

Predicting Risk of Chronic Hypertension in Women with Preeclampsia Based on Placenta Histology. A Prospective Cohort Study in Cuba.

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Abstract

Background: Chronic hypertension is one of the major sequelae of preeclampsia with associated long term morbidity and mortality among previously normotensive women diagnosed with preeclampsia. We identified the predictors of developing this complication in women with preeclampsia admitted at the Carlos Manuel de Céspedes Teaching Hospital in Cuba based on histological assessment of their placenta so as to guide the health care providers in early identification of the patients at risk for timely intervention against this vicious condition.

Methods: A three-year prospective cohort study was conducted between March 2017 and March 2020. A cohort of 178 women diagnosed with preeclampsia was recruited and followed up at 12 weeks postpartum for chronic hypertension. Histological studies were done on their placenta following delivery and the respective result forms used to collect the data. Cox's hazards regression model was applied to estimate the risk using STATA version 14.2.

Results: Chorioamnionitis (HR=1.697, 95%CI: 1.443-3.416, $p=0.038$), villositary infarcts (HR=1.657, 95%CI: 1.264-2.848, $p=0.048$), intervillous thrombus (HR=1.529, 95%CI: 1.231-3.197, $p=0.020$), and endarteritis (HR=1.242, 95%CI: 1.115-1.804, $p=0.025$) placental lesions were predictive of chronic hypertension at 12 weeks postpartum.

Conclusion: Placental histology in women with preeclampsia is key towards improving the ability to diagnose and monitor those likely to develop chronic hypertension before its onset for timely intervention.

Background

Chronic hypertension and preeclampsia remain one of the most intriguing hypertensive disease conditions among obstetricians all over the world with associated high maternal and neonatal morbidity and mortality (1). The two are part of the four classification criteria for the different forms of hypertensive disorders of pregnancy; the other two being gestational hypertension and preeclampsia superimposed on chronic hypertension (2)(3)(4). Chronic hypertension is defined as one (systolic blood pressure more than or equal to 140 mmHg and diastolic blood pressure more than or equal to 90 mmHg taken four to six hours apart) that is diagnosed before pregnancy or before 20 weeks of gestation; or one that is first diagnosed after 20 weeks' gestation and persists for greater than 12 weeks postpartum (5)(6)(7). In Cuba, preeclampsia is among the leading causes of maternal deaths and there has been an apparent rise in the proportion of maternal mortality related to hypertensive disorders of pregnancy since 2009 even though numbers are small (for example, a rate of 3.2 per 100,000 live births was reported in 2012) (8). Generally, a high future risk of up to 14.8% of developing chronic hypertension in women with preeclampsia (versus 5.6% in those without preeclampsia) has been reported (9). This persistent (chronic) hypertension has been noted to be a major threat to the quality of life of the women (10) with greatly increased risk of adverse cardiovascular events such as stroke, renal failure and coronary heart diseases (11)(12)(7)(13)(14)(15).

The predictive factors for chronic hypertension following preeclampsia pregnancies however remain not very clear; not only in Cuba but even to most of the other parts of the world. For quite a long time, the placenta has attracted a lot of attention among many scholars world over with regard to its role in the aetiopathology of preeclampsia. Most theories relate to a failed transformation of the spiral arteries during placentation with subsequent release of certain factors which lead to endothelial dysfunction, generalized vasospasms and ultimately impaired multiple organ function (16)(17)(18)(19). The altered organ function can lead to persistence of hypertension depending on the severity of the endothelial dysfunction even after delivery of the placenta (13). Early interventions tailored at controlling the high blood pressure during the postpartum period may result in reduction in associated morbidity and mortality resulting from this chronic hypertension (20)(21). The aim of the current study was to identify the histological predictors of this persistent hypertension based on the patient's placenta following delivery so as to guide in easy and timely identification of those at risk for early initiation of relevant interventions so as to minimize associated complications.

Methods

This was a prospective cohort study conducted collaboratively between Granma University of Medical Sciences in Cuba and Kampala International University in Uganda over a period of three years in the months of March 2017 to March 2020. The study was conducted in the hypertension unit of Obstetrics and Gynaecology department of Carlos Manuel de Céspedes Teaching Hospital located in Bayamo city, Granma Province, Southeastern Cuba. This is a public tertiary teaching hospital for the University of Medical Science of Granma with a bed capacity of 879. The obstetric unit where the study was done has a bed capacity of 234 and conducts about 5000 deliveries per year according to the hospital records of 2019. A total of 178 pregnant women above 24 weeks of gestation admitted in the hypertension unit with a diagnosis of preeclampsia that consented to participate in the study were enrolled. Consecutive enrolment of all the pregnant women who met the inclusion criteria for the study was done until the required sample size was realised. Diagnosis of preeclampsia was made following the American College of Obstetricians and Gynaecologists' protocol 2016 (12). Preeclampsia was defined as the presence of hypertension of 140/90 mmHg or more repeated four hours apart with proteinuria of + 1 or more in a previously normotensive patient above 20 weeks of gestation (22)(23). Only women above 24 weeks of gestation were however included in the study since we also targeted doppler ultrasound scan results at 24 weeks of gestation. Women with preeclampsia superimposed on chronic hypertension were excluded from the study since they were already chronically hypertensive. Women with known history of kidney disease were also excluded from the study since serum creatinine was one of our study variables. This is usually deranged in patients with kidney disease. These three variables were particularly being considered in a different investigation. Sample size was 178, estimated using Daniel's formula (24).

Voluntary recruitment of all the study participants was done. Informed written consent from the participants was obtained after fully explaining the details of the study in Spanish, the national language for Cuba. An informed consent document in Spanish language approved by the research ethics committee of Carlos Manuel de Céspedes Teaching Hospital was signed by every participant, the

investigator and a witness. Participants were not forced to enroll if they did not want to. The participant was free to withdraw from the study at any time she wished, without coercion or compromise of care that she was entitled to. Blood pressure measurements were done using a manual mercury sphygmomanometer using the right hand at the level of the heart with the patient in sitting position. All the enrolled participants were managed according to the hospital protocol which includes antihypertensive drugs, administration of magnesium sulfate for those with severe preeclampsia and subsequently delivery. A histopathologist was notified of any impending delivery. On delivery, the placenta was received on a bowl and then assessed for any gross abnormalities. Samples were then collected in 10% formaldehyde solution and transported to the histopathology laboratory within ten minutes for further analysis. Here, the tissues were stained using Haematoxylin and Eosin (H&E) and analyzed for any abnormalities such as intervillous thrombus, villous infarcts, tennar parker changes, placental hypermaturity, chorioamnionitis, meconium, decidual necrosis and endarteritis. 10% of our samples were sent to an independent histopathologic laboratory in Bayamo province for analysis for purposes of quality assurance. To avoid bias, every 10th sample was submitted for this cause. Laboratory forms were used to collect the data. Participants were followed up at twelve weeks post-delivery and their blood pressure measurements re-taken as already explained above so as to ascertain their blood pressure status. Those whose blood pressure were still above or equal to 140 mmHg systolic and 90 mmHg diastolic were considered to have chronic hypertension. Individuals with a systolic blood pressure lower than 140 mmHg and diastolic blood pressure lower than 90 mmHg were defined as normotensive. All the collected data were entered into Microsoft excel version 2010 and then imported into STATA version 14.2 for analysis. Both univariate and Cox's multivariate model analyses were carried out to estimate the risk. The variables in the final multivariate model were significant when $p < 0.05$. The measure of association was reported as hazard ratios with corresponding 95% confidence interval and *p-value*.

Results

A total of 178 women with preeclampsia were enrolled over the period of three years. Nine patients were however excluded from the study due to superimposed preeclampsia on chronic hypertension. Four women had history of isolated renal disease (that is, had history of only renal disease without chronic hypertension) and were also excluded while three patients failed to attend the postnatal follow-up at twelve weeks. Therefore, only 162 patients were successfully studied and data analyzed. Out of a cohort of 162 participants, 45(27.8%) had chronic hypertension at twelve weeks postpartum. The most common pathological findings were endarteritis 93(57.4%), followed by villous infarcts 42(25.9%) and chorioamnionitis 25(15.4%). We noted very few cases of decidual artery disease 3(1.9%) and this was the lowest histopathological finding found. These are shown in Table 1.

We run a univariate analysis model for risk of chronic hypertension in this cohort of women with preeclampsia based on the placenta histopathological findings which revealed four variables statistically significant; that is, intervillous thrombus, villous infarcts, endarteritis, and chorioamnionitis ($p < 0.001$). This is shown in Table 2. Cox's multivariate model analysis showed that placental lesions, that is; chorioamnionitis (HR = 1.697, 95%CI: 1.443–3.416, $p = 0.038$), villous infarcts (HR = 1.657, 95%CI:

1.264–2.848, $p = 0.048$), intervillous thrombus (HR = 1.529, 95%CI: 1.231–3.197, $p = 0.020$), and endarteritis (HR = 1.242, 95%CI: 1.115–1.804, $p = 0.025$) were independently associated with high risk for developing chronic hypertension at twelve weeks postpartum. This is shown in Table 3.

Table 1

Characterization of the samples for Predictors of Risk of Chronic Hypertension in Women with Preeclampsia based on Placenta Histology at Manuel de Céspedes Teaching Hospital (N = 162)

Variable	Category	Frequency	Percent (%)
Decidual artery diseases	Yes	3	1.9
	No	159	98.1
Tenney parker changes	Yes	21	13
	No	141	87
Placental hypermaturity	Yes	6	3.7
	No	156	96.3
Intervillous thrombus	Yes	24	14.8
	No	138	85.2
Villositary infarcts	Yes	42	25.9
	No	120	74.1
Chorioamnionitis	Yes	25	15.4
	No	137	84.6
Meconium	Yes	6	3.7
	No	156	96.3
Placenta disruption	Yes	4	2.5
	No	157	97.5
Vasculitis linfocitary, Thrombosis and/or Decidual necrosis	Yes	10	6.2
	No	152	93.8
Endarteritis	Yes	93	57.4
	No	69	42.6

Table 2

Univariate Analysis for Predictors of Risk of Chronic Hypertension in Women with Preeclampsia based on Placenta Histology at Manuel de Céspedes Teaching Hospital

Variable	Hypertension	No Hypertension	RR	95%CI	<i>p</i> -value
	N %	N %			
Tenney parker changes	5 23.8	16 73.2	0.839	0.374–1.884	0.663
Placental hypermaturity	2 33.3	4 66.7	1.209	0.379–3.857	0.757
Intervillositary thrombus	16 66.7	8 33.3	3.172	2.064–4.875	< 0.001
Villositary infarcts	25 59.5	17 40.5	3.571	2.229–5.723	< 0.001
Chorioamnionitis	16 64.0	9 36.0	3.023	1.953–4.680	< 0.001
Meconium	2 33.3	4 66.7	1.209	0.379–3.857	0.757
Vasculitis linfocitary, Thrombosis and/or Decidual necrosis	7 70.0	3 30.0	2.8	1.715–4.572	0.002
Endarteritis	39 41.9	54 58.1	4.823	2.165–10.745	< 0.001

Table 3

Cox's Multivariate Model Analysis for Predictors of Risk of Chronic Hypertension in Women with Preeclampsia based on Placenta Histology at Manuel de Céspedes Teaching Hospital

Variable	Hazard Ratio	95% Confidence Interval		<i>p</i> -value
		Lower	Upper	
Chorioamnionitis	1.697	1.443	3.416	0.038*
Villositary infarcts	1.657	1.264	2.848	0.048*
Intervillositary thrombus	1.529	1.231	3.197	0.02*
Endarteritis	1.242	1.115	1.804	0.025*
* <i>p</i> <0.05				

Discussion

The precise relationship between preeclampsia and later onset of hypertension remains an intriguing issue. The placenta has remained a point of emphasis among scholars with regard to both the aetiopathology of, and the later sequelae of, preeclampsia. Our study assessed the predictive histopathologic lesions of the placenta for chronic hypertension in women with preeclampsia admitted at Carlos Manuel de Céspedes Teaching Hospital at twelve weeks postpartum. Results indicated that placental abnormalities, that is; chorioamnionitis (HR = 1.697, 95%CI: 1.443–3.416, $p = 0.038$), villous infarcts (HR = 1.657, 95%CI: 1.264–2.848, $p = 0.048$), intervillous thrombus (HR = 1.529, 95%CI: 1.231–3.197, $p = 0.020$), and endarteritis (HR = 1.242, 95%CI: 1.115–1.804, $p = 0.025$) were independently associated with high risk for developing chronic hypertension at twelve weeks. Despite paucity of information regarding relatively similar studies conducted previously, we noted supportive findings by Krielessi et al. (25) at Alexandra Maternity University Hospital in Greece who in their study to investigate the extent of placental histological lesions associated with blood pressure levels in pregnancies complicated by hypertension, histological abnormalities such as the presence of villous fibrinoid necrosis, villous hypermaturity and placental infarction were observed significantly more often in the hypertensive placentas. Their study noted that the extensive placental lesions were significantly associated with higher levels of hypertension. Similarly also, in Venezuela, Castejón and Pérez's (6) placental histopathology studies revealed severe degenerative changes to the placental villi with disorganized placenta structure provoked by chronic hypertension. In their study, the placenta showed a significant number of syncytial knots, fibrinoid necrosis, calcification and hyalinization. Meanwhile, Obiri et al. (26) in Ghana revealed syncytial knots as the main contributor to placental pathology in women diagnosed with preeclampsia; this was about ten-fold more frequent in preeclampsia than non-preeclampsia placentas. For our case however, endarteritis 93(57.4%) was the most common pathological lesion noted.

Based on these findings therefore, and as it has been suggested by Garovic and August (27), it is possible that the preeclampsia induced long-term irreversible vascular changes arising from these placental lesions may be responsible for the overall increased risk for chronic hypertension and other related long-term cardiovascular sequel of preeclampsia.

Conclusion

A remarkable number of patients with preeclampsia are candidates for future chronic hypertension and its related cardiovascular complications. Recognition of these predictors therefore may be of value towards early diagnosis for early interventions.

Abbreviations

H&E

Haematoxylin and Eosin, mmHg:Millimeters of Mercury

Declarations

Ethics approval and consent to participate in the study

Voluntary enrollment of all the study participants was done. Informed written consent from participants was obtained after fully explaining the details of the study in Spanish, the national language for Cuba. An informed consent document in Spanish language approved by the research ethics committee of Carlos Manuel de Céspedes Teaching Hospital was signed by every participant, the investigator and a witness. Participants were not forced to enroll for the study if they did not want to. A participant was free to withdraw from the study at any time she wished, without coercion or compromise of care that she was entitled to. The study was approved by the Research Ethics Committee of Carlos Manuel de Céspedes Teaching Hospital, approval number; 11 of 2016.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

We bear no any competing interests to declare.

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No funding was obtained for this study.

Authors' contributions

SB was involved in conceptualization and design of the study, analysis, manuscript writing, and coordination of the study team. YF participated in conceptualization, design, data collection, and analysis of the study. DN and AA made substantial contribution during data collection and analysis. YC contributed towards study design, data and sample collection, and analysis of samples in the histopathology laboratory. RS made substantial contribution towards study design, literature search and general revision of the manuscript. All the authors had sufficient time to read and approve the final manuscript.

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