Out of the

Dr. von Hauner Children's Hospital

Intrauterine growth and postnatal nutritional status of Ethiopian preterm infants: a prospective cohort study.

Doctoral Thesis

for the awarding of a Doctor of Philosophy (Ph.D.)

at the Medical Faculty of

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Presented by

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Abstract

Background: Severe nutritional deficit experienced in early life results in growth restriction and long term metabolic and neurodevelopmental complications. Establishing enteral feeding is often difficult in neonatal intensive care units, and recent advances in nutritional support are unavailable in low income countries.

Method: This was a hospital-based multi-center descriptive study, under SIP project (Study of causes of illness and death of preterm infants in Ethiopia). Neonatal outcomes of 1336, 1:1 matched, singleton small for gestational age (SGA) and appropriate for gestational age (AGA) preterm infants were compared. The incidence and associated factors of extrauterine growth restriction (EUGR) was assessed in 436 preterm infants at the time of discharge from the hospital.

Result: The SGA infants had increased risk of hypoglycemia (OR and 95% CI) 1.6 (1.2-2.0), necrotizing enterocolitis (NEC) 2.3 (1.2-4.1), polycythemia 3.0 (1.6-5.4), late onset neonatal sepsis (LOS) 3.6 (1.1-10.9)) and prolonged hospitalization 2.9 (2.0-4.2), whereas, the incidence of respiratory distress syndrome (RDS), apnea and mortality were not different in the SGA and AGA groups. Over all 86.2% of the infants had EUGR, those who were SGA, VLBW, and stayed in the hospital over 21 days had increased risk of EUGR (p-value <0.01). SGA infants had the highest risk of developing EUGR at the time of discharge compared to non-SGA (OR (95% CI) = 15.2 (4.6-50.1).

Conclusion: The high incidence of EUGR observed in this study indicates that the nutritional support of the preterm infants was inadequate. SGA preterm infants are at particular risk for neonatal morbidities such as failure to thrive, hypoglycemia, NEC, LOS and polycythemia. Guidelines on preterm infants feeding in Ethiopia need to be updated and nutritional practices in the NICUs have to be improved. Further studies are needed to explore better approaches on nutritional support of sick preterm infants in low income settings.

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I hereby declare, that the submitted thesis entitled

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List of abbreviations

AGA = Appropriate for gestational age

EUGR = Extrauterine growth restriction

IUGR= Intrauterine growth restriction

GA= Gestational age

HM= Human milk

LGA= Large for gestational age

LON= Late onset neonatal sepsis

NEC= Necrotizing enterocolitis

NICUs = Neonatal intensive care units

RDS= Respiratory distress syndrome

SGA = Small for gestational age

VLBW= Very low birth weight

1. Your contribution to the publications

Contribution to paper I

The first paper "Comparison of neonatal outcomes of small for gestational age and appropriate for gestational age preterm infants born at 28 to 36 weeks of gestation, a multicenter study in Ethiopia", I conceptualized, designed, analysed the data, drafted the manuscript and I was both the first and corresponding author.

Contribution to paper II

My contributions for the second paper "Incidence and associated factors of extrauterine growth restriction (EUGR) in preterm infants, a cross-sectional study in selected NICUs in Ethiopia" include conceptualization, designing, data analysis and drafting of the manuscript. I was both the first and corresponding author.

Contribution to paper III (Appendix)

Similarly for the third paper "preterm nutrition and clinical outcomes", I was involved in the designing, data collection and I had analysed the data, drafted the manuscript, and I was both the first and corresponding author.

2. Introductory summary

2.1 Background

Complications of preterm births account for the 35% of the world's 3.1 million neonatal deaths a year (1). And neonatal mortality contributes for 45% of the under-five deaths. The risk of being born preterm in Africa is 12%, which is almost double the frequency of European countries. The likely reasons for this are higher rate of infections like sexually transmitted infections, malaria and HIV/AIDS (2). Premature infants are prone to nutrient deficiencies due to inadequate stores, inability to feed adequately and digest due to immaturity of the digestive system from being born to soon. The goal of nutritional support of preterm infants is to achieve growth similar to that of normally growing fetuses of the same gestational age (3).

Small for gestational age (SGA) is commonly defined as birthweight-for-gestational-age measure below the 10th percentile compared to a gender-specific reference population (4). Intra uterine growth retardation (IUGR) refers to a condition in which the fetal growth is slower than normal, a common cause of SGA (5). IUGR occurs due to compromised fetal growth related to hypoxia and ischemia experienced in utero, common causes include maternal hypertension, diabetes, cardiopulmonary disease, anemia, malnutrition and multiple pregnancies (5). IUGR and SGA are commonly used interchangeably, most of the SGA infants are considered to have had IUGR, and they have increased risk of neonatal morbidity and mortality, and chronic diseases in adulthood (6).

Even though expressed breast milk is the first choice for feeding preterm infants, human breast milk alone does not contain the required protein, energy, minerals, vitamins, and

trace elements preterm infants need (7), slower growth rates and lesser increase in head circumference are observed in preterm babies fed only on human milk as compared to those on fortified human milk (8). The brain is the main organ affected from undernutrition, as it is the most highly metabolic organ in the preterm neonates requiring adequate nutrient resources for proper function and growth. Historic control studies have showed that growth and neurodevelopmental outcomes of preterm infants' correlate with nutritional intake (9).

In the past few decades nutritional support for preterm infants have been improved, parenteral nutrition, enriched preterm formula, and fortification of human milk have been proven to be critically important to improve outcomes of preterm infants admitted to NICU. Unfortunately, unfortified human breast milk is the only option available in resource poor countries, which does not contain adequate nutrients for the growth and development of preterm infants with the small volumes they can take (10, 11).

Table 1. Comparison of preterm human milk composition and recommendations for a normal growth

Component	Preterm HM /150 ml (routine enteral volume)	Recommendations for enteral feeding
Energy, kcal/kg/day	100.5	110-135
Carbohydrate, g/kg/day	7.34	11.6-13.2
Fat, g/kg/day	3.5	4.8-6.6
Protein, g/kg/day	1.8-2.1	3.5-4.5
Calcium, mg/kg/day	25-30	120-140
Phosphorus, mg/kg/day	6.2-6.8	60-90
Vitamin D, IU/kg/day	Trace	800-1000

HM=human milk

Starting small amount of enteral feeding earlier as a means of preparing the immature intestine for full enteral feeding has been recognized beneficial (13). Beyond survival, providing optimal protein and energy during the first week of life is associated with higher mental development and lower likelihood of growth restrictions (14).

2.2 Statement of the problem

Currently, in in low income countries, there is inevitable suboptimal feeding of preterm infants, which contributes significantly to the incidence of neonatal morbidity and mortality. Addressing preterm nutrition should be considered vital, as there is obvious demand to reduce nutritional deficiencies in these susceptible infants (15). Nutritional status of neonates is poorly defined and often difficult to assess. In resource limited setting, where currently recommended nutritional support through parenteral nutrition or fortification of breast milk is not available, the extent of the problem is unknown. The finding of this study will help to show the magnitude of undernutrition in preterm neonates and advocate the need for appropriate strategy and guideline to address this critical problem.

2.3 Objectives

The objectives of the publications were:

- To assess morbidity and mortality pattern of SGA infants in comparison to AGA infants of same gestational age (GA).
- To assess incidence of EUGR in preterm infants in five NICUs in Ethiopia, at the time of discharge from hospital.
- To identify factors associated with EUGR in preterm infants.
- To explore the nutritional support of preterm infants in five NICUs in Ethiopia.
- To assess the association of pattern of feeding and neonatal outcomes.

2.4 Methods

This PhD project was a sub study under a multi-site descriptive study of causes of illness and death of preterm infants in Ethiopia (SIP). The five study sites were government referral hospital NICUs located in capital city Addis Ababa, northwest and south west of Ethiopia. The protocol and the primary result have been published (16, 17). GA of the infants was estimated by a combination of last menstrual period, ultrasound and New Ballard Score assessment. The practice in the NICUs was according to the national neonatal guideline, preterm infants are put on 10% dextrose intravenously, those who can breast feed will be on exclusive breast milk, infants weighing less than 1500gms are given expressed breast milk 10 ml/kg per day, which is then increased by 20ml/kg/day until full volume feeding is achieved. Otherwise donor milk, parenteral nutrition and breast milk fortification were not available. Diagnoses of

neonatal morbidities were made based on clinical findings and investigations such as chest x-ray, blood culture and white blood cell count. Data on feeding and other clinical status of the preterm infants was collected daily.

2.4.1 Method used in Publication I

We analyzed maternal obstetric and clinical data of 1336, 1:1 matched, singleton SGA and AGA preterm infants admitted to neonatal intensive units (NICUs). Weight for GA was assessed based on gender and GA specific Fenton growth charts (18). Infants with birth weight for GA below the 10^{th} percentile were considered SGA, while those between the 10^{th} and 90^{th} percentile were diagnosed as AGA. Infants who were multiple births, had congenital malformations and/or chromosomal disorders and large for gestational age (LGA) were excluded from the analysis. Data was analysed using the SPSS statistical program version 23. Chi-square tests, Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to identify clinical variables associated with SGA, a p-value of <0.05 was considered significant.

2.4.2 Method used in publication II

A cross-sectional study design was used to assess the incidence of EUGR at the time discharge from the hospital, 436 preterm infants were included. After exclusion of infants with congenital malformation and chromosomal abnormalities, preterm infants with a GA of 28 to 36 weeks, who were discharged alive from the hospitals after a minimum of two weeks hospital stay, were considered for the analysis. EUGR was diagnosed when weight at discharge for corrected age Z score was less than -1.29 or less than 10th percentile. Univariate logistic regression and subsequent stepwise

multivariate logistic regression was done to identify factors associated with EUGR with significance level of 5% and 95% confidence interval (95% CI).

2.4.3 Ethical considerations

Ethical approval was obtained from Addis Ababa University College of health Sciences institutional review board (Ethics ID: AAUMF 03-008), and LMU Institutional Review Board (Ethics ID: 19-649). Parents of the infants were given adequate information about the study and only those who gave written informed consent were enrolled to the study.

2.5 Results

2.5.1 Result of publication I

Out of a total of 1336 singleton SGA and AGA preterm infants included, 763 (57%) were females. Most of the infants 1094 (81.9%) were born close to term (32 to 36 weeks of GA), and about two third, 893 (67%) of the infants had a birthweight greater than 1500 grams. Compared to female infants male preterm infants had a higher risk of SGA (p-value <0.001). The morbidity pattern and outcome of SGA and AGA groups were not different in terms of incidence of RDS, apnea, early onset neonatal sepsis and mortality. However SGA infants had increased risk of hypoglycemia (p-value<.001, OR = 1.58, 95% CI (1.23-2.04)), NEC (p-value =.007, odds ratio = 2.25 95% CI (1.24-4.11)), polycythemia (p- value <.001, OR=3.00 95% CI (1.65-5.45)), late onset neonatal sepsis (p-value=.018, OR = 3.55 95%CI (1.16-10.85)), and prolonged hospitalization (p-value<.001, OR=2.90, 95%CI (1.98-4.24)).

2.5.2 Result of publication II

After exclusion of those who were discharged in less than two weeks, died in the hospital or have had chromosomal abnormalities and congenital malformations, 436 preterm infants were considered eligible for the analysis. The distribution by gender was almost equal, 223(51%) were male. Close to half, 205 (47%) of the infants were born at GA of 28 to 32 weeks, and the rest being moderate to near term, and 224 (51.4%) of them had birth weight less than 1500gms.

Significant proportion of the infants (42.4%) was born SGA, while 55.5% were AGA and 2.1% LGA. The common morbidities the infants had include neonatal infections, 214 (49.1%); RDS, 190 (43.6%); feeding problems, 111 (25.6%); and hypothermia, 253 (58%). The average time the infants stayed in the hospital was 21.5 ±days and the average corrected age at discharge was 35.4 ±1.9 weeks. The mortality rate of preterm infants admitted to NICUs in Ethiopia was 29% and most of survivors (86.2%) had EUGR at the time of discharged from the hospital. The rate of EUGR did not depend on the morbidities the infants had. Birth weight, birth weight for GA and duration of hospital stay had statistically significant association with EUGR (p-value <0.01), and on stepwise logistic regression analysis, being SGA, very low birth weight, and hospital stay over 21days were independent risk factors for development of EUGR.

2.6 Discussion

Outcomes of SGA and AGA preterm infants compared showed similar rates of RDS and mortality, while SGA infants had increased risk of hypoglycemia, NEC, late onset neonatal sepsis, polycythemia and prolonged hospitalization. Similarly, increased risk morbidities SGA infants experience more frequently than AGA infants have been reported in literatures (19-21).Mothers of the SGA infants were given prophylactic

dexamethasone for lung maturation more often (p-value = .017), and mode of delivery was not similar in the two groups, as cesarean section delivery was more common in AGA groups (p-value<.001), this may have improved the overall outcome of the SGA infants in this study.

Regarding comparison of outcomes of SGA and AGA preterm infants, there has been conflicting results in literatures, similar pattern, more risk of death and morbidities in SGA groups and in the contrary some investigators have reported better outcomes of SGA infants related to accelerated maturity of the brain and the lungs (6, 22-25). These inconsistent reports could be explained by the difference in settings of the studies, the duration and severity of the intrauterine insult the infants might have experienced, and the timing and quality of obstetric interventions made to prevent complications.

The mortality rate of preterm infants admitted to the NICUs was very high (29%) (17); and most of the infants (86.2%) who survived the immediate complications of prematurity had EUGR at the time of discharge from the hospital. That shows the infants were having severe caloric and protein deficits. The rate of EUGR in this study is higher than similar reports from China and Brazil (26, 27). Most of the studies on the incidence of EUGR included very low birth weight infants and those with extreme prematurity, unlike the current study; more than half the infants were born at GA of 32 to 36 weeks and we did not include those who were born before 28 weeks of gestation. This shows the rate of EUGR in this study was unacceptably high in preterm infants who could have had a better growth.

Studies have shown that aggressive nutritional support of preterm infants promotes growth without increased risk of adverse effects (3). A combination of parenteral nutrition, early advancement of enteral feeding and fortification of human milk are the

current standards of care in developed countries (10, 28, 29), these interventions are often not available in low-income countries (10). In addition to the growth failure, preterm infants who experience undernutrition in early life are prone to develop impaired cognitive function, school achievement, and increased risk of behavioral problems later in life (30). Further study is required to identify all the predictors of EUGR, to identify those at increased risk and develop a strategy to tackle this major problem.

Almost all of the trials on preterm nutrition are conducted in high income countries, while the magnitude of the problem disproportionately high in low income countries. The interventions studied in high income countries are expensive and require highly trained professionals, for these reason it is difficult to apply the findings in low income settings (8). Studies on new approaches to improve nutritional support of sick preterm infants in low income countries are highly needed.

2.6.1 Strength and limitations of the study project

This study addresses a very common neonatal problem that has not been given adequate attention, the effect of intrauterine growth restriction and postnatal nutritional status of preterm infants in a low income country; where neonatal mortality is one of the highest in the world. The study was multisite, conducted in five governmental hospitals; this makes the result generalizable reflecting the status of preterm nutrition in Ethiopia. The sample size was large, 4919 preterm infants were enrolled to SIP project, of which the two publications had adequate sample size after excluding those who did not fulfill the inclusion criteria.

The limitations of the study include, the fact that gestational age determination was made with the combination of LMP, early ultrasound and New Ballard Score rather than

a uniform GA determination with the most reliable method. For the extrauterine growth restriction, we analysed weight for corrected age at the time of discharge from the hospital rather than at a specific age when they have reached term, follow up for longer time might have showed their status at term corrected age. For assessment of incidence and associated factors of EUGR, a cross sectional study design was used, though the sample size was adequate for analysis of incidence of EUGR, the study design and sampling technique was not suitable to identify other important predictors of EUGR, further study with appropriate design and sampling technique is needed to understand characteristics of the infants who are at higher risk and specific practices that are predisposing the infants to growth restriction.

2.7 Conclusion

The findings of these publications indicate nutritional support of sick preterm infants in a low income setting was not adequately addressed and preterm infants who are born SGA have increased risk of neonatal morbidities and growth faltering. Undernutrition is contributing for death of preterm infants and those who survive the immediate complications of prematurity continue to suffer from growth and development failure and associated chronic illnesses that hinder the chance to attain once genetic potential. New approaches and guidelines are needed to improve preterm nutrition for low income settings, where the worlds' majority of preterm infants are born. Achieving sustainable development goal, ending preventable death of newborns and children requires improving care of preterm infants.

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Comparison of neonatal outcomes of small for gestational age and appropriate for gestational age preterm infants born at 28–36 weeks of gestation: a multicentre study in Ethiopia

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ABSTRACT

Purpose The aim of this study was to assess morbidity and mortality pattern of small for gestational age (SGA) preterm infants in comparison to appropriate for gestational age (AGA) preterm infants of similar gestational age.

Method We compared neonatal outcomes of 1336, 1:1 matched, singleton SGA and AGA preterm infants based on their gestational age using data from the study 'Causes of Illness and Death of Preterm Infants in Ethiopia (SIP)'. Data were analysed using SPSS V.23. ORs and 95% CIs and χ^2 tests were done, p value of <0.05 was considered statistically significant.

Result The majority of the infants (1194, 89%) were moderate to late preterm (32–36 weeks of gestation), 763 (57%) were females. Male preterm infants had higher risk of being SGA than female infants (p<0.001). SGA infants had increased risk of hypoglycaemic (OR and 95% CI 1.6 (1.2 to 2.0), necrotising enterocolitis (NEC) 2.3 (1.2 to 4.1), polycythaemia 3.0 (1.6 to 5.4), late-onset neonatal sepsis (LOS) 3.6 (1.1 to 10.9)) and prolonged hospitalisation 2.9 (2.0 to 4.2). The rates of respiratory distress syndrome (RDS), apnoea and mortality were similar in the SGA and AGA groups.

Conclusion Neonatal complications such as hypoglycaemic, NEC, LOS, polycythaemia and prolonged hospitalisation are more common in SGA infants, while rates of RDS and mortality are similar in SGA and AGA groups. Early recognition of SGA status, high index of suspicion and screening for complications associated and timely intervention to prevent complications need due consideration.

What is known about the subject?

- Intrauterine growth restriction is one of the common perinatal complications associated with increased neonatal morbidity and mortality.
- As an adaptation to early extrauterine life, in utero stress associated with placental insufficiency increases secretion of steroid hormones in the fetus.
- This results in acceleration of brain and lung maturation, however several studies have reported contradictory findings on the morbidity and mortality patterns of small for gestational age (SGA) infants.

What this study adds?

- Accelerated maturity associated with intrauterine growth restriction expected in SGA preterm infants did not protect them from RDS and mortality.
- Rather, SGA infants have significantly increased risk of hypoglycaemic, necrotising enterocolitis, polycythaemia, late-onset neonatal sepsis and prolonged hospitalisation.

INTRODUCTION

Globally, intrauterine growth restriction (IUGR) occurs in about 24% of newborns per year, and the majority are born in low-income and middle-income countries (LMICs).[1] IUGR is one of the rising public health challenges, because it contributes to increased risk of neonatal morbidity and mortality, and chronic diseases in adulthood.[2–4] Small for gestational age (SGA) is commonly defined as birthweight-for-gestational-age measure below the 10th percentile compared with a gender-specific reference population.[5] IUGR refers to a condition in which the fetal growth is slower than normal, a common cause of SGA; while SGA includes constitutionally small babies.[2] IUGR and SGA can only be distinguished if serial prenatal ultrasound evaluations are done. IUGR occurs due to compromised fetal growth usually related to placental malfunction for various reasons, such as maternal hypertension, diabetes, cardiopulmonary disease, anaemia, malnutrition and multiple pregnancies.[6 7] Congenital

malformations and fetal infection may also lead to SGA. IUGR and SGA are commonly used interchangeably and for this paper we will refer to these conditions as SGA.[6]

Conditions, such as multiple pregnancies or pregnancies complicated by maternal hypertension or other placental dysfunction, cause increased secretion of glucocorticoids, other steroid hormones and catecholamines that results in acceleration of brain and lung maturation by as much as 3–4 weeks or more when compared with the appropriate for gestational age (AGA) infants of the same gestational age (GA); this is considered an adaptation to early extrauterine life.[8–10] However, this adaptive response may fail if the placental dysfunction progresses and the fetus experiences severe anoxia and malnutrition that could result in increased risk of complications and death.[2 10]

Several studies have reported contradictory findings on the effect IUGR on neonatal respiratory distress syndrome (RDS).[11] The risk of RDS has been reported to be same or lower in SGA infants compared with AGA infants of similar GA,[12–14] but numerous studies have reported increased risk of morbidity and mortality in SGA infants.[3 13 15–19]

The reported conflicting findings of neonatal outcomes of SGA infants could be due to the differences in the timing of the onset of placental insufficiency, the severity of growth restriction and the degree of cardiovascular adaptation.[20] Differences in settings of the studies could play a role in terms of early diagnoses of high-risk pregnancies and timely intervention, which could abort the progression of the insult and prevent complications.

SGA infants are at higher risk of metabolic and haematological disturbances and those with severe SGA are more likely to die during the neonatal period.[10 18] Those who survive the neonatal period have a high risk of growth and developmental impairment in childhood, and metabolic, hormonal and cognitive disorders later in adulthood.[7 21] Reports from high-income countries show no significant mortality difference between preterm SGA and AGA infants. However, in LMICs preterm SGA infants have increased risk of mortality.[6] Most of the studies on preterm infants' health and SGA are reported from high-income countries and there is a paucity of data from LMICs where the burden is very high.[22] The aim of this study is to assess morbidity and mortality pattern of preterm SGA infants in comparison to AGA infants of similar GA in five neonatal intensive care units (NICUs) in Ethiopia.

METHOD

We analysed maternal obstetric and clinical data of GA-matched SGA and AGA preterm infants admitted to NICUs from a study on Causes of Illness and Death of Preterm Infants in Ethiopia (SIP). SIP was a prospective descriptive multisite hospital-based study conducted in five selected hospitals in Ethiopia. The protocol and the primary result have been published.[23 24]

After exclusion of multiple births, those with congenital malformations and chromosomal disorders and large for gestational age infants, SGA infants were identified and 1:1 match with AGA preterm infants was done randomly. Weight for GA was assessed based on gender-specific and GA-specific Fenton growth charts.[25] SGA was defined as a birth weight below the 10th percentile for GA, and AGA birth weight was defined as between the 10th and 90th percentile for GA. The association of SGA with gender, mortality, length of hospital stay, clinical diagnoses such as RDS, necrotising enterocolitis (NEC), neonatal infections, hypoglycaemic, perinatal asphyxia and polycythaemia were analysed. Maternal obstetric variables such as maternal age, marital status, pregnancy-induced hypertension, premature rupture of membranes (PROM), antepartum haemorrhage, chorioamnionitis, dexamethasone administration and mode of delivery were assessed for association with birth weight for GA.

GA estimation was based on maternal menstrual history, early fetal ultrasound or New Ballard Score examination. Complications of preterm birth such as RDS and neonatal infections were diagnosed based on clinical findings and investigations including chest X-ray, blood culture and white blood cell count. Death before the 28th day of life was defined as neonatal mortality. Statistical analysis was done using the SPSS V.23 statistical program. Differences in association of the variables were analysed with χ^2 tests and a p value of <0.05 was considered significant. ORs and 95% CIs were calculated to identify clinical variables associated with SGA.

Patient and public involvement statement

Patients were not involved in the design, recruitment and conduct of this study.

RESULT

A total of 1336 singleton SGA and AGA preterm infants were eligible for the study (figure 1); 763 (57%) were females. The majority of the infants, 1094 (81.9%) were moderate to late preterm (32–36 weeks of GA), and 893 (67%) of the infants had a birth weight >1500 g. The common complications the infants had are shown in table 1.

The male preterm infants had a higher risk of SGA than female infants (p<0.001). Maternal age and marital status were not associated with SGA, while pregnancy induced hypertension had a statistically significant association with SGA. SGA infants were more likely to be delivered by caesarian section than AGA preterm infants (p<0.001). Prophylactic dexamethasone was given more often to the mothers of the preterm infants who were SGA (p=0.017). Other obstetric factors studied such as PROM, antepartum haemorrhage and chorioamnionitis were more common in mothers of AGA preterm infants (p<0.01) (table 2).

The rates of RDS, apnoea and mortality were similar among the SGA and AGA groups. While SGA infants

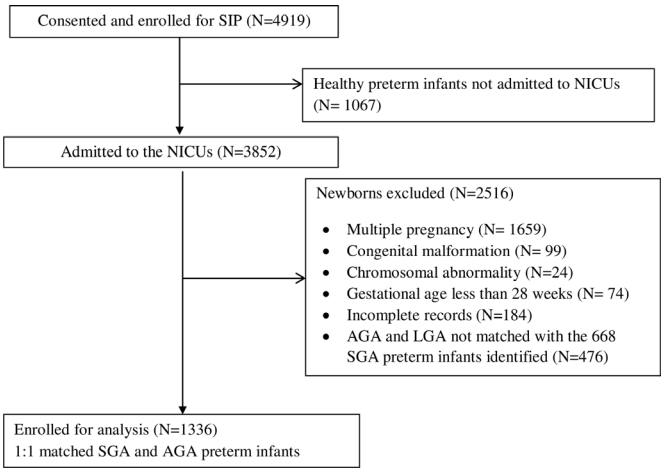

Figure 1 A total of 1336 singleton SGA and AGA preterm infants were eligible for the study. AGA, appropriate for gestational age; NICU, neonatal intensive care unit; SGA, small for gestational age; SIP, Causes of Illness and Death of Preterm Infants in Ethiopia.

had a 1.6 times higher risk of developing hypoglycaemic, p<0.001, OR 1.58, 95% CI 1.23 to 2.04. NEC was diagnosed in 5.2% of SGA and 2.4% of AGA infants, p=0.007, OR 2.25, 95% CI 1.24 to 4.11. Polycythaemia was seen more often in SGA infants, p<0.001, OR 3.00, 95% CI 1.65 to 5.45. Similar rates of neonatal infections were seen in both groups, while SGA infants had 3.6 times higher risk of developing late-onset neonatal sepsis than AGA preterm infants, p=0.018, OR 3.55 95% CI 1.16 to 10.85. SGA infants were more likely to be hospitalised for >21 days than AGA preterm infants, p<0.001, OR 2.90, 95% CI 1.98 to 4.24 (table 3).

Table 1 Preterm infants' perinatal data

Variables	No (%)
Infants' sex	
Male	573 (42.9)
Female	763 (57.1)
Birth weight (g)	
<1000	78 (5.8)
1000–1499	365 (27.3)
1500–1999	538 (40.3)
≥2000	355 (26.6)
Gestational age (weeks)	
28–32	242 (18.1)
33–34	562 (42.1)
35–36	532 (39.8)
Common morbidities	
Neonatal infections	696 (52.1)
Respiratory distress syndrome	514 (38.5)
Hypoglycaemic	326 (24.4)
Hyperbilirubinaemia	417 (31.2)
Perinatal asphyxia	98 (7.3)
Polycythaemia	58 (4.3)
Distribution of study subjects by hospitals	
Gondar University Hospital	373 (27.9)
Saint Paul Millennium College Hospital	358 (26.8)
Black Lion Hospital	307 (23.0)
Ghandi Memorial Hospital	158 (11.8)
Jimma University Medical Center	140 (10.5)

DISCUSSION

Comparison of neonatal outcomes of SGA and AGA preterm infants remains controversial, as several investigators have reported conflicting results. In the current study, the rates of RDS and mortality among the two groups were similar, unlike the 2 to 4 times,[6] and 16 times increased mortality of SGA preterm infants reported from LMICs.[22] The mortality rate in this study could have been partly modified related to the antenatal dexamethasone the SGA groups had received more than the AGA infants. These findings were in line with the report of Bartal *et al* among late preterm neonates.[14] And our findings contradict the reports of Tsai *et al* and Tayson *et al*, who reported an increased risk of RDS and mortality among SGA infants.[13 26] However, Bartels *et al* and *Sharma et al* reported increased risk of death and decreased risk of RDS.[12 19] The contradicting findings in the literature might be due to the multifactorial nature of outcome of SGA, the cause of SGA and severity of the condition, duration of intrauterine hypoxia and variations in settings of the studies. The GA at birth could modify the physiological changes and adaptation to extrauterine environment.

The SGA infants were more likely to be delivered by caesarean section (p<0.001) and their mothers were given prophylactic dexamethasone more often compared with mothers of AGA infants (p=0.017), this may have improved the overall outcome of the SGA infants. Pregnancy-induced hypertension was associated with the SGA (p<0.001), whereas acute obstetric condition such as antepartum haemorrhage, chorioamnionitis and PROM were more common in mothers of AGA infants. This finding is similar to the report of Boghossian *et al*.[27]

The rate of early onset neonatal infection was comparable in both groups, however SGA infants had a higher risk of late-onset neonatal sepsis. Similarly, SGA infants had an increased risk of NEC and hypoglycaemic compared with AGA infants. These findings are consistent with reports of Hasthi *et al* from India and Boghossian *et al* from USA.[15 27] These can likely be explained by the severe undernutrition the infants experienced predisposing them to infection, although the mechanisms of how undernutrition is related to immune suppression is not well understood, there are strong epidemiological data supporting the link.[28] The increased risk of NEC might be associated with immature gut development that has resulted from intrauterine chronic fetal hypoxia and

Table 2 Factors associated with birth weight for gestational age

Variables, no (%)	Total	SGA N=668	AGA N=668	P value
Maternal age (years)				0.303
<20	236 (17.7)	115 (17.2)	121 (18.1)	
20–34	980 (73.4)	485 (72.6)	495 (74.1)	
≥35	120 (9.0)	88 (13.2)	52 (7.9)	
Marital status				0.207
Married	1283 (96.0)	637 (95.4)	647 (96.9)	
Single	53 (4.0)	31 (4.6)	21 (3.1)	
Mode of delivery				<0.001
Caesarean section	509 (38.1)	283 (42.3)	226 (33.3)	
Vaginal delivery	827 (61.9)	385 (57.3)	442 (66.1)	
Major obstetric complications				
Pregnancy-induced hypertension	445 (33.3)	290 (43.4)	155 (23.2)	<0.001
PROM	191 (14.4)	72 (10.8)	120 (17.9)	<0.001
Antepartum haemorrhage	158 (11.8)	63 (9.4)	95 (14.2)	0.007
Chorioamnionitis	61 (4.6)	14 (2.1)	47 (7.0)	<0.001
Mother received dexamethasone	435 (32.6)	238 (35.6)	197 (29.5)	0.017
Sex of the infant				<0.001
Male	573 (42.9)	353 (52.8)	220 (32.9)	
Female	763 (57.1)	315 (47.2)	448 (67.1)	

AGA, appropriate for gestational age; PROM, premature rupture of membranes; SGA, small for gestational age.

consequent cardiovascular redistribution of blood flow away from the gastrointestinal tract to vital organs.[29]

SGA infants had a statistically significant increased risk of prolonged hospitalisation for >21 days, likely related to the severity of the morbidities they had; Sharma *et al* from the USA reported a similar finding in a retrospective study involving 2530 infants born at ≤36 weeks.[19] Polycythaemia (a venous haematocrit >65%) can occur as a response to intrauterine hypoxia, the hyperviscosity of blood associated might result in serious complications.[30] SGA infants are at higher risk of developing polycythaemia.[2] Similarly, we found a threefold increased risk

Table 3 Comparison of neonatal outcomes of small for gestational age and appropriate for gestational age preterm infants

Variables	SGA (N=668)	AGA (N=668)	P value	OR	95% CI	
					Lower	Upper
RDS	257 (38.5)	257 (38.5)	1.00	1.00	0.80	1.25
Apnoea	66 (9.9)	54 (8.0)	0.251	1.25	0.86	1.82
Hypoglycaemic	191 (28.6)	135 (20.2)	<0.001	1.58	1.23	2.04
NEC	35 (5.2)	16 (2.4)	0.007	2.25	1.24	4.11
Polycythaemia	43 (6.4)	15 (2.2)	<0.001	3.00	1.65	5.45
EOS	275 (41.2)	271 (40.6)	0.824	1.03	0.82	1.28
LOS	14 (2.1)	4 (0.6)	0.018	3.55	1.16	10.85
Hyperbilirubinaemia	196	221	0.140	0.84	0.67	1.06
Perinatal asphyxia	48	50	0.834	0.96	0.63	1.44
Mortality	51 (7.6)	51 (7.6)	1.00	1.00	0.67	1.50
Length of hospital stay						
<21 days	564 (84.4)	628 (94.0)	–	–	–	–
≥21 days	104 (15.6)	40 (6.0)	<0.001	2.90	2.98	4.24

AGA, appropriate for gestational age; EOS, early onset neonatal sepsis; LOS, late-onset neonatal sepsis; NEC, necrotising enterocolitis; RDS, respiratory distress syndrome; SGA, small for gestational age.

of polycythaemia in SGA compared with AGA infants. The observed complications could be prevented with improvement of neonatal care.

CONCLUSION

The SGA infants in this study had increased risk of hypoglycaemic, NEC, late-onset neonatal sepsis, polycythaemia and prolonged hospitalisation. The rates of RDS and neonatal mortality were similar in SGA and AGA infants. Proper antenatal care, timely recognition of high-risk pregnancies and right interventions are needed to prevent IUGR and the subsequent SGA-related complications. Screening for morbidities associated with SGA, preventive measures and adequate postnatal care could contribute for improvement of neonatal outcomes.

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Ethics approval Ethical approval was obtained from Addis Ababa University College of health Sciences institutional review board (Ethics ID: AAUMF 03-008) before the study was commenced. The parents of the infants were given adequate information and asked for informed consent prior to participation.

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Incidence and associated factors of extrauterine growth restriction (EUGR) in preterm infants, a cross-sectional study in selected NICUs in Ethiopia

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ABSTRACT

Background Preterm infants have high risk of developing growth restriction and long-term complications. Enteral feeding is often delayed in neonatal intensive care units (NICUs) for the fear of feeding intolerance and the associated necrotising enterocolitis, and recent advances in nutritional support are unavailable in low-income countries.

Objective The aim of this study was to assess the incidence and associated factors of extrauterine growth restriction (EUGR) among preterm infants in selected NICUs in Ethiopia.

Method This was a cross-sectional study involving a subgroup analysis of preterm infants admitted to hospitals, from a multicentre descriptive study of cause of illness and death in preterm infants in Ethiopia, conducted from 2016 to 2018. EUGR was defined as weight at discharge Z-scores <−1.29 for corrected age. Clinical profiles of the infants were analysed for associated factors. SPSS V.23 software was used for analysis with a significance level of 5% and 95% CI.

Result From 436 preterm infants included in the analysis, 223 (51%) were male, 224 (51.4%) very low birth weight (VLBW) and 185 (42.4%) small for gestational age (SGA). The mean (SD) of weight for corrected age Z-score at the time of discharge was −2.5 (1.1). The incidence of EUGR was 86.2%. Infants who were SGA, VLBW and longer hospital stay over 21 days had increased risk of growth restriction (p-value<0.01). SGA infants had a 15-fold higher risk of developing EUGR at the time of discharge from hospital than those who were appropriate or large for gestational age (OR (95% CI)=15.2 (4.6 to 50.1).

Conclusion The majority of the infants had EUGR at the time of discharge from the hospital, which indicates suboptimal nutrition. Revision of national guidelines for preterm infants feeding and improvement in clinical practice is highly required.

What is known about the subject?

- Preterm infants' growth is expected to be similar to that of the intrauterine foetus, however small preterm infants often develop extrauterine growth restriction (EUGR).
- EUGR is associated with increased risk of post-neonatal mortality and long-term morbidities such as adverse metabolic and neurodevelopmental outcomes in subsequent years.
- There is paucity of data regarding preterm nutrition in low-income and middle-income countries; parenteral nutrition and use of human milk fortifiers are often unavailable.

What this study adds?

- Neonatal mortality rate of hospital admitted preterm infants in Ethiopia is 29%, 86.2% of the infants who survived the immediate complications were discharged with extrauterine growth restriction (EUGR).
- The high incidence of EUGR indicates insufficient nutritional support of the preterm infants.
- Infants with very low birth weight, hospital stay over 21 days and small for gestational age had increased risk of developing EUGR.

INTRODUCTION

Complications of preterm births are the leading causes of newborn deaths worldwide. Survivors of preterm birth are at increased risk of adverse metabolic and neurodevelopmental long-term outcomes.[1] Ideally, growth of the preterm infant is expected to be similar to that of the intrauterine foetus at the same gestational age (GA) once birth weight has been regained. However, attaining that goal requires optimal nutritional support to address the increased needs of nutrients for catch-up growth.[2 3] Extrauterine growth restriction (EUGR) is a severe nutritional deficit during the first weeks after birth, commonly seen in small preterm infants.[4 5] Factors associated with EUGR reported from developed countries include caloric and protein deficits, intrauterine growth restriction (IUGR), neonatal morbidities and the

need for prolonged hospital stay.[6] EUGR is commonly defined as a growth measurement that is <10th percentile of the predicted value at the time of hospital discharge.[5]

Improved nutritional support may decrease the rate of EUGR. This support may include early administration of parenteral nutrition, use of human milk fortifiers and preterm formula when mother's milk is unavailable.[7 8] Identifying infants at risk of growth failure by monitoring weight and nutritional intake should guide clinicians to increase nutritional support that is individualised according to the need of the preterm infant.[9] Many mothers of preterm infants need support to produce and express enough milk as the babies are often too weak to suckle.[10 11] Recent evidence indicates that early, fast or continuous enteral feeding results in better neonatal outcomes compared with late, slow or intermittent feeding.[10 12] However, clinicians in many NICUs often delay enteral feeding for the fear of feeding intolerance and the associated necrotising enterocolitis (NEC).[13]

For LMICs WHO guidelines on feeding stable low birth weight infants whose birth weight is greater than 1000 g recommend feeding mother's own milk starting from the first day. Those who cannot be fed mother's own milk should be fed donor human milk (when available); if this is not possible standard infant formula has to be given, those who fail to gain weight despite adequate feeding with standard infant formula should be given preterm infant formula. And very low birth weight (VLBW) infants who fail to gain weight despite adequate breast milk feeding should be given human-milk fortifiers.[14] In Ethiopian neonatal guideline, mothers breast milk is the only option recommended for feeding preterm infants; however, the use of donors milk, standard infant formula milk, preterm formula milk and human milk fortifiers were not considered as options where indicated.[15] EUGR is associated with long-term morbidities such as adverse neurodevelopmental outcomes in subsequent years. Hence, assessment of the magnitude of the problem and recognising associated factors should help to identify and manage preterm infants at risk of growth restriction and consequently improve long-term outcomes.[16] The burden of preterm birth is increasing worldwide, and the highest average rate of preterm birth occurs in low-income countries (11.8%).[17] However, there is paucity of data regarding preterm nutrition and EUGR in low-income and middle-income countries, most of the literatures in this area are reported from high-income countries. Thus, the aim of this study is to assess the incidence and associated factors of EUGR in preterm infants in five NICUs in Ethiopia.

METHODS

Data source

This is a cross-sectional study involving the analysis of a subgroup of 436 preterm infants from a multicentre descriptive study conducted in five selected hospitals, 'Study of causes of illness and death in preterm infants (SIP)'. The primary study and methodology papers have been previously published.[18 19] The hospital practice of neonatal care was based on a national neonatal guideline. Stable preterm infants are fed on mothers own breast milk. For infants weighing <1.5 kg at birth, starting expressed breast milk 10 mL/kg per day and increasing the amount by 20 mL/kg/day according to the infants' condition until full volume feeding is achieved. The goal is to achieve, volume: 140–150 mL/kg/day and calorie: 110–120 kcal/kg/day. Other nutritional support methods, such as the use of donor milk, parenteral nutrition and breast milk fortification were not available.[15]

Preterm infants with a GA of 28–36 weeks, who were discharged alive from the hospitals, were considered for the analysis. The exclusion criteria included infants with a congenital malformation, chromosomal abnormalities; those who died before discharge from the hospital, and had a hospital stay less of than 2 weeks. GA estimation was done by a combination of last menstrual period, ultrasound and New Ballard Score assessment. Variables such as birth weight, discharge weight, estimated GA, clinical profile of the infants, corrected age and duration of hospital stay were analysed.

Statistical analysis

Weight for GA and weight for corrected age Z-scores were calculated using gender specific Fenton growth chart calculation spreadsheets.[20] Small for gestational age (SGA) and EUGR was defined as weight for GA and weight at discharge for corrected age <−1.29 or less than the 10th percentile, respectively.

Statistical analyses were done using SPSS V.23 software. Following descriptive analysis, the χ^2 test was used to check the cell count adequacy before performing univariate logistic regression. Factors that could be associated with the dependent variables were identified from univariate logistic regression (p-value<0.2). Stepwise multivariate logistic regression was performed to identify independent risk factors for EUGR with significance level of 5% and 95% CI.

Patient and public involvement statement

Study participants were not involved in the design of the study.

RESULTS

Figure 1 shows the flow chart of recruitment of study subjects, including those who were excluded because they were discharged early, died in the hospital or had chromosomal abnormalities and congenital malformations. A total of 436 preterm infants were eligible for the analysis, 223 (51%) were male. Nearly half 205 (47%) of the infants were very preterm (born at GA of 28–32 weeks) and 224 (51.4%) were VLBW (birth weight less than 1500 g). The rate of small for GA (SGA) among the study subjects was 42.4%, while 55.5% and 2.1% were appropriate for GA (AGA) and large for GA (LGA), respectively. The birth

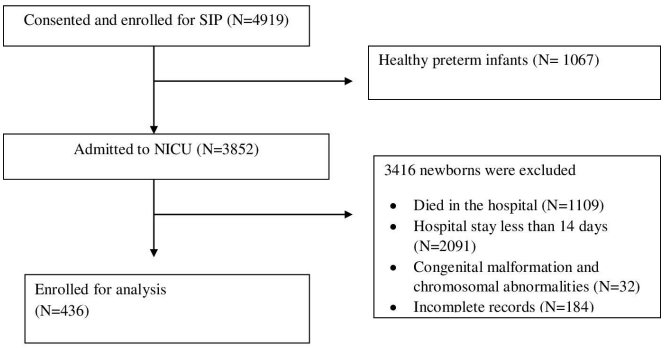

Figure 1 Flow chart of study subjects included in the analysis. NICU neonatal intensive care units; SIP study of illness in preterms.

weight for GA Z-score, mean (SD) was −1.1 (1.0), while weight for corrected age Z-score mean (SD) at the time of discharge was −2.5 (1.1) (table 1).

Nearly half of the infants, 214 (49.1%) had neonatal infections such as neonatal sepsis, pneumonia, meningitis and NEC, while 190 (43.6%), 111 (25.6%), 253 (58%) and 19 (4.4%) had respiratory distress syndrome, feeding problems, hypothermia and perinatal asphyxia, respectively. The mean (SD) duration of hospital stay was 21.5 (5.1) days and the mean (SD) of corrected age at discharge was 35.4 (1.9) weeks.

The overall incidence of EUGR was 86.2%. Almost all (98.4%) of the infants born SGA had EUGR at discharge, while fewer of the LGA cases (22.2%) were classified as EUGR at the time of discharge from the hospital. Comparable rates of EUGR were observed across the infants' major diagnoses. Birth weight, weight for GA and duration of hospital stay were found to be associated with the occurrence of EUGR (p-value<0.01) (table 2). Variables associated with a statistically significant increased risk of EUGR on univariate logistic regression include being SGA, VLBW and duration of hospital stay over 21 days. Similarly, on stepwise multivariate logistic regression, SGA, VLBW and longer hospital stay over 21 days were found to be independent risk factors for EUGR. SGA infants had a 15-fold increased risk of developing EUGR at the time discharge from hospital than those who were AGA or LGA (OR (95% CI)=15.2 (4.6 to 50.1) (table 3).

Table 1 Clinical characteristics of the preterm infants

Variables	Values
Female/male ratio (%)	49/51
GA (weeks), no. (%)	
28–32	205 (47.0)
32–34	148 (33.9)
35–<37	83 (19.0)
Birth weight (g), no. (%)	
<1000	28 (6.4)
1000–1500	196 (45.0)
1500–2000	164 (37.6)
≥2000	48 (11.0)
Weight for gestational age, no. (%)	
AGA	242 (55.5)
LGA	9 (2.1)
SGA	185 (42.4)
Pregnancy	
Singleton	260 (59.6)
Twins	166 (38.1)
Triplets	10 (2.3)
Weight for gestational age Z-score at birth, mean (SD)	−1.1 (1.0)
Weight for corrected age Z-score at discharge, mean (SD)	−2.5 (1.1)
Newborn major diagnosis, no. (%)*	
Neonatal infections	214 (49.1)
Respiratory distress syndrome	190 (43.6)
Feeding problems	111 (25.6)
Perinatal asphyxia	19 (4.4)
Hypothermia	253 (58.0)
Anaemia	82 (18.8)
Total duration of hospital stay, mean days (SD)	21.5 (5.1)
Corrected age at discharge, week, mean (SD)	35.4 (1.9)

*The percent does not add up to 100 since the infants may have had more than one diagnosis.
.AGA, appropriate for gestational age; GA, gestational age; LGA, large for gestational age; SGA, small for gestational age.

DISCUSSION

The SIP study has showed a very high mortality rate (29%) among hospital admitted preterm infants.[19] The current follow-up study revealed that most (86.2%) of the infants who survived the immediate complications were discharged with EUGR and associated severe caloric and protein deficits. Establishing adequate dietary intakes in preterm infants is a very common problem in NICUs; however, optimal nutrition is critically important to insure survival, normal growth and development in subsequent years.[21 22]

The incidence of EUGR observed in this study was comparable to the 89% EUGR rate in extremely low birth weight infants (birth weight less than 1000 gm) reported by Dusick *et al* from the USA,[23] however only 6.4% of the study population in the current study were extremely low birth weight. The rate of EUGR in this study was much higher than that reported from China by Shan *et al*; Lima *et al* from Brazil and Clark *et al* from the USA, 56.8%,[24] 26%,[6] 28%,[5] respectively. Nearly half the preterm infants in the current study had a birth weight greater than 1500 g, while the other studies included mainly VLBW infants and those with extreme prematurity. In addition, our study did not include infants with a GA less than 28

Table 2 Univariate logistic regression, factors associated with extrauterine growth restriction (EUGR)

Variables	Total no.	EUGR cases no. (%)	P value	OR (95% CI)
Overall incidence of EUGR	436	376 (86.2)	–	–
Gender				
Female	213	191 (86.9)	–	–
Male	223	185 (85.6)	0.71	0.9 (0.5 to 1.6)
Birth weight				
<1500	224	210 (93.8)	0<0.001	4.9 (2.2 to 11.1)
>1500	212	166 (78.3)	–	–
Weight for GA				
AGA and LGA	251	194 (77.3)	–	–
SGA	185	182 (98.4)	0<0.001	17.8 (5.4 to 57.9)
Pregnancy				
Singleton	260	226	–	–
Twins and triplets	176	150	0.61	1.2 (0.7 to 2.0)
Major diagnosis of the preterm infants				
Infection	214	184 (86.0)	0.87	1.0 (0.55 to 1.65)
Respiratory distress syndrome	190	162 (85.3)	0.60	0.8 (0.5 to 1.5)
Perinatal asphyxia	19	16 (84.2)	0.79	0.8 (0.2 to 2.9)
Feeding problems	131	111 (84.7)	0.55	0.8 (0.6 to 1.5)
Anaemia	82	67 (81.7)	0.18	0.7 (0.3 to 1.2)
Duration of hospital stay				
14–21 days	224	179 (79.9)	–	–
>21 days	212	197 (92.9)	0<0.001	3.3 (1.8 to 6.1)

AGA, appropriate for gestational age; EUGR, extrauterine growth restriction; GA, gestational age; LGA, large for gestational age; SGA, small for gestational age.

weeks. Thus, our study shows a rate of EUGR that was unacceptably high in higher GA preterm infants.

The mean Z-score of birth weight and weight at discharge in this study was significantly lower than the averages reported in other literature.[6 25] Shan *et al* have shown risk factors related to EUGR, such as male gender, low GA at birth, low birth weight and long length of hospital stay.[24] In this study, we found increased risk of EUGR in infants who were SGA, VLBW and hospitalised over 21 days (table 3). Sakurai *et al* from Japan have also reported lower GA, IUGR, severe chronic lung disease and poor nutrition as relevant risk factors associated with EUGR, the SGA infants in our study are likely to have had IUGR, but none of the comorbidities the infants had was associated with increased risk EUGR .[26] Generally, preterm infants born SGA have higher risk of morbidity and mortality compared with AGA preterm infants.[6 27] The rate of EUGR was higher (92.9%) in infants who stayed in the hospital over 21 days. This is probably due to the severity of the infants' morbidities and the inadequacy of nutritional support provided in the NICUs.

Aggressive nutritional support has been shown to promote growth without increased risk of adverse effects.[28] With optimal nutrition, postnatal growth failure could be prevented and extrauterine weight gain can be achieved similar to fetuses of same GA.[29] A combination of parenteral nutrition, early advancement of enteral feeding and fortification of human milk are the current standards of care in developed countries.[3 30] These interventions are often not available in low-income countries.

Table 3 Multivariate logistic regression analysis, independent risk factors of extrauterine growth restriction

Variables	P value	AOR (95% CI)
Birth weight		
Non-SGA	–	–
SGA	<0.001	15.2 (4.6 to 50.1)
Weight for GA		
≥1500 g	–	–
<1500 g	0.03	2.2 (1.1 to 4.3)
Duration of hospital stay		
<21 days	–	–
≥21 days	<0.001	2.7 (1.4 to 5.3)

AOR, adjusted OR; EUGR, extrauterine growth restriction; GA, gestational age; SGA, small for gestational age.

Under-nutrition experienced in infancy is known to impair cognitive function, school achievement and results in increased risk of behavioural problems later in life.[31]

This study has several limitations, the mean corrected age at discharge was 35.4 weeks, and follow-up at around 40 weeks could have possibly shown catch up growth. We used similar definition of EUGR for all infants in the study, SGA infants' growth velocity was not considered for diagnosis EUGR. Nutritional data, maternal conditions and delivery relating factors were not assessed as risk factors. This was a cross-sectional study design, the main aim was to assess the incidence of EUGR, associated factors were analysed with the available data. Further study is required to identify all the predictors of EUGR.

CONCLUSION

The high incidence of EUGR observed in this study indicates that the nutritional support of the preterm infants was insufficient. The risk of developing EUGR was higher in preterm infants who were VLBW, SGA and hospitalised for over 21 days . Much attention needs to be given to improve preterm nutrition in low-income countries. Country infant feeding guidelines need revision based on recent evidences to improve preterm nutrition. Regular monitoring of nutritional status and individualised timely nutritional intervention has to be the standard of care of preterm infants in the NICUs.

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Original Article

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Abstract

Background. In low-income countries, preterm nutrition is often inadequately addressed. The aim of the study was to assess the patterns of feeding and associated clinical outcomes of preterm neonates admitted to neonatal intensive care units in Ethiopia. *Method*. This was a multicenter, prospective study. Infants' clinical characteristics at birth, daily monitoring of feeding history, and weight measurements were collected. An outcome assessment was completed at 28 days. *Result*. For this analysis, 2560 infants (53% male) were eligible. The mean (SD) gestational age was 33.1 (2.2) weeks. During the hospital stay the proportion of infants on breast milk only, preterm formula, term formula, and mixed feeding was 58%, 27.4%, 1.6%, and 34.1%, respectively. Delay in enteral feeding was associated with increased risk of death (odds ratio [OR] = 1.92, 95% confidence interval [CI] = 1.33-2.78; $P < .001$) and (OR = 5.06, 95% CI = 3.23-7.87; $P < .001$) for 1 to 3 and 4 to 6 days of delay in enteral feeding, respectively, after adjusting for possible confounders. The length of delay in enteral feeding was associated with increased risk of hypoglycemia (OR = 1.2, 95% CI = 1.1-1.2; $P = .005$). The mortality rate was lower in hospitals providing preterm formula more often ($P = .04$). Half of the infants continued losing weight at the time of discharge. *Conclusion*. Delayed enteral feeding significantly increases the risk of mortality before discharge and hypoglycemia in preterm infants in resource-limited settings. Ensuring adequate nutritional support of preterm infants is highly needed.

Keywords

prematurity, infant feeding, preterm nutrition, neonatal mortality, low- and middle-income countries

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Introduction

Complications of preterm birth are responsible for the largest proportion of neonatal deaths in the world, accounting for 35% of the world's 3.1 million neonatal deaths per year.[1] Worldwide, 15 million preterm births occur every year, with those less than 32 weeks of gestation at the highest risk of morbidity and mortality.[2] Undernutrition in preterm infants is associated with serious consequences such as increased mortality and long-term neurodevelopmental, metabolic, and growth disorders.[3] Undernutrition largely affects the brain, resulting in poor brain growth and neurodevelopmental delay.[4] Regardless of the degree of prematurity, early postnatal growth (ie, during hospitalization) has been associated with neurological and cognitive outcomes in

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infancy and preschool-age.[5] Premature infants are prone to nutrient deficiencies due to inadequate stores, inability to feed adequately, and digest due to immaturity of the digestive system, while optimal nutrition of preterm infants is expected to result in growth similar to that of normally growing fetuses of the same gestational age.[6]

In recent years, the nutritional support for preterm infants has been improved. Parenteral nutrition, enriched preterm formula, and fortification of human milk have been proven to be critically important for preterm infants admitted to neonatal intensive care units (NICUs).[7] Unfortified human breast milk, the only option available in many low-income countries, does not contain adequate nutrients for the growth and development of preterm infants with the small volumes they can take in.[8-10] Human breast milk alone does not contain the required protein, energy, minerals, vitamins, and trace elements to promote growth and development of preterm infants.[11] Slower growth rates, including that of the head circumference, have been observed in preterm babies fed only on human milk as compared with those on fortified human milk.[12]

The advantage of starting small amount of enteral feeding earlier as a means of preparing the immature intestine for full enteral feeding has been recognized recently.[10] However, the nutritional assessment of preterm infants is challenging. For example, the body weight may vary based on fluid status, and changes in linear growth take time. Moreover, assessing body composition has usually been limited to research settings, and the biochemical nutritional assessments are not well established for clinical use.[13] Currently, in most settings in resource-limited countries, there is inevitable suboptimal feeding of preterm infants. This contributes significantly to the incidence of neonatal morbidity and mortality. Addressing preterm nutrition is vital, as there is an obvious need to reduce nutritional deficiencies in these susceptible infants.[14] Thus, we aimed to assess feeding patterns, extent of nutritional problems, and associated clinical outcomes using data from a study on illness among preterm infants in Ethiopia.

Methods

Our primary objective was to assess patterns of feeding of preterm neonates admitted to NICUs and associated clinical outcomes. The specific objectives were to investigate the type of feeding of preterm infants and associated clinical outcomes; to assess the time of initiation of enteral feeding; to assess the association of length of delay in enteral feeding (duration of nil per os [NPO] "nothing through the mouth") and clinical outcomes; and to review the weight changes of preterm infants during their hospital stay and finally to assess breast feeding prevalence at discharge.

Study Setting and Design

This was a hospital-based multicenter prospective study, known as the Study of Cause of Illness and Death of Preterm infants in Ethiopia (SIP). SIP was conducted in 5 teaching hospitals in Ethiopia. The methodology paper and primary outcomes have been published.[15,16]

The study participants for this analysis included a subgroup from the main study. Specifically, we included only preterm infants with a gestational age (GA) of less than 37 completed weeks admitted to one of the study hospitals with a minimum duration of hospital stay of 3 days in order to have sufficient time to measure undernutrition. Finally, only those infants whose parents gave informed consent for study participation were included.

Study Procedures

The clinical status of the infants, their general condition, vital signs, and oxygen saturation were monitored twice a day. Revisions of the diagnosis and pertinent investigations, assessment of the type and method of feeding, and weight measurements were done or collected daily. Specific clinical diagnoses of the infants were made with a combination of clinical data and laboratory results, and final diagnosis of cause of death for those who died was determined with additional data from a postmortem autopsy, among those with a completed autopsy. The assessment of the infants' GA was based on 3 methods: last menstrual period, physical examination using the New Ballard Score, and prenatal ultrasound when available.

Ethical Approval and Informed Consent

The study was conducted after ethical approval was obtained from Addis Ababa University College of Health Sciences Institutional Review Board (Ethics ID: AAUMF 03-008), and LMU Institutional Review Board (Ethics ID: 19-649). An information sheet and written consent for participation in the study was provided to potential participants in the 2 commonly spoken local languages. Only data from the women and infants of women who provided informed consent were included. Procedures were generally performed according to the national NICU management protocol.[17]

Statistical Analyses

Data were analyzed using SPSS version 23 and R software. Continuous variables were calculated as means

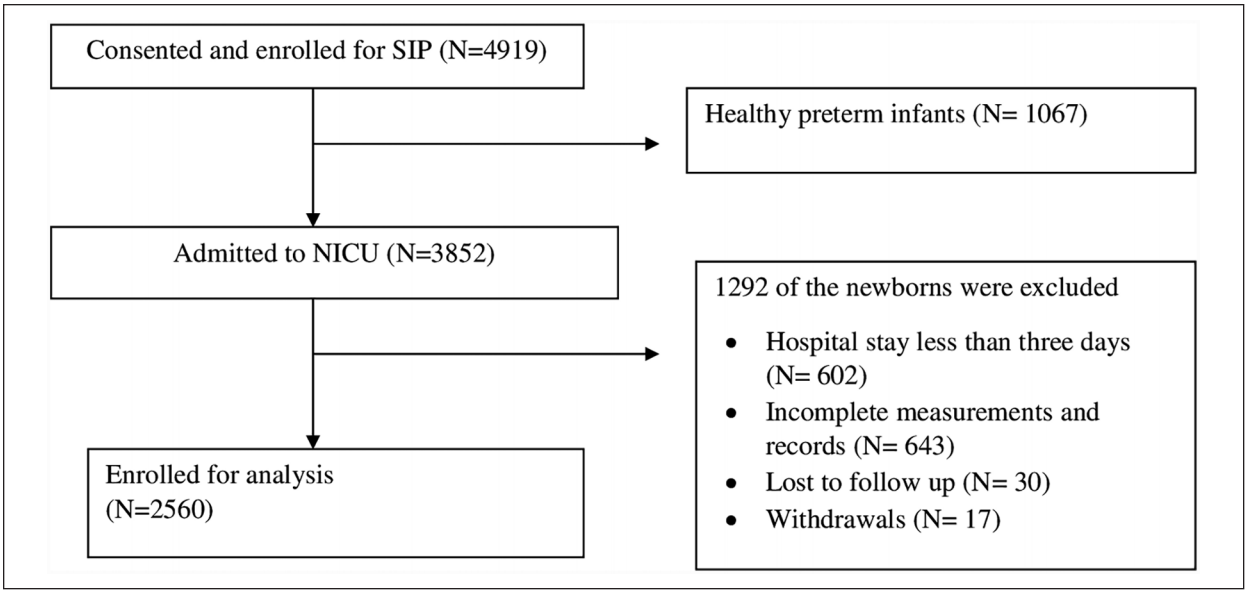

Figure 1. Flow chart of recruitment of study subjects.

and standard deviations, and other results were presented as the mean difference, with the calculated 95% confidence interval (CI), odds ratio (OR), and a *P* value. Binary logistic regression was done to investigate the associations of different variables related to the outcomes studied.

Results

Figure 1 and Table 1 show study participants selection and infants' characteristics. Out of a total of 2560 infants, 1225 (48%) were females and 1335 (52%) were males. During the first 24 hours, the majority of the infants, 1938 (76%), were kept NPO (nothing by mouth), and 559 (22%) were kept NPO for the subsequent 3 days after admission, getting only 10% dextrose intravenously. Overall, the infants were kept NPO 26.8% of the time they were in the hospital NICU. The percent of time the infants were kept NPO increased with lower GA. Similarly, 24.9% of those who had birth weight less than 1500 g were kept NPO for more than 3 days compared with 13.2% of the infants who weighed greater than 1500 g ($P < .001$).

During the hospital stay, 1485 (58%) of the infants were on exclusive breast feeding, while 201 (8%) were not given any enteral feeding at all; of the rest of the infants, 701 (27.4%), 41 (1.6%), and 874 (34.1%) received preterm formula, term formula, and mixed feeding (infants on more than one type of feeding), respectively. The pattern of feeding varied significantly by hospital. Preterm formula was given to more than one third of the infants admitted to the 3 hospitals located in Addis Ababa, while in 2 hospitals outside Addis Ababa (Jimma University Medical Center and Gonder University Hospital) only 3% to 6% of the infants were given preterm formula. Similarly, exclusive

Table 1. Clinical Characteristics of the Preterm Infants.

Variables	Values
Maternal age, mean (SD)	25.9 (5.4)
Gender	
Male, n (%)	1335 (52)
Gestational age (weeks), n (%)	
<28	80 (3)
28 to32	508 (20)
32 to 34	1159 (45)
35 to <37	813 (32)
Birth weight (g), n (%)	
<1000	150 (5.9)
1000 to <1500	728 (28)
1500 to <2000	1049 (41)
≥2000	591 (23)
Missing	42 (2)
Newborn major diagnosis, n (%)	
Respiratory distress syndrome	1405 (55)
Sepsis	918 (36)
Pneumonia	72 (3)
Necrotizing enterocolitis	103 (4)
Perinatal asphyxia	145 (6)
Hypothermia	1383 (54)
Total duration of hospital stay, mean days (SD)	10.0 (7)

Abbreviation: SD, standard deviation.

Table 2. Feeding Pattern and Outcome of Study Participants in Each Hospital, N (%).

Hospitals	N (%)	Exclusive breast feeding	Preterm formula	Term formula	Mixed feeding	No enteral feeding	Outcome	
							Alive	Died
Tikur Anbessa Hospital	659 (25.7)	330 (50.1)	223 (33.8)	14 (2.1)	260 (39.5)	69 (10.5)	530 (80.4)	129 (19.6)
Ghandi Memorial Hospital	276 (10.8)	102 (37.0)	148 (53.6)	7 (2.8)	162 (58.7)	12 (4.3)	233 (84.4)	43 (15.6)
St Paul Hospital	741 (28.9)	368 (49.7)	286 (38.6)	11 (1.5)	324 (43.7)	49 (6.6)	566 (76.4)	175 (23.6)
Gondar University Hospital	674 (26.3)	540 (80.1)	38 (5.6)	4 (0.6)	73 (10.8)	61 (9.1)	533 (79.1)	141 (20.9)
Jimma University Medical Center	210 (8.0)	145 (69.0)	6 (2.9)	5 (2.4)	55 (26.2)	10 (4.8)	150 (71.4)	60 (28.6)
Total	2560 (100.0)	1485 (58.0)	701 (27.4)	41 (1.6)	874 (34.1)	201 (7.9)	2012 (78.6)	548 (21.4)

Table 3. Duration of NPO and Associated Neonatal outcome.

NPO days[a]	Outcome		Crude odds ratio				Adjusted odds ratio[b]			
					95% CI				95% CI	
	Alive, n (%)	Died, n (%)	*P*	OR	Lower	Upper	*P*	OR	Lower	Upper
<1 day	476 (90.5)	50 (9.5)	—	—	—	—	—	—	—	—
1-3 days	1269 (79.6)	325 (20.4)	.000	2.44	1.78	3.34	.001	1.92	1.33	2.78
4-6 days	201 (59.1)	139 (40.9)	.000	6.58	4.58	9.46	.000	5.06	3.26	7.87
7-9 days	44 (71.0)	18 (29.0)	.000	3.90	2.09	7.25	.017	2.70	1.19	6.11
≥10 days	22 (57.9)	16 (42.1)	.000	6.92	3.42	14.04	.000	6.33	2.48	16.18

Abbreviations: NPO, nil per os; OR, odds ratio; CI, confidence interval.
[a]Days the infants were given 10% dextrose only without enteral feeding.
[b]Adjusted for birth weight, gestational age, and diagnoses such as respiratory distress syndrome neonatal infection, perinatal asphyxia, and hypothermia.

breastfeeding occurred in 69% and 80% of the infants in these 2 hospitals, while the infants in the other hospitals in Addis Ababa had 50% or less exclusive breast feeding. The in-hospital neonatal mortality rate observed in this study was also significantly different by hospital ($P = .004$). The lowest mortality rate (15.6%) was seen in the hospital with the highest rate of preterm formula feeding (54%; Table 2). At the time of discharge, the majority of infants (83%) was on breast milk feeding, while 14.9%, 5%, and 1.2% were given preterm formula, term formula, and mixed feeding, respectively.

Logistic regression analysis was done to determine the relationship of delayed enteral feeding to the risk of death in the hospital. Delay in enteral feeding by 1 to 3 days was associated with twice the risk of death (OR = 1.92, 95% CI = 1.33-2.78), while being kept NPO for 4 to 6 days was associated with a much higher risk of death (OR = 5.06, 95% CI = 3.23-7.87, $P < .001$), after adjusting for possible confounders, including GA, birth weight, and for the most common causes of death such as respiratory distress syndrome, neonatal infection, perinatal asphyxia, and hypothermia. Similarly, we found a statistically significant association between length of duration of NPO and hypoglycemia (OR = 1.2, 95% CI = 1.1-1.2; $P = .005$). We did not find a statistically significant association between risk of infection and types of feeding (Table 3).

Nearly half (47%) of the infants studied continued losing weight at the time of discharge or death, while only 22% of them regained their birth weight. The mean (SD) percentage weight loss and gain observed among the groups were 10.2% (8.6) and 13.0% (17.0), respectively. For those infants who stayed in the hospital for greater than or equal to 14 days, the mean weight at the 7th and 14th days across the GA classifications was found to be less than the mean birth weight. However, for these infants, the mean weight at the time of discharge was slightly higher than the mean birth weight (Table 4).

Discussion

The objective of preterm infant nutritional support is to achieve a rate of growth comparable to that found in

Table 4. Change in Mean Weight of Preterm Infants Who Had Been in the Hospital for 14 Days and More (N = 579), Mean ± SD.

GA (in weeks)	N	Days in NICU stay			
		At birth	7th day	14th day	Day of discharge
<28	24	1145 ± 290	1131 299	1130 ± 320	1261 ± 285
28 to 31	157	1381 ± 273	1328 ± 283	1357 ± 280	1442 ± 286
32 to 34	284	1612 ± 360	1523 ± 335	1543 ± 351	1619 ± 344
35 to <37	114	1869 ± 369	1778 ± 377	1807 ± 387	1872 ± 396

Abbreviations: SD, standard deviation; GA, gestational age; NICU, neonatal intensive care unit.

normally growing fetuses of similar GA. However, that goal is not attained in most of settings, even including high-resource settings where parenteral nutrition and human milk fortification is available.[6] Preterm infants face increased risk of death,[18] and survivors are at continued risk of growth restriction, unless provided with adequate nutrients required for growth. There is also an increased nutritional demand for preterm infants related to the serious illness they often suffer.[19] In low-income countries, where there are high rates of preterm birth,[20] poorly equipped NICUs and a shortage of trained health workers, the nutritional needs of preterm infants are often neglected. In our study, we found that none of the infants received parenteral nutrition or breast milk fortification.

The rate of breast feeding in this study is comparable to findings from NICUs in Europe and the United States, which ranged from 19% to 75% among mothers who gave birth to preterm infants.[21,22] Despite the recent study findings and the World Health Organization recommendation to give human milk fortifiers to very low birth weight (VLBW) infants who fail to gain weight while on adequate breast milk feeding,[23-25] none of the infants were given human milk fortifier. This is likely due to the fact that the Ethiopian national guidelines had not yet been revised, and human milk fortifiers were not available in the study NICUs.

The mortality rate of the infants in this study was very high (21.4%), and the risk of death of infants who were kept NPO longer while only getting 10% glucose was even higher. One in 5 of the infants received only 10% glucose intravenously, without enteral feeding for the first 3 days of admission. Glucose provides only 20% of an infant's energy requirement and has no protein. Several randomized controlled trials have shown the benefits of combined early parenteral and enteral nutritional support, without increased risk of adverse clinical outcomes.[26]

Minimal postnatal weight loss is expected in the first week of life, due to contraction of the extracellular compartment. However, exaggerated weight loss occurs in infants whose energy intake is inadequate.[27] At the end of the first week, more than half of the infants had a mean weight loss of 10% and only 30% of them gained weight by the second week. The initial postnatal weight loss observed in this study is comparable to a report of Shaffer et al,[28] which found a weight loss of 7.9% to 14.6% in the first few days. However, in our study, a significant proportion of the infants did not gain weight as expected even in the second week or thereafter. Recent studies show the benefits of early and enhanced nutrition of preterm infants in terms of improving neonatal outcomes and prevention of long-term complications, shorter hospital stay, better weight gain, and same or less risk of infection including necrotizing eneterocolitis.[6]

Preterm formula was given more often in the hospitals located in the capital city of Addis Ababa. This could be due to the influence of pharmaceutical companies' advertisement of the preterm formula in the capital city compared with the other regions. Though the hospitals had similar settings, the mothers in hospitals located in Addis Ababa could have had better income to afford the preterm formula. Lower mortality rates were seen in the hospitals providing preterm formula more often compared with those who had higher exclusive breast feeding rates. This is probably due to improved nutritional support as preterm formulas contain approximately 3.5 to 3.6 g/kg/day of protein when adequate energy is provided (120 kcal/kg/day). This is within the range of recommended daily protein intake (3.5-4.5 g/kg/day).[29] In addition to the improved nutrient content of the preterm formula, early feeding, and avoidance of unnecessary IV fluids and starvation may have contributed for the lower mortality rather than the preterm formula itself.

A limitation of the study was the fact that we did not capture the volumes of the feeds and the time infants achieved full enteral feeding. Preterm infants often start enteral feeding gradually based on the infants' general condition and tolerance, while receiving 10% dextrose intravenously in addition to the small amount of enteral feeding they received.

Conclusion

Unlike the general recommendation to initiate early enteral feeding, a considerable number of the infants were kept NPO in the first few days, receiving only maintenance fluid. This was associated with increased risk of death and development of hypoglycemia. We noted that the feeding patterns varied among the hospitals. A low death rate was observed in the hospital providing preterm formula feeding. Association of preterm formula feeding with improved survival may be only because earlier feeding is more easily achieved when formula feeding is used, as mothers often have difficulty to produce and express enough milk. In our opinion, the Ethiopian National Guideline on preterm nutrition should be revised, to promote more practices proven to be beneficial for survival and growth of the infants. These practices include the advancement of enteral feeding, the use of parenteral nutrition, human milk fortifiers, mixed feeding using preterm formula and breast milk, and enteral additives.

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Author Contributions

The study was conceptualized by NW, LMM, MS, and OG and reviewed by RLG, AM, EMM, BW, and AKN. The following authors contributed to data acquisition: LMM, AM, BW, AD, EMM, ZT, GM, AKN, EMM, and NW. ZTB contributed to data management, data analysis, and interpretation. NW drafted the manuscript, and RLG, LMM, AM, BW, AD, EMM, ZT, GM, ZTB, AKN, MS, and OG contributed to the writing and reviewing the manuscript. All authors have approved the final draft of the manuscript.

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