Original Research Article

Placental and umbilical cord morphometry in hypertensive diseases of pregnancy

ABSTRACT

Aims: Hypertensive diseases of pregnancy (HDP) may be characterized by changes in the morphometry of the placenta and umbilical cord which may affect normal foetal growth and development. This study aimed to determine changes in the morphometry of the placenta and umbilical cord in HDP.

Study Design: A case-control study

Place and Duration of Study: The study was conducted at the Bolgatanga Regional Hospital between September 2015 and May 2016.

Methodology: The study included 49 pregnant women (Control=30, HDP=19), aged between 18 to 41 years. The controls and cases were matched by maternal age at the time of sampling. Venous blood and placental tissue samples were analysed for markers of oxidative stress. Also, the morphometric variables of the placenta and the umbilical cord were collected.

Results: The independent factors that were associated with HDP [adjusted odds ratios (95% confidence interval)] included: caesarean delivery, relative to spontaneous vaginal delivery [AOR: 32.222(3.162-328.345)], placental malondialdehyde > 11 nmol/mL [AOR: 5.718(1.513-21.617)], total antioxidant capacity ≥13.0 mmol/L [AOR: 13.775(2.809-67.557)], oxidative stress index > 2, [AOR: 10.762(2.666-43.438)]. However, placental weight >0.50Kg [AOR: 0.146(0.037-0.581)] and non-central, relative to central umbilical cord insertion [AOR: 0.142(0.021-0.966)] were less associated with HDP.

Conclusion: Placental weight above 0.50 Kg and non-central umbilical cord insertion may be protective against HDP. These findings are useful references data for maternal and neonatal health and wellbeing among women of reproductive age in the Bolgatanga Municipality of Ghana.

Keywords: Hypertensive diseases of pregnancy, Morphometry, Placenta, Umbilical Cord, Bolgatanga

1.0 INTRODUCTION

Hypertensive diseases of pregnancy are among the leading causes of maternal and infant morbidity and mortality globally. The global prevalence of HDP is about 12-22% with Sub-Saharan African countries, even recording higher prevalence (Awuah et al., 2020; Mengistu & Kuma, 2020). HDP is characterized by the new onset of hypertension, with or without proteinuria, after 20 weeks of pregnancy. HDP is a syndrome of unknown aetiology and may include chronic hypertension of all causes, gestational hypertension, preeclampsia and superimposed preeclampsia and eclampsia (ACOG, 2019).

The placental and umbilical cord have been suggested as key players in the aetiopathology of HDP. Aberrant trophoblastic invasion, ischemia and hypoxia of the placenta may lead to the concomitant production of free radicals and subsequently oxidative stress and endothelial injury (Juan-Reyes et al., 2020). Also, the morphometry of the placenta and the umbilical cord have been associated with HDP. Previous studies that have investigated the association between placental weight, placental length, umbilical cord length, umbilical cord diameter and its insertion and HDP have reported mixed outcomes. (Maduray et al., 2016; Olaya-C et al., 2016),

Differences in outcomes in the association between the morphometry of the placental, umbilical cord and that of HDP may stem from differences in genetic and environmental factors across populations (Juan-Reyes et al., 2020). For these variabilities, population-specific studies are usually required to establish local reference data for purposes of diagnosis, prevention and management of HDP. This study sought to determine the changes in placental and umbilical cord morphometry in hypertensive diseases of pregnancy among women in the Bolgatanga Municipality in the Upper East region of Ghana, where fewer such studies have been conducted.

2.0 MATERIALS AND METHODS

2.1 Study design and setting

This was a case-control study from September 2015 to May 2016 at the Bolgatanga regional hospital in the Upper East Region of Ghana. The Bolgatanga Regional Hospital is a secondary level hospital and it's the main referral hospital in the Upper East Region. The catchment area of the hospital includes some parts of the Northern Region of Ghana and villages in Burkina Faso, particularly those villages around the Ghana-Burkina Faso border.

2.2 Participants

The study involved 49 pregnant women of whom 61.2% (30/49) had normotensive pregnancies (controls) and 38.8% (19/30) were found to have hypertensive diseases of pregnancy (cases). Women who had a history of chronic hypertension and other chronic conditions were excluded from the study.

2.3 Variables

The study considered the sociodemographic variables (e.g., age), obstetric history (e.g., parity, gravidity, gestational age, mode of delivery etc.), anthropometric variables (e.g., BMI), markers of oxidative stress such as malondialdehyde (MDA), total peroxides (TP), catalase, total antioxidant capacity (TAC) and oxidative stress index (OSI). The dependent variable was HDP while the independent variables included the morphometric parameters of the placenta and umbilical cord, markers of oxidative stress, obstetric and anthropometric variables.

2.4 Data collection

2.4.1 Socio-demographic and Anthropometric measurements

Socio-demographic data (age, parity, gravidity, gestational age, and adherence to anti-malarial prophylaxis) were collected using a structured interview and also from their medical records. A stadiometer and a bathroom scale were used to measure the standing height and body weight, respectively, of the pregnant women following standard guidelines (Melo et al., 2014). The maternal Body Mass Index (BMI) was calculated in Kg/m^2 by dividing the weight by the square of the height in meters.

2.4.2 Blood pressure measurement

Blood pressure was measured with the aid of a mercury cuff sphygmomanometer according to the fifth Korotkoff sound. The reading was repeated after 4 hours and then averaged. Blood pressures were measured twice in a seated position after 15 minutes of rest following the method of Chobanian et al. (2003).

2.4.3 Placentae and umbilical cord Examination

Placentae and umbilical cords were washed with normal saline and the umbilical cords were examined for insertion. The newly born babies and placentae were weighed with a weighing scale (Seka Alpha, GmbH&CO. Igni, France) to the nearest 0.1Kg. Placentae and umbilical cord lengths were measured with non-extensile tape. The umbilical cords diameter were

measured with a sliding calliper. About 25 to 60g (about 1-2 cotyledons) of placental tissue was then cut from each placenta from the villous tree in less than an hour after delivery and thoroughly rinsed to remove excess blood using phosphate-buffered saline (PBS). The tissues were then homogenized and used for the measurement of antioxidant enzymes and compounds.

2.4.4 Blood Sample collection

A venous blood sample of about 4.0 ml in volume was collected shortly after delivery into a gel separator tube. The blood was allowed to clot under room temperature and then centrifuged at 3000g for 5 minutes to obtain serum.

2.4.5 Biochemical and Antioxidant markers

The serum uric acid levels were assayed on the BT 5000® Random Access Chemistry Analyser (Biotecnica, Italy) using Envoy® 500 reagents (Vital Diagnostics, USA). We carefully followed the instructions of the manufacturer. The method used by Sinha (1972) was followed to measure placenta CAT activity. Measurement of placental of MDA was done following the procedure described by Ádám-Vizi and Seregi (1982). The placental TAC was estimated with the ferric reducing antioxidant power (FRAP) assay of Benzie and Strain (1999). Placental Total peroxide activity was determined with the ferrous oxidation (FOX2) method by Miyazawa (1989) as modified by Harma et al. (2005). The OSI value was estimated using the standard formula; OSI = [(TP (µmol L^{-1})/ (TAC, µmol Trolox equivalent L^{-1}) x 100] as described in a similar study(Devi et al., 2008).

2.4.6 Sickling test

The sickling slide test was performed following the recommendations of Cheesbrough (1984). Equal volumes of anticoagulated blood and freshly prepared 2% sodium metabisulphite were mixed on a clean glass slide. A glass coverslip was placed on the mixture, carefully excluding air bubbles. The slides were placed in a plastic box with damp tissue paper to prevent drying. The slides were first examined under a 10x objective lens followed by a 40x objective lens after 1 hour. Positive and negative controls were also examined.

2.4.7 Malaria microscopy

Malaria diagnosis by microscopy was performed following the WHO standard for malaria microscopy (Organization, 2010). Thick and thin blood films were prepared on clean microscope slides. The blood films were allowed to air dry before the thin film was fixed with absolute methanol. The slides were then stained with filtered, freshly prepared, quality controlled 1 in 10 diluted Giemsa Stain for 10 minutes. The slides were washed with a buffer (pH:7.2) and then air-dried. The slides were examined by 2 experienced Medical Laboratory scientists, firstly under a 40x objective lens followed by the 100x objective lens with oil immersion, for the presence of malarial parasites following standardized guidelines.

2.5 Bias mitigation

To mitigate any bias in the analysis, independent variables were controlled for covariates such as maternal age, BMI and gestational age before the results for odds ratios was presented including P-values. All interpretations were based on the adjusted results.

2.6 Statistical Analysis

The data were initially entered into Microsoft Excel before being exported to SPSS (v23) and GraphPad Prism (v8) for analysis. Descriptive statistics were performed for each variable and the differences between the means were determined using an unpaired student *t*-test (2-tailed). The associations between HDP and maternal variables were determined using binary logistic regression analysis. The response (dependent variable was No HDP/HDP and was

coded as zero (0) and one (1) respectively. Each independent variable was entered into the logistic regression model simultaneously with the age at sampling, body mass index and gestational age at sampling. The effect size was reposted as adjusted odds ratio (AOR) and the 95% confidence intervals (CI). A P-value < 0.05 was considered to be statistically significant.

3.0 RESULTS

3.1 General characteristics of the study population

The women were aged between 18-41years. Most of the women were multiparous (46.9%) and most have had a spontaneous vaginal delivery (73.5%). Most of the women had a history of multiparity (46.9%) and the majority had delivered vaginally (73.%%).

Table 1. The general characteristics of the study population

Variable	Descriptive statistics
Age (years)	27.8 (18-41)
GA (weeks)	38.0 (23-41)
BMI (Kg/m^2)	26.4 (18.3-47.2)
Parity	
Nulliparous	17(34.7)
Primiparous	9(18.4)
Multiparous	23(46.9)
Gravidity	
Primigravida	17(34.7)
Multigravida	32(65.3)
Sickling	
Negative	45(91.8)
Positive	4(8.2)
Mode of Delivery	
Spontaneous Virginal delivery (SVD)	36(73.5)
Caesarean Section (CS)	13(26.5)
Birth Outcome	
Normal	41(83.7)
Abnormal	8(16.3)
Sickling test	
Negative	45(91.8)
Positive	4(8.2)
Anti-malarial prophylactic	
No	46(93.9)
Yes	3(6.1)
Peripheral malaria	
No	47(95.9)
Yes	2(4.1)
Placental malaria	
No	43(87.8)
Yes	6(12.2)

Results were presented as mean(min-max) for parametric and number (%) for categorical variables. BMI; body mass index

3.2 Socio-demographics factors associated with hypertensive diseases of pregnancy

Sociodemographic characteristics that are associated with HDP are summarized in Table 2. The odds of caesarean delivery were greater among women with HDP when compared to the controls [AOR: 32.222(3.162-328.345)].

Table 2. Socio-demographic characteristics that are associated with hypertensive diseases of pregnancy

Variable	Control n=30	HDP n=19	AOR (95%CI)/P-value
Parity			
Nulliparous	12(70.6)	5(29.4)	1
Primiparous	7(77.8)	2(22.2)	0.331(0.033-3.307)
Multiparous	11(47.8)	12(52.2)	1.214(0.248-5.949)
Gravidity			
Primigravida	12(70.6)	5(29.4)	1
Multigravida	18(56.3)	14(43.8)	0.863(0.194-3.846)
Mode of delivery			
SVD	29(80.6)	7(19.4)	1
CS	1(7.7)	12(92.3)	32.222(3.162-328.345) *
Sickling positive			
No	29(64.4)	16(35.6)	1
Yes	1(25.0)	3(75.0)	9.802(0.738-130.097)
Peripheral Malaria			
No	29(61.7)	18(38.3)	1
Yes	1(50.0)	1(50.0)	0.076(0.000-1823.257)
Placental malaria			
No	25(58.1)	18(41.9)	1
Yes	5(83.3)	1(16.7)	0.029(0.000-15.842)

Variables in asterisks were presented as Mean ± SD for parametric and number (%) for categorical variables. Differences in means were determined using an unpaired t-test (2-tailed) and binary logistic regression for the adjusted (maternal age, gestational age and BMI) odds ratios (AOR). HDP; hypertensive diseases of pregnancy, BMI; body mass index, CI; confidence interval. *Significance at the level of P<0.010.

3.4 Differences in oxidative stress markers

The adjusted odds ratios of the markers of oxidative stress that were associated with HDP are summarized in Table 3. An increase in placental MDA levels was associated with the presence of HDP [AOR: 5.718(95%CI: 1.513-21.617)]. Also, there was a general state of oxidative stress among women with HDP [AOR: 10.762(95%CI: 2.666-43.438)].

Table 3. Differences in markers of oxidative stress between normotensive and hypertensive diseases of pregnancy

Variable	Control n=30	HDP n=19	AOR (95%CI)
Uric acid (mg/dL)	17.8±6.36	14.3±5.23	
≤17	13(54.2)	11(45.8)	1
>17	17(68.0)	8(32.0)	0.619(0.182-2.105)
MDA (nmol/mL)	10.4±4.49	15.0±5.50	
≤11	17(77.3)	5(22.7)	1
>11	13(48.1)	14(51.9)	5.718(1.513-21.617) *
TAC (mmol/L)	14.1±1.81	6.6±2.22	

<13	22(88.0)	3(12.0)	1
≥13	8(33.3)	16(66.7)	13.775(2.809-67.557) **
Catalase (U/g)	7.0±2.78	4.7±3.34	
≤6	12(54.5)	10(45.5)	1
>6	18(66.7)	9(33.3)	0.667(0.201-2.206)
Total Peroxides (mmol/L)	22.0±9.64	23.1±7.29	
≤20	15(65.2)	8(34.8)	
>20	15(57.7)	11(42.3)	1.118(0.333-3.747)
Oxidative stress index	1.6±0.74	4.2±2.43	
≤2	23(92.0)	2(8.0)	1
>2	7(29.2)	17(70.8)	10.762(2.666-43.438) **

Results were presented as Mean ± SD for parametric and number (%) for categorical variables. The adjusted (maternal age, gestational age and BMI) odds ratios (AOR) were determined using logistic regression. HDP; hypertensive diseases of pregnancy, BW/PW; birth weight to placental weight ratio, CI; confidence interval. *Significant at the level of P<0.050, **significant at the level of P<0.010

3.5 Differences in placental and umbilical cord morphometric indices

The adjusted odds ratios of the association between the placenta and umbilical cord morphometry are shown in table 4. The odds that a woman with HPD would have a high placenta weight was reduced [AOR: 0.146(95%CI 0.037-0.581)]. Also, HDP was less associated with any other form of umbilical insertion either than central insertion [AOR: 0.142(0.021-0.966)].

Table 4. Differences in placental and umbilical cord morphometric indices between normotensive and hypertensive diseases of pregnancy

Variable	Control n=30	HDP n=19	AOR (95%CI)
Birth weight (Kg)	3.1±0.56	2.8±0.84	
<2.5	3(30.0)	7(70.0)	1
≥2.5	27(69.2)	12(30.8)	0.879(0.244-3.169)
Placenta Length (cm)	20.0±3.38	19.8±5.88	
<20	15(60.0)	10(40.0)	1
≥20	15(62.5)	9(37.5)	0.929(0.273-3.157)
Placenta weight (Kg)	0.63±0.15	0.57±0.19	
≤0.50	8(40.0)	12(60.0)	1
>0.50	22(75.9)	7(24.1)	0.146(0.037-0.581) **
BW/PW	5.1±1.22	5.2±1.58	
≤5.0	13(52.0)	12(48.0)	1
>5.0	17(70.8)	7(29.2)	0.481(0.138-1.680)
Cord Insertion			
Central	18(52.9)	16(47.1)	1
Non-central	12(80.0)	3(20.0)	0.142(0.021-0.966) *
Cord Length (cm)	50.1±10.89	52.1±13.35	
≤50	16(61.5)	10(38.5)	1
>50	14(60.9)	9(39.1)	1.248(0.372-4.187)
Cord diameter (cm)	1.2±0.58	1.2±0.47	
≤1.0	1555.6)	12(44.4)	1
>1.0	15(68.2)	7(31.8)	0.557(0.161-1.930)

Results were presented as Mean ± SD for parametric and number (%) for categorical variables. The adjusted (maternal age, gestational age and BMI) odds ratios (AOR) were determined using logistic regression. HDP; hypertensive diseases of pregnancy, BW/PW; birth weight to placental weight ratio, CI; confidence interval. *Significant at the level of P<0.050, **significant at the level of P<0.010

4.0 DISCUSSION

The study aimed to determine changes in the morphometry of the placenta and umbilical cord in HDP. Women with HDP were characterized by increased caesarean deliveries, high placental MDA, oxidative stress index and reduced placental weight.

The study observed that the weight of the placenta was lower among women with HDP (Awuah et al., 2020; Maduray et al., 2016). There is a dysfunction of the placenta in HDP. The development of placenta spiral arteries is poor and inappropriate in HDP and pseudovasculogenesis is incomplete. These and other factors may lead to placental infarcts, maternal radial arthrosis, loss of smooth muscle modifications and the impairment of diastolic blood flow to the placenta (Ives et al., 2020). As a consequence, there is a reduced placental blood flow resulting in ischemia and hypoxia which finally culminates in stress in the endoplasmic reticulum and also oxidative stress (Juan-Reyes et al., 2020; Rana et al., 2019). Reduced blood flow to the placenta implies a reduction in the supply of requisite nutrients for both placental and foetal development. This occurrence may be responsible for the reduced placental weight, low birth weight and intrauterine growth restriction (IUGR) among women with HDP (Getaneh et al., 2020; Maduray et al., 2016; Wagata et al., 2020). Changes in the morphometry of the umbilical cord have been observed among women with HDP in previous studies (Olaya-C et al., 2016). Unlike this study, HDP was associated with other forms of cord insertions including eccentric (Udainia & Mehta, 2013) while some previous studies did not find any significant differences in cord insertions between HDP and controls (Paiker et al., 2016)

The state of placental hypoxia in HDP may promote the production of free radicals in the placenta. The free radicals such as reactive oxygen species (ROS) cause lipid peroxidation and endothelial injury (Aouache et al., 2018; Tenório et al., 2019). Increased peroxidation in HDP is marked by the increased levels of products of lipid peroxidation such as MDA. There is an oxidant-antioxidant imbalance in HDP as anti-oxidant compounds are continuously consumed creating a state of generalized oxidative stress (Hariharan et al., 2017).

Hypertensive diseases of pregnancies may be characterized by increased CS (Dassah et al., 2019; Gemechu et al., 2020). HDP is characterized by placental insufficiency, abruption and non-reassuring foetal heart tracing pattern that may necessitate CS as the rate of foetal intolerance to labour is increased. Women with HDP may suffer worsening conditions as compared to normotensive pregnant women. And as such the provider's threshold for the decision to conduct a CS is reduced as labour in such women will further aggravate their already precarious condition (Kim et al., 2010). Also, magnesium sulphate, which is usually administered to HDP women as seizure prophylaxis may reduce foetal heart rate variability and subsequent non-reassuring foetal heart tracing leading to the decision to perform a CS (Guzman et al., 1993; Hiett et al., 1995).

This study is among a few studies to be conducted in the Bolgatanga municipal area regarding the factors associated with HDP. Given the observation that HDP varies from one population to another due to genetic and environmental factors, there is a need for population-specific studies (Juan-Reyes et al., 2020). Due to the smaller sample size, the findings cannot be generalized for the entire population of Ghana. Further studies should focus on specific HDPs such as preeclampsia, gestational hypertension or eclampsia, using a larger sample size.

CONCLUSION

In conclusion, hypertensive diseases of pregnancy are significantly associated with low placental weight and central umbilical cord insertion. These findings are useful for subsequent HDP research, diagnosis and management in the Bolgatanga Municipality of the Upper East Region of Ghana.

ETHICAL APPROVAL

The study followed the recommendations of the 1964 Helsinki declaration and its later amendments on the use of human subjects in research. Institutional guidelines were followed for all procedures and approval was given by the Navrongo Health Research Centre Institutional Review Board (Ref#: NHRCIRB216). All pregnant women who took part in the study gave their verbal consent before they were enrolled on the study.

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DEFINITIONS, ACRONYMS, ABBREVIATIONS

DEFINITIONS

Hypertensive disease of pregnancy was defined per the classification by the International Society for the Study of Hypertensive Disorders in Pregnancy (ISSHP) (Brown et al., 2018). HDP is described as the new onset of hypertension (≥ 140/90 mmHg) with/without proteinuria and/or evidence of liver dysfunction, haemolysis, neurological features, foetal growth restriction, maternal acute kidney injury or thrombocytopaenia at ≥20 weeks of gestation. Gravidity was used to refer to the number of times that a woman had been pregnant and parity was used to describe the number of times that a woman has given birth to a foetus at ≥24 weeks, either alive or stillborn. Gestational age was measured based on the date of the last menstrual period as well as reports from ultrasonography. Stillbirths and birth deformities were regarded as abnormal birth outcomes.

ACRONYMS, ABBREVIATIONS

AOR	Adjusted odds ratio
BMI	Body mass index
BW	Birthweight
CAT	Catalase
CD	Cord diameter
CI	Confidence interval
CL	Cord length
HDP	Hypertensive diseases of pregnancy
IUGR	Intrauterine growth restriction
MDA	Malondialdehyde
OSI	Oxidative stress index
PL	Placental length
PW	Placental weight
ROS	Reactive oxygen species
TAC	Total antioxidant capacity
TP	Total peroxide
WHO	World health organization