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INCIDENCE, ASSOCIATED FACTORS AND OUTCOMES OF ANEMIA AMONG PRETERM NEONATES ADMITTED TO THE NEWBORN UNIT OF MOI TEACHING AND REFFERAL HOSPITAL, KENYA

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ABSTRACT

Background: **Each year witnesses a growing number of preterm births. Approximately 1million children die each year due to complications of preterm birth including anemia.**

Objective: **To determine the incidence, associated factors and outcome of anemia among preterm neonates admitted to the newborn unit of Moi Teaching and Referral Hospital, Kenya**

Methodology: **This was a hospital based prospective observational study which was conducted in the newborn unit of Moi Teaching and Referral Hospital in Eldoret, Kenya from October 2023 to April 2024. Study participants were preterm neonates born before 37 completed weeks enrolled consecutively after consenting their mothers and followed up for a period of 28 days while in the unit or until discharge, referral, transfer or death. Gestational age was based on either last normal menstrual period, Ballard's score or obstetric ultrasound scan of the mother done before delivery.**

A standard tool was used to abstract information from files and document interview responses from the mothers. Complete blood Count tests done on 0, 7, 14, 21, 28 days of life. *Results*: **The incidence of anemia among the 385 study participants who at baseline had normal hemoglobin levels was 44.7% (95% CI39.76 – 49.69). The incidence density rate was 28.3% per 1000 person-days. Of the 172 neonates who developed anemia, 33 (19.2%) received packed red blood cells. There were 95 (55.2%) who completed 28 days of follow-up, 60 (34.9%) discharged home and 17 (9.9%) died in the unit.**

Low gestational age, low birth weight and increased phlebotomy blood loss were significantly associated with development of anemia in preterm neonates (p<0.001).

***Conclusion*: The incidence of anemia was nearly half the total number of preterm neonates admitted in the unit during the study period.**

INTRODUCTION

Preterm neonates, defined as infants born alive before completing 37 weeks of gestation, exhibit various subcategories based on gestational age: extremely preterm (< 28 weeks), very preterm (28 to 32 weeks), moderate (32 to 33 weeks), and late preterm (34 to 36 weeks) [1]Additionally, neonates are classified by birth weight into low-birth-weight (1500–2500 grams), very low-birth-weight (1000–1500 grams), and extremely low-birth-weight (less than 1000 grams).Each year witnesses a growing number of preterm births, with an estimated 15 million globally [2]. Preterm birth complications stand as the primary cause of death among children under 5 years old, contributing to around 900,000 deaths in 2019 [3]. Among these complications, anemia emerges as a significant contributor to morbidity and mortality in preterm neonates. In premature babies, anemia corresponds to a hemoglobin level of less than 13.5 grams / decilitre [4, 5]. Anemia is a common and fatal disease in premature neonates if it is not properly and carefully managed [5]. Anemia development and its ultimate severity is determined by a combination of physiological and pathological processes including: hemorrhage, infections, insufficient nutrient intake and cardiorespiratory disease and iatrogenic causes [4] Anemia becomes symptomatic when there is an imbalance between oxygen delivery and consumption which may not occur universally at the same hemoglobin for every preterm infant but once below a certain level of hemoglobin is reached [6]. Symptoms of anemia (e.g., desaturations, bradycardias, and tachycardia) are non-specific and can be due to alternative causes including sepsis, evolving lung conditions [7].A study carried out in Yaounde found a high prevalence rate of anemia in premature babies (24.2%) [8]. Preterm neonates are prone to both short term and long term complications.

In the third trimester of pregnancy, most fetal iron is transferred from the mother to the fetus leading to low iron stores at birth in preterm infants as pregnancy is interrupted [9].After birth, rapid growth and phlebotomy losses lead to a high risk of iron deficiency anemia (IDA) [9]. The risk of anemia is higher in infants born small for gestational age (SGA) or those with intrauterine growth retardation (IUGR) [10]. Approximately 90% of extremely low birth weight (ELBW) neonates will receive at least one red blood cell (RBC) transfusion. [11]. Physiologic and non-physiologic factors related to prematurity are responsible for anemia in prematurity and high transfusion rate, with phlebotomy blood loss for laboratory testing. [12]In a study done in Tanzania, the proportion of preterm infants (38%) with anemia. Anemia was prevalent among moderate preterm infants (born at gestation age 32 to <34 weeks) and those with multiple phlebotomies. [13]

Methods:

Settings: This study was conducted in the newborn unit of Moi Teaching and Referral Hospital (MTRH) which is located in Eldoret city, Kenya

Study design

This was a hospital based prospective observational study.

Target Population

All the preterm neonates born before 37 completed weeks.

Inclusion criteria

a) Preterm neonates born before 37 completed weeks of gestational age.

Exclusion criteria

a) Preterm babies with surgical conditions
b) Preterm neonates who were severely ill on admission for example neonates with low APGAR Score (Appearance, Pulse, Grimace, Activity, Respiration) of less than 5 at 5,10,15 minutes after birth
c) Readmitted babies to the ward
d) Preterm babies with low hemoglobin levels of < 13.5grams/decilitre on admission at day 1 of life

Sampling procedure

Consecutive sampling procedure was used on all preterm babies whom their parents consented to participate in the study.

Study procedure

Preterm neonates admitted were recruited by principal investigator or research assistant
Consented all preterm babies who met the inclusion criteria Followed by doing Ballard's score, babies measurements weight, head circumference and length Reviewed complete blood counts done within the 24 hours, interviewed mothers whose babies had been included in the study. On subsequent days 7, 14, 21 and 28; reviewed complete blood count done for each week. Estimation of phlebotomy loss for the tests done per week by following up laboratory samples which were taken off to read the volume of blood collected then added up the total. Babies (Diagnosis) collected in filHistory of blood transfusion and hematinic (iron) use

DATA MANAGEMENT

Data was collected using data collection tools which were checked on a daily basis by the principal investigator for completion and consistency. The data was then double entered into an electronic database and backups were created to safeguard against loss of information. The data entered was de- identified and the database password protected to ensure confidentiality.
Data was exported to STATA (Statistics and Data) version 16 where coding, cleaning and analysis was done.

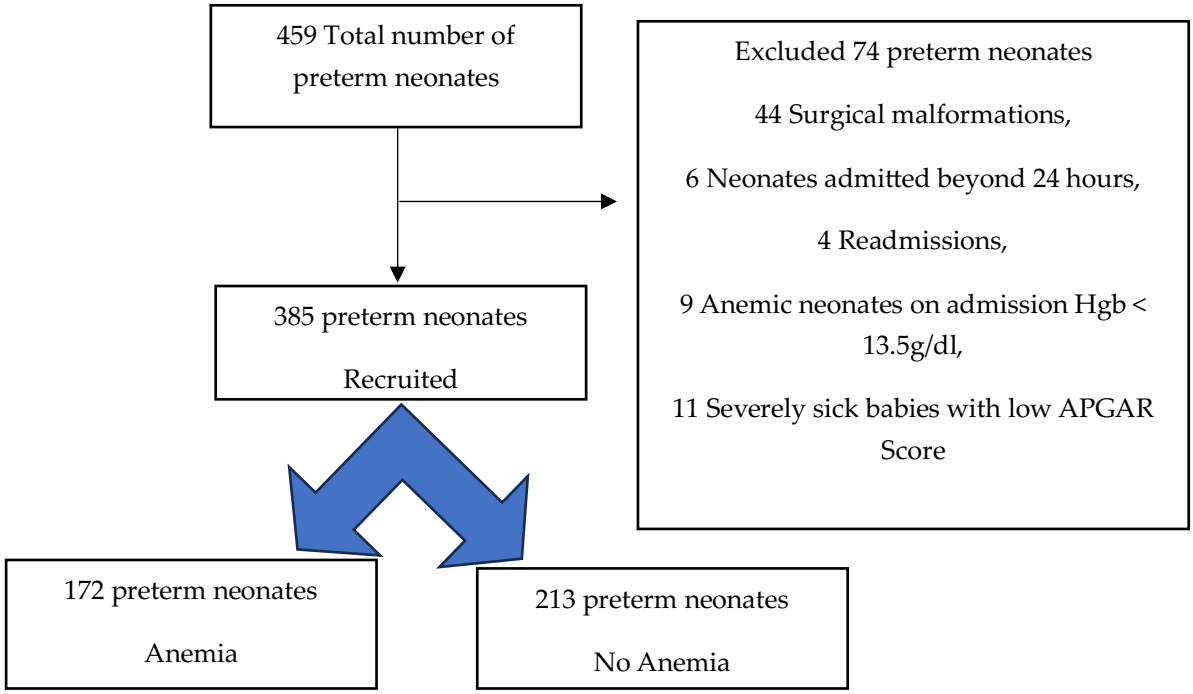
Statistical analysis

Categorical variables such as maternal level of education, antenatal care attendance were summarized as frequencies and their corresponding percentages.
Numerical variables such as maternal age, gestation age were summarized using means/median and their standard deviation/ interquartile ranges.
Incidence proportion of anemia in preterm neonates was expressed as a percentage with corresponding 95%Confidence Interval.
Binary logistic regression was used to determine factors associated with anemia in preterm neonates where crude and adjusted Odd ratios were reported for bi-variable and multivariable analysis respectively. Variables with a P-value of less than 0.2 at bivariable analysis were included in the multivariable analysis. A multinomial logistic regression was used to test association between anemia and outcome.
All test results with P-values <0.05 were considered statistically significant.

ETHICAL CONSIDERATION

Approval from MTRH Institutional Research and Ethics Committee(0004442), National Commission for Science, Technology and Innovation(NACOSTI/P/23/30859), Chief Executive Officer of Moi Teaching and Referral Hospital, newborn Unit in charge and the mothers of the preterm babies with low birth weight who met the criteria. Confidentiality of the patients' data was adhered to Informed written consents were administered to the mothers of the preterm neonates.

RESULTS: RESULTS FLOW CHART



There were 459 Total number of preterm neonates Recruited 385, excluded 74 preterm neonates. Resulted in 172 anemic and 213 non anemic preterm neonates.

To determine the incidence of anemia among preterm neonates admitted in newborn unit at Moi Teaching and Referral Hospital

The incidence of anemia among preterm neonates admitted in newborn at Moi Teaching and Referral Hospital was 44.7% [95%CI 39.76-49.69]

Association between individual characteristics and development of anemia

Table 1: ***Bi-variable table comparing babies who developed anemia to those who maintained normal hemoglobin status***

Variables	**No Anemia**	**Anemic neonates**	**uOR[95%CI]**	**p-value**
	N=213	**N=172**		
Sex				
Male	104/213 (48.8%)	85/172 (49.4%)	1.02(0.68-1.53)	0.908
Female	109/213 (51.2%)	87/172 (50.6%)	1	
Gestation Age-Ballards Score				
Mean(SD)	32.8 (2.9)	**31.5 (2.5)**	0.84(0.78-0.91)	<0.001
Range	25-36	26-36		

Mode Of Delivery				
Cesarean Section	79/213 (37.1%)	51/172 (29.7%)	1	
Vaginal	134/213 (62.9%)	121/172 (70.3%)	1.39(0.91-2.14)	0.126
Birth weight(Grams)				
Mean(SD)	1602.2 (497.8)	**1380.4 (400.0)**	0.99(0.99-0.99)	<0.001
Range	580 – 2600	670 – 2500		
Maternal Hemoglobin level (g/dl)				
Mean(SD)	13.5 (1.4)	13.2 (1.4)	0.85(0.69-1.05)	0.143
Range	9.8 – 16.1	8.6 – 15.6		
HIV Results				
Negative	191/213 (89.7%)	155/172 (90.1%)	1	
Positive	1 /213(0.5%)	2/172 (1.2%)	2.46(0.22-27.43)	0.463
Antenatal complication				
No	27/213 (12.7%)	22/172 (12.8%)	1	
Yes	185 /213(86.9%)	149/172 (86.6%)	0.98(0.54-1.80)	0.970
PPROM				
No	197/213 (92.5%)	152/172 (88.4%)	1	
Yes	16/213 (7.5%)	20 /172(11.6%)	1.62(0.81-3.23)	0.171
Pregnancy Iron supplements				
No	149/213 (70.0%)	134/172 (77.9%)	1.51(0.95-2.40)	0.080
Yes	64/213 (30.0%)	38/172 (22.1%)	1	
Antenatal corticosteroids				
No	196/213 (92.0%)	155/172 (90.1%)	1	
Yes	17/213 (8.0%)	17/172 (9.9%)	1.23(0.62-2.54)	0.523
Total blood withdrawn				
Mean(SD)	3.5 (1.8)	**8.0 (3.0)**	**1.95(1.72-2.20)**	**<0.001**
Range	1.3 – 10	1.7 – 16.9		

KEY
SD-Standard Deviation
PPROM-Preterm Premature Rupture of Membrane
HIV-Human immunodeficiency Virus
uOR-Unadjusted Odds Ratio

Factors associated with development of anemia

Table 2: In a multivariate analysis

Variables	aOR	p-value	95% CI
Gestation Age by Ballards Score	0.980	0.881	0.754- 1.274
Mode Of Delivery			
Cesarean Section	Ref		
Vaginal	1.270	0.579	0.545 - 2.961
Birth weight(Grams)	1.000	0.907	0.998 - 1.002
Hemoglobin level(gdl)	0.949	0.716	0.716 - 1.258
PPROM			
No	Ref		
Yes	1.046	0.949	0.264 - 4.149
Pregnancy Iron supplements			
Yes	Ref		
No	2.416	0.054	0.984 - 5.933
Total blood withdrawn	**1.773**	**<0.001**	**1.504 - 2.091**

KEY
aOR- Adjusted Odds Ratio
CI-Confidence Interval
g/dl- grams per deciliter
PPROM-Preterm Premature Rupture of Membranes

Phlebotomy blood loss was an independent factor directly associated with anemia in preterm neonates with an adjusted Odds ratio of 1.773.
Gestation age by Ballard's Score has an adjusted Odd's ratio of 0.98, 95%CI (0.754-1.274) and P-value of 0.881, birth weight (adjusted OR 1.0, 95% CI 0.998-1.002 P value 0.907), hemoglobin level (adjusted OR 0.949, 95%CI 0.716-1.258 and a P-Value of 0.716) Preterm neonates delivered by Spontaneous vaginal delivery had a 1.27 risk of developing anemia than those delivered by cesarean section with a non-significant P-Value of 0.579. Preterm neonates delivered by mothers with preterm premature rapture of membranes (PPROM) had a 1.046 risk of developing anemia with a P-Value of 0.949 Preterm neonates delivered by mothers not taking iron supplements during pregnancy had a 2.416 risk of developing anemia than those who were on medications with a non- significant P-Value of 0.054 and 95%CI 0.984-5.933

Outcome of preterm neonates

Out of a total of 385 preterm neonates enrolled, 172 developed anemia. Among those who developed anemia, 49 (28.5%) were discharged without any anemia treatment modality, 79 (45.9%) received packed red blood cells and platelets, 33 (19.2%) received only packed red blood cells. Fifty two (44.4%) neonates were on iron supplements. Of the 172 preterm neonates who developed anemia, 95 (55.2%) completed the

28-day follow-up in the unit before discharge, while 60 (34.9%) were discharged home. Unfortunately, 17 (9.9%) of those who developed anemia died while admitted in the newborn unit. Evidently, those who developed anemia were more likely to receive blood transfusion and were also more likely to remain admitted after 28 days compared to those who did not develop anemia. Both outcomes being statistically significant (P-Value of <0.001)

Table 3: Association between outcome and anemia

Outcome	**No Anemia**	**Anemia**	**Total**	**RRR(95% CI)**	**p-value**
	N=213	**N=172**	**N=385**		
Still in ward	9 (4.2%)	**95 (55.2%)**	104 (27.0%)	26.21 (12.42,55.29)	<0.001
Discharged home	149 (70.0%)	**60 (34.9%)**	209 (54.3%)	1	
Died	55 (25.8%)	17 (9.9%)	72 (18.7%)	0.76 (0.41,1.42)	0.404

KEY
RRR-Relative Risk Ratio
CI-Confidence Interval

DISCUSSION

Incidence of anemia in preterm neonates

The incidence of anemia in this study was 44.68% (95% CI 39.76 – 49.69). This finding was consistent with the proportion of anemia in preterm neonates at the newborn unit of Moi Teaching and Referral Hospital, where a proportion of 40.6% was reported in a study done on early neonatal complications [14]. The similarity in findings could be attributed to the use of similar clinical protocols in both settings.

In contrast, a study conducted at Tibebe Ghion Specialised Hospital in Northwest Ethiopia reported a lower prevalence of anemia (23.2%) among preterm neonates [15]. This difference could be explained by several factors, including the study design used was cross sectional study where by it was a one term test for neonates.

Similarly, a study conducted in Dar es Salaam, Tanzania, showed a prevalence proportion of anemia among preterm infants at 6 weeks of age to be 38.4% (142/370) [13]. This was slightly lower than the current study, which may be attributed to differences in the study populations. The Tanzanian study focused on stable infants who were being followed up in outpatient clinics, while the present study involved a broader range of preterm infants at various stages of care, likely influencing the prevalence of anemia.

Additionally, other studies reported significantly higher anemia proportions. For instance, a study done in Indonesia reported a 70% prevalence in preterm infants aged two months [16]. The higher prevalence in Indonesia may be related to the timing of the study, which coincided with a period of post-natal catch-up growth, a phenomenon that can exacerbate anemia in preterm infants.

Among the factors examined, blood withdrawal through phlebotomy was notably associated with the occurrence of anemia. It revealed a mean blood withdrawal of 8mls (3.0), ranging from 1.7 to 16.9mls in preterm neonates who developed anemia, with an odds ratio of 1.88.

These findings were consistent with a study conducted in Iowa, United States of America where blood loss equivalent to 2 to 4 ml/kg/week contributed to anemia in preterm infants [17]. Higher phlebotomy value observations were made in Tanzania, where anemia was observed among preterm infants with phlebotomy blood loss of 11 to 22ml/kg/week in the intensive care unit during their first 6 weeks of life [18].

Mean gestation age among neonates who developed anemia was 31.5weeks and 32.8 weeks in neonates without anemia.

Mean birth weight of preterm neonates with anemia was 1380.4gms (SD 400) while 1602.2gms (SD 497.8) for those without anemia. This finding was consistent with a study done at Muhimbili National Hospital in Dare-es Salaam, Tanzania where a higher proportion of anemia among moderate preterm infants was found compared to late preterm infants [13].

According to the study done in Sargevo , showed an average birth weight of preterm neonates 1394grams for the group which was prone to developing anemia [19].

This could be a reflection of the fact that hemoglobin increases with advancing gestation age, thus babies who are born before the 3rd trimester of gestation are deprived of most of the iron transported from the mother and a great deal of in utero fetal erythropoiesis.

Among mothers of preterm neonates who developed anemia, 149 (44.6%) had antenatal complications, with preterm premature rupture of membranes (PPROM) contributing 20 (55.6%), while 22 (44.9%) did not experience any complications during pregnancy

PPROM was associated with 30% to 40% of premature births and responsible for neonatal problems resulting from prematurity, including fetal distress, prematurity, infection and pulmonary hypoplasia. These complications often lead to prolonged stays in the ward, predisposing preterm neonates to repeated phlebotomies and subsequent anemia. [20]. This study's findings were consistent with the current study and other research, which also highlights the significance of PPROM and preterm birth.

The study showed significant findings regarding preterm neonates who developed anemia, with 172 (44.7%) of the neonates affected. Of these, 33 (19.2%) received packed red blood cell (PRBC) transfusions. The percentage of preterm neonates who were transfused was similar to the proportion of preterm neonates who required blood transfusions in a study conducted in Sargevo, where 21% of preterm neonates needed blood transfusions during hospitalization [19]. In this study, 13.1% of neonates born at less than 32 weeks and 7.9% of neonates born after 32 weeks required transfusions.

Additionally, 95 (55.2%) of the 172 preterm neonates who developed anemia completed the 28-day follow-up in the Newborn Unit. before being discharged. A total of 60 (34.9%) anemic preterm neonates were discharged home. Prolonged stays in the unit were primarily observed in extremely low birth weight neonates, a finding consistent with a study done at Kenyatta National Hospital in Kenya [21]. This was likely due to the high morbidity associated with the complications of extreme prematurity, as well as the time required for neonates to reach the recommended weight for discharge.

These findings aligned with other studies done in Sargevo and United States [19, 22], which highlight the role of complications like nosocomial infections in prolonging hospital stays for preterm neonates.

In the current study, the discharge rate among preterm neonates was 209 (54.3%), with 60 (34.9%) anemic and 149 (70.0%) non-anemic preterm neonates being discharged. This suggested a lower discharge rate for preterm neonates, particularly those with anemia complications. A study conducted in Ethiopia reported a higher discharge rate, which could be attributed to the lack of restriction follow-up timeline for the enrolled neonates [15]. The current study involved maximum follow-up of preterm neonates to 28 days in the newborn unit.

In a study done at Moi Teaching and Referral Hospital, it was found that two-thirds (60.6%) of premature infants admitted to the newborn unit survived to discharge [14].This was similar to the current study of discharged preterm neonates.

The proportion of preterm neonates who died in current study was 72 (18.7%), with 17 (9.9%) of these having developed anemia. This mortality rate was similar to the findings in Sargevo, which showed that 21% of preterm neonates died [19]. The proportion of preterm neonatal mortality in the current study was also consistent with a study conducted at Mbarara Regional Referral Hospital in Uganda, which reported a cumulative incidence of preterm neonatal mortality of 19.8% at 28 days after birth [23]. Other studies, such as those in Ivory Coast and Sarjevo, reported mortality rates of 25.8% and 21%, respectively [24,19]. These differences may be linked to varying preterm care protocols and treatment practices, with the Ivorian study noting a 60% co-infection rate.

Study Limitation

Follow up of preterm neonates admitted in a single level six facility of newborn unit of Moi Teaching and Referral Hospital.

No follow up of preterm neonates was done after discharge, transfer, and referral.Anemia developed by preterm neonates with-in 28days of life while admitted in the unit.

Conclusion

The incidence of anemia in preterm neonates was approximately half the total number of preterm neonates admitted in the unit during the study period. Half of the preterm neonates who developed anemia completed 28 days of follow up while in newborn unit.Low gestation age, low birth weight and increased blood loss through phlebotomy were significantly associated with development of anemia in preterm neonates.

Recommendation

Adoption of micro-sampling methods for phlebotomy. Further long term follow up studies on anemia in preterm neonates to evaluate for long term complications.

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