death rather than NEC prevalence and it contains a large number of late preterm and stable neonates(17-20).

Infants who develop NEC experience more nosocomial infections, have lower levels of nutrient intake, grow more slowly, and have longer durations of intensive care and hospital stay than gestation-comparable infants who do not develop NEC. The associated mortality rate is high (20%) compared with their match and have a higher incidence of long-term neurological disability, which may be a consequence of infection and under-nutrition during a critical period of brain development (21).

Advanced neonatal care, improved survival of preterm neonates and necessity of providing adequate nutritional regimes has made feeding strategies one of the major clinical challenges facing NICU staff (22).

The introduction of enteral feeds for very preterm (less than 32 weeks' gestation) or very low birth weight (VLBW; less than 1500g) infants is often delayed for several days or longer after birth due to concern that early introduction may not be tolerated and may increase the risk of necrotizing enterocolitis (NEC). However, delaying enteral feeding could diminish the functional adaptation of the gastrointestinal tract and prolong the need for parenteral nutrition with its attendant infectious and metabolic risks (23).

Studies are lacking to determine factors associated with necrotizing enterocolitis and Analysis of nine trials have no evidence that early or delayed feeding practice increases the risk of a severe bowel disorder called necrotizing enterocolitis (24).

Although several studies have verified the potential benefits of trophic feeding, there is no general agreement about the optimal timing to start enteral feeds (2, 25). A systematic review revealed that only time to full enteral feeding, number of days that feedings were withheld and total hospital stay were significantly reduced following trophic feeding (25). Another review results revealed that early feeding had no significant effect on weight gain, necrotizing enterocolitis, mortality, or age at discharge and did not provide any evidence to affect feed tolerance or growth rates in VLBW infants, although important effects cannot be excluded with the small number of patients studied (26).

Establishing feeding is a central component of care for preterm or very low birth weight infants. In our clinical setup many very premature and VLBW neonates are kept NPO for long period due to lack of consideration for the initiation of very premature and VLBW infants feeding; though many of them are suffering from NEC during periods of NPO.

Although NEC prevalence estimates in Ethiopia are not well define due to, lack of separate studies pertaining to magnitude and factors associated with necrotizing enterocolitis. Knowing the prevalence and associated factors of necrotizing enterocolitis in the neonatal intensive care unit (NICU) helps to use available resources and can make requisite efforts to reduce morbidity and mortality; little known about the prevalence of necrotizing enterocolitis and their outcomes and associated factors in Addis Ababa, Ethiopia.

Therefore, this study is aims to assess the prevalence and associated factors of necrotizing enterocolitis among premature infants in selected public hospital, Addis Ababa, Ethiopia.

1.3 Significance of the study

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Unfavorable outcomes was seen in premature neonates admitted to the NICU that develops necrotizing enterocolitis secondary to many associated factors during neonatal intensive care; hence anticipating contributing factors is an essential aspect of the clinical management of preterm neonate.

Still, little attention given to NEC prevalence among preterm neonates even after contributing factors was shown to be associated with increased morbidity and mortality in premature, low birth weight and very low birth weight neonates, including a higher risk of nosocomial infections (24).

NEC prevalence estimates in Ethiopia are not well defined due to, lack of study and other factors. There is limited evidence about the burden and to the knowledge of the investigator no data is available on the burden of necrotizing enterocolitis, the effect of early enteral feeding and the associated risk of NEC among premature infants admitted to the NICU. The determination of clinical course associated to the occurrence of NEC may permit to the selection of neonates at risk for NEC and could contribute to the development of strategies aimed at the prevention and early treatment of NEC (17-20).

Hence, we aimed to determine the prevalence of necrotizing enterocolitis and to identify independent variables that are associated with the development of NEC among premature, low and very low birth weight neonate admitted to the NICU.

The study will give an insight and assist to the health service manager, nurse, physician, quality team, hospital stakeholders and ministry of health to design enteral feeding strategies and NEC prevention guidelines pertaining to premature, very premature, LBW and VLBW infants and can help to fill the gap. This study will provide benchmark data for other future researchers.

CHAPTER: 2. LITERATURE REVIEW

Premature and VLBW infants have fewer nutrient reserves at birth than full-term infants and frequently receive parenteral maintenance within the absence of expressed breast milk. The introduction of enteral feeds for very preterm (less than 32 weeks' gestation) or very low birth weight less than 1500g infants is usually delayed for several days or longer after birth thanks to concern that early introduction might not be tolerated and should increase the danger of inflammatory intestinal disease (NEC) (23).

However, delaying enteral feeding could diminish the functional adaptation of the digestive tract thereby ends up in inflammation and necrotizing enterocolitis; delaying the establishment of full enteral nutrition and increasing and prolonged use of parenteral nutrition is related to infectious and metabolic risks that will have adverse consequences for survival, growth, and development. It's been argued that the danger of NEC shouldn't be considered in isolation of those other potential clinical outcomes when determining feeding policies and practice for very preterm or VLBW infants (27).

2.1 Prevalence of Necrotizing Enterocolitis:

The incidence of NEC varies among US centers and across continents, but ranges between 3% and 28%, with a mean of roughly 6% to 10% in infants born weighing below 1500 grams, with mortality rates of 20–30% and approaching 50% in infants who require surgery. Both incidence and case fatality rates of NEC increase with decreasing birth weight and age of gestation, the incidence increases dramatically within the smallest and most premature infants, and intrauterine growth restriction confers the next risk of disease than that of a normally grown preterm neonates (1, 2).

NEC is more prevalent in preterm infants (28), with; 85% of cases occurring in infants born <35 weeks gestation, whereas only 7–15% of cases occur in late-preterm (35–36 weeks gestation) or term infants (37–42 weeks gestation) (29, 30).

In a study conducted at Addis Ababa public hospital preterm prevalence accounts 16.15%, among this 32.3% and 12.2% of them are very preterm and extremely preterm respectively (17).

Study conducted in Tikur Anbesa hospital neonatal intensive care unit from 2001 through 2005 have identified 52.5% of death among very preterm(<= 32wks of GA) and 50.3% of death of VLBW (<= 1500gm) (19). A study conducted in Tigray region, have identified that two thirds of deaths were due to prematurity (34%) (18).

In other SIP study on major reason for preterm death conducted in four public hospitals, have identified that a high prevalence of preterm death (22·7%). Of the infants admitted to the NICU 28·8% died; of the infants enrolled within the study, mortality was 85·6% for infants younger than 28 weeks of gestation, 53·7% for infants of 28 to 32 weeks of gestation. Similarly, mortality was inversely related to birth weight with the death of 83% of preterm infants who weighed less than 1000 g, and 47·6% of infants who weighed between 1000 g to but 1500gm. Prevalence of NEC was estimated as 4% and associated death prevalence accounts 22.2% in 28–31 weeks, 55.6% in 32–34 week, and 22.2% in 35 to <36 weeks (20). Although prevalence of necrotizing enterocolitis estimates in our country, do not seem well-defined thanks to lack of separate study in Ethiopia and other factors.

2.2 Associated factors of Necrotizing Enterocolitis:

Although the pathogenesis of inflammatory intestinal disease (NEC) remains unknown, it's probably a heterogeneous disease resulting from multiple factors that result in mucosal injury during a susceptible host. Current studies have identified prematurity and milk feeding as consistent risk factors for NEC (1, 31).

2.2.1 Prematurity

Several studies demonstrated that prematurity and low birth weight may be a predominant risk factor for NEC, but several other medical risk factors identified. An infant with high clinical acuity or severe co-morbidities is also at a greater risk for NEC (32-34).

Low birth weight (1500–2499 g), very low birth weight (VLBW) (1000–1499 g), and extremely low birth weight (<1000 g) are linked to many morbidities, including chronic lung disease, retinopathy of prematurity, sepsis, and inflammatory intestinal disease (NEC) (35).

Meta-analysis study significant prognostic factors for NEC reported in a minimum of two studies and other related study identified that a high risk of developing NEC were closely related to low

birth weight, very low birth weight. Small gestational age, low gestational and with inflammation of the amnion during labor and it reveals a high mortality in low birth weight preterm infants presenting as necrotizing enterocolitis, especially in VLBW infants (36-38).

2.2.2 Enteral feeding

A systematic review conducted in 2011 showed that over 90 percent of premature neonates who develop NEC have received milk feeding. Enteral feeding provides substrates for bacterial proliferation within the gut which can contribute to the pathogenesis of NEC, although NEC also occurs in infants who have not been fed (31).

Newborns, especially premature infants, have not developed the power to completely digest and absorb nutrients. Within the intestine of the preterm, bacterial fermentation products of incompletely digested carbohydrates and lipids like reducing substances, organic acids, short chain fatty acids, carbon dioxide, and hydrogen gas may cause mucosal injury, which may exacerbated by delayed transit time thanks to impaired intestinal motility. Animal model study demonstrated that a combination of casein, organic acids, and low pH led to mucosal injury with infiltration of cellular elements and vasoactive compounds (39).

Systematic review and single studies suggested that human milk, compared to formula, provided a transparent protective effect against NEC in premature infants with an approximate 4% reduction in incidence. Enteral feeding containing a minimum of 50% HM within the first 14 days of life was related to a six fold decrease within the odds of NEC (40-42).

Protective factors within human milk like, platelet activating factor acetyl hydrolase, secretory immunoglobulin A, cytokines (IL-10, IL-11), nucleotides, glutamine, and antioxidants like vitamin E, carotene, glutathione and epidermal growth factors repair disruptions during this layer (40). Human milk feeding related to a lower intestinal pH to facilitate the expansion of non-pathogenic bacteria, which counteract pathogenic bacteria and reduce inflammation or the introduction of foreign antigens within the gut. Improves intestinal motility, which avoids milk stasis and reduces intestinal permeability and stimulates the mucosal weapons system so local immune activation is prevented; the mucus coat of the intestine is less affected with human milk (40, 41).

A better proportion of HM was more effective than lower amounts with a 4% ARR in any NEC and 2% reduction in severe NEC. Human milk also provided a possible 5% reduction in LOS, severe retinopathy of prematurity (ROP) and severe NEC. Particularly for NEC, any volume of HM is healthier than exclusive preterm formula (EPTF), and also the higher the dose the greater the protection (41). On the opposite hand, evidence exists that artificial formula feeding and prolonged duration of parenteral feeding were related to an increases risk of NEC (6, 43) .

The risk-benefit balance of enteral feeding strategies may differ between human milk-fed and formula-fed very preterm or VLBW infants (6). Currently there are insufficient data to treat on whether there's a differential effect of the timing of the introduction of enteral feeds betting on whether infants received human breast milk versus formula (44).

In several current systematic review studies demonstrated that providing minimal enteral or trophic feeding doesn't increase the incidence of necrotizing enterocolitis (31). On the opposite hand, delay within the introduction of enteral feeds (after four days of age) and slow rate (15 to twenty mL/kg/d) advancement of feeds failed to reduce the danger of NEC compared with faster rates (30 to 40 mL/kg/d) of enteral feed volumes failed to show an impact on all-cause mortality. Pre specified subgroup analyses revealed no statistically significant effects on risk of NEC or death among extremely low birth weight (ELBW) or extremely preterm infants, nor among infants with growth restriction. Rather it absolutely was related to two to four days delay in regaining birth weight, longer time to determine full enteral feeds and borderline higher risk of late-onset infection compared with faster rates of advancement but the long-term clinical importance of those effects is unclear. However, only limited data are available on the effect of this intervention on outcomes for extremely preterm or ELBW infants (31,44-46).

A randomized control trial, comparative study and other studies conducted in United Kingdom, Ireland, Azerbaijan, Bangladesh and India on the advantages of early trophic feeding showed strong support for its use for preterm infants without adding complications. There have been no statistically significant differences in maternal characteristics of infants within the two groups and has the advantage of optimizing nutrition with marked reduction in incidence of NEC (14 VS 4%); sepsis; and hospital stay in stable preterm, VLBW infants and doesn't appear to extend the danger of NEC in growth-restricted preterm infants. The time to achieve birth weight (13.75±5.21 VS 20.53±6.31), duration of parenteral nutrition (9.26±4.572 days VS 14.11±6.415

days), hospital stay (12.14±8.612 VS 21.11±1.156), day of feat of full feeds and antibiotic therapy were significantly shorter in early compared to late feeding group with comparable mortality and incidence of late onset sepsis in each group (47-49)

In other hand, several randomized control trial and Cochrane systematic review of meta-analysis available data demonstrated that early trophic feeding failed to detect a statistically significant effect on the incidence of necrotizing enterocolitis and failed to provide any evidence that early trophic feeding affected feed tolerance or growth rates in VLBW infants. Early colostrum and progressive feeding significantly reduce mortality, the utilization of parenteral nutrition (4 compared with 8 d) and the need for central venous access (9 compared with 13 d). Time to succeed in full feeds within the study population was 6.90 ± 4.4 days as compared to 9.80 ± 4.86 days within the control group with significant weighted mean difference of ± 2.4 days (−0.8: −3.9) (24, 26, 50, 51).

2.2.3 Prenatal and Intrapartum risk Factors

A systematic review and meta-Analysis conducted in 2013 suggested that Clinical chorioamnionitis and histologic confirmed chorioamnionitis with fetal involvement were highly related to NEC, but the association between histologic confirmed chorioamnionitis and NEC was not statistically significant. However, Multivariate analyses in single studies generally weakened the reported associations. Several associations between other markers of antenatal inflammation and NEC are reported. In other study high umbilical cord artery, base deficit found to contribute to NEC in growth-restricted infants. Intrapartum risk factors related to NEC include maternal cardiac arrest, umbilical cord prolapse, placental abruption, and chorioamnionitis (52, 53).

Because NEC was, hypothesize to result from a reperfusion injury that stimulates an inflammatory cascade with resultant damage to the vasculature and therefore the intestinal mucosa in watershed areas of the intestine, any maternal condition that stimulates such an incident could considered. Possible risk factors present within the prenatal course include maternal drug use (specifically cocaine) (54), maternal hypertensive disease including pregnancy-induced hypertension and problems associated with placental blood flow (55).

Placental disease restricts the standard and quantity of nutrition to the developing fetus, results in a growth-restricted newborn, and will cause metabolic compromise if combined with other risk

factors. Maternal hypertension may cause placental disease, but it's unclear what impact it's on NEC (54, 55).

2.2.4 Clinical Course Factors

Although, prematurity could be a predominant risk factor for NEC, several other medical risk factors are identified. Infants with high clinical acuity or severe co-morbidities and who had a critical start (i.e. required resuscitation at delivery, mechanical ventilation within the first days of life, were born due to placental accidents including placental abruption and cord prolapsed, or were born growth-restricted due to placental insufficiency in utero) are at a greater risk for NEC. Low Apgar scores at birth (56), cardiac lesions, bowel obstruction, the utilization of inotropes, and compromised respiratory function are some indicators of clinical severity (57, 58).

A hemodynamic significant patent blood vessel (PDA) has been shown to increased risk of NEC (59). Indomethacin has been administered medically to close PDA, and when compared with ibuprofen, the risk for NEC decreased with ibuprofen (60, 61).

Meta-analysis study suggested that significant prognostic factors for NEC reported in a minimum of two studies were: nosocomial infection (62), erythrocyte transfusions(63), small for GA (64), assisted ventilation, premature rupture of membranes, sepsis, out born, hypotension are all increased risk, and cesarean section (lower risk) (36).

Studies on potential effects of postnatal antibiotics on NEC incidence have shown conflicting results and in other case control study contrary to expectations, the initiation of treatment with antibiotics within 24 hours after birth was inversely related to NEC (43, 65). In other study early-onset sepsis, drug exposure, and respiratory distress were all related to NEC, and infants who developed NEC were significantly less likely to own received breast milk and more likely to own been fed only formula (66).

2.3 Conceptual framework:

The factors that contribute for the development of necrotizing enterocolitis among premature and low birth weight infants summarized as newborn factors, enteral feeding, clinical factors, prenatal and intra partum related factors.

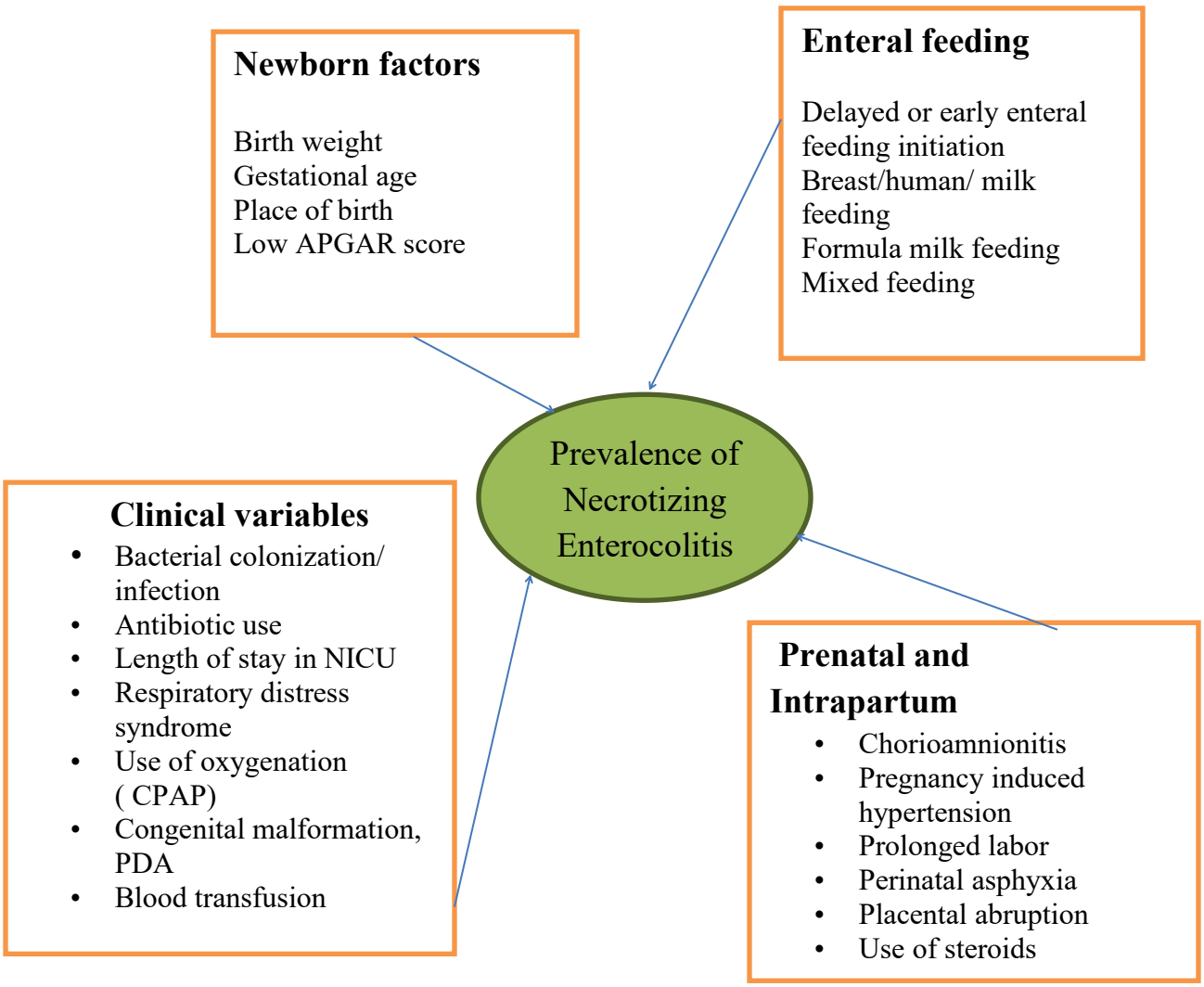

Figure 1. Schematic presentation of conceptual framework.

Source: Adapted after reviewing different literature's (24, 26, 27, 31, 32, 36, 41, 43, 44, 46-53, 55, 56, 58, 60, 62-64, 66) .

CHAPTER 3. OBJECTIVE OF THE STUDY

3.1 General Objective:

- To assess prevalence and associated factors of necrotizing enterocolitis among enteral feed preterm and low birth weight neonates admitted in selected public hospitals neonatal intensive care unit, Addis Ababa, Ethiopia, 2020.

3.2 Specific Objective:

- To assess the prevalence of necrotizing enterocolitis among enteral feed preterm and low birth weight neonates admitted in selected public hospitals intensive care unit, Addis Ababa, Ethiopia, 2020.
- To identify factors associated with necrotizing enterocolitis among enteral feed preterm and low birth weight neonates admitted in selected public hospitals intensive care unit, Addis Ababa, Ethiopia, 2020.

CHAPTER 4. MATERIALS AND METHODS

4.1 Study Area

The study conducted in governmental hospitals that found in Addis Ababa capital city of Ethiopia. Addis Ababa has an estimated area of 526.99 square kilometers, lies between 2326-3000 meters above sea level with lowest and highest annual temperature of 10c and 32c respectively and annual rainfall around 1200mm. Addis Ababa is rapidly growing urban city in terms of both population and economy. According to census 2007 (EFY) figure from the central statistical agency (CSA) of Ethiopia, Addis Ababa has an estimated total population of 3,384,569. The city has through recent years, seen vigorous annual growth rate, and population counts as of 2017 are growing closer to 4 million. 100% of the populations are urban dwellers (CSA 2007) and an estimated density of 5,535.8 people per square kilometer (67). There are 13 governmental public hospitals in Addis Ababa, those are one university hospital; six federal hospitals and the rest six are regional hospitals. Out of those, nine of them are deliver neonatal intensive care services. Currently; the total number of preterm, very preterm and very low birth weight infants average annual admission in Gandhi memorial hospital, Yekatit 12 hospital medical college and Tikur Anbesa specialized hospital are 425, 650 and 820 respectively, making a total of 1895 preterm admission per year with in those three selected hospitals.

4.2. Study design and period

An institutional based cross-sectional retrospective study design with document review method was used among preterm, very preterm, low birth weight and VLBW infants who were admitted to the NICU of selected public hospitals. The study was conducted from March 25/2020 to May 10/2020. Data collection was done by chart review using data abstraction form.

4.3. Source of Population

The source of population included all neonates' card were admitted and treated in the NICUs of selected hospitals.

4.4. Study population

The study population included all preterm, very preterm, low birth weight and VLBW infants' cards who were admitted to the NICU from January 2019 to January 2020 and who fulfilled the inclusion criteria.

4.5. Inclusion and exclusion criteria

4.5.1. Inclusion criteria

All preterm neonates' cards less than 37 completed weeks of gestation and birth weight below 2500gm neonate's card were admitted in neonatal intensive care unit. All very preterm and VLBW infants card between the ages of birth to discharge who were admitted to the selected hospitals NICU from January 2019 to January 2020 for whom, gestational age and weight parameters were available and stayed for more than 72 hours were included in the study.

4.4. 2. Exclusion criteria

Preterm neonates' cards who died or were discharged before 72 hours of age, and neonates cards for whom the gestational age and weight measurements and/or other relevant clinical data were not documented or were incomplete were excluded from the study.

4.5. Sample size determination

The sample size was calculated by using single population proportion formula. Due to absence of studies done in Ethiopia, the prevalence was considered to be 50% to calculate the sample size;

$$In = \frac{\left(z^{\alpha}/_{2}\right)^{2} P(1-P)}{d^{2}} = In = \frac{(1.96)^{2}(0.5)(1-0.5)}{(0.05)^{2}} = 384$$

Since the sample is taken from a small population that is less than 10,000 a smaller sample size will be required thus, using correction formula **n final,** $\mathrm{nf} = 1 + \frac{\frac{n}{n}}{N}$

$$= 1 + \frac{384}{\frac{384}{1895}} = 319.3$$

Considering 10% contingency the sample size was calculated to be 350.

Where: **n**= required sample size

Zα /2= 1.96 (Z=score corresponds to 95% confidence level)

P= prevalence (50% is preferred to obtain the largest possible sample size)

d2= margin of error (0.05)

N= total population

4.6. Sampling procedure and technique

A simple random sampling technique was used to select sampling units and study participants' medical card for document review. There are a total of 13 public hospitals in Addis Ababa city and 9 hospitals have giving NICU service, from those 3 hospitals are selected by using simple random sampling (lottery) method and the calculated sample size was distributed to each hospitals by proportion to size then study participants' card was selected using simple random sampling method. When term neonates' card has chosen during random selection, subsequent preterm medical cared was used as the study participant.

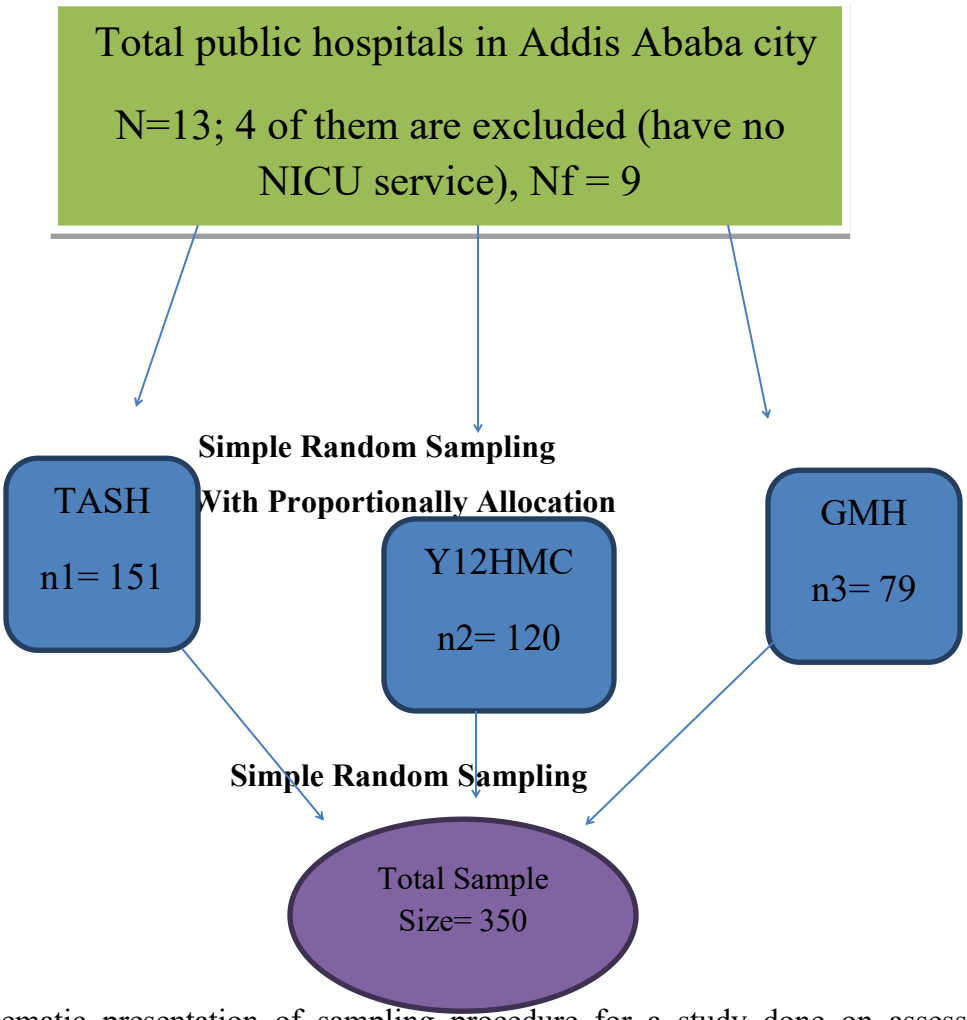

Figure 2 Schematic presentation of sampling procedure for a study done on assessment of prevalence and associated factors of necrotizing enterocolitis among enteral feed preterm and very low birth weight neonates admitted in neonatal intensive care unit in selected public hospitals of Addis Ababa city, 2020.

4.7. Study variables

4.7.1. Dependent variable

- Prevalence of Necrotizing enterocolitis

4.7.2. Independent variables

4.7.2.1New born factors

- Birth weight
- Gestational age
- Place of birth
- Low APGAR score

4.7.2.2Enteral feeding

- Delayed or early enteral feeding initiation
- Breast/human/ milk feeding
- Formula milk feeding
- Mixed feeding

4.7.2.3 Clinical variables

- Bacterial colonization/ early or late onset infection
- Antibiotic use
- Length of stay in NICU
- Respiratory distress syndrome
- Use of oxygenation (CPAP)
- Congenital malformation, PDA
- Blood transfusion

4.7.2.4 Prenatal and Intrapartum

- Chorioamnionitis
- Pregnancy induced hypertension

- Prolonged labor
- Perinatal asphyxia
- Placental abruption
- Use of steroids

4.8 Operational definition

Necrotizing Enterocolitis: In this study necrotizing enterocolitis is declared when a medical diagnosis of the neonate's card are stated as stage I, II, and III NEC by the physician in the neonate's medical record chart.

- **Suspected Necrotizing Enterocolitis:** Is defined as those neonates' card stated with the diagnosis of stage one necrotizing enterocolitis by the treating physician based on referring documented diagnosis from the neonate's card.
- **Confirmed Necrotizing Enterocolitis:** Is declared when a medical diagnosis of the neonate' card is stated as stage II or stage III NEC by the physician in the neonate's medical record chart or NEC diagnosed with confirmed evidence through abdominal X-ray finding which suggested the necrotizing enterocolitis.
- **No Necrotizing Enterocolitis:** Is declared when the neonates' card have no diagnosis with necrotizing enterocolitis by the physician or have no any abdominal X-ray finding for NEC during card document review.

4.9 Data collection tool

Structured chart review questionnaire format was adapted from different literatures after being modified to the local context and to the research objective by the investigator.

4.10 Data collection procedure

Three BSC nurse data collectors and one BSC nurse supervisor having possible experience in data collection was selected. One day training was given for data collectors and supervisor about the research objective, data collection tool and sampling procedure. Chart numbers of infants' card admitted to the NICU of selected public hospitals from January 1, 2019 to January 30, 2020 were retrieved from the NICU HMIS and medical record storeroom. Selection were made according to inclusion and exclusion criteria. Data was collected between March to May/2020 by

the data collectors. Relevant data were recorded in a data collection sheet designed for the study; infant characteristics, relevant feeding practice, NEC and other clinical data was retrieved and documented.

To ensure the validity of the study, pre-testing was conducted in Zewuditu memorial hospital on 5% (18 participants' card) of sample size participants' card before data collection, based on that the questionnaires was revised and edited. The supervisor made continuous supervision of data collectors and collected data. The principal investigator for its completeness and missing information during data collection checked data. The data was crosschecked and corrected by the investigator prior to analysis.

NB: prolonged data collection period (from March 25 to May 10/2020) was due to interruption of data collection for greater than a month because of lockdown command due to COVID-19 outbreak and restriction commands not to collect the data by each hospitals administration.

4.12 Data analysis and interpretation

The collected data was checked manually for its completeness, entered into Epi-data version 4.6, and then coded. Data was exported in-to SPSS version 26 statistical software for further analysis. Continuous data was summarized using descriptive statistics of percentile, frequency, mean, median and standard deviation. An association of dependent and independent variables was measured using bi-variate and multivariate logistics regression analysis. Statistical significance was declared with p value less than 0.05 at 95% CI. Finally, the result was presented using tables, texts and other representation.

4.13 Ethical consideration

Ethical clearance was obtained from department of nursing IRB, school of nursing and midwifery, Addis Ababa University and Addis Ababa public health research and emergency management directorate. Permission letter was provided to Tikur Anbessa specialized hospital, Yekatit 12 hospital medical college and Gandhi memorial hospital to proceed for data collection. Anonymity was assured on the data retrieval form by omitting names, telephone numbers and chart number of patients and confidentiality of the information from individual chart is maintained.

4.14 Dissemination of results

The finding of the study will be disseminated to Addis Ababa University, department of nursing and midwifery, Addis Ababa public health research and emergency management directorate and to NICU departments of each study area hospitals. In addition, efforts will be made to disseminate the results through presentations in different seminars, workshops, and scientific conference. Attempts will also be made to publish the information on reputable peer reviewed journals for further utilization.

5. Result

5.1. Characteristics of neonates admitted to NICU

Three hundred fifty eligible participants were selected for the study based on inclusion and exclusion criteria. Out of which 184 (52.6 %) were male and the rest 166 (47.4%) of the respondents were female. Majority of 290 (82.9%) of neonates born in hospital or inborn and the rest 60 (17.1%) of the neonates were born outside of study area hospital. There is look into case document, 13.1 % of the babies have in utero growth restriction. Majority of neonate's (35.1%) were 32+1-34 weeks gestational age and the rest 32.6% and 4.3% of them were 28+1-32 and less than or equal to 28 weeks gestational age respectively. Were as about 53.1% were LBW and the rest 32.9% and 145 were VLBW and ELBW respectively. About 48.3% of neonates APGAR score was above 7and the rest 47.1% and 4.6% of them were between 4-6 and less than or equal to 3 respectively. In other hand, average postnatal age at admission to NICU was 5.64 hour.

Table 1: Characteristics of neonates admitted to NICU (N=350)

Study variable	**Category**	Frequency	Percent(%)
Sex	Male	184	52.6
	Female	166	47.4
Place of birth	Inborn	290	82.9
	out born	60	17.1
In-utero growth restriction	Yes	46	13.1
	No	304	86.9
Gestational age in weeks	<=28wks	15	4.3
	28+1-32wks	114	32.6
	32+1-34wks	123	35.1
	34+1-36+6	98	28
Birth weight Classification	LBW(1500-2499g)	186	53.1
	VLBW(1000-1499g)	115	32.9
	ELBW(<1000gm)	49	14
APGAR score	<=3	16	4.6
	4-6	165	47.1
	>=7	169	48.3

Descriptive statistics	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**
Age at admission to NICU / hours	0.08	192.00	5.6407	20.17970

5.2. Prenatal and Intrapartum factors

Results regarding to mode of delivery, a majority of (56.9%) have a provision of C/S care, followed by 42.3% of SVD and 0.9% of them had instrumental assisted. Majority of (56.9%) of neonates were born from primipara mother and the rest 43.1% of them were adjusted with multipara. Among 350 study subject neonate's mother, 63 (19.1%) had prolong labor and 65 (18.6%) of neonate's mothers had maternal chronic disease during pregnancy. Out of this, 14.9% and 2% of the mother had pregnancy induced hypertension and gestational diabetes mellitus respectively. Maternal infection during pregnancy was 123(35.1%), of which 33.4% was PPROM followed by 8.6% of chorioamnionitis and 2.6% of UTI and foul smelling vaginal discharge. Similarly, about 50.6% mothers took drug during pregnancy. In the other hand, 16% of neonates had birth related complication during delivery process.

Table 2: Description of Prenatal and Intrapartum factors (N=350)

Study variable		Frequency	Percent %
Mode of delivery	SVD	148	42.3
	C/S	199	56.9
	Instrumental Assisted	3	0.9
Parity	Primipara	199	56.9
	Multipara	151	43.1
Prolonged labor	Yes	67	19.1
	No	283	80.9
Maternal chronic disease during pregnancy	Yes	65	18.6
	No	285	81.4
Gestational diabetes	Yes	7	2
	no	58	16.6
	missing	285	81.4
Hypertensive disorder	Yes	52	14.9
	No	13	3.7
	missing	285	81.4
Presence of maternal infection during pregnancy	Yes	123	35.1
	No	227	64.9
PPROM	Yes	117	33.4
	No	6	1.7
	Missing	227	64.9
Chorioamnionitis	Yes	30	8.6
	No	93	26.6
	Missing	227	64.9

UTI, fever, abdominal pain, foul-vaginal discharge during pregnancy	Yes	9	2.6
	no	114	32.6
	missing	227	64.9
Mother took any drug during pregnancy	Yes	177	50.6
	No	173	49.4
Use of Antenatal antibiotics	Yes	148	42.3
	No	29	8.3
	Missing	173	49.4
Use of Magnesium sulfate	Yes	35	10
	No	142	40.6
	Missing	173	49.4
Use of Steroid drugs	Yes	60	17.1
	No	117	33.4
	Missing	173	49.4
Babies' birth related complications	Yes	56	16
	No	294	84
Antepartum hemorrhage/ abruption placenta	Yes	20	5.7
	No	36	10.3
	Missing	294	84
Umbilical cord prolapse	Yes	2	0.6
	No	54	15.4
	Missing	294	84
MAS	Yes	11	3.1
	No	45	12.9
	Missing	294	84
Perinatal asphyxia with any stage of HIE	Yes	30	8.6
	No	26	7.4
	Missing	294	84

5.3. Description of Neonates' characteristics by enteral milk feed initiation

Among 350 of babies who were admitted to neonatal intensive care unit 93.1% of babies were received trophic feeding at mean age of 34.54 ± 34.62 hours with a minimum of one hour and maximum of 240 hours. An average of 18± 13.57ml/kg/day volume of milk was used with a minimum of 2ml/kg/day and maximum of 86ml/kg/day to start feeding. Majority of neonates were breast milk fed users (73.7%) whereas formula milk and mixed milk fed users were 13.1%) and 6.3% respectively. The rest 24 (6.9%) of them were not yet start enteral feeding. The study result found that higher proportions, (72%) of premature neonates admitted to neonatal intensive care unit had been feed by NGT with an average mean duration of 7.74 ± 7.88 days (minimum 1 and maximum 64 days). Study result was evaluated that 77.4% of the baby established full enteral milk feeds at the mean age of 6.48 ± 6.45 with a minimum of one and maximum of 58 days variation. From those started milk feeding 23.7% of the babies had feeding intolerance. In regarding to enteral feed volume before onset of NEC; 5.4% of them done full feeding, other 16.9% of them done trophic feeding and the rest 3.1% of them were NPO. Where it comes to duration of parenteral (IV MF) nutrition by day were in minimum of 1 and maximum of 38 days with an average 6.38±5.838 days.

Table 3: Description of infants characteristics by milk feed initiation (N=350)

Study variable		Frequency	Percent %
Babies have receive trophic feeds during Postnatal admission to NICU	Yes	326	93.1
	No	24	6.9
Type of milk feeding	Breast milk feed	258	73.7
	Formula milk	46	13.1
	Mixed milk feed	22	6.3
	Missing	24	6.9
Mode of feeding	Cup	27	7.7
	Direct breast	47	13.4
	NGT feed	252	72
	Missing	24	6.9
Baby established full enteral milk feeds.	Yes	271	77.4
	No	55	15.7
	Missing	24	6.9
Babies have feeding intolerance.	Yes	83	23.7
	No	243	69.4
	Missing	24	6.9
Enteral feed volume before onset of NEC	Full feeding	19	5.4
	Trophic feeding	59	16.9
	NPO	11	3.1
	Missing	261	74.6
If the baby establish weight gain	Yes	117	33.4
	No	233	66.6

Descriptive Statistics	N	Minimum	Maximum	Mean	Std. Deviation
Duration of parenteral (IV MF) nutrition by days	350	1.00	38.00	6.3829	5.83800
Age of trophic enteral feeding started /hours	326	1.000	240.000	34.5429	34.6286
First enteral feed volume used to start trophic feeding by ml/kg/day	326	2.00	86.00	18.0000	13.5789
Age of full Enteral feed established	271	1.00	58.00	6.4871	6.45087
Duration of NGT feeding bay day	252	1.00	64.00	7.7421	7.88266
Age baby establish weight gain	117	3	66	14.196	9.508

5.4. Description of clinical factors to the diagnosis of NEC

From the study participant neonates admitted to NICU, 14 (4.0%) of babies had congenital anomalies, 83 (24.9%) of the babies had developed failure to breath or resuscitated after birth. Significantly, 257(73.4%) of them had respiratory distress, of which 220 (62.9%) of the neonates required CPAP ventilation support. Days on CPAP varied between a minimum of one and maximum of 24 days with an average mean duration of 4.49± 2.924 days. The data showed 321(91.7%) of the baby had diagnosed with early/late onset neonatal sepsis. Regarding medication, 326 (93.1%) of babies were receive antibiotics; out of which five (1.4%) of them were not diagnosed with sepsis. From the total study subject's 89 (25.4) of them were diagnosed with NEC, which were 30 (8.6%) of them were developed leukocytosis/ leukopenia, 28 (8%) were developed anemia and 60 (17.1%) were developed thrombocytopenia. About 31(8.9%) of babies make sure of blood/exchange transfusion in the 48 hours prior to NEC diagnosis. Moreover, day of life at diagnosis of NEC were a minimum of two days and maximum of 46 days and average day were 8.4± 5.760 days. In other hand, Total number of antibiotics days prior to diagnosis of NEC was 8.4±6.0 days in average and minimum of one and maximum of 46 days.

Table 4: Description of clinical factors to the diagnosis of NEC on Premature and Low Birth Weight infants (N=350)

Study variable		**Frequency**	**Percent %**
Baby have Congenital anomalies	Yes	14	4
	No	336	96
Failure to breath/Resuscitation after birth	Yes	87	24.9
	No	263	75.1
Presence of Respiratory distress	Yes	257	73.4
	No	93	26.6
Use of CPAP support	Yes	220	62.9
	No	130	37.1
Baby have diagnosed with Early/Late onset neonatal sepsis	Yes	321	91.7
	No	29	8.3
Baby receive antibiotics	Yes	326	93.1
	No	24	6.9
Did the baby have diagnosed with NEC?	Yes	89	25.4
	No	261	74.6
How the NEC was diagnosed	Clinically	57	16.3
	Imaging/x-ray/us	32	9.1
	Missing	261	74.6
Type and stage of NEC	Stage I	57	16.3
	Stage II	30	8.6
	Stage III	2	0.6
	Missing	261	74.6
Blood/exchange transfusion in the 48 hours prior to NEC diagnosis	Yes	31	8.9
	No	58	16.6
	Missing	261	74.6
Leukocytosis/ Leukopenia during diagnosis of NEC	Yes	30	8.6
	No	59	16.9
	Missing	261	74.6
Anemia during diagnosis of NEC	Yes	28	8
	No	61	17.4
	Missing	261	74.6
Thrombocytopenia during diagnosis of NEC	Yes	60	17.1
	No	29	8.3
	Missing	261	74.6
Outcome of NEC	Improved	49	14%
	Death	40	11.4%
	Missing	261	74.6

Descriptive Statistics	N	Minimum	Maximum	Mean	Std. deviation
Duration of CPAP used by day	220	1	24	4.49	2.924
Total number of antibiotics days prior to diagnosis of NEC	89	1.00	46.00	8.1461	6.00672
Day of life at diagnosis of NEC; specify by day	89	2.00	46.00	8.4944	5.76061

5.5. Prevalence of Necrotizing Enterocolitis

Out of 350 study participants 89 (25.4%) of infant found developed NEC. Of neonates who developed NEC; <=28 weeks, 28+1-32 weeks, 32+1-34 weeks and 34+1-36+6 weeks of gestational age accounts 2%, 10.6%, 10.2% and 2.6% respectively. Likewise most of them were VLBW (1000 to 1499gm) 41(11.7%) and the rest 29(8.3%) and 19(5.4%) of them were 1500 to 2499gm and less than or equal to 1000gm birth weight neonates respectively. Of which neonates, 57(16.3%) of them was diagnosed via clinically (Sign/symptom) and the rest 32 (9.1%) of the babies had diagnosed via imaging (x-ray/ US). Regarding to type and stage of NEC; 57(16.3%) of the babies were developed Suspected (stage I), and other 30(8.6%) were Confirmed (stage II) and the rest of 2(0.6%) were Advanced (stage III) of NEC. Majority of the neonates, 78 (22.28%) who develop NEC had started enteral feeds and the rest of 11(3.14%) were NPO.

Between January 2019 to January 2020, 89 infants were diagnosed with NEC, 49(14.0%) recovered from NEC and 40 (11.4%) died due to NEC.

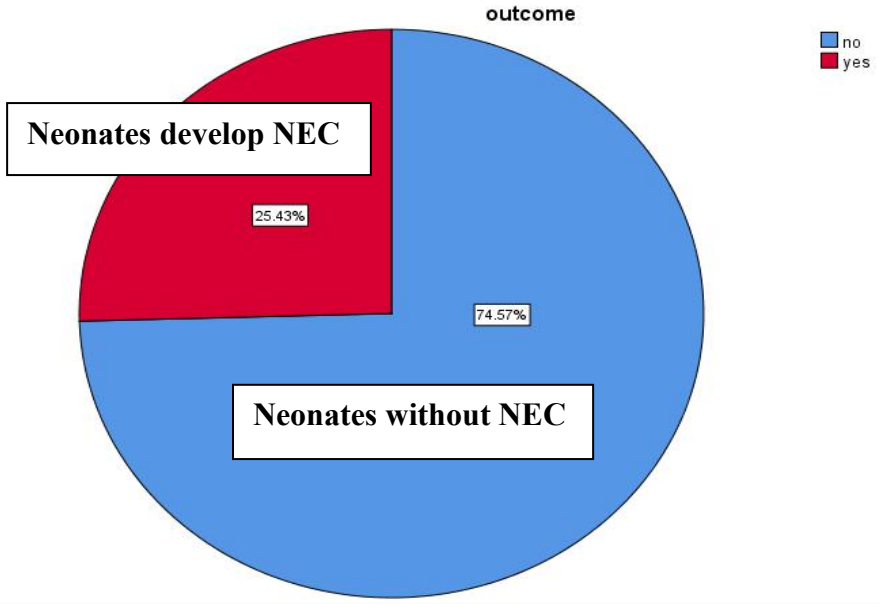

Figure 3: Prevalence of NEC among premature and low birth weight neonates admitted in NICU of public hospitals Addis Ababa, Ethiopia, from January 2019 to January 2020(N=350).

5.6. Factors Associated with Necrotizing Enterocolitis (NEC) Among Premature and Low Birth Weight Neonates

In multivariate analysis gestational age less than 37 completed weeks, very low birth weight (1000gm to 1499gm), low APGAR score (4 to 6) and neonates of mother with prolonged labor and hypertension during pregnancy were significantly associated to necrotizing enterocolitis. Those premature neonates gestational age less or equal to 28 weeks (P=0.025, AOR=4.94, 95% CI: 1.22, 19.97), 28+1 to 32 weeks (P=0.011, AOR=3.15, 95% CI: 1.31, 7.61) and 32+1 to 34 weeks (P=0.006, AOR=3.26, 95% CI: 1.40, 7.66) develop NEC 4.9, 3.2 and 3.3 times respectively compared to 34+1 to 36+6 weeks of gestational age neonates. Those preterm neonates 1000 to 1499gm birth weight (P=0.010, AOR=2.29, 95% CI: 1.22, 4.33) were 2 times more likely develop NEC compared to those 1500 to less than 2500gm birth weight neonates. Neonates low Apgar score of 4 to 6 (P=0.004, AOR=2.34, 955 CI: 1.32, 4.16) were 2 times more likely at risk for NEC compared to those greater than 7score. Those preterm and low birth weight neonates born from mothers who had prolonged labor (P=0.006, AOR=2.94, 95% CI: 1.35, 6.38), maternal chronic disease especially hypertension (P=0.000, AOR=3.20, 95% CI: 1.70, 5.90) and chorioamnionitis (P=0.000, AOR=14.8, 95% CI: 4.9, 44) were 2.9, 3 and 15 times more likely increase the risk of acquiring NEC compared to those who had no any maternal disease.

CPAP ventilation used by preterm and low birth weight neonates and neonatal sepsis were significantly associated to necrotizing enterocolitis. Those preterm and low birth weight neonates had used CPAP ventilation (P=0.012, AOR=6.70, 95% CI: 1.50, 29.70) and who had late or early onset neonatal sepsis (P=0.040, AOR=8.4, 95% CI: 1.1, 64.60) were 7 and 8 times more likely increase risk of develop NEC compared to those who hadn't CPAP ventilation and neonatal sepsis.

Only breast (human) milk was significantly associated to decreased risk of necrotizing enterocolitis. Those neonates used breast milk fed at any age (P=0.000, AOR=0.02, 95% CI: 0.003, 0.05) were 98% less likely acquired necrotizing enterocolitis compared to those mixed milk fed neonates.

Table 5: Bi-variate and multivariate analysis of factors associated with necrotizing enterocolitis among enteral fed premature and low birth weight neonates admitted in NICU of public hospitals in Addis Ababa, Ethiopia, 2020(N=350)

Characteristics		Prevalence of NEC		COR(95% CI)	AOR(95% CI)	P-value
		No	Yes			
Gestational Age in week	<=28wks	8 (53.3%)	7 (46.7%)	8.65(2.54,29.43)*	4.94(1.22,19.97)**	**0.025**
	28+1-32wks	77 (67.5%)	37(32.5%)	4.75(2.16,10.47)*	3.15(1.31,7.61)**	**0.011**
	32+1-34wks	87 (70.7%)	36(29.3%)	4.09(1.86,8.99)*	3.26(1.40,7.66)**	**0.006**
	34+1-36+6wks	89 (90.8%)	9 (9.2%)	1	1	
Birth weight in In gram	<1000gm	30 (61.2%)	19(38.8%)	3.43(1.71,6.89)*	1.68(0.73,3.85)	0.219
	1000-1499gm	74 (64.3%)	41(35.7%)	3.00(1.73,5.19)*	2.29(1.22,4.33)**	**0.010**
	1500-2499gm	157 (84.4%)	29(15.6%)	1	1	
Sex	Male	132 (71.7%)	52(28.3%)	1.4(0.80,2.20)*	1.36(0.79,2.33)	0.265
	Female	129 (77.7%)	37(22.3%)	1	1	
APGAR score	<=3	11 (68.8%)	5 (31.3%)	2.3(0.74,7.10)	1.48(0.39,5.49)	0.558
	4-6	109 (66.1%)	56(33.9%)	2.6(1.54,4.34)*	2.34(1.32,4.16)**	**0.004**
	>=7	141 (83.4%)	28 (16.6)	1	1	
Intrauterine growth Restriction(IUGR)	Yes	31 (67.4%)	15(32.6%)	1.5(0.77,2.90)	1.3(0.62,2.84)	0.460
	No	230 (75.7%)	74(24.3%)			
Prolonged labor	Yes	43 (64.2%)	24(35.8%)	1.9(1.06,3.31)*	2.94(1.35,6.38)**	**0.006**
	No	218 (77%)	65 (23%)	1	1	
Maternal chronic disease/Hypertension	Yes	35 (53.8%)	30(46.2%)	3.26(1.72,6.17)*	3.2(1.70,5.90)**	**0.000**
	No	226 (79.3%)	59(20.7%)	1	1	
Maternal infection	Yes	84 (68.3%)	39(31.7%)	1.6(1.04,2.70)*	1.5(0.90,2.50)	0.136
	No	177 (78%)	50 (22%)	1	1	
Chorioamnionitis	Yes	8 (26.7%)	22(73.3%)	12.3(4.70,32.3)*	14.8(4.9,44)**	**0.000**
	No	76 (81.7%)	17(18.3%)	1	1	
	Missing	227 (64.9%)				
Mother took drug	Yes	124 (70.1%)	53(29.9%)	1.6(0.99,2.65)*	1.1(0.24,4.90)	0.907
	No	137 (79.2%)	36(20.8%)	1	1	

Steroid drug	Yes	37 (61.7%)	23(38.3%)	1.8(0.9,3.5)*	1.5(0.7,3.1)	0.288
	No	87 (74.4%)	30(25.6%)	1	1	
	Missing	173 (49.4%)				
Perinatal Asphyxia	Yes	16 (53.3%)	14(46.7%)	10.5(2.1,52.6)*	4.5(0.2,108.6)	0.349
	No	24 (92.3%)	2 (7.7%)	1	1	
	Missing	294 (84%)				
Failure to breath/	Yes	54 (62.1%)	33(37.9%)	2.3(1.3,3.8)*	1.3(0.7,2.4)	0.371
resuscitated	No	207 (78.7%)	56(21.3%)	1	1	
Respiratory distress	Yes	180 (70%)	77 (30%)	2.9(1.5,5.6)*	0.34(0.07,1.63)	0.177
Syndrome	No	81 (87.1%)	12(12.9%)	1	1	
Use of CPAP	Yes	145 (65.9%)	75(34.1%)	4.3(2.31,7.99)*	6.7(1.50,29.70)**	**0.012**
Ventilation	No	116 (89.2%)	14(10.8%)	1	1	
Early or Late onset	Yes	233 (72.6%)	88(27.4%)	10.6(1.4,78.9)*	8.4(1.1,64.6)**	**0.040**
Neonatal sepsis	No	28 (96.6%)	1 (3.4%)	1		
Received	Yes	238 (73%)	88 (27%)	8.5(1.1,64)*	5.5(0.69,43.12)	0.106
Antibiotic	No	23 (95.8%)	1 (4.2%)	1		
Received	Yes	248(76.1%)	78(23.9%)	0.37(0.14,0.86)	0.49(0.19,1.28)	0.149
trophic feed	No	13 (54.2%)	11(45.8%)	1	1	
Age of milk fed started						
	<=24hrs	166 (81%)	39 (19%)	0.32(0.14,0.75)*	1.2(0.29,4.76)	0.804
	25-48hrs	52 (74.3%)	18(25.7%)	0.47(0.18,1.21)*	0.51(0.09,2.70)	0.431
	49-72hrs	15 (60%)	10 (40%)	0.91(0.29,2.77)*	1.44(0.28,7.26)	0.658
	>72hrs	15 (57.7%)	11(42.3%)	1	1	
	Missing	24				
Type of milk fed used by						
neonates	Human milk	237 (84.9%)	42(15.1%)	0.02(0.01,0.07)*	0.01(0.003,0.05)**	**0.000**
	Formula milk	8 (28.6%)	20(71.4%)	1.06(0.28,3.97)	1.34(0.32,5.85)	0.680
	Mixed milk	3 (15.8%)	16(84.2%)	1	1	
	Missing	24				

NB: *Significant Association with Bivariate; **Significant Association with Multivariate;

1=Reference category ; CPAP=continuous positive airway pressure

6. Discussions

This study attempted to assess the prevalence and factors associate with necrotizing enterocolitis among enteral feed preterm and low birth weight neonates admitted in neonatal intensive care unit in selected public hospitals of Addis Ababa, Ethiopia, 2020.

In this study it was summarized that Out of 350 preterm and low birth weight neonates admitted to the neonatal intensive care units, 89 (25.4%) of neonates found developed NEC. Majority of neonates who developed NEC are 28+1 to 32(10.6%) weeks, and those who are 32+1 to 34 weeks, 34+1 to 36+6 and less than or equal to 28 weeks of gestational age accounts 10.2%, 2.6% and 2% respectively.

This finding was closely related to the study conducted across US centers and worldwide (1, 2). The similarity in finding might be due to the relations of study subjects those with low gestational age neonates are highly at risk for NEC because of poor intestinal motility and adaptation; but previous study in Addis Ababa showed that the prevalence was estimated as 4% (20).

This difference might be explained due to previous study asses all cause of premature death, was not separated study pertaining to NEC, and was not able to identify associated factors for NEC. Likewise, most of them were VLBW (1000 to 1499gm) 11.7% and the rest 8.3% were 1500 to 2499gm and less than 1000gm birth weight neonates' accounts 5.4%. This was closely related with previous meta-analysis studies which revealed that low birth weight was closely related with necrotizing enterocolitis {(35), 36-38)}.

In this study, gestational age, low Apgar score, and birth weight were observed significantly determining newborn factors associated with Necrotizing enterocolitis on multivariate analysis. This study is almost consistent with several systematic review and other meta-analysis studies which were demonstrated that high risk of developing NEC is closely related to LBW, VLBW and low gestational age and are a predominant risk factors for NEC {(28, 29, 30) 32-34, 36-38)}. This similarity may be explained by the similarity of study subject as well as in preterm and LBW neonate's immature intestinal immunity, microbial dysbiosis and mucosal ischemia favors bacterial proliferation within the gut, which can contribute to the pathogenesis of NEC.

This study was revealed that breast (human) milk fed was significantly associated to decreased risk of NEC. Those neonates used breast milk fed was 98% less likely develop necrotizing enterocolitis among premature and low birth weight infants in neonatal intensive care units.

This study result was comparable with systematic review studies, which were human milk compared to formula milk, provided a transparent protective effect against NEC in premature infants with an approximate 4% reduction in incidence (40-42). Likewise, the study result was consistent with randomized control trial and comparative studies conducted in United Kingdom, Ireland, Azerbaijan, Bangladesh and India on the advantages of early trophic feeding showed strong support for its use for preterm infants without adding complications (47-49). And also the result was congruent with Cochrane systematic review of meta-analysis which were demonstrated that early trophic feeding failed to detect a statistically significant effect on the incidence of necrotizing enterocolitis (24, 26, 50, 51).

This similarity might explained by protective factors within human milk like, platelet activating factor, acetyl hydrolase, antioxidants and epidermal growth factors repair disruptions of intestinal mucosal layer. Likewise, human milk feeding is related to a lower intestinal PH to facilitate the expansion of non-pathogenic bacteria, which counteract pathogenic bacteria and reduce inflammation that leads to improve intestinal motility. Also avoids milk stasis and reduces intestinal permeability also stimulates the mucosal weapons system so local immune activation is prevented; the mucus coat of the intestine is less affected with human milk thereby decrease risk of NEC. However, this study failed to demonstrate statistical significance on artificial formula milk feeding which was contradicted with previous study findings, which were revealed that artificial formula feeding were related to an increase risk of NEC (6, 43).

This difference might be explained by majority of neonates are breast milk users and very small formula milk was used in the study area participants; with this small formula feeding user sample the difference may not exist.

This study identified that prolonged labor, pregnancy induced hypertension and chorioamnionitis were observed as significant predictors of necrotizing enterocolitis. This finding is almost consistent with systematic review and meta-analysis studies conducted in 2013 {(52, 53), 54, 55)} . This might be explained due to maternal infection and prolonged labor increase the likely hood of neonatal infection which results clinical severity and hypertension predisposed to being preterm thereby increase sever co-morbidity and compromised respiratory functions which are increasing determinant factors of necrotizing enterocolitis.

According to this study, bacterial colonization/ early or late onset infection was significant predictors of NEC among preterm and low birth weight neonates. Likewise use of CPAP ventilation was associated to increase odds of NEC to the premature and low birth weight neonates. This is similar with meta-analysis studies{ (36) 57, 58), (59), 62) 66)}. The similarity might be due to immature gut as well as re-per-fusion injury and different complications related to prematurity that predispose them to inflammatory cascades of the preterm and low birth weight neonates gut that leads to NEC. Neonates who had severe co-morbidities and who had a critical start are at greater risk for NEC.

7. Conclusion and Recommendation

7.1 Conclusion

In this study it was summarized that Out of 350 preterm and low births weight neonate, 89 (25.4%) of them found developed NEC. Majority of neonates who developed NEC are 28+1 to 32 weeks (10.6%) and those who are 32+1 to 34 weeks, 34+1 to 36+6 and <=28 weeks of gestational age accounts 10.2%, 2.6% and 2% respectively. Likewise, most of them are VLBW (1000 to 1499gm) (11.7%), the rest are 15000 to 2499gm (8.3%), and less than 1000gm birth weight neonate's accounts 5.4%. From the 89 infants with NEC 49(14.0%) of them were improved and 40 (11.4%) of neonate's was died. Gestational age, low Apgar score, and birth weight were observed significantly determining newborn factors associated with Necrotizing enterocolitis. Neonates with mother who had prolonged labor, pregnancy induced hypertension and chorioamnionitis was found that a significant perinatal and intra partum factors which increase the likely hoods of developing NEC. Premature neonates being colonized by pathogenic bacteria/ having early or late onset infection and use of CPAP were found significantly predicting factor associated to NEC in the study area. On the other side breast milk, fed user neonates are 98% less likely to develop NEC.

7.2. Recommendations

Based on the finding the following recommendations will be forwarded to concerned bodies.

For Health Institutions

It is better to regularly screen out pregnant mothers for infection and maternal chronic disease like hypertension so that they will be alarmed as this can put in risk of delivery being preterm and low birth weight which may lead to poor neonatal adaptation and so many associated co-morbidity that leads to necrotizing enterocolitis even up to end with death.

For Health professionals who are working in NICU and Obstetrics Unit:

Paying detail attentions to identify associated factors and giving priority treatment for these factors as well as giving attention about enteral feeding initiation for those premature and low birth weight neonates will significantly decrease proportion risk of necrotizing enterocolitis.

It is better to encouraging early initiation of breast milk feeding for every premature neonate, as it has a clear protective effect on the occurrence of NEC.

For Further Researchers:

It will be more valuable if studies will be conducted on this subject matter with alternative institutional based prospective observational, case control as well as randomized control trial study design to find more preventable factors associated with the risk of NEC among premature and low birth weight neonates.

8. Strength and Limitation of the Study

8.1 Strength

This study assessed factors associated with necrotizing enterocolitis among premature and low birth weight neonates which is important in the context of this country. In addition as this is the first study in the context of this subject matter it will be used as a base line data for future researchers.

8.2 Limitation

The findings of this study should be interpreted in the light of a number of limitations.

Firstly, since it was a retrospective document review study institutional and health professional factors were not included. Secondly, the study was cross-sectional which didn't address the cause and effect of the factors. Thirdly, the study reviewed data of one year only.

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ANNEX

Annex 1: English Version Data Collection Format

General information for the study participation

Hello, my name is ----------; I am a nurse and I am collecting data from a patient's individual card record in the NICU for the purpose of research being conducted on necrotizing enterocolitis and associated factors among enteral feed premature and low birth weight neonates. The result of the study will be helpful to the study population by helping identify the prevalence and factors associated in the same population with necrotizing enterocolitis. Results may also be used as base line data for the planning and intervention for prevention of necrotizing enterocolitis in the same population in the local area as well as nationally.

If you have any questions or more clarification about this study you may ask a data collectors or the principal investigator.

(Tel. 0923421196, E-Mail- giftu21@gmail.com).

Consent form for the study subjects

I the undersigned have been informed about the purpose of this particular research project and I have been informed that the information I give will be used only to the purpose of the study. In addition I am also informed that my identity as well as the information I will be providing will be kept confidential. Based on this, I agree to participate in the research voluntarily.

Witnesses

Signature: ……

Data collection format for Addis Ababa University, MSc research project on necrotizing enterocolitis and associated factors among preterm, very preterm, low birth weight and very low birth weight neonates in selected Addis Ababa public hospital neonatal intensive care unit.

Date of Admission----------

Study Number----------

Part 1)Infant characteristics

No	Questions	Coding categories	Remark
101	Gestational age in weeks	----------weeks	Specify
102	Birth weight in gm	----------gm	Specify
103	Birth weight classification	A. LBW C. ELBW B. V LBW	
104	Sex	A. Male B. Female	
105	Mode of delivery	A. C/S B. SVD B. Instrumental assisted	
106	APGAR score at 5th minutes	----------	Specify
107	Place of birth	A. Inborn B. Out born	
108	Postnatal Age at admission to NICU	----------	Specify
109	Did the baby have in utero growth restriction	A. Yes B. No	

Antepartum and Interapartum Factors

No	Questions	Coding categories	Skip to
201	Parity	A. Primipara B. Multipara	
202	Prolonged Labor	A. Yes B. No	
203	Presence of maternal chronic disease during pregnancy	1. Yes 2. No	205
204	If yes, what type of maternal chronic disease the mother had during pregnancy (Chose more than one)	A. Gestational diabetes B. Hypertensive disorder C. Cardiac failure/ hypotension D. Other specify……..	
205	Presence of maternal infection during pregnancy	A. Yes B. No	
206	If yes, what type of maternal infection the mother had during pregnancy (Chose more than one)	A. PPROM B. Chorioamnionitis C. UTI, fever, abdominal pain or foul smelling vaginal discharge during pregnancy D. No maternal infection	
207	Did the mother took any drug during pregnancy	A. Yes B. No	
208	Did the mother took any drug during pregnancy (Chose more than one)	A. Antenatal antibiotics B. Magnesium sulfate C. Maternal drug or substance abuse D. Steroid drugs E. Specify others….. F. No drug history intake	
209	Did the baby have birth related complications	A. Yes B. No	
210	Did the baby have birth related complications (Chose more than one)	A. Antepartum hemorrhage or abruption placenta B. Umbilical cord prolapse C. Meconium aspiration syndrome (MAS) D. Perinatal asphyxia (PNA) with any stage of hypoxic ischemic encephalopathy (HIE) E. previous intrauterine exchange transfusion F. No birth complication	

Clinical factors prior to the diagnosis of NEC

301	Did the baby have any type of Congenital anomalies	A. Yes B. No	if no, skip to Q.no.303
302	Specify if yes, what type of Congenital anomalies?	…….	Specify
303	Failure to breath or Resuscitation after birth	A. Yes B. No	
304	Presence of respiratory distress	A. Yes B. No	
305	Use of CPAP support	A. Yes B. No	If no, skip to Q. NO.307
306	Duration of CPAP ventilation use by day	----------	Specify by day
307	Did the baby have diagnosed with Early/Late onset neonatal sepsis	A. Yes B. No	
308	Did the baby receive antibiotics	A. Yes B. No	If no, skip to Q.no 309
308	Day of life baby was started on antibiotics	----------	Specify by days
309	Duration of parenteral (IV MF) nutrition by days	----------	Specify by days
310	Duration of central/peripheral venous access by days	----------	Specify
311	Presence of CBC investigation derangement at admission	A. Leukocytosis / Leukopenia B. Anemia C. Thrombocytopenia	Chose more than one

Infant characteristics by milk feed initiation and outcome characteristics

No	Question	Coding categories	If no, Skip to Q.NO.
401	Did baby receive trophic feeds,	A. Yes B. No	413
402	At what age was trophic enteral feeding started? Specify by day	----------day	Specify by day
403	How much first enteral feed volume was used to start trophic feeding? Specify by ml/kg/day	----------ml	Specify by ml/kg/day
404	Type of milk feeding	A. Breast B. Formula milk C. Mixed milk feeding	
405	Mode of feeding	A. Cup B. direct breast feed C. NGT feed	If not NGT 407
406	If NGT, Duration of NGT feeding	----------days	Specify
407	Did the baby established full enteral milk feeds?;	A. Yes B. No	409
408	If yes at what age? Specify by day	----------days	Specify
409	Did the baby establish weight gain?	A. Yes B. No	411
410	If yes, at what postnatal age of life baby establish weight gain?	----------Day	Specify by day
411	Did the baby have feeding intolerance?	A. Yes B. No	413
412	If yes, at what age feeding intolerance happened? Specify by day	----------day	
413	Did the baby have sign and symptoms of NEC?	A. Yes B. No	
414	Did the baby have diagnosed with NEC?	A. Yes B. No	422
415	Day of life at diagnosis of NEC; specify by day	----------day	Specify
416	Total number of antibiotics days prior to diagnosis of NEC	----------day	Specify by days
417	Blood or exchange transfusion in the 48 hours prior to NEC diagnosis	A. Yes B. No	Specify
418	How the NEC was diagnosed	A. Clinically(Sx/symptom B. By imaging (x-ray/ US)	

419	Type and stage of NEC	A. Suspected (stage I) B. Confirmed (stage II) C. Advanced (stage III)	
420	Enteral feed volume during the diagnosis of NEC	A. Full feeding B.Trophic feeding	
421	CBC investigation derangement at time of NEC diagnosis	A. Leukocytosis Leukopenia / B. Anemia C. Thrombocytopenia	Chose more than one
422	Outcome of NEC	A. Improved B. Death	If death.424
423	Length of hospital stay	----------days	
425	Postnatal age of death	Days	Specify

THE END

THANK YOU!!!!

APPROVAL SHEET

ADDS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCE

SCHOOL OF NURSING AND MIDWIFERY

DEPARTMENT OF NURSING

I, the undersigned MSc student, declare that I have submitted my original work on a title necrotizing enterocolitis and associated factors among enteral fed preterm and low birth weight neonates admitted in selected public hospitals, Addis Ababa, Ethiopia, 2020 for the examination.

Submitted by:

Sitotaw Molla _____ _____

Name of student Signature Date

This thesis work has been submitted for examination with my approval as an advisor.

Approved by:

1. _____ _____ _____

Name of Major Advisor Signature Date

2. _____ _____ _____

Name of Co-Advisor Signature Date

APPROVAL BY THE BOARD OF EXAMINATION

This thesis by Sitotaw Molla is accepted in its present form by the board of examiners as satisfying thesis requirement for the degree of masters in neonatal nursing.

INTERNAL EXAMINER:

_____	_____	_____	_____
NAME	RANK	SIGNITURE	DATE

EXTERNAL EXAMINER:

_____	_____	_____	_____
NAME	RANK	SIGNITURE	DATE

RESEARCH ADVISORS:

_____	_____	_____	_____
NAME	RANK	SIGNITURE	DATE

_____	_____	_____	_____
NAME	RANK	SIGNITURE	DATE

DEPARTMENT HEAD

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