Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 25 (2021) 129–135

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

# Metabolic syndrome following hypertensive disorders in pregnancy in a low-resource setting: A cohort study

Salisu M. Ishaku [a,1,*], Tunau Karima [b,1], Khadijat A. Oboirien [b], Agbo P. Innocent [c], Oyeneyin Lawal [d], Tukur Jamilu [e], Joyce L. Browne [a], Kayode A. Gbenga [a,f], Onyebuchi K. Azubuike [g], Dattijo M. Lamaran [h], Aminu M. Baffah [h], Owa O. Olorunfemi [i], Odusolu O. Patience [j], Warren E. Charlotte [k], Hanifah D. Abubakar [l], Abdulkarim Musa [m], Arie Franx [n], Diederick E Grobbee [a]

[a] Julius Global Health, Julius Center for Health Science and Primary Care, UMC Utrecht, Utrecht University, the Netherlands
[b] Usmanu DanFodio University Teaching Hospital, Sokoto, Sokoto State, Nigeria
[c] Population Council-Nigeria, Nigeria
[d] University of Medical Sciences Teaching Hospital, Ondo, Ondo State, Nigeria
[e] Bayero University/Aminu Kano Teaching Hospital Kano, Kano State, Nigeria
[f] Translational Health Sciences, Bristol Medical School, University of Bristol, Southmead Hospital, Bristol, United Kingdom
[g] Federal Teaching Hospital, Abakaliki, Ebonyi State, Nigeria
[h] Abubakar Tafawa Balewa University Teaching Hospital, Bauchi, Bauchi State, Nigeria
[i] Mother and Child Hospital, Akure, Nigeria
[j] University of Calabar Teaching Hospital, Calabar, Cross River State, Nigeria
[k] Population Council-Washington DC, USA
[l] Muhammad Abdullahi Wase Teaching Hospital, Kano, Kano State, Nigeria
[m] Federal Medical Center, Lokoja, Kogi State, Nigeria
[n] Erasmus Medical Center, University Medical Center Rotterdam, the Netherlands

ARTICLE INFO

*Keywords:*
Hypertensive disorders in pregnancy
Metabolic syndrome
Nigeria

ABSTRACT

*Objectives:* Hypertensive disorders in pregnancy (HDPs) are associated with risk of future metabolic syndrome. Despite the huge burden of HDPs in sub-Saharan Africa, this association has not been adequately studied in this population.

*Study design:* This was a prospective cohort study on pregnant women recruited between August 2017 - April 2018 and followed up to one year after their deliveries and evaluated for presence of metabolic syndrome at delivery, nine weeks, six months and one year.

*Main outcome measures:* Prevalence of metabolic syndrome

*Results:* A total of 488 pregnant women were included: 410 and 78 with HDPs and normotensive, respectively. None of the normotensive had metabolic syndrome until one year (1.7% = 1 out of 59 observations), while among those with HDPs were 17.4% (71 of 407), 8.7% (23 of 263), 4.7% (11 of 232) and 6.1% (17 of 278), at delivery, nine weeks, six months and one year postpartum, respectively. High BMI and blood pressure were the drivers of metabolic syndrome in this population. The incidence rate in HDPs versus normotensive at one year were, respectively, 57.5/1000 persons' year (95%CI; 35.8 – 92.6) and 16.9/1000 persons' years (95%CI; 2.4-118.3), with incidence rate ratio of 3.4/1000 person's years. Only parity significantly predicted the presence of metabolic syndrome at one year [(aOR= 3.26/delivery (95%CI; 1.21-8.79)].

*Conclusion:* HDPs were associated with a higher incidence of metabolic syndrome up to one year postpartum. Women with HDPs should be routinely screened for metabolic syndrome within the first year postpartum to reduce cardiometabolic risks.

* Corresponding author.
*E-mail address:* salisuishaku@yahoo.com (S.M. Ishaku).
[1] First and second authors contributed equally.

https://doi.org/10.1016/j.preghy.2021.05.018
Received 16 November 2020; Received in revised form 26 January 2021; Accepted 24 May 2021
Available online 4 June 2021
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## 1. Introduction

Metabolic syndrome is a group of clinical, metabolic and biochemical abnormalities with negative impact on global health [1]. Based on the International Diabetes Federation (IDF) consensus statement, it is defined as the presence of body mass index > 30 kg/m$^2$ with any two of the following: triglycerides ≥ 1.7 mmol/L, high-density lipoprotein < 1.29 mmol/L, hypertension (systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg) or fasting blood glucose ≥ 100 mg/dL or 5.6 mmol/L [2]. Normal pregnancy adaptations to cater for nutritional needs of the growing fetus induces cardiometabolic stress reminiscent of metabolic syndrome with increased insulin resistance, hyperlipidemias and changes in protein and amino acid metabolism [3,9]. As such, pregnancy is sometimes considered a 'stress test'. Hypertensive disorders in pregnancy (HDP) may therefore be manifestations of underlying metabolic and cardiovascular disease (CVD) risks due to constitutional predisposition [4–8,10].

There is growing evidence that abnormalities in cardiometabolic markers during pregnancy can persist in HDP including pre-eclampsia well beyond the *peri*-partum period [4,9,10]. In fact, metabolic syndrome has been shown to be commoner among these women [4,7,10]. In addition, HDP without initial aberrations may begin to exhibit abnormal metabolic profiles postpartum, some of which result in metabolic syndrome [10]. Consequently, many authorities, including the American Heart Foundation, have included HDP as indicator risk factors for cardiovascular diseases (CVDs) [8]. The International Society for the Study of Hypertension in Pregnancy (ISSHP) and the National Institute for Health and Care Excellence (NICE) guidelines also recommend long-term postpartum follow up for women with HDP due to heightened cardiovascular and metabolic disease risks associated with prior HDP [11,12].

Following HDP, varying prevalence rates of metabolic syndrome have been reported from around the world depending on the postpartum interval the evaluation was made, with values ranging from 13.9% in the Netherlands (median of 8 months postpartum) and 14.5% in the United States of America [9,13]. Fourteen years after pre-eclampsia, an 82.3% prevalence of metabolic syndrome has been reported in Brazil [14]. Udenze et al. reported a prevalence range from 10.9% to 27.3% after a pre-eclamptic pregnancy in an inter-continental systematic review [15].

Evidence on the burden of metabolic syndrome in prior HDP in sub-Saharan African setting is limited. One study from Ghana was conducted during the second half of pregnancy and reported a prevalence of 61% based on the National Cholesterol Education Program (NCEP) definition [16]. Two Nigerian cross-sectional studies are also available with reported prevalence of metabolic syndrome ranging from of 24.3% to 31.7% [17,18]. However, they were conducted among semi-urban non-pregnant women.

Given that metabolic syndrome is considered an intermediate and modifiable risk factor for future cardiovascular and metabolic diseases and its proven association with prior HDP, a prospective cohort was conducted among women with prior HDP who delivered at tertiary facility settings, in order to determine the prevalence and risk factors of metabolic syndrome.

## 2. Methods

### 2.1. Study design

This was a prospective cohort study on pregnant women recruited between August 2017 and April 2018 up to one year after deliveries. They were evaluated for metabolic syndrome at pre-determined intervals and the last recruited participant completed the study on March 31, 2019.

### 2.2. Study setting

The study was conducted in eight tertiary hospitals in Nigeria namely: Abubakar Tafawa Balewa University Teaching Hospital, Bauchi State, University of Calabar Teaching Hospital, Cross River State, Federal Teaching Hospital, Ebonyi state, Federal Medical Center, Kogi State, Aminu Kano Teaching Hospital Kano State, Usmanu Danfodiyo University Teaching Hospital Sokoto as well as Mother and Child Hospital and the University of Medical Sciences Teaching Hospital, both in Ondo State. The health facilities were high-volume sites with well-functioning clinics, delivery rooms and laboratory services with combined annual deliveries averaging 38,400.

### 2.3. Participants

This study recruited women 18 years old and above who delivered with diagnoses of HDP. Multiple pregnancies and medical disorders in pregnancy other than hypertensive disorders such as diabetes mellitus, sickle cell anemia, heart disease, kidney and other connective tissues disorders were excluded. The normotensive cohort comprised of pregnant women who also delivered in the study sites.

### 2.4. Study procedures

Participants (both women with HDP and normotensive) were informed of the study during the antenatal period (for registered clients) or after delivery but all recruitments were done within 24 h of delivery. Intending participants were individually counseled, informed consent obtained - either signed or thumb printed – (consent rate over 95%) and enrollment forms (comprising information on socio-demographic and obstetric variables) was completed. After enrollment, the women underwent baseline clinical evaluations to assess their symptoms and signs. In addition, laboratory investigations were performed before discharged from the hospitals. They were subsequently followed-up during which the same clinical and laboratory investigations conducted at baseline were repeated at nine weeks, six months and one year postpartum. To enhance follow up, the participants were requested to provide their contact information (particularly personal and spousal mobile telephone numbers). They were reminded of their follow up appointments through phone calls. Participants' contact information was not linked to their clinical records while all clinical information was linked to unique identifiers.

### 2.5. Exposure variables

The main exposures of interest were the presence of any HDP subtype namely, chronic hypertension, gestational hypertension and pre-eclampsia as defined by the ISSHP [11]. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg and or diastolic blood pressure of ≥ 90 mmHg measured on two consecutive periods 4–6 h apart. Chronic hypertension in pregnancy was defined as any hypertension with onset before the index pregnancy or diagnosed within the first 20 weeks of the index pregnancy. Gestational hypertension was defined as any hypertension occurring after the first 20 weeks of pregnancy without significant proteinuria (<2++ of proteinuria on urine dipstick measurement) or any hematological or biochemical abnormality. Pre-eclampsia was defined as hypertension with onset after the first 20 weeks of pregnancy with significant proteinuria (≥2++ of proteinuria on urine dipstick measurement) or the presence of any hematological and biochemical abnormality.

### 2.6. Outcome variables

We assessed the prevalence and incidence of metabolic syndrome at three time–periods after delivery: nine weeks, six months and one year. Metabolic syndrome was as defined by the International Diabetes Federation [2], the presence of BMI > 30 kg/m$^2$ with any two of; triglycerides ≥ 1.7 mmol/L, high-density lipoprotein (HDL) < 1.29 mmol/L, hypertension (systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg) or

fasting blood glucose ≥ 100 mg/dL or 5.6 mmol/L. We used the IDF definition for ease of use in our setting as other commonly used definitions require measurements not readily available such as measures of insulin resistance, insulin concentration (the World Health Organization criteria) and waist circumference (the National Cholesterol Education Program – NCEP ATP III) [19].

### 2.7. Data source/data collection

At each data collection period, participant's BMI (weight (kg)/height ($m^2$)), was measured along with urine protein estimation (using meditest combi 10 dipsticks) and blood pressure (BP) by auscultation technique using mercury sphygmomanometer. The first and fourth Korotkoff sounds were taken as systolic and diastolic values, respectively. A general physical examination for signs was also conducted. In addition, blood samples were collected for laboratory tests which included fasting blood glucose and serum lipids (total cholesterols, HDL and low-density lipo-proteins (LDL) cholesterols, triglycerides). All clinical examinations and blood sample collection were performed by trained medical officers (research assistants). Laboratory investigations were performed by scientists based on laid down protocols following standard practices used in all the study sites.

### 2.8. Risk of bias

The women with HDPs and the normotensive cohort were recruited from a similar maternity population. In Nigeria, access to such health facilities is based on women's preferences, places of residence and socioeconomic status (not necessarily based on referrals), with the more educated and high-income group typically attending tertiary care centers. Because women of particular risk strata could self-select themselves for tertiary care delivery, estimates of metabolic syndrome in this population may not be generalized. However, recruitment proceeded independently in all facilities. Case identification was done by specially trained midwives using standard diagnostic criteria. Outcomes assessors were blinded of participants' HDP status. The results of medical and laboratory investigations were entered in the electronic data capturing platform by trained research assistants as soon as the data were available to reduce the incidence of missing data. The hard copies of all medical and laboratory results were retained as source documents at the facilities for future reference when necessary.

### 2.9. Sample size

Given that on average 14% of pregnant women develop metabolic syndrome postpartum across previously conducted studies with varying follow up time [9,13], it is estimated that 185 women in each arm were required to participate in the study in order to detect a similar level of postpartum metabolic syndrome in our Nigerian population after HDP and compare it to women after normotensive pregnancy, at alpha level of 5% and power of 80%. Considering a potential 10% loss to follow up, 204 women were needed. As the study was only observational with minimal risks, many women as could consent to participation within available resources and time, were enrolled.

### 2.10. Data analysis plan/statistical methods

The women with HDP and the normotensive followed-up for each period were successfully analyzed. Laboratory results reported in mg/dl were converted to mmol/L before the analyses were carried out. Frequencies, percentages, proportions and means (standard deviations) were used to describe participants' obstetric and demographics variables as well as the prevalence of metabolic syndrome. Independent *t*-test was used to compare mean differences between the HDP and the normotensives. For comparing categorical data, chi square or Fisher's exact test was used. In addition, the incidence rates of metabolic syndrome (in person years experienced) for each period were calculated to delineate between new onset metabolic syndrome attributable to hypertensive disorders from the persistent effects of pregnancy adaptation that could influence prevalence. Univariable and multivariable logistic regression analyses to identify factors that predict metabolic syndrome at six months and one year postpartum were performed. Confounders' selection was hypothesis-driven, and the following variables were included: age, parity, gestational age at delivery, gestational age at onset of HDP, booking status, gestational hypertension, pre-eclampsia and eclampsia. The data was analyzed using SPSS IBM version 25.0.

## 3. Results

In this cohort, 410 women with hypertensive disorders and 78 normotensives ones (due to differential consenting rates between the two cohorts ((95% and 38% for HDPs and normotensive respectively) participated. Fig. 1 shows flowchart of follow up of women with HDPs versus the normotensive over the one-year period. The number of women assessed at various time points varied based on follow up rates: 263 (65%), 232 (57%), 278 (68%) and 53 (68%), 43 (55%), and 58 (74%) for HDPs and control at nine weeks, six months and one year, respectively.

Table 1 shows the baseline characteristics of the women. The mean

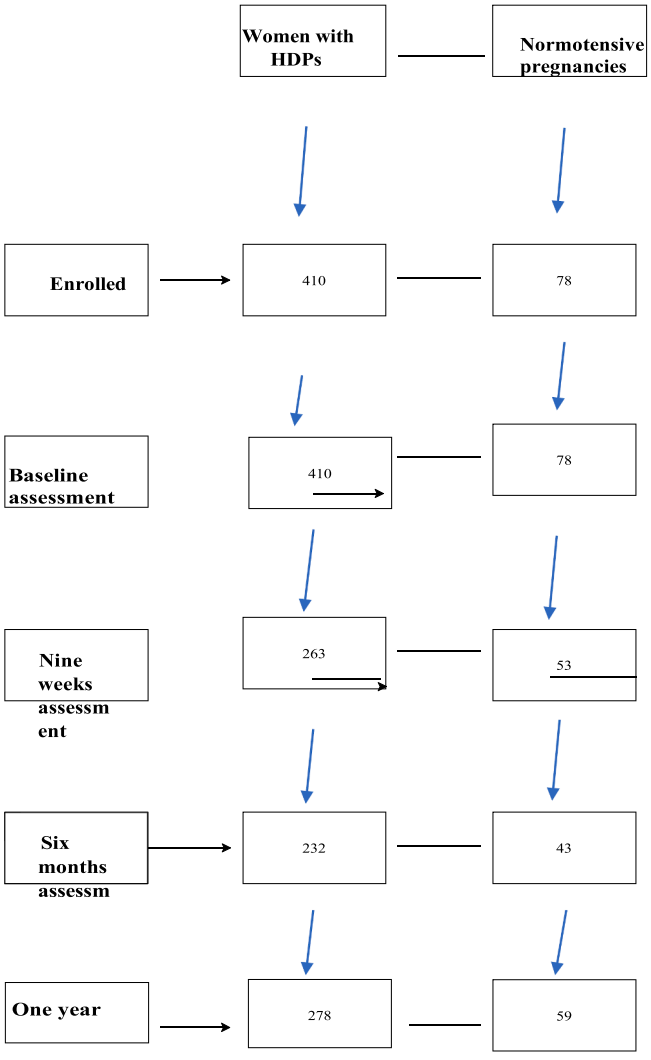


**Fig. 1.** Follow up rate among women with HDPs and women with normotensive pregnancies from delivery until 1 year.

**Table 1**
Baseline characteristics of women with hypertensive disorders in pregnancy (N=410) and the normotensives (N=78).

| Variables | Number (%) | | Mean (SD) | | P- | GHT (N=75) | CHT(N=33) | PE(N= 200) | EC(N=58) |
|---|---|---|---|---|---|---|---|---|---|
| | HDP | Normotensive | HDP | Normotensive | | | | | |
| Age, Mean(SD) | | | 29.4(0.58) | 28.3(0.59) | 0.480 | 33.3(3.34) | 35.2(1.18) | 28.4(0.41) | 24.6(0.83) |
| BMI at booking, Mean(SD) | | | 28.8 (0.51) | 26.7(0.81) | 0.050 | 31.6(1.16) | 31.7(2.61) | 27.7(0.59) | 24.9(0.93) |
| *Parity* | | | | | 0.230 | | | | |
| Para 0 n(%) | 86 (21) | 10(12.8) | – | – | | 9(12.0) | 1(3.0) | 45(22.5) | 23(40.3) |
| Para 1 – 3 n(%) | 226 (55) | 49(62.8) | – | – | | 51(68.0) | 14(42.4) | 108(54) | 27(47.4) |
| ≥para 4 n(%) | 98(24) | 19(24.4) | – | – | | 15(20.0) | 18(54.6)) | 47(23.5) | 7(12.3) |
| *ANC Registration. n(%)* | | | | | 0.001 | | | | |
| Booked/Registered | 247(60.2) | 66(89.7) | – | – | | 60(80.0) | 23(70.0) | 117(58.5) | 21(36.8) |
| Unbooked/Not registered | 163 (39.8) | 8(10.3) | | | | 15(20.0) | 10(30.0) | 83(41.5) | 36(63.2) |
| GA at booking, Mean(SD) | – | – | 23.7(0.41) | 22.8(0.75) | 0.280 | 24.9(0.86) | 23.8(0.97) | 23.1(0.58) | 23.0(1.46) |
| *GA at booking n(%)* | | | | | 0.794 | | | | |
| ≤12 weeks | 14 (3.4) | 3 (3.8) | | | | 3(4.0) | 0(0.0) | 7(3.5) | 2(3.5) |
| 13 – 20 weeks | 73 (17.8) | 23 (29.5) | – | – | | 14(18.7) | 6(18.2) | 43(21.5) | 6(10.3) |
| >20 weeks | 323 (79) | 52 (66.7) | – | – | | 58(77.3) | 27(81.8) | 150(75.0) | 50(86.2) |
| GA of HDP onset Mean(SD) | | | 33.2 (8.7) | – | | 36.9(4.1) | 23.8(13.4) | 33(8.5) | 34.5(6.5) |
| *GA at onset of HDP n (%)* | | | | | | | | | |
| ≥ 34 weeks | 239(65.5) | – | – | – | | 61(84.7) | 10(30.3) | 122(61.3) | 42(73.7) |
| <34 weeks | 126(34.5) | | | | | 11(15.3) | 23(67.7) | 77(38.7) | 15(26.3) |
| GA at delivery, Mean(SD) | – | – | 36.5(4.1) | 38.3(1.7) | 0.301 | 38.7(1.9) | 36.1(3.9) | 36(4.3) | 35.5(4.3) |
| *Apgar Scores at 1 minute* | | | | | 0.790 | | | | |
| ≥7 n(%) | 224(61.4) | 36(88.72) | – | – | | 58(77.3) | 20(60.6) | 117(58.5) | 29(50.9) |
| <7 n(%) | 141(38.6) | 7(16.28) | – | – | | 17(22.7) | 13(39.4) | 83(41.5) | 28(49.1) |
| *Apgar Score at 5 minutes* | | | | | 0.950 | | | | |
| ≥7 n(%) | 308(84.4) | 42(97.7) | – | – | | 72(96.0) | 29(87.9) | 163(81.5) | 44(77.2) |
| <7 n(%) | 57(16.6) | 1(2.3) | – | – | | 3(4.0) | 4(12.1) | 37(18.5) | 13(22.8) |
| *Perinatal deaths n(%)* | | | | | | | | | |
| Stillbirths | 29 (7.1) | 0.0 (0.0) | – | – | 0.008 | 2(6.9) | 1(3.4) | 20(69) | 6(20.7) |
| Early neonatal deaths | 12 (2.9) | 1.0 (1.3) | – | – | 0.7028 | 1(8.3) | 2(16.7) | 9(75) | 0(0.0) |

HDP = Hypertensive disorders in pregnancy, SD = standard deviation, HTN = Hypertension, GA = gestational age, BP = Blood pressure, GHT = Gestational hypertension, CHT = Chronic hypertension, PE = Pre-eclampsia, EC = Eclampsia

age and booking BMI of women with HDPs and normotensive women were similar [age: (29.4; Sd = 0.58) versus (28.3; Sd = 0.59), BMI: (28.8; Sd = 0.51) versus (26.7; Sd = 0.81)]. The proportion of women who were primigravidae was higher in the HDP group (21%, n = 86/410) than in the normotensive counterpart (13%, n = 10/78). About 40% (163) and 10% (8) of the HDP and the normotensive women, were not registered for antenatal care (ANC). Of those who registered, similar proportions of HDPs and normotensives did so within the first trimester (3.4%, n = 14 versus 3.8%, n = 3). The mean gestational age at booking were similar (23.7 (Sd = 0.41) versus 22.8 (Sd = 0.75)). Women with HDPs were more likely to deliver preterm compared to normotensive women (mean delivery gestational age of 36.5 (Sd = 4.1) versus 38.3 (Sd = 1.7)].

At baseline (within 24 h of delivery, Table 2), women with HDPs significantly differed from the normotensive in some components of metabolic syndrome. HDPs had significantly higher mean BMI [29.1 kg/m$^2$ (Sd = 7.3) versus 27.3 kg/m$^2$ (Sd = 6.2) p = 0.047], mean systolic [159.6 mmHg (Sd = 22.2) versus 113.7 mmHg (Sd = 10.9), p = 0.001] and mean diastolic blood pressure [102 mmHg (Sd = 15.8) versus 71.5 mmHg (Sd = 6.9), p = 0.001], with no significant differences with respect to serum cholesterol, triglycerides and fasting blood glucose levels, although the proportions of women with high abnormal values for these three components are higher among the HDP at baseline and at 1 year (with the exception of FBS at baseline). Similarly, at one year after delivery, women with HDPs as compared to the normotensives had significantly higher mean BMI [28.5 kg/m$^2$ (Sd = 7.1) versus 26.4 kg/m$^2$ (Sd = 5.5), p = 0.035], mean systolic [132.86 mmHg (Sd = 26.8) versus 112.07 mmHg (Sd = 13.8), p = 0.001] and mean diastolic blood

**Table 2**
Prevalence of abnormally high components of metabolic syndrome and their mean differences between women with hypertensive disorders in pregnancy and the normotensives at baseline and one year after delivery.

| | Baseline | | | | | 1 year | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | HDP High n (%) | Normotensive High n (%) | HDP Mean (SD) | Normotensive Mean (SD) | P-value | HDP High n (%) | Normotensive High n (%) | HDP Mean (SD | Normotensive Mean (SD | P-value |
| BMI | 270(65.9) | 33(42.3) | 29.1(7.3) | 27.3(6.2) | 0.047 | 233(83.8) | 39(67.2) | 28.5(7.1) | 26.4(5.5) | 0.035 |
| SBP | 365(89.0) | 1(1.3) | 159.6 (22.2) | 113.7(10.9) | 0.001 | 265(95.3) | 26(44.8) | 132.86 (26.8) | 112.07(13.8) | 0.001 |
| DBP | 365(89.0) | 1(1.3) | 102(15.8) | 71.5(6.9) | 0.001 | 265(95.3) | 26(44.8) | 86.75 (18.5) | 72.55(11.52) | 0.001 |
| Chol (mmol/l) | 22(5.4) | 1(1.3) | 4.4(1.6) | 4.4(1.3) | 0.748 | 1(0.4) | 0 | 4.40(1.2) | 4.29(1.3) | 0.513 |
| TGC (mmol/l) | 198(48.3) | 34(43.5) | 1.8(0.9) | 1.6(0.6) | 0.0917 | 174(62.6) | 26(44.8) | 1.15(0.6) | 1.06(0.6) | 0.330 |
| FBS (mmol/l) | 130(31.7) | 26(33.3) | 5.3(3.5) | 5.3(2.1) | 0.999 | 196(70.5) | 32(55.2) | 5.0(1.9) | 4.9(1.2) | 0.478 |

pressure [86.8 mmHg (Sd = 18.5) versus 72.6 mmHg (Sd = 11.5), p = 0.001], but similar cholesterol, triglycerides and fasting blood glucose concentrations. At both the baseline and at 1 year postpartum, higher proportion of women with HDP, as compared to the normotensive, had abnormality in all the components of metabolic syndrome (Table 2).

Women with normotensive pregnancies had no metabolic syndrome at baseline, nine weeks and six months after delivery, but 1.7% (n = 1/59) had it at one year postpartum. For women with HDPs, this was 17.4% (71/410), 8.7% (15/263), 4.7% (11/232) and 6.1% (17/278), respectively. The incidence rates for metabolic syndrome among women with HDPs dropped from 329.7/1000 person years (95%CI; 217.8 – 498.9) to 57.5/1000 person years at one year. For women with a normotensive pregnancy the incidence rate at one year was 16.9/1000 person years (95%CI; 2.4 – 118.3).

The incidence and prevalence rates of metabolic syndrome among the different HDP categories differed (Table 3). At 6 months postpartum, women with pre-eclampsia were more likely to have metabolic syndrome [(IR = 444/1000 person years (95%CI; 214 – 923), followed by chronic hypertension [(IR = 111/1000 person years (95%CI; 18 – 705) and finally gestational hypertension [(IR = 37.7/1000 person years (95%CI; 5.5 – 258)]. While no woman with chronic hypertension developed new onset metabolic syndrome at one year, the rate in gestational hypertension, pre-eclampsia and eclampsia were, respectively, 71/1000 person years (95%CI; 27.8 – 183.7), 60/1000 person years (95%CI; 30.7 – 118) and 29/1000 person years (95%CI; 4.3 – 203).

Table 4 describes the overall prevalence and incidence rates of metabolic syndrome for the HDP and normotensive at each of the time points. At nine weeks, six months and one year postpartum, the prevalence of metabolic syndrome was higher in the HDP category than in the normotensive but only significantly so at nine weeks (p-0.019). Similarly, development of new onset metabolic syndrome (incidence) occurs significantly more among the HDP at all postpartum times with p < 0.0001.

While Table 5 describes the results of univariable and multivariable logistic regression analyses of maternal demographic and obstetric factors as predictors of metabolic syndrome at six months and one year postpartum. At six months postpartum, none of the possible predictors were associated with metabolic syndrome. At one year postpartum, only parity significantly predicted the development of metabolic syndrome [(aOR = 3.26/delivery (95%CI; 1.21–8.79)].

**Table 4**
Overall prevalence and incidence rates (per 1000 persons year of exposure) of metabolic syndrome among women with hypertensive disorders in pregnancy versus normotensive at 9 weeks, 6 months and 1 year postpartum.

| Timelines | Prevalence n (%) | | | | |
|---|---|---|---|---|---|
| | HDP | Normotensive | Risk Difference | 95% Confidence Interval | P-value |
| **9 weeks** | 23/263 (8.7%) | 0/53(0.0) | 0.09 | 0.05 – 0.12 | 0.019 |
| **6 months** | 11/232 (4.7%) | 0/43(0.0) | 0.05 | 0.20 – 0.07 | 0.223 |
| **1 year** | 17/278 (6.1%) | 1/58(1.7%) | 0.04 | 0.0001 – 0.0877 | 0.331 |
| **Timelines** | **Incidence per 1000 person years** | | | | |
| | *HDP* | *Normotensive* | *Incidence Rate Difference* | *95% Confidence Interval* | *p-value* |
| **9 weeks** | 329.7 (217.8 – 498.9) | 0.0 | 0.33 | 0.29 – 0.36 | P<0.0001 |
| **6 months** | 69.0 (35.3 – 134.6) | 0.0 | 0.07 | 0.05 – 0.09 | P<0.0001 |
| **1 year** | 57.5 (35.8 – 92.6) | 16.9(2.4 – 118.3) | 0.04 | 0.02 – 0.6 | P<0.0001 |

## 4. Discussion

This study showed a relatively high prevalence (6.1%) of (persistent) metabolic syndrome up to one year postpartum. In contrast, only 1.7% of women in the comparison group developed metabolic syndrome the year following birth. The prevalence of metabolic syndrome after puerperium among our cohort of women with HDPs was lower than the reported global proportion of about 15% [2,9,13]. These differences may be reflective of differences in the criteria used and the postpartum time periods during which measurements were taken. The IDF criteria was used in this study, whereas others used the NCEP ATP III (defined as presence of any three of the following: hypertension ≥ 130/85 mmHg; fasting plasma glucose ≥ 6.1 mmol/L; fasting plasma triglycerides ≥ 1.69 mmol/L; fasting HDL cholesterol < 1.29 mmol or subjects were receiving treatment for their condition and waist circumference > 88 cm) and the World Health Organization definition (hyperinsulinemia - the upper fourth of the fasting insulin level among nondiabetic subjects or hyperglycemia - fasting glucose ≥ 110 mg/dl- in addition to at least two of the following: waist girth ≥ 94 cm, dyslipidemia - triglycerides ≥ 150 mg/dl or HDL cholesterol ≥ 40 mg/dl, or BP ≥ 140/90 mmHg or taking BP medication [19]. The two criteria could potentially lead to higher estimates of metabolic syndrome than IDF criteria. For instance, the WHO criteria utilize insulin resistance which, in pathogenesis term, precede raised fasting blood glucose used by the IDF definition, and while the NCEP definition uses waist circumference to measure obesity, the IDF utilizes the BMI.

The 1.7% prevalence of metabolic syndrome among normotensive women at one year is lower than the 24.3% reported from a non-pregnant women population in Nigeria in which the IDF definition was also used [17]. This disparity could be explained by the fact that the normotensive population in our study had fewer risk factors compared to women in this random survey of sub-urban population in whom 42% were overweight with mean systolic blood pressure of 131 mmHg (112 mmHg in our normotensive cohort after one year of follow up) [17].

Because the cardiometabolic changes (reminiscent of metabolic syndrome) in HDP also occur in normal pregnancies and the effects could persist throughout puerperium and for variable length of postpartum period, we assessed metabolic syndrome from nine weeks postpartum up to one year - after which most pregnancy-related metabolic changes are expected to have waned off; and included normotensive women as a control group. The finding that only one new onset metabolic syndrome occurred out of fifty-nine normotensive observations at one year (IR = 16.9/1000 person years) as opposed to sixteen out of 278 HDP observations (IR = 57.5/1000 person years) - with

**Table 3**
The prevalence and Incidence rate per 1000 person years of exposure (with 95% confidence interval) of metabolic syndrome across HDPs sub-types (chronic hypertension, gestational hypertension, pre-eclampsia, eclampsia) at 9 weeks, 6 months and 1 year postpartum.

| | Chronic hypertension | | Gestational hypertension | | Pre-eclampsia | | Eclampsia | |
|---|---|---|---|---|---|---|---|---|
| Timelines | *Prevalence n (%)* | *incidence* | *Prevalence n(%)* | *incidence* | *Prevalence n(%)* | *incidence* | *Prevalence n(%)* | *incidence* |
| 9 weeks | 5(22.7) | 525 (202 – 1365) | 4(7.5) | 327(129.1 – 827.5) | 12(9.2) | 409(247.6 – 676) | 1(3.4) | 199(34.5 – 1151) |
| 6 months | 2(11.1) | 111 (18 – 705) | 1(1.9) | 37.7(5.5 – 258) | 6(5.6) | 444(214 – 923) | 0 | 0.0 |
| 1 year | 5(20.8) | 0.0 | 4(7.1) | 71(27.8 – 183.7) | 12(9.0) | 60(30.7 – 118) | 1(2.9) | 29(4.3 – 203) |

**Table 5**
Univariable and Multivariable logistic regression on predictors of metabolic syndrome in women with HDP at six months and one year postpartum.

| | 6 months | | | | 1 year | | | |
|---|---|---|---|---|---|---|---|---|
| | *Univariate analysis* | | *Multivariate analysis* | | *Univariable analysis* | | *Multivariable analysis* | |
| Variables | *OR (95%CI)* | *P-value* | *OR (95%CI)* | *P-value* | *OR (95%CI)* | *P-value* | *OR (95%CI* | *P-value* |
| Age | 1.01(0.99-1.03) | 0.459 | 1.09(0.95-1.25) | 0.216 | 1.01(0.99-1.03) | 0.321 | 1.00(0.98-1.03) | 0.844 |
| Parity | 1.21(0.42-3.50) | 0.730 | 0.81(0.19-3.41) | 0.768 | 2.15(0.99-4.68) | 0.054 | 3.26(1.21-8.79) | 0.020 |
| GA at delivery | 0.93(0.83-1.05) | 0.229 | 1.01(0.85-1.21) | 0.905 | 1.06(0.89-1.26) | 0.504 | 1.0.(0.83-1.20) | 0.967 |
| GA at onset HDP | *** | *** | *** | *** | 2.68(0.58-12.41) | 0.209 | 2.83(0.43-18.60) | 0.278 |
| Booking status | 3.83(0.47-31.39) | 0.211 | 2.87(0.20 -28.08) | 0.364 | 1.31(0.45-3.77) | 0.621 | 1.38(0.38-5.00) | 0.625 |
| Gestational hypertension | 0.44(0.03-7.23) | 0.564 | 3.38(0.15-78.32) | 0.448 | 3.14(0.34-28.93) | 0.312 | 1.74(0.16-18.95) | 0.649 |
| Pre-eclampsia | 0.65(0.07-6.03) | 0.707 | 2.88(0.19-43.89) | 0.447 | 2.30(0.28-18.82) | 0.436 | 1.40(0.16-12.45) | 0.764 |
| Eclampsia | *** | *** | *** | *** | *** | *** | *** | *** |

*** Omitted variables due to small number of observations.

incidence rate ratio of 3.4/1000 person years- further strengthened the association between metabolic syndrome with prior HDPs.

We observed that at six months post-delivery of an HDP-complicated pregnancy, the likelihood of developing metabolic syndrome diminishes in the order of HDP sub-type severity: pre-eclampsia, chronic hypertension in pregnancy and gestational hypertension. Although pre-eclampsia has the highest risk at six months postpartum, the prevalence of metabolic syndrome among pre-eclamptic cohort was only 3.7%. Other studies reported both higher and lower levels: a study in the Netherlands observed 13.9% prevalence at six months based on the WHO definition [13], and a Korean study reported no association with development of metabolic syndrome postpartum among women with pre-eclampsia who had two or more components of metabolic syndrome-pre-pregnancy [20]. Although we had no information on the pre-pregnant status of our cohort, the prevalence of 17.4% metabolic syndrome at delivery may suggest a population with already pre-exiting abnormal metabolic components which might have conferred some protection against metabolic syndrome developing postpartum.

Only parity significantly exerts independent influence on occurrence of metabolic syndrome one year postpartum in our HDP cohort. By intuition, this should be expected as increasing parity is typically associated with advancing maternal age, hypertension, and abnormal BMI which, in turn, increases the risk of abnormal cardiovascular surrogate marker, including metabolic syndrome. Studies of Hispanic/Latino women in the United States [21] and Chinese women [22] have established significant association between higher parity and some components of metabolic syndrome independent of age. The American study observed that higher parity accompanied with abdominal obesity suggest high risk of metabolic dysregulation [21].

### 4.1. Clinical and research implication

West Africa in general, and Nigeria in particular, carry a heavier burden of CVDs risk compared to other regions [23]. It is projected to be the leading cause of premature mortality and disability-adjusted life years (DALY) burden by 2050 [24]. In addition, West Africa has one of the highest fertility rates with 5.2 children per woman (in contrast to 4.4 for Africa overall) [23]. Given the association between parity, HDP, metabolic syndrome and future risk of adverse cardiometabolic disorders [24], routine screening and management of metabolic syndrome following HDP – and especially when associated with multiparity - is essential, and should be included in any strategy to reduce the CVD burden in sub-Sahara Africa. Although screening for CVD risk markers following HDP-complicated pregnancies is an established practice in many high-income countries, there is no agreement on timing of commencement of screening and of ongoing follow up processes [25]. Guidelines for screening strategies for postpartum detection of metabolic syndrome following HDPs in high-income country settings are currently limited with only one template suggested by Dutch researchers which entails a stepwise approach starting at a younger age [25]. For the Nigerian, and possibly other (West) African health care contexts, commencement of screening during the pre-conceptional and antenatal periods would be recommendable, as the modification of risk for future CVDs based on body weight and blood pressure management, also reduces the risk of HDP in the shorter term. Importantly, up to 40% of our HDP cohort did not receive antenatal care. A general continued effort to promote (early) antenatal care attendance remains urgent. For pregnancies complicated by HDP, secondary prevention could commence within first year of delivery for a timely detection and management of metabolic syndrome in order to mitigate future risks of cardiovascular and metabolic disorders.

### 4.2. Strengths and limitations

This unique study prospectively followed over five hundred women with HDP and normotensive pregnancies in sub-Saharan Africa for one year and evaluated their health at three different time periods: nine weeks, six months and one year postpartum. It allowed the exploration of both prevalence and incidence rates and risk factors, including the comparison between women with hypertensive disorders and those with normal BP during pregnancy. However, some limitations need to be considered in the interpretation of these findings. First, that one year of follow up after delivery is not adequate to detect transition beyond the intermediary risk factors on the pathways to develop cardiovascular diseases to outcomes itself. Secondly, while we aimed for a minimum of 185 normotensive pregnancies, less than half were recruited. This was due to lower consent rates to participate in the study by women in that category ((95% and 38% for HDPs and normotensive respectively - due to low perception of risk and threat among the normotensive). This could have led to insufficient power to detect metabolic syndrome at different time intervals given the low(er) prevalence. At the same time, our sample size is sufficient to suggest that these will be at the very low ends and still justifies our conclusion to focus efforts on reducing the metabolic syndrome prevalence primarily among women with HDP at highest risk.

### 4.3. Conclusion

Hypertensive disorders in pregnancy are associated with increased risk of metabolic syndrome after delivery, and this is augmented by parity independent of age. Maternal BMI and blood pressure are the main drivers of metabolic syndrome in these women. Given the growing burden of cardiovascular disease on morbidity and mortality in sub-Saharan Africa, as well as availability of risk reducing strategies, screening of all women with HDP for metabolic syndrome should routinely take place starting within the first year of delivery (but also during pre-conceptional and antenatal periods).

## Funding

This work was conducted as part of the Ending Eclampsia project (2014–2019), supported by the US Agency for International Development (USAID), under the terms of cooperative agreement number [USAID APSOAA-14-000048]. This article reflects the views of the authors and does not represent the views of the U.S. Government. Salisu Ishaku was also supported by the UMC Utrecht Global Health Fellowship Program.

## Authors contribution

First and fifth authors made substantial contributions in the conception of the work. Second and third authors made the first draft. First, second, fifth and sixth authors revised critically for important intellectual contents. First and fourth authors conducted the data analysis while the remaining authors provide final revision and approval of the version to be published.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

[1] J.D. Hernández-Camacho, M. Hernández-Camacho, Clinical update on metabolic syndrome, Rev. Esp. Nutr. Hum. Diet 21 (4) (2017) 384, https://doi.org/10.14306/renhyd.21.4.392.

[2] The International Diabetes Federation consensus worldwide definition of the metabolic syndrome. Retrieved from https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome.html on February 03, 2020.

[3] M.-E. Nijdam, M.R. Timmerman, A. Franx, H.W. Bruinse, M.E. Numans, D. E. Grobbee, M.L. Bots, Cardiovascular risk factor assessment after pre-eclampsia in primary care, BMC Fam. Pract. 10 (1) (2009), https://doi.org/10.1186/1471-2296-10-77.

[4] D.R. Barry, K.M. Utzschneider, J. Tong, K. Gaba, D.F. Leotta, J.D. Brunzell, T. R. Easterling, Intraabdominal fat, insulin sensitivity, and cardiovascular risk factors in postpartum women with a history of preeclampsia, Am. J. Obstet. Gynecol. 213 (1) (2015) 104.e1–104.e11.

[5] L. Sjónsdóttir, R. Arngrimsson, R.T. Geirsson, H. Slgvaldason, N. Slgfússon, Death rates from ischemic heart disease in women with a history of hypertension in pregnancy, Acta Obstet. Gynecol. Scand. 74 (10) (1995) 772–776.

[6] G. Libby, D.J. Murphy, N.F. McEwan, S.A. Greene, J.S. Forsyth, P.W. Chien, A. D. Morris, Preeclampsia and the later development of type 2 diabetes in mothers and their children: an intergenerational study from the Walker cohort, Diabetologia 50 (3) (2007) 523–530.

[7] D.B. Carr, K.M. Newton, K.M. Utzschneider, J. Tong, F. Gerchman, S.E. Kahn, T. R. Easterling, S.R. Heckbert, Preeclampsia and risk of developing subsequent diabetes, Hypertens. Pregnancy 28 (4) (2009) 435–447.

[8] C. Bushnell, L.D. McCullough, I.A. Awad, M.V. Chireau, W.N. Fedder, K.L. Furie, V. J. Howard, J.H. Lichtman, L.D. Lisabeth, I.L. Piña, M.J. Reeves, K.M. Rexrode, G. Saposnik, V. Singh, A. Towfighi, V. Vaccarino, M.R. Walters, A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association, Stroke 45 (5) (2014) 1545–1588.

[9] P.F. Erin, J.J. Emily, L.H. Teri, Pregnancy reveals evolving risk for cardiometabolic disease in women, JOGNN 45 (2016) 413–425, https://doi.org/10.1016/j.jogn.2016.02.004.

[10] F. Jean-Claude, G. Joël, M. Jacques, et al., Early occurrence of metabolic syndrome after hypertension in pregnancy, Obstet. Gynecol. 105 (6) (2005) 02227.f8, https://doi.org/10.1097/01.AOG.0000163252.

[11] L.A. Magee, P.V. Dadelszen, W. Stones, et al., An evidence-based guide to monitoring, prevention and management, The FIGO textbook of pregnancy hypertension (2016) 5–6.

[12] National Institute for Health and Care excellence. Hypertension in pregnancy: diagnosis and management. Published: 25 June 2019, retrieved August 10, 2020 from www.nice.org.uk/guidance/ng133.

[13] S. Al-Nasiry, C. Ghossein-Doha, S.E.J. Polman, S. Lemmens, R.R. Scholten, W. M. Heidema, J.J. Spaan, M.E.A. Spaanderman, Metabolic syndrome after pregnancies complicated by pre-eclampsia or small-for-gestational-age: a retrospective cohort, BJOG 122 (13) (2015) 1818–1823.

[14] H.A.C.P. Teixeira, C.F.H. Costa, H.N. Feitosa, et al., Metabolic syndrome after pre-eclampsia: a cohort study with a mean follow up of 14 years, J. Metabolic Syndrome 3 (3) (2013) 1–7.

[15] I.C. Udenze, Association of pre-eclampsia with metabolic syndrome and increased risk of cardiovascular disease in women: a systematic review, Niger. J. Clin. Pract. 19 (2016) 431–435.

[16] C.A. Turpin, L. Ahenkorah, W.K.B.A. Owiredu, E.F. Laing, N. Amidu, The Prevalence of the metabolic syndrome among Ghanaian pregnancy-induced hypertensive patients using the World Health Organisation and the National Cholesterol Education Program III Criteria, Journal of Medical Sciences 8 (5) (2008) 443–451.

[17] Ayokunle Dada, Daisi Ajayi, Peter Areo, Taiwo Raimi, Eyitayo Emmanuel, Olusola Odu, Olusegun Aremu, Metabolic syndrome and Framingham risk score: observation from screening of low-income semi-urban African Women, Medicines 3 (2) (2016) 15, https://doi.org/10.3390/medicines3020015.

[18] V.M. Oguoma, E.U. Nwose, R.S. Richards, Prevalence of cardio-metabolic syndrome in Nigeria: a systematic review, Public Health (2015) 413–423.

[19] P.L. Huang, A comprehensive definition for metabolic syndrome, Dis. Model. Mech. 2 (5–6) (2009) 231–237, https://doi.org/10.1242/dmm.001180.

[20] J.C. Geum, S.J. Un, Y.S. Jae, et al., Is preeclampsia itself a risk factor for the development of metabolic syndrome in the postpartum period? Obstet. Gynecol. Sci. 62 (4) (2019) 233–241.

[21] Catherine J. Vladutiu, Anna Maria Siega-Riz, Daniela Sotres-Alvarez, Alison M. Stuebe, Andy Ni, Karen M. Tabb, Linda C. Gallo, JoNell E. Potter, Gerardo Heiss, Parity and components of the metabolic syndrome among us Hispanic/Latina women: results from the Hispanic community health study/study of Latinos, Circ. Cardiovasc. Qual. Outcomes 9 (2 suppl 1) (2016) S62–S69, https://doi.org/10.1161/CIRCOUTCOMES.115.002464.

[22] Jing Wu, Guiqiang Xu, Lijun Shen, Yanmei Zhang, Lulu Song, Siyi Yang, Handong Yang, Jing Yuan, Yuan Liang, Youjie Wang, Tangchun Wu, Parity and risk of metabolic syndrome among Chinese women, J. Women's Health 24 (7) (2015) 602–607, https://doi.org/10.1089/jwh.2014.5134.

[23] A.R. Gregory, D.H. Mark, E.M. Andrew, et al., Global and regional patterns in cardiovascular mortality from 1990 to 2013, Circulation 132 (2015) 1667–1678, https://doi.org/10.1161/CIRCULATIONAHA.114.008720.).

[24] H. Suzan, G. Wim, P. Milena, Trends in cardiovascular diseases and associated risks in sub-Saharan Africa: a review of the evidence for Ghana, Nigeria, South Africa, Sudan and Tanzania, Aging Male 22 (3) (2019) 169–176, https://doi.org/10.1080/13685538.2019.1582621.

[25] T Katrien J Groenhof, Bas B van Rijn, Arie Franx, Jeanine E Roeters van Lennep, Michiel L Bots, A Titia Lely, Preventing cardiovascular disease after hypertensive disorders of pregnancy: searching for the how and when, Eur. J. Prev. Cardiol. 24 (16) (2017) 1735–1745.