Hematological profile derangement in newborns as an outcome of hypertensive disorders of pregnancy.

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Research note

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Abstract

Objectives This study aimed at determining the changes of hematological parameters in newborns of mothers with HDP compared to normotensive mothers.Results This was a hospital-based comparative cross-sectional study conducted from December 2017 to May 2018. The study groups consisted of 70 normotensives and 73 hypertensive pregnant women as a comparison and index group respectively. The male to female ratio for the newborns was 1:1. Newborns of the hypertensive mothers had a lower birth weight, lower APGAR score and had a lower median gestation age at the time of birth compared to the newborns of normotensive mothers (P < 0001). White blood cell and differential counts were lower in cord blood of the newborns of HDP group than in the normotensive group (P≤0.001). Approximately 50% of newborns of hypertensive mothers had thrombocytopenia. Furthermore, hypertensive disorders of pregnancy were found to independently predict neutropenia [OR=6 (2.1 – 19.4), p<0.05] and thrombocytopenia [OR=4.3(1.7 – 11.1), p<0.001] in the newborns.

Background

Hypertensive disorders of pregnancy (HDP) are multi-system disorders which not only have effects on pregnant mothers but they also affect their newborns. The fetus and newborn of a woman with HDP is at risk of intrauterine growth restriction, placental hypoxia and being small for gestational age which is thought to be a result of utero-placental insufficiency (1) . In HDP, delivery is the most favorably considered option to avert the progression of the condition and to save mother and child (2), as the definitive treatment of HDP remains unknown. However, this decision subjects the newborns to unfavorable outcomes such as premature deliveries, high rate of operative delivery, low birth weight (LBW) , low APGAR score and worst of all: a high mortality which is over 300 per 1000 live births in low-income countries (3)

Derangement of hematological parameters is among the complications suffered by neonates of HDP mothers with neutropenia and thrombocytopenia being the most commonly reported hematological derangements in newborns. As a consequence, these newborns have an increased susceptibility to bleeding disorders and infections compared to newborns of normotensive pregnant women (2,4,5).

Differences have been reported in the hematological parameters of newborns of hypertensive and normotensive mothers. These differences are mainly seen in Hemoglobin, neutrophil, red cell distribution width (RDW), packed cell volume (PCV) mean cell volume (MCV), red cell count and platelet counts (6). However, findings from different studies are not consistent with each other, probably due to variations in ethnicity, nutrition, genetic and environmental factors (7). It is not known to what extent these differences exist in Tanzania. Therefore, the aim of this study was to determine the changes in hematological parameters in newborns of mothers with HDP compared to normotensive mothers.

Methods

Study design, settings and participant's recruitment.

This was a hospital-based comparative cross-sectional study conducted from December 2017 to May 2018. The study groups consisted of 70 normotensives and 73 hypertensive pregnant women as a comparison and index group respectively. All pregnant women in the first stage of labor, who consented to participate in the study, were recruited from maternity wards of Amana regional referral hospital and the Muhimbili National Hospital in Dar-es-salaam. Pregnant women with history of blood transfusion in the current pregnancy and/or pre-existing chronic diseases such as heart failure, hypertension, diabetes and renal failure, were excluded from the study

Amana hospital where most of the neonates born to normotensive mothers were recruited from is in Ilala district and is among three governments regional referral Hospital in Dar es Salaam Region. The Hospital acts as a regional referral from 18 lower government-owned health facilities, and 145 private health facilities. It has maternity wards with 110 beds (including Neonatal unit). Whenever needed the patients, including complicated maternal cases from ARH are referred to MNH

Muhimbili National Hospital (MNH) where most of the neonates born to hypertensive mothers were recruited caters to a population of over five million Dar es Salaam residents (according to NBS 2017 data) and neighboring coastal regions. MNH is a national referral hospital, also serves as a teaching hospital for Muhimbili University of Health and Allied Sciences (MUHAS). It has a special pre-eclampsia/eclampsia ward with a capacity of 15-beds, to which patients with HDP are admitted.

Procedures and data collection

Participants' data on socio-demographic characteristics, blood transfusion history, parity, blood pressure, gestational age, and number of missed pregnancies were collected. Data were obtained through structured questionnaires and/or by extracting information from antenatal clinic cards and the hospital files.

Three mls of cord blood was drawn into a 5ml vacutainer tube containing 0.5ml of tri-potassium ethylene-di-amine tetra acetic acid (K3EDTA) during delivery. Full blood count was done using Abbott Cell dyne 3700 at the Central Pathology Laboratory in MNH which is ISO 15189 accredited

In this study, neutrophil count of <1500 was considered as neutropenia, platelet count of <150 X 10^{9}/L - thrombocytopenia, hematocrit value of < 40% - anemia, LBW was considered as <2500g and birth of < 37 weeks was considered premature.

Data Analysis

The data was analyzed using SPSS version 23; Continuous variables were checked for normality. Differences in hematological parameters were compared between the HDP and normotensive groups using Student's independent t-test and Mann–Whitney U-test when the data were normally and abnormally distributed respectively.

Logistic regression analysis was used to assess the association between newborns hematological parameters and the hypertensive disorders after controlling for birth weight and prematurity. Odds ratios and confidence intervals were used to present. A p-value of < 0.05 was considered to be statistically significant

Results

Demographic, socio-economic and clinical characteristics of Newborns mothers

A total of 143 study participants were recruited. Median age of the participants was 26 years. Mothers in the hypertensive group were significantly younger than their normotensive counterparts (P= 0.025). Approximately half (70) of the participants had a secondary school education and above. The median systolic and diastolic blood pressure were significantly higher in hypertensive pregnant women (P <0.001) (Table 1).

The male to female ratio for the newborns was 1:1. Newborns of the hypertensive mothers had a lower birth weight, lower APGAR score and had a lower median gestation age at the time of birth compared to the newborns of normotensive mothers (P < 0001) (Table 1).

Hematological parameters of newborns of hypertensive and normotensive mothers

White blood cell and differential counts were lower in cord blood of the newborns of HDP group than in the normotensive group (P≤0.001), with median total white cell count and median absolute neutrophil count showing a 50% reduction. This difference was not observed in the monocytes (Table 2, additional file 1). The same trend is observed in the platelet count, where newborns of the hypertensive mothers had a significantly lower mean platelet count (161x10⁹/L) compared to newborns from normotensive mothers (241x10⁹/L).

The median RBC count and HCT were lower in newborns of the hypertensive group compared to the normotensive group, whilst RDW and MCHC were significantly higher in the hypertensive group as compared to the normotensive group. No significant differences were observed in Mean Hb, MCV and MCH parameters (Table 2, Additional file 1).

Univariable and multivariable regression of the factors associated with newborns hematological parameters

Results for univariate and multivariate analysis on the three factors that were measured for association are summarized on table 3. After adjusting for prematurity and LBW, newborns of hypertensive mothers were still more likely to have neutropenia at birth [OR=6 (2.1 – 19.4), p<0.05] Both LBW and prematurity

were also found to be positively associated with neutropenia on univariate analysis, but after adjusting for the other factors, newborns with a LBW were found to be 5 times more likely to have neutropenia [OR=4.5(1.4-14.8), p<0.05] than those born with a normal birth weight.

The adjusted OR for association between maternal hypertension and thrombocytopenia, showed that maternal hypertension was strongly associated with thrombocytopenia in the newborn [OR=4.3(1.7 – 11.1), p<0.001]. No significant association was found with LBW or prematurity. There was no association found between maternal hypertension and a low haematocrit in the newborn. However, newborns born prematurely were found to be 6 times more likely to have a low haematocrit at birth [OR=6.1(1.6-23), p<0.05] compared to newborns born at term.

Discussion

We have observed that newborns of the hypertensive mothers had lower median birth weight, lower median Apgar score and were delivered prematurely. A significant difference was also observed in the cord blood hematological parameters of newborns of mothers with HDP compared to normotensive mothers

Low birth weight and premature delivery

In the present study, newborns of hypertensive mothers had a significantly lower median birth weight compared to newborns of normotensive mother. The findings are consistent with those of previous studies whereby HDP's was found to be a risk factor for LBW. This is due to utero-placental failure which consequently causes poor fetus nourishment in the womb (2,4).

Hypertensive disorder of pregnancy is a risk factor for indicated premature delivery. This explains the observed, low median gestation age at delivery in hypertensive mothers of our study. This is similar to findings from a study by Elgari et al (8) The positive association of LBW and premature delivery with neutropenia that was observed in this study is also consistent with other studies: which reported that neonatal stage of maturation and development, specifically VLBW is associated with neutropenia (9,10).

Poor neonatal granulocyte production as an outcome of maternal hypertensive disorder of pregnancy

In our study newborns of the hypertensive mothers had statistically and clinically significant lower median neutrophil count when compared to their normotensive counterpart. The prevalence of neutropenia was 50% and 9.8% in cord blood of newborns of hypertensive and normotensive mothers respectively. This is similar to other studies done in both Africa Asia and Europe (10–12). Among the neutropenic cases, more than half (55%) had severe neutropenia; Moreover, to the best of our knowledge the observed median neutrophil count in our HDP population is the lowest compared to those observed elsewhere. The reason as to why the neutrophil count is lowest in our population remains as the subject for future studies.

Neonatal neutropenia due to HDP can be self-limiting in less than 60 hours after birth; however, higher risk of nosocomial and other infections is also present in these newborns as neutropenia is known to independently predict sepsis. The risk is known to be there even after normal neutrophil levels has been attained (13). Neonatal neutropenia due to hypertensive disorders may be explained by several mechanisms such as:- a) Inhibition of fetal production of neutrophils by unidentified inhibitor which is present in cord blood serum of newborns of hypertensive mothers (9), b)Reduced numbers of circulating colony-forming unit-granulocyte macrophage (CFU-GM) and reduced neutrophil storage pools (14), c) Interaction of Fas to Fas ligand for apoptosis activation which cause the presence of raised Fas associated protein in the mother and infant. Fas associated proteins are associated with both chronic and congenital neutropenias (15,16), d) Shift into direction balance of erythropoiesis more than granulopoiesis due to placenta hypoxia which induce stem cell favoring the earlier and as a result dysgranulopoiesis's develops (17)

We found significantly low count in other granulocytes (basophil & eosinophil) and consequently leukopenias in cord blood of hypertensive mother's newborns as compared to normotensive mother's, These findings are similar to findings by Bolat et al (4). We anticipate that the above-mentioned mechanisms can also be used to explain the difference observed in these other granulocytes.

Neonatal thrombocytopenia due to hypertensive disorders of pregnancy

Newborns of hypertensive mothers had low median platelet count compared to newborns of normotensive mothers. Moreover, thrombocytopenia prevalence was 50% and 18.3% in newborns of hypertensive and normotensive mothers respectively. Similar findings have also been reported by other studies (2,4,18).

This is attributed to placental dysfunction and hypoxia which results in impairment of platelet production by several mechanisms such as a) Adherence of thrombocyte to the damaged endothelial region caused by segmental vasospasm and vasodilatation in the placenta of hypertensive mothers(19,20) b) Undefined factor which leads to DIC which is said to be transported to the baby by the placenta and cause thrombocytopenia in the newborn (19). (c) Depression of megakaryocyte proliferation due to placental hypoxia as a consequence of hypertension (21)

Conclusions

Newborns of hypertensive mothers are more likely to be premature and to have a low birth weight. They are at higher chances of neutropenia (which may be severe) and thrombocytopenia. It is therefore important that these hematological parameters are tested. Following up these newborns in cohort studies may give us more insight in the progression of these derangements that can further guide management and establish whether there is a need to institute screening all neonates born to hypertensive mothers for neutropenia and thrombocytopenia

Limitations

This study was limited in that it was cross-sectional: therefore, we cannot elaborate how our findings will correlate with the clinical course of newborns with deranged hematological profiles.

Abbreviations

BMI– Body Mass Index

CFU-GM - Colony-forming unit-granulocyte macrophage

DIC- Disseminated intravascular coagulation

EDTA – Ethylene-diamine-tetra-acetic Acid

GH – Gestational Hypertension

Hb – Hemoglobin

HDP – Hypertensive Disorders of pregnancy

IUGR – Intrauterine Growth Retardation

LBW- Low birth weight

MCH – Mean Cell Hemoglobin

MCHC – Mean Cell Hemoglobin concentration

MCV – Mean Cell Volume

MNH – Muhimbili National Hospital

MUHAS – Muhimbili University of Health and Allied Sciences

PE- Pre-eclampsia

PLT – Platelet

RDW – Red cell distribution width

SPSS – Statistical Package for Social Sciences

WBC – White Blood Cell

WHO –World Health Organization

Declarations

Ethics approval and consent to participate

This study was ethically cleared by MUHAS senate research and publication committee (SRPC) with reference number 2017-05-24/AEC/Vol.XII/71. Permission to collect data was issued by Muhimbili National hospital directorate of research. All participants were asked for and signed informed consent form before they were included in the study.

Consent to publish

Not Applicable

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no competing conflict of interest. The authors alone are responsible for the content and writing of the paper.

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Author's contributions

YSM initiated and designed the study, collected and analyzed the data and wrote the paper.CCC participated in laboratory data review, and manuscript writing. MAL Participated in proposal writing and supervised data collection and manuscript writing. SNM participated in proposal writing, supervision in data collection, Data analysis and paper writing. All authors reviewed and approved the final manuscript for submission

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Tables

Table 1: **Demographic, socio-economic and clinical characteristics of study participants**

Variable	All	Hypertensive	Normotensive	P value
Overall		**N=70(50%)**	**N=73(50%)**	
Median age (SD)	26	24.3(23.5,32.7)	28.1(21.5,31.3)	0.023
Education	**N=143**			0.014
Primary and below n (%)	73 (100)	34(46.6)	39(53.4)	
Secondary n (%)	59(100)	26(44.1)	33(55.9)	
College n (%)	11 (100)	10(90.9)	1(9.1)	
Marital status	**N=142**			0.014
Married n (%)	130 (100)	60(46.2)	70(53.8)	
Single n (%)	12 (100)	10(83.3)	2(16.7)	
Employment	**N=140**			0.006
Formal work n (%)	21 (100)	16 (76.2)	5 (23.8)	
Self employed (%)	59 (100)	31(52.5)	28(47.5)	
No formal work n (%)	60 (100)	22(36.7)	38(63.3)	
Gravidity	**N=153**			0.297
1 n (%)	65(100)	32(49.2)	33(50.8)	
2+ n (%)	76 (100)	38(50)	38(50)	
Median systolic blood pressure (IQR)	120.0 (99, 235)	147(131,157)	118(113,120)	<0.001
Median diastolic blood pressure (IQR)	78.0 (64.0, 89.0)	92(82,102)	70(60,73)	<0.001
Median Gestational age (IQR)	38.0 (25.0, 39.0)	36(33,39)	39(38,40)	<0.001
Sex of the baby				
Male n (%)	76	36(47.3)	40(52.7)	0.163
Female n (%)	67	34(50.7)	33(49.3)	
Median Birth weight(IQR)	2.9(2.3,3.3)	2.41(1.6,3)	3(2.8,3.35)	<0.001
Median APGAR Score (IQR)	8(8,10)	8(7,8)	10(8,10)	<0.001

Table 2: **Hematological parameters of cord blood from newborns of hypertensive and normotensive mothers**

	Newborns of		
Variable	**Normotensive mother (n=77)**	**Hypertensive mother (n=76)**	***P value**
RBC count and RBC's indices			
Median RBC (IQR)	4.41(4.09,4.75)	4.16(3.7,4.6)	0.014
Mean Hb ± SD	15.06(1.4)	14.6(3.2)	.280
Median MCHC (IQR)	31.8(31.2,32.5)	32(31.5,33.5)	0.004
Mean HCT ± SD	47.7(5.4)	43.38(8.7)	.001
Median MCV (IQR)	108(103,114)	107.5(100.7,114.8)	0.366
Mean MCH SD	34.5(2.2)	35.9(7.3)	.133
Median RDW (IQR)	17.8(16.7,19.5)	18.6(17.1,20.4)	0.047
White blood cell counts			
Median WBC count (IQR)	12.7(9.16,15.3)	6.25(3.99,13.4)	<0.001
Median Neutrophil count (IQR)	6.24(3.7,8.0)	1.58(0.34,3.6)	<0.001
Median Basophil (IQR)	0.161(0.12,0.25)	0.07(0.03,0.26)	0.001
Median Eosinophil count (IQR)	0.16(0.09,0.27)	0.09(0.03,0.17)	<0.001
Median monocytes count (IQR)	0.88(0.58,1.34)	0.8(0.34,1.29)	0.39
Median lymphocyte count (IQR)	4.9(4.3,6)	3.7(2.1,6.03)	0.001
Platelets counts			
Mean platelets count SD	241(94)	161(98.9)	<0.001

Table 3: Univariate and multivariate regression of the factors associated with newborns hematological parameters

	Neutropenia		Thrombocytopenia		Low hematocrit	
	Crude oR, *95% CI*	AoR, 95% CI	Crude oR, 95% CI	AoR, 95% CI	Crude oR, 95% CI	AoR, 95% CI
Hypertensive status	9.1(3.7-22.7)**	6.3(2.1-19.4)*	6.3(2-9)	4.3(1.7-11.1)**	9.1(1.6-11.6)*	2.1(0.6-7.5)
Birth weight	8.2(3.5-18.9)**	4.5(1.4-14.8)*	4.5(1-4.6)	1.6(0.5-4.9)	8.2(1.1-6.6)*	0.5(0.1-1.7)
Gestational age	4.8(2.2-10.7)**	0.8(0.2-2.8)	0.8(0.9-3.8)	0.5(0.2-1.7)	4.8(2.2-14.6)**	6.1(1.6-23)*

AOR= adjusted odd ratio, CI= Confidence interval, **P<0.001, *p<0.05

Supplementary Files

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- Figure1.docx