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Association between Germinal Matrix Hemorrhage and Perinatal Risk Factors in Preterm Neonates, in a Southwestern Nigerian Hospital

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Authors' contributions

This work was carried out in collaboration between all authors. Author AA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AY and IJ managed the analyses of the study. Author KS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine the incidence of Germinal matrix hemorrhage (GMH) among preterm neonates and the associated perinatal risk factors.
Study Design: Prospective cross sectional study.
Place and Duration of Study: This study was carried out in the (two) neonatal units of Lagos

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University Teaching Hospital (LUTH), Idi-Araba, from May 2011 – April 2012.
Methodology: Transfontanelle Ultrasonography was done for 300 preterm neonates (136 male and 164 females) within the first 24 hrs of life and subsequently on the 2nd, 3rd, 4th and 7th days of life. Thereafter weekly until discharge or corrected 40 weeks. Sonographic findings and pertinent perinatal history from the case note of each neonate were documented using a proforma. Gestational age was determined from maternal dates (last menstrual period) and gestational assessment by Ballard score. Data were analyzed using IBM SPSS Statistic software, version 20.0 and Chi – square test with desired degree of accuracy at 0.05.
Results: GMH occurred in 95/300 neonates, giving an incidence of 31.7%. Anemia (33/50, p<0.001) and perinatal HIV exposure (100%, p<0.001) were the most significant risk factors. Antenatal corticosteroid administration had significant protective effect (p= 0.001). Gender however did not significantly determine the occurrence of GMH (p = 0.40).
Conclusion: The incidence of GMH in preterm neonates is higher than previously reported. Preventable perinatal risk factors are significant contributors. Antenatal steroid administration was found to be protective.

Keywords: Transfontanelle ultrasonography; germinal matrix hemorrhage; preterm neonate; perinatal.

1. INTRODUCTION

Preterm neonates are babies delivered at gestational age less than 37 weeks. [1] Approximately fourteen percent (14%) of annual deliveries in Nigeria are Preterms, [2] compared to 7% in United Kingdom [3]. Twenty five percent of all infants having very low birth weight (<1.5 kg) die by one year compared to 2% for babies of similar birth weight and 0.3% for infants weighing 2.5 kg in United Kingdom [2,3]. This is as a result of better perinatal care.

Germinal matrix is located in the subependyma of the ventricular walls and predominantly localized at the caudothalamic groove at gestational age of about 32 weeks. These metabolically active vessels are prone to varying degrees of haemorrhage, termed germinal matrix haemorrhage (GMH) also called subependymal or intra-ventricular haemorrhage (IVH) [1,4,5]. GMH, an intracranial hemorrhage, is the leading etiology of morbidity and mortality in preterm babies [1,5-9]. GMH has been reported at autopsy in 50 to 70% of preterm neonates [10].

There has been variation in the prevalence of GMH, which was previously reported to be stable, between 15-20%, for over 2decades (1960 - 1980). [1] Nzeh and Ajayi reported an incidence of 29.5% in Nigerian preterm neonates in 1992-1994 [11]. The incidence reported recently shows higher incidence [12,13]. This variation has been reported to be the result of variation in the quality of perinatal care and not only prematurity [1,11,12,14-16]. Previous studies also show no statistical correlation between incidence of GMH and birth weight or gestational age at birth [11,15,16]. There is also no association between the degree of prematurity and degree (grades) of GMH [11, 12,15]. These indicate a causative lacuna, attributed to perinatal risk factors. Although perinatal risk factors have been reported [4,11-15], similar study has not been done in Lagos a cosmopolitan and commercial centre in southwest Nigeria.

The sensitivity and specificity of ultrasound in the diagnosis of intracranial haemorrhage greater than 5 mm is 96% - 100% and 91% - 94% respectively [6,10]. Ultrasound is non-ionizing and does not require use of sedation to investigate uncooperative newborns as may be necessary for cranial Magnetic Resonance Imaging (MRI) [5,10].

The study is aimed at reporting the incidence of GMH, identify perinatal risk factors in this environment and determine the association between GMH and the identified perinatal risk factors. This will also help identify possible preventable risk factors in this environment and promote effective management of mothers during the perinatal period and possibly averting the risk of GMH in preterms.

2. METHODOLOGY

This prospective, cross-sectional study was conducted in the neonatal units of the Lagos University Teaching Hospital (LUTH), Idi- Araba, over a period of 12 months, following health research and ethics committee's approval and

written informed consent by the parents. The procedure was carried out using a portable ``PCO 90" ultrasound system equipped with a 7.5MHz broadband curvilinear 11mm scan head transducer.

Three hundred neonates were used in this study using the sample size formula ($n=z^2pq/d^2$) as described by ``Cochran" [17]. The constants: n, z, p, q and d as defined in the reference article. The prevalence (p) of GMH in a similar study in the country by Ajayi and Nzeh [11] was 24.4%.

The babies included in the study are consecutive preterm neonates admitted in LUTH during the study period, having obtained informed consent from their parents. The exclusion criteria are preterms whose parents declined consent, preterms with congenital malformations, metabolic disorders, central nervous system infections, and unknown perinatal data.

Positioning the baby in the cot such that the baby`s anterior fontanel can be easily accessed through the chosen side hole. The transfontanelle ultrasound scan for each child was performed in both coronal and sagittal planes. All scans were carried out by the researcher to avoid inter-observer error.

The first scan on each neonate was within the first 24 hrs of life and serial scans done on the 2nd, 3rd, 4th and 7th days of life. Thereafter once weekly until discharged or till the corrected 40 weeks was attained. Sonography was also repeated on days when there was any condition such as apnoea, decreased level of Hemoglobin (<12 mg/dl i.e PCV < 36%) [1,8], asphyxia- low oxygen saturation (SPO^2 < 90%) [1,8] and on institution of any significant intervention such as intermittent or continuous positive pressure ventilation. Other perinatal factors considered are: sex, jaundice, sepsis (early onset of neonatal infection with raised WBC > 11000), intra uterine growth restriction, respiratory distress syndrome (confirmed by radiography), patent ductus arteriosus (diagnosis by physical examination and echocardiogram), sodium bicarbonate administration, blood transfusion, intermittent positive pressure ventilation, history of fetal distress, antepartum haemorrhage, premature rupture of membrane, antenatal steroid administration (two doses given at 24 hours interval for 48hours before delivery), multiple pregnancy, preeclampsia, apnoea, aminophylline administration, mode of delivery and human immunodeficiency virus (HIV). The sonographic findings and pertinent perinatal history from the case note of each neonate were documented using a proforma.

Gestational age was determined from maternal dates (last menstrual period) and gestational assessment by Ballard score [18]. Data were analyzed using IBM SPSS statistic software, version 20.0. Chi – square test was used to determine association between the Incidences of GMH and the perinatal risk factors.

3. RESULTS AND DISCUSSION

3.1 Results

The 300 preterm neonates recruited had gestational age at birth ranged between 24 and 36 completed weeks with incidence of 31.7% (95) (Table 1).

Table 1. Incidence of GMH per group of gestational age recruited and the overall Incidence of GMH

Gestational age at birth (completed weeks)	Frequency recruited per group (F)	GMH per group (N)	Incidence per group (%) N/F X100
24.00	9	4	44.4
26.00	5	0	0
27.00	4	0	0
28.00	42	12	28.6
29.00	29	16	55.2
30.00	42	29	69.1
31.00	34	8	23.5
32.00	37	10	27.0
33.00	17	4	23.5
34.00	27	12	44.4
35.00	14	0	0
36.00	40	0	0
Total	300	95	31.7

There is statistical significant difference in the incidence of GMH in neonates with birth weight less than 1.5 Kg and those with birth weight greater than 1.5 Kg (p= 0.004) (Table 2). Out of 136 males recruited, 46 (33.8%) had GMH while 49 (29.9%) of the 164 females had GMH with insignificant statistical difference (P= 0.40) (Table 3).

Fifty (16.7%) had anaemia and 33 (66%) of these anemic neonates had GMH. This indicates a statistical significant difference (P < 0.001) in patients with GMH and those without GMH in terms of anaemia (Table 4). Asphyxia occurred in 30 (10.0%) babies and twenty five (83.3%) of these babies had GMH. It shows significant statistical association (P < 0.001) between GMH and low SPO_2.

Forty (13.3%) were treated with aminophylline and twenty (50%) of these had GMH which was not statistically significant (P = 0.21).

There is statistical significant difference in patients with GMH and those without GMH in terms of Jaundice (P - 0.002), IUGR (P - 0.003), PDA (P- 0.002), Sodium bicarbonate administration (P- 0.000), Sepsis (P - 0.001) and Respiratory distress (P-0.008). Statistically significant difference (p<0.001) between preterms who were perinatally exposed to HIV and those who were not was noted, as fifteen (5%) of the 300 preterm neonates were perinatally exposed to HIV infection and all the 15 (100%) babies had GMH. No statistical significant difference is seen in the preterm neonates who had GMH and those without GMH in terms of apnoea (p= 0.36) and mothers who had premature rupture of membrane (P = 0.21). Fetal distress (P <0.001), and Blood transfusion (P <0.001) (Table 4,5 and 6).There is also statistical significant difference in patients with GMH and those without GMH in terms of those delivered by mothers who had Multiple pregnancy (P<0.001), Antepartum haemorrhage (P - 0.004) and Preeclampsia (P = 0.01) (Table 6).

Out of 300 cases 161 preterms (53.7%) were delivered via the vaginum while 139 (46.3%) were through Caesarean section. Out of the former, 50 developed GMH (52.6% of GMH population) and 45 of the latter (47.4% of GMH population). No statistical significant association (P=0.17) between GMH and mode of delivery (Table 7). Forty five (45) babies were delivered by mothers who received antenatal steroid and only 5 (11.1%) of these babies had GMH. This is statistically significant (P =0.001) with inverse relationship between GMH and antenatal steroid administration to mothers (Table 6).

Figs. 1 and 2 illustrate transfontanelle scan with normal and inyraventricular hemorrhage.

3.2 Discussion

The incidence (31.7%) of GMH in this study is high, which is in- keeping with high incidence (29.5%) found by Ajayi and Nzeh, [11] in a study carried out in North Central part of Nigeria in 1992 -1994. These incidences are higher when compared with WHO report of a stable range of 15% -20% between 1960 -1980. This upward trend is observed in similar publications in this century by Akadri et al. [13] and Joidery et al. [12] with incidence of 44.1% and 36.7% respectively. This trend is also contrary to the report of Di salvo [19] in 2001 that GMH has decreased steadily. Hence this study corroborates the fact that incidence of GMH is increasing.

Table 2. Relationship between risk factors (GA and BW) and GMH

Factors	Status(N)	GMH		P-values
		With GMH N (%)	Without GMH N (%)	
Gestational age (weeks)	<32 (165)	69 (41.8%)	96 (58.2%)	<0.001
	≥32 (135)	26 (19.3%)	109 (80.7%)	
Birth weight (kg)	<1.5KG	54(40.3%)	80(59.7%)	0.004
	≥1.5KG	41(24.7%)	125(75.3%)	

Table 3. Incidence of GMH according to gender

Presence of GMH	Male N (%)	Females N (%)
GMH present (n=95)	46 (48.4)	49 (51.6)
GMH absent (n=205)	90 (43.9)	115 (56.1)
TOTAL RECRUITED (300)	136 (45.3)	164 (54.7)

P=0.40

Table 4. Frequency of Postnatal risk factors and Relationship with GMH

Factors	Status	GMH		Total	P –values
		With GMH N (%)	Without GMH N (%)		
Anaemia	Yes	33(66%)	17(34%)	50	< 0.001
	No	62(24.8%)	188(75.2%)	250	
Jaundice	Yes	24(51.1%)	23(48.9%)	47	0.002
	No	71(28.1%)	182(71.9%)	253	
Sepsis	Yes	20(55.6%)	16(44.4%)	36	0.001
	No	75(28.4%)	189(71.6 %)	264	
Asphyxia	Yes	25(83.3%)	5(16.7%)	30	< 0.001
	No	70(25.9%)	200(74.1%)	270	

Table 5. Relationship between other postnatal risk factors and GMH

Factors	Status	GMH		Total	P- values
		With GMH N (%)	Without GMH N (%)		
IUGR	Yes	8(66.7%)	4(33.3%)	12	0.003
	No	87(30.2%)	201(69.8%)	288	
RD	Yes	39(42.4%)	53(57.6%)	92	0.01
	No	56(26.9%)	152(73.1%)	208	
PDA	Yes	25(50%)	25(50%)	50	0.002
	No	70(28%)	180(72%)	250	
$NaHCO_3$	Yes	23(28%)	109(72%)	132	<0.001
	No	72 (42.9%)	96 (57.1%)	168	
BT	Yes	16 (66.7%)	8 (33.3%)	24	<0.001
	No	79 (28.6%)	197 (71.4%)	276	
IPPV	Yes	20 (80%)	5 (20%)	25	0.04
	No	75 (27.3%)	200 (72.7%)	275	
Aminophylline administration	Yes	20 (50%)	20 (50%)	40	0.21
	No	75 (28.8%)	185 (71.2%)	260	
Apnoea	Yes	18(38.3%)	29 (61.7%)	47	0.36
	No	77(30.4%)	176(69.6%)	253	
HIV Status	Yes	15 (100%)	0	15	<0.001
	No	80 (28.1%)	205(71.9%)	285	

IUGR-Intrauterine Growth Restriction, RD – Respiratory Distress, PDA – Patent Ductus Arteriosus, BT – Blood Transfusion, IPPV – Intermittent Positive Pressure Ventilation.

Table 6. Relationship between antenatal risk factors and GMH

Factors	Status	GMH		Total	P –values
		with GMH N (%)	without GMH N (%)		
Foet. Dist.	Yes	5 (50%)	5 (50%)	10	<0.001
	No	90 (31%)	200 (69%)	290	
Antep.Haem.	Yes	16 (55.2%)	13 (44.8%)	29	0.004
	No	79 (29.2%)	192 (70.8%)	271	
Prom	Yes	34 (27.6%)	89 (72.4%)	123	0.21
	No	61 (34.5%)	116 (65.5%)	177	
Anten. Steroid	Yes	5 (11.1%)	40 (88.9%)	45	0.001
	No	90 (35.3%)	165 (64.7%)	255	
Mult.Preg.	Yes	14 (17.3%)	67 (82.7%)	81	0.001
	No	81 (37%)	138 (63%)	219	
Pre Eclampsia	Yes	8 (61.5%)	5 (38.5%)	13	0.01
	No	87 (30.3%)	200 (69.7%)	287	

Foet.Dist. – Foetal Distress ANTEP.HAEM- Antepartum haemorrhage, PROM – Premature rupture of membrane, Anten. Steroid - Antenatal steroid administration, MULT. PREG – Multiple pregnancies,

Table 7. The relationship between mode of delivery and Germinal Matrix Haemorrhage

Mode of delivery	GMH present (%)	GMH absent (%)	Total
Vaginal delivery	50 (31.1)	111 (68.9)	161
Caesarean Section	45 (32.4)	94 (67.6)	139

P = 0.17

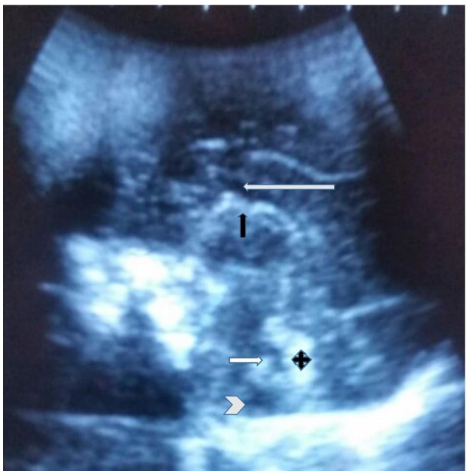

Fig. 1. A sagittal section in the mid line showing the caudothalamic groove (black arrow) and characteristic echogenic cerebellum (+) with the fourth ventricle (white arrow) anterior to it. A normal fluid-filled cisterna magna (chevron). The midline cystic cavum septum pellucidum (long white arrow)

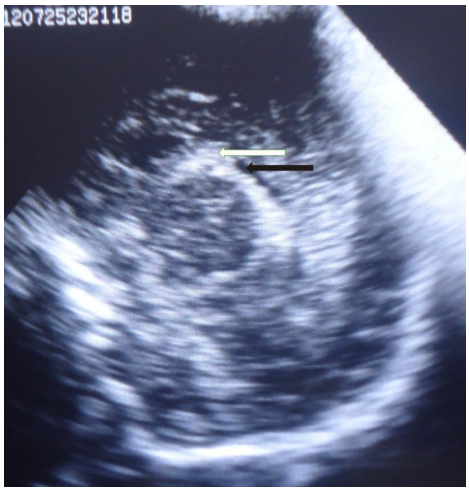

Fig. 2. Illustrating GMH grade II (i.e. bleed (white arrow) in the ventricle (black arrow) but no ventricular dilatation)

As shown in Table 2, when the gestational age are grouped into ≤32 weeks and > 32 weeks and the birth weight grouped into Very low birth weight (≤1.5 Kg) and Low birth weight (>1.5 Kg), there is significant statistical relationship between prematurity and incidence of GMH as generally known and accepted. This observation is most probably due to inclusion of preterms up to gestational age of 36 weeks and higher sample size which enable proper comparison of prematurity. However a critical analysis of Table 1 supports the fact that there is no linear relationship between GMH and prematurity, meaning that there is a factor to be considered apart from prematurity for the incidence of GMH.

Twenty one perinatal risk factors were identified in this study. This is unlike Ajayi and Nzeh[11] who studied only the association between GMH and mode of delivery. Joideiry B et al. [12] considered fourteen while Yelik Pekcevik et al. [20] considered seventeen. Many studies and recent reports [19,20] show no association between GMH and SexThis is also found in this study. Out of the recruited preterm neonates, 16.7% had anaemia, 66% of these anaemic babies had GMH (P = 0.000). Soni et al. [6] and Vergani [16] had similar findings. Etiology of anaemia in preterm neonates include; immature erythropoiesis, decreased survival of red blood cells in premature infant, deficiencies of folate, vitamin B12 and iron, as well as multiple blood draws during hospitalization [21]. Anaemia causes increase in cerebral blood flow and the vascular endothelium is extremely vulnerable to hypoxic-ischemic injury in anemic preterm neonate [1,21]. Due to inadequate auto regulatory mechanisms in sick preterm infants, all alterations in systemic blood pressure are transmitted directly to the fragile germinal matrix vasculature [1,21,22]. These explain the pathophysiological basis of positive association between GMH and anaemia. In view of these any drop in packed cell volume in Preterm neonates should be an indication for transfontanelle ultrasound scan to rule out GMH. This study also corroborate the need for the use of hematinics by pregnant women throughout pregnancy, however tasking compliance to the drugs may be. This helps the fetus to build high PCV and negates GMH in case of premature delivery.

Fifty percent of patients with Patent ductus arteriosus (PDA) had GMH and positive statistical association (P- 0.002) was observed between PDA and GMH. Jodeiry et al. observed similar relationship between PDA and GMH. In their study, 54.5% of patient with PDA had GMH [12]. The patency of the ductus arteriosus causes fluctuation in cerebral blood flow [21]. Fluctuating cerebral blood flow (CBF) is associated with the development of GMH [21,22-25]. Other conditions in preterm neonates, causing fluctuation in cerebral blood flow, with positive statistical association with GMH in this study include: low oxygen saturation pressure (83.3% of babies with low SPO2 had GMH), intermittent positive pressure ventilation (80% of preterm neonates who had this administered, had GMH), sepsis (55.6% of the babies that had septicemia, had GMH), foetal distress (50% of babies who had history of foetal distress in utero, had GMH) and Jaundice [22,26,27]. Of the recruited babies, 15.7% had jaundice and a statistically significant percentage (51.1%) of the jaundiced preterm neonates had GMH.

Significant percentage (66.7%) of those who had blood transfusion had GMH. In a single center study of 103 infants randomized to liberal versus restrictive transfusion guidelines, no difference was found in the incidence of GMH or worsening GMH grades III and IV combined in the restrictive transfusion group, but did note a trend for more infants with grade IV GMH in this group.[28] Some studies suggest that maintaining a higher Pack Cell Volume(PCV) (by transfusion) level in the first week of life might protect preterm neonates from GMH, [29,30] unlike the observation in this study. However, being unable to determine whether the post transfusion GMH observed in this study is primarily due to the transfusion procedure or as a result of high incidence of GMH in the first one week of life, this report could not negate the established facts by previous studies that transfusion and high PCV in the first week of life is protective against GMH. The finding on transfusion in this study, being contrary to the previous studies, also advocates the need for protocols in the transfusion of these babies and encourages the procedure to be carried out by skillful and experienced members of the neonatal team.

Asphyxiated babies with GMH were 83.3% of those with asphyxia in the total preterm neonates recruited in this study and statistical significant positive association (P- 0.000) was found. Several studies corroborate this finding [1,5,31, 32]. The immature blood vessels in the germinal matrix are believed to have limited vasodilatation capability, a normal physiological response to anoxia that results in increased intravascular pressure. This increase in pressure can easily rupture the thin walled vessels [1,5,21].

About sixty seven percent (66.7%) of the preterm neonates with IUGR had GMH and significant positive association (P=0.003) was observed. There are 2 major categories of IUGR: symmetrical and asymmetrical. Asymmetrical IUGR is more common. In asymmetrical IUGR, there is restriction of weight followed by length. The head continues to grow at normal or near-normal rates (head sparing). This is a protective mechanism that may have evolved to promote brain development If the cause of IUGR is extrinsic to the fetus (maternal or uteroplacental, transfer of oxygen and nutrients to the fetus is decreased) [1,3,21]. This causes a reduction in

the fetus' stores of glycogen and lipids. This often leads to hypoglycemia at birth [1]. Polycythemia can occur secondary to increased erythropoietin production caused by the chronic hypoxemia. Although this type of IUGR is head sparing, Impaired auto regulation of cerebral blood flow and fragility of germinal matrix as a result of prematurity and effect of thrombocytopenia are possible contributory factors to IVH in these babies [1,3,19].

In this study, 24.2% of the preterm neonates that had IVH had intravenous sodium bicarbonate to correct for acidosis. There is statistical significant difference (P=0.000) between preterm neonates with GMH and those without GMH in terms of sodium bicarbonate administration. Rapid infusion of hyperosmolar solution increases cerebral flow which usually leads to GMH due to loss of cerebral auto-regulation in these babies as well as fragility of germinal matrix [1,21].

In this study 61.5% of preterm neonates delivered by preeclamptic mothers had intraventricular haemorrhage and this is statistically significant (P = 0.010). This is in-keeping with previous studies [1,8,16,33]. David A. et al. [34] and June Kepler et al. [35] reported reduced incidence of intraventricular hemorrhage in preterm neonates delivered by mothers who had preeclampsia. Although in their studies they acknowledge the preeclamptic protective effect as possibly secondary to higher gestational age, administration of $mgso_4$, antenatal steroid administration and high PCV in the first week of life. In the current study, most of the preeclamptic mothers were delivered at relatively low gestational age.

All the babies who were perinatally exposed to HIV were diagnosed of GMH. This finding suggests a strong positive statistical significant association between HIV and GMH. Further research into the possible explanations for this is necessary.

About thirty eight percent (37.5%) of the babies with apnoea had GMH, hence no statistical difference (P = 0.49) between preterm neonates that had IVH and those without IVH in terms of apnoea. This is inconsistent with some previous studies [4,8,10,23]. Apnoea of prematurity is a manifestation of developmental immaturity of respiratory control mediated by the brainstem although it can also be due to airway obstruction [19,23]. This persists for several weeks in some premature infants especially in extremely low birth weight infants (ELBW). Episodes of apnea may be induced by hypoxia, sepsis, hypoglycemia, temperature disturbances or neurologic lesions [23]. Assisted ventilation or suctioning is the immediate intervention [23]. In view of this, apnoea predisposes these infants to high incidence of GMH contrary to the observation in this study. The possible reason for this is the percentage of ELBW recruited in this study (1.3%) and also because none of the babies had mechanical ventilation as this is presently not available in the hospital.

Out of the babies with GMH, 52.5% were delivered vaginally while 47.4% were delivered through caesarean section. No significant difference in the incidence of GMH in these modes of delivery. This is similar to the findings of Linder et al. [29] and Yeliz Pekcevik et al. [22]. This is however contrary to the finding of Jodeiry et al. [12] who reported a statistically significant higher incidence of GMH in babies delivered vaginally. In another study, vaginal delivery was reported as a risk factor of GMH, however general anesthesia used during caesarean section was found to be a risk factor for GMH [36]. In this centre spinal anesthesia is generally used for caesarean section and this may be responsible for the difference observed.

There is low occurrence of GMH in newborn with maternal prenatal steroid therapy, which shows the protective effect of steroid. The steroid therapy stimulates lung maturity of fetus and this is usually administered, especially when preterm delivery is anticipated or inevitable [21]. This finding is consistent with the study by Yeliz Pekcevik et al. [20] Koskal et al. [37] and Jodeiry et al. [12] In the study by Vural et al. on 103 premature neonates, maternal corticosteroid therapy was found to be significantly protective against GMH. In the study from Iran, antenatal steroid had protective effect on the occurrence of GMH [38].

We have limitations in this study such as single centre study, inability to determine whether the post transfusion GMH observed in this study is primarily due to the transfusion procedure or as a result of high incidence of GMH in the first one week of life. We strongly recommend another study to determine the association of GMH and perinatal HIV infected preterms involving large sample size.

4. CONCLUSION

The incidence of GMH in preterm neonates is increasing, 31.7% in this study. Perinatal maternal and neonatal conditions are important predisposing factors. The following risk factors had association with GMH: Anaemia, Patent Ductus Arteriosus (PDA), Sodium Bicarbonate administration, Intermittent positive pressure ventilation, Blood transfusion, Jaundice, Asphyxia, Respiratory distress, Low SPO2, Intra Uterine Growth Restriction, Foetal distress, Antepartum haemorrhage, sepsis, multiple pregnancy and preeclampsia. There was an inverse association with prenatal steroid administration and no association with apnoea, aminophylline administration, premature rupture of membrane and mode of delivery. All the babies who were perinatally exposed to HIV had GMH. Further research into the possible explanations for this is necessary.

CONSENT

All authors declare that 'written informed consent was obtained from the parent(s) of the patients recruited in the study.

ETHICAL APPROVAL

Ethical clearance was obtained from LUTH Health research and ethics committee. The protocol number is ADM/DCST/HREC/VOL.XV/287

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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