ANTHROPOMETRIC, HEMATOLOGICAL AND BIOCHEMICAL PREDICTORS OF HYPERTENSIVE DISORDERS OF PREGNANCY AMONG WOMEN IN IFE-IJESA DISTRICT

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ABSTRACT: Background & Objectives: Hypertensive disorders complicate six to 12% of pregnancies. This study is aimed at providing information on the predictive ability of ABO blood group, body mass index (BMI) category and plasma calcium in identifying women at risk of developing hypertensive disorders (HDP) in pregnancy in the study population. **Methods**: a longitudinal study involving 80 pregnant women (divided equally into O, A, B and AB) recruited between 20 and 34 weeksof pregnancy at the Obafemi Awolowo University Teaching Hospitals using homogenous purposive sampling method. They were followed up till delivery or onset of HDP whenvenous blood was obtained from each participant for plasma Calcium analysis using Ion Selective Electrode. BMI was calculated using the Quetelet formula. Chi square test and Pearson correlation were determined as appropriate. **Results and Interpretation:** Seventeen women (21.3%) developed HDPs. Out of the 20 women in each blood group type, 1 (5%), 3 (15%), 6 (30%) and 7 (35%) developed HDP in blood group type AB, O, A and B respectively. The mean total plasma calcium in the group that developed HDP and the normotensive women were 2.19 $\pm$ 0.07mmol/L and 2.43 $\pm$ 0.19mmol/L respectively with no statistically significant difference between them (p=0.226). There was weak negative correlation between the blood pressure at delivery/onset of hypertensive disorder and the total plasma calcium at delivery, with Pearson correlation coefficient (r) of -0.352 (p=0.002) and -0.362 (p=0.001) respectively for SBP and DBP. The risk of HDP increased with BMI category. **Conclusion**: There is potential predisposition of blood group types B>A>O>AB respectively to the development of HDP. Overweight and obese, blood group A or B pregnant women should have closer surveillance for HDP especially in the setting of additional risk factors.

Keywords: hypertension, pre-eclampsia, pregnancy, blood group, body mass index, calcium.

Abbreviations: HDP, Hypertensive disorders of pregnancy; BMI, Body Mass Index; BP, Blood Pressure; DBP, Diastolic Blood Pressure; SBP, Systolic Blood Pressure; OAUTHC, Obafemi Awolowo University Teaching Hospitals Complex.

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INTRODUCTION

Hypertensive disorders of pregnancy (HDPs) contribute significantly to both maternal and perinatal morbidity and mortality. These disorders range from pregnancy-induced hypertension, to proteinuric new onset hypertension in pregnancy - pre-eclampsia; which poses an especially high risk for adverse complications. Hypertensive disorders complicate six to 12% of pregnancies.[1] Pre-eclampsia is the occurrence of gestational hypertension with significant proteinuria after 20 weeks of gestation in a woman with previously normal blood pressure. They are progressive diseases which if not diagnosed and managed appropriatelycould result in fatal consequences.[2]

The prediction of occurrence of HDPs in women at risk affords close surveillance and institution of preventive strategies. It also allows for risk assessment which implies that women at increased risk should be managed at a tertiary health institution well-equipped with facilities for surveillance and intervention. Prediction could be made from the woman's previous medical and obstetric history, examination findings and some investigations.

Historically, family history of hypertension and previous history of HDPs in the woman confer some degree of risk in index pregnancy. Similarly, the incidence is higher in primigravidae and those that are having new partners. On examination, a significant change in blood pressure following a cold-pressor test or roll-over test could be predictive. Investigations could be biophysical or biochemical. Biophysical tests include a notch in the uterine artery doppler waveform in early pregnancy. Serum Calcium, uric acid, Placental Insulin-Like Growth Factor (PIGF) and others like antiphospholipid antibodies, Insulin-like Growth factors, soluble fms-like Tyrosine kinase, Transferrin, Vitamin D could be measured as biochemical markers for prediction. Varying degree of reliability have been found with the available prediction models. Although studies have explored the relationship between blood group and hypertension in the non-pregnant population, the relationship between blood group and occurrence of HDPs in the study population is yet to be explored, hence this study. Similarly, the role of BMI and serum Calcium level.Prediction of women at risk will afford institution of preventive strategies and appropriate surveillance to detect its occurrence at its earliest onset. This study therefore assessed the relationship between the anthropometry (body mass index), biochemical (Plasma Calcium level) and hematological (blood group type) parameters and occurrence of hypertensive disorders of pregnancy.

STUDY DESIGN

The study was a longitudinal study involving 80 consented normotensive pregnant women (divided equally into O, A, B and AB) who were recruited between 20 and 34 weeks of pregnancy at the booking/antenatal clinics of the OAUTHC using homogenous purposive sampling method. Exclusion criteria included pregnant women who did not consent to the study and those with chronic hypertension or chronic kidney disease. Sample size of 80 was obtained after accounting for attrition using the appropriate statistical method.

MATERIALS AND METHODS

Ethical clearance was obtained from the Ethics and Research committee of the OAUTHC (Protocol Number: ERC/2019/09/01). Informed written consent was obtained from willing participants after due counseling. The study was carried out in the Department of Obstetrics, Gynaecology and Perinatology of the OAUTHC. Analysis of plasma calcium was done at the Chemical Pathology department of the same hospital. At recruitment, BP was measured using standard procedures and the BMIwas calculated as the volunteer's weight in kilograms (kg) divided by the square of the height in metres (m) with the unit as kg/m^2 as measured at the first clinic visit while adopting standardized steps for the measurements.

Blood group determination by observation of agglutination on white tiles was done using blood sample obtained for routine booking blood tests. The women were then followed up till delivery or development of HDP and at either of these points, the blood pressure was noted, while the blood sample was also obtained for plasma calcium assay. Laboratory analysis of Calcium level was done using Ion Selective Electrode (ISE) with the aid of GE 300 Electrolyte Analyzer (Shenzhen Genius Electronics Company, China). Data obtained was analyzed using IBM SPSS version 23. Both descriptive and inferential statistical techniques were adopted in data analysis. Frequencies and proportions were generated for categorical data and these were compared using Chi square. Correlation test was done where appropriate and P-value less than 0.05 was taken to be significant.The results were presented in appropriate tables and charts.

RESULTS

The age range of the study participants was between 18 and 39 years with mean of 29.06 ± 5.50 years. About four out of every five participants were within the age bracket of 20 to 35 years with teenagers constituting about 2.5%.The average gestational age at recruitment was 24.2 ± 4.6 weeks with a mean gestational age of 38.1 ± 2.3 weeks at the end of the study. The gestational age at delivery/onset of hypertensive disorder ranged from 29 to 44 weeks.

Out of the 80 study participants, 17 women (21.3%) developed HDPs. Figure 1 is a composite bar chart of the blood pressure pattern at completion of follow-up across the blood group types. Out of the 20 women in each blood group type, 1 (5%), 3 (15%),

6 (30%) and 7 (35%) developed HDP in blood group type AB, O, A and B respectively.

The mean BMI at booking was 27.34 ± 5.22 kg/m^2. The Body Mass Index Distribution is presented in Table 1. Figure 2 depicts the Blood Pressure pattern of the participants (at delivery) across the BMI Categories at Booking.

None of the women had oral calcium supplementation in pregnancy.The total plasma calcium ranged between 2.10mmol/L and 2.75mmol/L with a mean value of 2.38 ± 0.20 mmol/L. The mean total plasma calcium in the group of women that developed HDP was 2.19 ± 0.07mmol/L and ranged from 2.10 to 2.31mmol/L while the mean total plasma calcium in the group of women that remain normotensive was 2.43 ± 0.19mmol/L and ranged from 2.10 to 2.75mmol/L. There was no statistically significant difference in the mean total plasma Calcium in hypertensive and normotensive women (p=0.226).

There was a weak negative correlation between the systolic blood pressure at delivery/onset of hypertensive disorder and the total plasma calcium at delivery, with Pearson correlation coefficient of -0.352 (p=0.002). Similarly, there was a weak negative correlation between the diastolic blood pressure at delivery/onset of hypertensive disorder and the total plasma calcium at delivery, with Pearson correlation coefficient of -0.362 (p=0.001).

Table 2 shows the statistical analysis of the relationship between specific anthropometric, hematological and biochemical parameters and the development of hypertensive disorders of pregnancy.

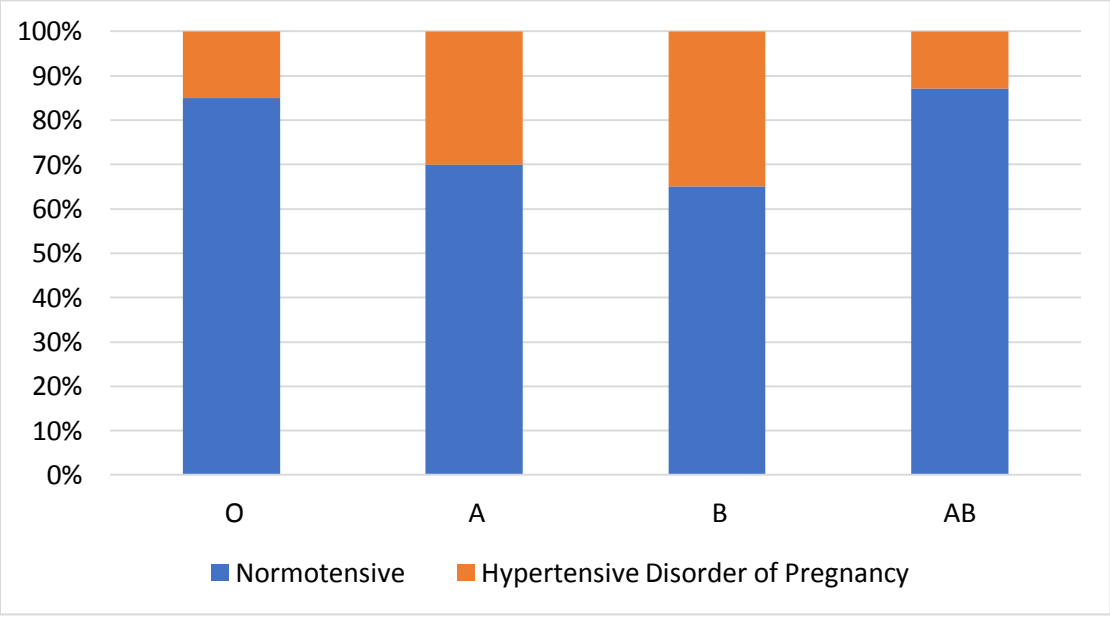

Figure 1. Blood Pressure Pattern of the Participants across the Blood Group types at Delivery.

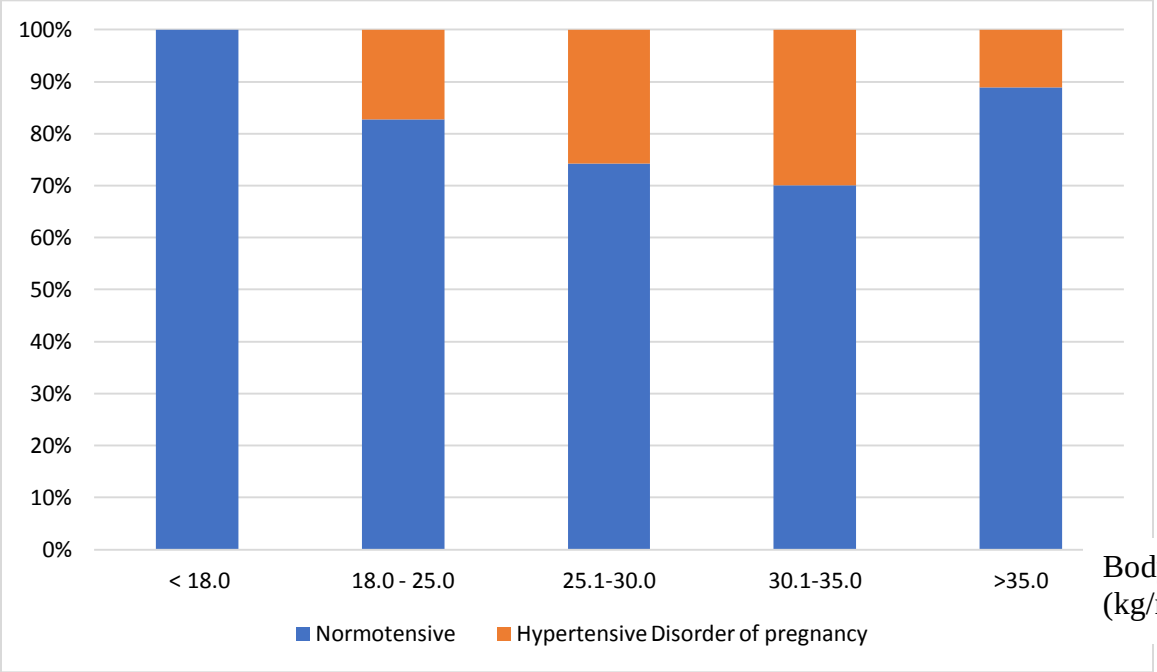

Figure 2. Blood Pressure Pattern of the Participants (at delivery) across the Body Mass Index Categories at Booking.

Table 1

Body Mass Index Distribution of Study Participants at Booking/recruitment

BMI Category (kg/m^2)	Frequency	Percentage (%)
< 18.0	1	1.3
18.0 - 25.0	29	36.3
25.1 – 30.0	31	38.8
30.1 - 35.0	10	12.5
> 35.0	9	11.3
Total	**80**	**100**

Table 2

Relationship between specific parameters and occurrence of hypertensive disorders of pregnancy among study participants

Parameters	**χ2**	**p-value**
Blood Group and Occurrence of Hypertensive disorder	6.797	0.079
BMI Category and Occurrence of Hypertensive disorder	1.943	0.746
Absolute weight and Occurrence of Hypertensive disorder	70.040	0.312
Age and Occurrence of Hypertensive disorder	26.467	0.189
Parity and Occurrence of Hypertensive disorder	2.301	0.806

χ2=Chi square

DISCUSSION

The average gestational age at recruitment into the study (24 weeks) allowed for a reasonable period of follow-up given the mean gestational age at completion of study, being 38 weeks. Being a longitudinal study, which recruited normotensive women ab initio, the findings could be of stronger recommendation profile than previous studies which were cross-sectional studies and therefore prone to multiple confounders including non-consideration of pre-pregnancy blood pressure profile of the women and non-uniform distribution of the blood group types.[3-5]

The prevalence of HDP was 21.3% in this study. This is higher than the global prevalence of six to 12% in previous studies.[1] It is higher than the prevalence of between 5 and 17% reported from different parts of Nigeria. This finding further supports the growing burden of hypertensive disorders. Similarly, the amorphous nature of local prevalence studies could explain the prevalence of hypertensive disorders in the country. While cross-sectional studies reported incidences between 2% and 16.7%, available longitudinal studies which were hospital-based reported incidences as high as 17%, and up to 28.93% in reviews focusing on nulliparous parturients.[6-8]

The occurrence of HDP with each blood group type was in the order of B>A>O>AB with incidence of 35%, 30%, 15% and 5% for blood group B, A, O, and AB respectively as shown in Figure 1. This implies that blood group B carries the highest risk for the development of HDP in the study population with the least risk among the blood group AB individuals. The differences were however not statistically significant as shown in Table 2. This could be explained by the hypothesis that non-O blood groups have higher levels of vWF, a known inciting agent for vascular disorders, in the serum.[9]It however does not explain the observation of AB being the least prone blood group.

In a review of the relationship between types of ABO blood group with hypertensive disorders among pregnant women in Bani Suef Egypt, authors found blood group B to have the highest risk of development of HDP among other blood group types, accounting for 71.5% of all cases. While the study design was cross-sectional, recruited all women who have already developed HDP and grouped them based on ABO blood group type thus generating the proportion of women in each blood group type, the study did not allow for uniform representation of all blood group types. The blood group B was over-represented as it constituted 51.3% of all study participants while blood group A women constituted only 2.9% of all participants. Although the finding of the most susceptible blood group as type B in a study agrees with index research, the equal representation of all blood group types and longitudinal design of index study confer higher reliability and reproducibility.[10]

Of note is the work of Mishra and Pradhan on the association of maternal ABO blood group and HDP among antenatal clinic attendees in Burla. The study found a statistically significant relationship between ABO blood group type and HDP with blood group A having the highest risk when compared with blood group O with a relative risk of 2.02.[11] The study grouped women into unexposed control made up of blood group O individuals, which are known to lack ABO antigens on the surface of the red blood cells; and the exposed group which comprise blood group A, B and AB which have the corresponding ABO antigenic variants on the surface of the erythrocytes. The exposed groups were then compared individually (A, B or AB) with the unexposed group (blood group O) thereby generating the relative risk. The study is however limited by the over-representation of blood group A which accounted for about 42% of the women with hypertensive disorders. This may therefore explain the study findings.

A retrospective case-control study found no statistically significant association between ABO blood group types and risk of Pre-Eclampsia in an Iranian obstetric population. In the review, blood group O showed higher risk of development of HDP with Odds Ratio of 1.0 after adjustment for age of participants and parity. The review, as with previous studies adopted the methodology of non-uniform distribution of blood group types, wherein blood group O individuals constituted half of all the cases and about 44.3% of the controls.[12]

Contrary to index study findings, researchers at Kayseri Turkey in a cross-sectional study reviewing

the relationship between ABO blood group and development of hypertension among newly delivered mothers found that the risk of developing hypertension was significantly higher in blood group AB women than other non-AB blood group mothers. While the rationale for the categorization was not spelt out, blood group AB was under-represented in the study. This is contrary to the index study finding wherein blood group AB had the lowest risk of development of HDP.[13]

Similar to the index research findings, a study evaluating the effect of maternal ABO blood type on birth weight and pre-eclampsia found the highest incidence of HDP among the blood group B category wherein hypertension was recorded at advanced gestation in 9.4% of all women with blood group B as against 8.8% for blood group AB, 7.9% for blood group O and 6.7% for blood group A. Blood group A therefore had the least probability as against blood group AB in index study. These findings were similarly not statistically significant as observed in this study.[14] Hentschke and colleagues in a study involving a large cohort of pregnant women in a Southern Brazilian population refuted the perceived correlation between blood groups and pre-eclampsia.[15] The research was borne out of the non-uniform inclusion criteria for recruitment of women in previous studies and the conflicting findings. The report therefore highlights the role of other factors that could contribute to the aetiopathogenesis of HDP.

From this work, although inferencesfrom numerical findings favour a higher risk of HDP among blood group B (and similarly for blood group A) pregnant women, the absence of statistically significant relationship implies weak link between blood group type and HDP among Ife-Ijesa pregnant population. By extension, a review by Asafa and colleagues among a non-pregnant population in the same locality found the highest blood pressure indices among individuals with blood group O, but the association was not statistically significant.[16]

There was no statistically significant relationship between BMI category and occurrence of HDP (p=0.746), although the proportion of women with HDP increased with increasing BMI with a change in the trend for morbid obesity group as shown in Figure 2. These findings agree with those reported at the Lagos University Teaching Hospital, South-Western Nigeria, in a review of obesity and pre-eclampsia exploring role of fibrinogen and C-Reactive Protein. The authors found higher average BMI in the pre-eclamptics than the normotensive women.[17] The change in trend for the morbidly-obese group could be attributed to the under-representation of the BMI category in index study.

In the great obstetrical syndromes study evaluating the relationship between BMI and the risk of HDP in Quebec Canada, obesity was associated with increased risk of hypertension although the association with preterm pre-eclampsia was not statistically significant. It was further established that combination of other maternal characteristics including age, ethnicity, smoking status and other chronic medical conditions could improve the predictive ability of BMI.[18]Similar to index study, a study on blood pressure pattern and BMI status in pregnancy at the antenatal clinic of Korle-Bu Teaching Hospital found that BMI alone at 20 weeks of gestation and beyond did not reveal any statistically significant relationship with the risk of HDP.[5]

Converse with the index study findings, a study evaluated BMI and Hypertensive disorders in a cohort of white European women with singleton pregnancies and concluded that hypertensive disorders were common in obese women compared with those who had normal BMI.[19]Although the BMI is considered the gold standard for measuring body fat, pregnancy-associated weight gain and relative fluid retention of pregnancy coupled with predominantly unavailable pre-pregnancy weight among our population greatly challenge the use of BMI in pregnancy. This is even more worrisome in the study environment considering the fact that women often present for booking very late in pregnancy as against the WHO recommendation of antenatal booking after the second missed period. Investigators have examined the correlation between Mid-Upper Arm Circumference (MUAC) and BMI towards finding a better substitute for nutritional assessment in the pregnant population. MUAC which was originally designed for use in children less than five years of age has been

reported to have a correlation of 0.92 with BMI in pregnant women of < 30 weeks of gestation[20]; and correlation coefficient of 0.836 by Cooley et al.[21] MUAC is however challenged by the observation that body fat redistribution imposed by previous pregnancies often persist in women beyond the successive pregnancies and can negatively impact on the MUAC reading in multiparous women by falsely elevating the MUAC readings.[22] Furthermore, there are no established internationally agreed MUAC cut-off in adults or pregnant women for classification, communication and global comparison. Hence BMI remains the widely accepted index till date.

Although the absolute blood pressure value increased with decreasing calcium level, the correlation was weak with correlation coefficient of -0.352 for SBP and -0.362 for the DBP. These findings align with the observations in a comparative study of serum magnesium and calcium in 60 pregnant women at Korle-Bu teaching hospital in Ghana wherein the total calcium level in 30 pre-eclamptics and 30 normotensive women in third trimester had no statistically significant difference.[23] A similar study on comparison of serum calcium and magnesium between 40 pre-eclamptic women and 40 normotensive pregnant women in Abakaliki South-Eastern Nigeria revealed comparable mean serum calcium between the two groups.[24]

A research in Owerri South-Eastern Nigeria compared the serum level of Calcium between pregnant women with HDP and normotensive women. They demonstrated significant negative correlation between serum calcium level and SBP and DBP.[25]

Independent studies in Iran in Western Asia, and in Gwagwalada North-central Nigeria West Africa, recorded significantly lower serum calcium levels in women with HDP in comparison with normotensive women.[26-28]

While reports on calcium and its role in HDP are still fraught with controversies, it is not unexpected that the trials on its supplementation towards the reduction in the risk of HDP in women at risk also have findings with varying outcomes. For example, a systematic review and network meta-analysis of calcium and vitamin D supplementation for prevention of pre-eclampsia with 16 randomised controlled trials focusing on calcium has majority of the studies in favour of calcium versus placebo and a few negating its role. The analysis was in favour of calcium and its beneficial role.[29]

CONCLUSION

This study demonstrated a potential predisposition of blood group types B>A>O>AB respectively to the development of HDP, although the association was not significant. Review of literature was also controversial in this regard. Overweight and obesity increase the risk of development of HDP as it is established in other medical conditions in pregnant and non-pregnant population. Unlike blood group, BMI offers a significant opportunity for prevention as it is a modifiable risk factor and by extension it also improves women's lifelong risks. Although plasma calcium level is lower in women with hypertension in this series in comparison with the normotensive pregnant women, the strength of the association between systolic/diastolic blood pressure and plasma calcium level does not affirm routine plasma calcium analysis in the population of pregnant women except if additional risk factors for HDP are identified.

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