Journal of Medical Laboratory Science, 2021; 31 (1): 1-9
http://jomls.org; info@jomls.org Adjekuko ***et al***
http://doi.org/10.5281/zenodo.4641282

Evaluation of Some Maternal and Neonatal-Associated Risk Factors in Early On-Set Neonatal Thrombocytopenia in Delta State, Nigeria

Collins Ohwonigho Adjekuko[*1], Emmanuel Asuquo Etim[2], Mathias Abiodun Emokpae[3] Humphrey Benedo Osadolor[3], Zaccheaus Awortu Jeremiah[4]

1. *Department of Medical Laboratory Services, General Hospital, Okwe-Asaba, Nigeria.*
2. *Department of Haematology, Federal Medical Centre Yola, Adamawa State, Nigeria.*
3. *Department of Medical Laboratory Science, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Benin City, Nigeria.*
4. *Haematology and Blood Transfusion Science Unit, Department of Medical Laboratory Sciences, College of Health Sciences, Niger Delta University, Wilberforce Island, Bayelsa State, Nigeria.*

ABSTRACT

Background: The growing prevalence of neonatal thrombocytopenia at birth in recent times is a source of concern. Hence, the assessment of maternal and neonatal risk factors associated with early on-set neonatal thrombocytopenia to forestall any complications that may lead to lifelong residual defects or even death among new-borns in this locality. **Methods**: From a total of 374 newborns at birth, 35 (9.4%) newborns developed thrombocytopenia and served as cases while, 339 (90.6%) were non-thrombocytopenic newborns and served as controls for this study between April 2016 and November 2016. Platelet count was determined on cord blood immediately after delivery using Sysmex KX-21N auto-haematology analyzer. Platelet count from the analyzer correlated with the estimated platelet count from the peripheral blood film evaluation. **Results:** Incidence of twin delivery (33.3%) was higher among the risk factors associated with neonatal thrombocytopenia. Twin gestation was significantly associated with neonatal thrombocytopenia (P = 0.0062). **Conclusion:** New-borns from mothers with multiple pregnancies should be thoroughly evaluated for any possible complications of thrombocytopenia at birth to reduce perinatal morbidity and mortality.

Keywords: Neonatal thrombocytopenia, maternal and neonatal risk factors.

***Correspondence:** adjekukocollins27@gmail.com; +2348037111026; ORCID: 0000-0003-3619-4591

Author's contributions:
This work was conducted and approved in collaboration between all the authors, who takes responsibility for its accuracy and integrity. ACO and EEA designed the study; ACO and EEA sourced for funding; ACO and EMA wrote the protocol; ACO, EEA and OHB contributed in literature search; ACO and EEA did the lab experiments; ACO and JZA did statistical analysis; ACO, EEA and EMA drafted the manuscript; EMA, OHB and JZA supervised the study; ACO, EEA Wrote the final manuscript; All authors proofread the final manuscript for publication.

Received: Jan/10, 2021; **Accepted**: Mar/03, 2021; **Published**: Mar/28, 2021.

Citation: Adjekuko CO, Etim EA, Emokpae MA, Osadolor HB, Jeremiah ZA**.** Evaluation of Some Maternal and Neonatal-Associated Risk Factors in Early On-Set Neonatal Thrombocytopenia in Delta State, Nigeria. **J Med Lab Sci, 2021; 31 (1): 1-9**

INTRODUCTION

There is a growing concern on the increasing prevalence of neonatal thrombocytopenia at birth. A recent study in Nigeria indicates a higher prevalence of thrombocytopenia (9.4%) among newborns at birth [1] compared to previous incidence of 0.9% thrombocytopenia at birth [2]. However, Sharma and Thapar [3] reported a prevalence of thrombocytopenia to be between 1% and 5% among high-risk neonates in Sri Lanka.

Thrombocytopenia in a newborn of any viable gestational age is defined as a platelet count less than 150×10^9/L [4, 5] and this may present within 72 hours of birth (early on-set thrombocytopenia) or 72 hours after birth (late on-set thrombocytopenia).

In evaluating neonatal thrombocytopenia, the clinical presentation of newborn; the severity of thrombocytopenia; the underlying mechanism responsible for thrombocytopenia (consumption, increased destruction, decreased production) and the maternal as well as the neonatal risk factors are important considerations. [6]

Maternal risk factors such as pregnancy-induced hypertension, premature rupture of membrane, multiple gestations, pre-eclampsia, intrauterine growth restriction (IUGR) may predispose new-borns to developing early on-set thrombocytopenia [7].

Full-term newborns are those with gestational age of 37 - 42 weeks and birth weight of 2.5 - 4.0kg [8] while preterm newborns are those with gestational age below 37 weeks and birth weight less than 2.5kg. The gestational ages are determined by the last menstrual period according to mother's statement and record of ultrasound estimation. Low birth weight newborns (LBW) are those weighing less than 2.5kg [9], while birth asphyxia are babies born with Apgar score less than 8 at 5 minutes. Pregnant women with pre-eclampsia are those with hypertension (systolic pressure elevated above 140 mmHg and diastolic greater than 90 mmHg) and proteinuria appearing for the first time after 20 weeks gestation [10].

There is however paucity of information on risk factors associated with neonatal thrombocytopenia at birth in our setting. This study therefore, seeks to evaluate some maternal and neonatal risk factors associated with thrombocytopenia at birth in Delta State, Nigeria to minimise complications associated with neonates.

MATERIALS AND METHODS

Study population

This is a cross-sectional study conducted on 374 apparently healthy neonates at birth in Central Hospital, Warri and Federal Medical Centre, Asaba, Delta State, Nigeria between April 2016 and November 2016.

The clinical and provisional diagnosis was provided by the attending consultant paediatrician and the consultant gynaecologist attached to the labour ward. Characteristics of the studied population included newborns at birth with platelet counts less than 150×10^9/L (thrombocytopenia) and were considered cases while those with platelet counts of $\geq 150\times10^9$/L (non-thrombocytopenia) were considered as controls.

Ethical Approval

The study was approved by the ethics committees of Federal Medical Centre, Asaba and Central Hospital, Warri (FMC/ASB/28, 20th April, 2016; CHW/ECC VOL1/095, 4th August, 2016) while,

informed consent was obtained from the mothers of every newborn prior to delivery and before specimen collection.

Sample collection and processing

Five millilitres (5mL) of cord blood was collected from the umbilical cord of every neonate using vacutainer, immediately after delivery by a trained hospital phlebotomist attached to the labour room, and dispensed into ethylene di-amine tetra-acetic acid (EDTA) container and mixed. Platelet counts and mean platelet volume were analysed within 3 hours of sample collection at the hospital medical laboratory, according to the manufacturer's instruction using haematology auto-analyser model Sysmex KX-21N, manufactured by Sysmex Corporation, Kobe, Japan. Platelet count from the analyzer correlated with the estimated platelet count from the peripheral blood film stained by Leishman staining technique [10]. The examination of the thin blood film was to rule out platelet clumping that may result in pseudo-thrombocytopenia.

Statistical analysis

The association between risk factors and neonatal thrombocytopenia was determined by Chi-square test using the statistical software INSTAT® (Graph Pad Inc., La Lolla, CA, USA). The level of significance was set at $p < 0.05$.

RESULTS

Out of the 374 newborns studied, 35 (9.4%) had thrombocytopenia (platelet count $\leq 150 \times 10^9$/L) while 339 (90.6%) newborns were not thrombocytopenic (platelet count above 150 $\times$ 10^9/L). Among the 35 newborns with thrombocytopenia, 19 (54.2%) had mild thrombocytopenia (platelet count 100 – 150 $\times$ 10^9/ L) while 16 (45.7%) had moderate thrombocytopenia (platelet counts 50 – 99 $\times$ 10^9/L). No severe thrombocytopenia (platelet count below 50 $\times$ 10^9/L) was recorded in this study.

Table 1.0 shows the incidence of pregnancy induced hypertension (21.4%), low birth weight (19.4%), birth asphyxia (25.0%), premature rupture of membrane (22.2%), twin delivery (50%), placenta abruption (20.0%), preterm delivery (9.6%), pre-eclampsia (25.0%) and other unidentified risk factors (2.6%) as probable risk factors for neonatal thrombocytopenia. The incidence of twin delivery was higher, followed by preeclampsia and birth asphyxia among the risk factors studied.

The associations between pregnancy induced hypertension, low birth weight, birth asphyxia, premature rupture of membrane, placenta abruption, preterm delivery, pre-eclampsia and other unidentified risk factors and neonatal thrombocytopenia in the study population was not statistically significant ($p > 0.05$) as shown in table 2.0. However, there was a statistically significant association between twin delivery and neonatal thrombocytopenia ($p = 0.0062$).

In table 3.0, the incidence of maternal and neonatal risk factors associated with severity of neonatal thrombocytopenia are shown. The incidence of twin delivery (33.3%) was significantly higher among newborns with moderate thrombocytopenia (platelet count between 50 – 100 $\times$ 10^9/L), while pre-eclampsia (25.0%) was significantly higher among newborns with mild thrombocytopenia (platelet count between 100-150 $\times 10^9$/L). However, case of severe thrombocytopenia (platelet count $<50 \times 10^9$ /L) was not observed in this study.

Table 1.0: Incidence of maternal and foetal clinical conditions associated with neonatal thrombocytopenia.

Maternal and neonatal risk factors	Number of subjects (n)	Neonatal thrombocytopenia n (%)
Pregnancy induced hypertension	14	3 (21.4)
Low Birth Weight (LBW)	36	7 (19.4)
Birth Asphyxia	16	4 (25)
(PROM)	9	2 (22.2)
Twin Delivery	6	3 (50.0)*
Placenta Abruption	5	1 (20.0)
Preterm	94	9 (9.6)
Pre-eclampsia	4	1 (25.0)
Unidentified causes	190	5 (2.6)

KEY: PROM= Premature Rupture of Membrane

Table 2.0: Association of maternal and neonatal risk factors with neonatal thrombocytopenia

Maternal and neonatal risk factors	Category	Thrombocytopenia $\leq 150\times10^9$/L n(%)	Non-thrombocytopenia $> 150\times10^9$/L n (%)	χ^2	p-value
Pregnancy-Induced Hypertension	Present	3 (8.6)	11 (3.2)	1.238	0.2658
	Absent	32 (91.4)	328 (96.8)		
Pre-elampsia	Present	1 (2.9)	3 (0.9)	0.04705	0.8283
	Absent	34 (97.1)	336 (99.1)		
Birth Weight	Low	7 (20.0)	29 (8.6)	3.552	0.0595
	Normal	28 (80.0)	310 (91.4)		
Birth asphyxia	Present	4 (11.4)	12 (3.5)	3.087	0.0789
	Absent	31 (88.6)	327 (96.5)		
Twin gestation	Present	3 (8.6)	3 (0.9)	7.504	0.0062*
	Absent	32 (91.4)	336 (99.1)		
Gestational age	Preterm	9 (25.7)	85 (25.0)	0.006917	0.9337
	Full term	26 (74.3)	254 (75.0)		
Premature rupture of membrane	Present	2 (5.7)	7 (2.1)	0.5807	0.4460
	Absent	33 (96.3)	332 (97.9)		
Placenta abruptio	Present	1 (2.9)	4 (1.2)	0.002460	0.9604
	Absent	34 (97.1)	335 (98.8)		

*significant

Table 3.0: Incidence of maternal and neonatal risk factors according to severity of neonatal thrombocytopenia.

Maternal and neonatal risk factors	Moderate $50\text{-}100\times10^9$/L n (%)	Mild $100\text{-}150\times10^9$/L n (%)	Normal $>150\times10^9$/L n(%)
Pregnancy induced hypertension	2 (14.3)	1 (7.1)	11 (78.6)
Low birth weight	5 (13.9)	2 (5.6)	29 (80.5)
PROM	0 (0)	2 (22.2)	7 (77.8)
Twin Delivery	2 (33.3)	1 (16.7)	3 (50.0)
Placental Abruption	0 (0)	1 (20)	4 (80.0)
Birth Asphyxia	3 (18.8)	1 (6.3)	12 (75.0)
Preterm delivery	6 (6.4)	3 (3.2)	85 (90.4)
Pre-eclampsia	0 (0)	1 (25.0)	3 (75.0)
Unidentified causes	1 (0.5)	4 (2.1)	185 (97.4)
Total	19 (5.1)	16 (4.3)	339 (90.6)

DISCUSSION

Maternal risk factors such as pregnancy-induced hypertension, premature rupture of membrane, multiple gestations, pre-eclampsia may predispose new-borns to developing early on-set thrombocytopenia. However, neonatal risk factors include, birth asphyxia, intra uterine growth restriction and sepsis [6, 7]. Pregnancy-induced hypertension (PIH) and pre-eclampsia are complications following pregnancy, and could cause neonatal thrombocytopenia as a result of foetal hypoxia having direct depressant effects on megakaryocyte [12] or due to disorders associated with placental insufficiency [13, 14]. This study has shown that 21.4% of neonates born to mothers with pregnancy-induced hypertension developed neonatal thrombocytopenia which is similar to the reports of Bhat *et al.* [15] who observed that 36% of neonates born to mothers with PIH had neonatal thrombocytopenia. However, pregnancy induced hypertension from our study was not significantly associated with neonatal thrombocytopenia at birth. However, this is in contrast with the study of Sharma and Thapar, [3] who reported a significant association between PIH and thrombocytopenia. The reason for the difference remains unclear, however, our study was on new-borns at birth while, Sharma and Thapar [3] investigated high risk new-borns in the neonatal intensive care unit (NICU).

Pre-elampsia is a maternal risk factor associated with neonatal thrombocytopenia. The mechanism

of neonatal thrombocytopenia resulting from maternal pre-eclampsia may be attributed to a possible disruption of the haematopoietic progenitor cell commitment to megakaryopoiesis [13]. In this study, the incidence of pre-eclampsia as a risk factor was higher among newborns with mild thrombocytopenia (Table 3.0). This is in agreement with the study by Mouna *et al*., [10] who reported a higher incidence of neonatal thrombocytopenia among pre-eclamptic mothers. They attributed it to a pathology that arises at the placental level, in which thrombocytes gets attached to endothelial cells which are damaged due to segmental vasoconstriction and dilatation of the blood vessel in the placenta of pre-eclamptic mothers leading to thrombocytopenia. Other studies have also shown that, the severity as well as the duration of hypertension plays a vital role in influencing the platelet counts of babies born to mothers with gestational hypertension, preeclampsia and eclampsia syndrome [12]. However, our study did not determine the duration or severity of these risk factors. Therefore, more studies need to be done to verify these assertions.

Low birth weight infants have been associated with thrombocytopenia from previous studies [16, 17]. This agrees with our study, where 19.4% low birth weight newborns developed thrombocytopenia. However, low birth weight was not significantly associated with neonatal thrombocytopenia at birth. This finding is in agreement with the earlier report of Sharma and Thapar [3] which showed that low birth weight was not significantly associated with thrombocytopenia ($p = 0.471$). In contrast with our findings, Nadkarni *et al.* [18] found thrombocytopenia to be significantly associated with low birth weight while Tirupathi *et al*. [19] reported that low birth weight was significantly associated with moderate to severe thrombocytopenia.

Our study has revealed that 25% of newborns with birth asphyxia developed thrombocytopenia. This is in agreement with the findings of Nadkarni *et al*. [18] who reported that, a quarter of asphyxiated babies in NICU developed thrombocytopenia and Castle *et al*. [20] who observed that thrombocytopenia occurs more frequently among neonates with history of birth asphyxia than in non-asphyxiated neonates while, Jeremiah and Oburu [17] observed severe birth asphyxia as the most common provisional diagnosis among thrombocytopenic neonates. The study has further shown that, birth asphyxia was not significantly associated with neonatal thrombocytopenia, and this is in agreement with the findings of Phelan *et al*. [21] and Tirupathi *et* al. [19] who revealed that, thrombocytopenia was inconsistent with acute birth asphyxia and therefore, not a sensitive marker in cases of a mild degree of acute asphyxia. Our result is however in contrast with Sharma and Thapar [3] who observed perinatal asphyxia to be significantly associated with neonatal thrombocytopenia. The reason for the contrast is unclear, but severity and duration of birth asphyxia may influence the degree of thrombocytopenia. One of the limitations is that our study did not determine the severity of birth asphyxia among newborns.

Twin delivery may cause neonatal thrombocytopenia following impaired platelet production secondary to tissue hypoxia, slow spleen blood flow and decreased plasma fraction with normal concentrations following inter-twin placental transfusion before or during delivery [22, 23]. Twin delivery was significantly associated with neonatal thrombocytopenia in this study. This is in contrast with the report of Sharma and Thapar [3]. The reason for the contrast is however unclear.

This study also showed that 9.6% of preterm babies developed thrombocytopenia at birth. This is however in contrast with the report by Nadkarni *et al*. [18] who reported more frequencies of thrombocytopenia among preterm babies in NICU. The reason for the difference may be due to differences in population of newborns studied. In this study, newborns sampled at birth exhibited early on-set thrombocytopenia occurring within 72 hours of birth while, Nadkarni *et al*. [18] reported on newborns sampled after three days of birth and exhibits late on-set thrombocytopenia occurring after 72 hours of birth. Our report of low frequency of preterm developing thrombocytopenia is also in contrast with the studies by Sharma and Thapar [3] who reported a frequency of 58.2% newborn preterm babies who

developed thrombocytopenia. The difference may again be attributed to the different population of babies studied. Our study was on apparently healthy newborns at birth while Sharma and Thapar [3] studied high risk newborn in NICU.

Premature rupture of the membrane (PROM) and placenta abruption were not significantly associated with neonatal thrombocytopenia at birth in our study.

CONCLUSION

There was significant association of twin delivery with neonatal thrombocytopenia at birth. While, pregnancy induced hypertension, pre-eclampsia, birth weight, birth asphyxia, gestational age, premature rupture of membrane and placenta abruption showed no significant association with neonatal thrombocytopenia. New-borns from mothers with multiple pregnancies should be thoroughly evaluated for any possible complications of thrombocytopenia at birth to reduce perinatal morbidity and mortality.

FINANCIAL SPONSORSHIP

This study was not sponsored. The equipment used was provided by the hospitals in which this work was conducted.

ACKNOWLEDGEMENT

The authors are very grateful to management and staff of Federal Medical Centre, Asaba and Central Hospital, Warri for providing the enabling environment and equipment for the research work.

REFERENCES

1. Adjekuko CO, Emokpae MA, Osadolor HB, Jeremiah ZA. Prevalence of thrombocytopenia among apparently healthy newborns in Delta state, Nigeria. New Zeal J Med Lab Sci. 2018; 72(2).
2. Dreyfus M, Kaplan C, Verdy E, Schlegel N, Durand-Zaleski I, Tchernia G. Frequency of immune thrombocytopenia in newborns: a prospective study. Immune Thrombocytopenia Working Group. Blood 1997; 89 (12): 4402–4406.
3. Sharma A, Thapar K. A prospective observational study of thrombocytopenia in high risk neonates in a tertiary care teaching hospital. Sri Lanka J Child Health. 2015; 44(4):213-219.
4. Kotwal J. Approach to neonatal thrombocytopenia: Immature platelet fraction has a major role. Med J Armed Forces India. 2011; 67(3): 212-214.
5. Veneri D, Franchini M, Randon F, Nichele I, Pizzolo G, Ambrosetti A. Thrombocytopenias: A clinical point of view. Blood Transfus. 2009; 7(2):75-85.
6. Eslami Z, Lookzadeh MH, Noorishadkam M, Hashemi A, Ghilian R, Pirdehghan A. Thrombocytopenia and Associated Factors in Neonates Admitted to NICU during Years 2010_2011. Iran J Pediatr Hematol Oncol. 2013; 3(1):205-20515.
7. Robert I, Murray NA. Neonatal thrombocytopenia. Diagnosis and management. Arch Dis Child Fetal Neonatal. 2007; 88: 359-364.
8. Adewumi A, Titilope A A, Akinsegun AA, Abidoye G, Ebele U, Sulaimon AA. Cord blood full blood count parameters in Lagos, Nigeria. Pan Afr Med J. 2014; 17:192.
9. Gupta A, Mathai SS, Kanitkar M. Incidence of thrombocytopenia in the neonatal intensive care unit. Med J Armed Forces India. 2011; 67(3):234-236.
10. Mouna K, Doddagowda SM, Junjegowda K, Krishnamurthy L. Changes in hematological parameters in newborns born to preeclamptic mothers - A case control study in a rural hospital. J Clin Diagnostic Res. 2017; 11(7):
11. Bajpai R, Rajak C, Poonia M. Platelet estimation by peripheral smear : Reliable, rapid, cost-effective method to assess

degree of thrombocytopenia. 2015; 2(2):2013-2016.
12. Sunil KP, Haricharan KR. Neonatal thrombocytopenia associated with gestational hypertension, preeclampsia and eclampsia: a case-control study. Int J Contemp Pediatr. 2016;3(1):16-21.
13. Wong W, Glader B. Approach to the newborn who has thrombocytopenia. Neoreviews. 2004; 5: 444-450.
14. Chakravorty S, Murray N, Roberts I. Neonatal thrombocytopenia. Early Hum. Dev. 2005; 81: 35-41.
15. Bhat YR, Cherian CS. Neonatal thrombocytopenia associated with maternal pregnancy induced hypertension. Indian J Paediatr.2008; 75: 571-573
16. Beiner ME, Simchen MJ, Sivan E, Chetrit A, Kuint J, Schiff E. Risk factors for neonatal thrombocytopenia in preterm infants. Am J Perinatol. 2003; 20(1):49-54.
17. Jeremiah Z, Oburu JE. Pattern and prevalence of neonatal thrombocytopenia in Port Harcourt, Nigeria. Pathol Lab Med Int. 2010; 27.
18. Nadkarni J, Patne S, Kispotta R. Hypoxia as a predisposing factor for the development of early onset neonatal thrombocytopenia. J Clin Neonatol. 2012; 1(3):131. 2249-4847
19. Tirupathi K, Swarnkar K, Vagha J. Study of risk factors of neonatal thrombocytopenia. Int J Contemp Pediatr. 2016; 4(1):191.
20. Castle V, Andrew M, Kelton J, Giron D, Johnston M, Carter C. Frequency and mechanism of neonatal thrombocytopenia. J Pediatr. 1986; 108 (5):749-55.
21. Phelan JP, Kirkendall C, Korst LM, Martin GI. Nucleated red blood cell and platelet counts in asphyxiated neonates sufficient to result in permanent neurologic impairment. J Matern-Fetal Neonatal Med.2007; 20(5): 377-380.
22. Lopriore E, Slaghekke F, Oepkes D, Middledrop JM, Vandenbussche FP, Walther FJ. Haematological characteristics in neonates with twin anemia-polycythemia sequence. Prenat Diagn. 2010; 30: 251-255.
23. Sarkar S, Rosenkrantz TS. Neonatal polycythemia and hyperviscosity. Semin Fetal Neonat Med. 2008; 13: 248–255