Influence of Maternal and Perinatal Characteristics on Risk of Postpartum Chronic Hypertension Following Pre-eclampsia

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Synopsis: Biochemical, hemodynamic or echocardiographic biomarkers should be evaluated, as a weak association with peripartum clinical characteristics on postpartum chronic hypertension in pre-eclamptic women is only noted

Keywords: Pre-eclampsia; postpartum, hypertension; chronic hypertension; severe pre-eclampsia.

Abstract

Objective: To assess the prevalence of postpartum, new-onset chronic hypertension following pre-eclampsia and to determine whether maternal, fetal and peripartum factors are associated with it.

Methods: This study was conducted in a tertiary center in south India, between June 2018 and February 2019, including pre-eclamptic women who completed at least three months follow-up as a part of an ongoing cohort. Demographic, medical and laboratory details were collected. Primary outcome was a diagnosis of new-onset chronic hypertension at three months.

Results: Postpartum chronic hypertension at three months was noted in 32(18.1%) women. During postnatal follow-up, two (1.1%) women suffered hemiplegia from stroke and 19(10.7%) had elevated serum creatinine levels (>1.1mg/dl) at three months. On multivariate analysis, advancing maternal age (aOR=1.10, 95%CI 1.01-1.21), multiparity (aOR=2.79, 95%CI 1.07-7.24) and eclampsia (aOR=3.07, 95%CI 1.03-9.13) significantly increased the risk of chronic hypertension at three months post-partum.

Conclusion: One-in-five women present with a diagnosis of new-onset chronic hypertension within three months postpartum in a cohort of predominantly preterm and/or severe pre-eclampsia. A significant but weak association of chronic hypertension with peripartum clinical characteristics was noted. Role of biochemical, hemodynamic and echocardiographic biomarkers should be evaluated for prediction of postpartum chronic hypertension after pre-eclampsia in future studies.

INTRODUCTION

Pre-eclampsia, a progressive multi-systemic disorder, complicates 3-5% of the pregnancies and increases the risk of cardiovascular morbidity/mortality in mothers [1]. Recent evidence suggests that the maternal cardiovascular system is not only dysfunctional at the time of pre-eclampsia diagnosis, but that it also plays an important role in the pathogenesis of the disorder [2,3]. The latter hypothesis is consistent with the finding that women whose pregnancies were complicated by pre-eclampsia are at increased lifetime risk of chronic hypertension, stroke, myocardial infarction and other cardiovascular events [4-7]. The risk of future cardiovascular disease is eight-times higher than after normotensive pregnancies, and much higher when pre-eclampsia occurred preterm or was associated with fetal growth restriction [4,8].

Following pre-eclamptic pregnancy, maternal blood pressure typically normalizes within three months postpartum – persistent hypertension beyond this period is an indication for referral for further evaluation [9,10]. Even though the postpartum maternal cardiovascular legacy of pre-eclampsia is well recognized, it has always been presumed that this occurs several years remote to the index pregnancy. International Federation of Gynecology and Obstetrics (FIGO) in the postpartum initiative on the future risk on maternal health from pregnancy comorbidities suggest the lack of evidence regarding the strategies as when and how often to follow up these women which would be the most cost-effective at a population level [11].

More recent reports suggest that maternal chronic hypertension has suggested that the peak incidence may occur much earlier and that the magnitude of the risk is much higher [12,13]. Early diagnosis and treatment of chronic hypertension are associated with a reduction in the individual risk for developing cardiovascular disease of up to 50% [14]. This study aimed to assess the prevalence of postpartum, new-onset chronic hypertension following pre-eclampsia and to determine whether maternal, fetal and peripartum factors can influence this risk.

MATERIAL AND METHODS

This study was based on the data of women with pre-eclampsia followed up as a part of the on-going cohort study in the Women and Children's Hospital attached to the Jawaharlal Institute of Postgraduate Medical Education & Research, Pondicherry, India. Women with pre-eclampsia diagnosed based on the American College of

Obstetricians and Gynecologists (ACOG) 2013 criteria [15], referred and admitted between June 2018 and February 2019, were recruited before discharge from hospital to the primary study with planned follow-up for 12 months. Records of all women who were recruited were reviewed for blood pressure at less than 20 weeks and those women with chronic hypertension diagnosed at less than 20 weeks or during the pre-pregnancy period were excluded. The Ethics Committee (Human Studies) approved the primary research proposal leading to the work submitted (certificate (JIP/ IEC/2013/3/173). Informed consent was obtained from all women before recruitment for follow-up in the study. As per the hospital protocol, women with preeclampsia were followed up at two weeks and 6 weeks postpartum and then monthly if the blood pressure remain elevated. Anti-hypertensives were titrated according to the blood pressure values and were monitored in the local primary health centers.

Maternal demographic details, obstetric/medical history, and pregnancy outcomes were collected from the medical records. Details of laboratory investigation at diagnosis and need for postpartum anti-hypertensives medication were also collected. Calculation of body mass index (kg/m2) was performed using the height and weight noted before 15 weeks of pregnancy. Blood pressure at the time of admission to hospital, highest blood pressure recording in the antenatal period (highest reading at admission or after admission before the onset of labor), intrapartum period (during labor and delivery) and at the time of discharge were recorded.

A trained research assistant measured blood pressure in the upright sitting position after at least 5 minutes of rest. The appropriate arm cuff was placed around the left upper arm to measure blood pressure. Two reading five minutes apart, in the same arm, with a validated automatic oscillometric blood pressure monitor device (OMRON HEM-8712, Omron Healthcare Co Ltd, Japan). Women were classified as hypertensive if they met the following criteria: systolic blood pressure >140mmHg, diastolic blood pressure >90mmHg or requiring anti-hypertensive medication. The primary outcome was chronic hypertension defined as the persistence of hypertension at 3 months postpartum. [15]

Statistical Analysis

Data analysis was done using STAT 13.1 (StataCorp, Texas, USA). The normality of continuous data was checked with Kolmogorov–Smirnov tests and presented either

as mean ± standard deviation, or as median and range. Association of the continuous data with chronic hypertension was assessed using wither Student t-test or Mann Whitney test. Categorical data are presented as frequencies and percentages and chi-square or Fisher exact test was used to assess its association with postpartum chronic hypertension. Multivariable logistic regression analysis was done to study the association of various risk factors with the persistence of hypertension at 3 months. A p-value of < 0.05 was considered significant.

RESULTS

One hundred and ninety-one women with pre-eclampsia during the study period completed at least three months follow-up and after excluding 14 women with preexisting or chronic hypertension 177 women with preeclampsia was included in the final analysis.(Figure 1) Maternal demographic and pregnancy characteristics are shown in Table 1. The majority of women were nulliparous (n=115, 65.0%) with preterm preeclampsia (n=116, 68.6%), mean age of 25.7 years and mean gestation at the birth of 34.1 weeks. Eclampsia and hemolysis elevated liver enzymes, and low platelet (HELLP) syndrome complicated 39 (22.3%) and 22 (12.6%) pregnancies, respectively. At the time of discharge, 103 women were on antihypertensives, with the majority of them receiving either labetalol (n=30) and/or amlodipine (n=26).

Persistence of hypertension at three months was noted in 32 (18.1%) women. Among these women 27 needed anti-hypertensives (Tab Amlodipine 2.5mg [n=20] or 5mg [n=7] once daily) at three months. During the postnatal period, two (1.1%) women suffered from hemiplegia due to stroke, 19 (10.7%) had elevated serum creatinine level (>1.1mg/dl) and 41.5% had abnormal urine protein creatinine ratio values (>0.3). In bivariate analysis, maternal age, parity, and chronic kidney disease were significantly associated with postpartum chronic hypertension (Tables 2 and 3). On multivariate analysis after adjusting for other parameters, only advancing maternal age (aOR=1.10), multiparity (aOR=2.79) and eclampsia (aOR=3.07) were significantly associated with the diagnosis of new-onset, postpartum chronic hypertension (Table 4).

DISCUSSION

This study investigated the postpartum cardiovascular morbidity in a cohort of referred women with predominantly preterm, severe pre-eclampsia. The findings demonstrate

high cardiovascular morbidity with approximately one in five women diagnosed with new-onset chronic hypertension and two women with stroke-induced hemiplegia within three months of delivery. Although maternal age, parity, and eclampsia were statistically associated with adverse postpartum cardiovascular outcomes, they were poorly predictive for the development of postpartum chronic hypertension.

After a pregnancy complicated with hypertensive disorders, maternal blood pressure typically returns to normal within three months [8-10]. Hypertension per se is regarded as an important causal factor for cardiovascular and cerebrovascular disease, with timely reduction with antihypertensive shown to have a significant reduction in the major events regardless of age and class of drug used. Women and healthcare workers are usually unaware of the risk of persistent postpartum hypertension and subsequent cardiovascular morbidity is high, especially in low to middle-income countries [16]. It is typically assumed that the cardiovascular legacy of preeclampsia occurs several decades after the index pregnancy. The rate and timing of postpartum chronic hypertension in this study were more severe than that reported in the literature [16-22]. Variation in prevalence from previous studies may occur because of differences in the timing/severity of pre-eclampsia, the presence of co-morbidity and the longer-term outcomes available from large epidemiological databases. More recently, in a large population-based study from Denmark assessing shorter-term outcomes, the risk of hypertension was found to be highest in the first one to two years postpartum and that about thirty percent of women developed hypertension within a decade of delivery of a pre-eclamptic pregnancy [12]

Various risk factors were reported in the earlier studies to be associated with the development of postpartum chronic hypertension several years to decades later. These include maternal age, ethnic origin, body mass index (BMI), pregnancy/postpartum blood pressure, HELLP syndrome and delivering a small for gestational age baby [16-21]. Hwang *et al.*[17] noted that pre-pregnancy BMI, history of smoking along with early-onset preeclampsia with end-organ dysfunction to be associated with progression to a diagnosis of chronic hypertension postpartum. Obesity was found to increase the long-term risk of chronic hypertension in a study of 54,000 women participating in the Nurses' Health Study II - regardless of a history of hypertensive disorders of pregnancy [18]. Only two previous studies investigated immediate or short-term postpartum chronic hypertension rates after preeclampsia

[16,19]. The authors showed that persistent postpartum hypertension occurred in 21-27% of women and was associated with maternal age, Afro-Caribbean ethnicity, serum creatinine, need for antihypertensive medication at discharge and those with severe pre-eclampsia. However, both studies failed to exclude women with pre-existing chronic hypertension from the analysis, but they did confirm the poor predictive ability of these associations.

There is only limited data available in the literature regarding the immediate postpartum development of new-onset chronic hypertension. Hypertension is part of a current epidemic of non-communicable disease and is known to be associated with an increased long-term risk of severe cardiovascular disease [22]. Furthermore, most of the existing data is derived from high-income countries and may not be generalizable to low and middle-income populations. The high rate of new-onset postpartum hypertension within three months in our cohort suggests that systematic screening for cardiovascular in the postpartum period after severe preterm preeclampsia in the low to middle-income countries is justified. The study findings also support a more immediate and significant impact on maternal postpartum renal morbidity with high rates of elevated serum creatinine level and abnormal urine protein creatinine ratio values. Consideration should also be given to postpartum maternal renal assessment at follow-up visits.

The current data confirm that routinely collected information on maternal, fetal and delivery characteristics may be associated with postpartum cardiovascular outcomes, but do not appear to be useful in determining a high-risk sub-population for targeted follow-up. As cardiovascular diseases and pre-eclampsia share common pathophysiologic/risk factors, the role of maternal biomarkers for dyslipidemia, insulin resistance, hypercoagulability, and inflammation may help in the prediction of hypertension [23,24]. Maladaptation to the cardiovascular load and changes in pregnancy as noted in echocardiographic evaluation is observed as one of the pathophysiological processes in pre-eclampsia [13]. In the future, the evaluation of these factors as a predictor for the persistence of maternal hypertension into the postpartum period needs to be studied. Identifying such women will provide an opportunity to initiate preventive measures/modify the risk to reduce the subsequent development of cardiovascular events in later life.

This is a well-defined prospective study that contained high enough rates of preterm pre-eclampsia and severe complications such as eclampsia and HELLP syndrome to evaluate the contribution of such factors to the development of postpartum new-onset chronic hypertension. There is a concern that the observed rate of postpartum chronic hypertension in the study may be higher than anticipated for a routine pre-eclampsia population because of the high prevalence of preterm and/or severe preeclampsia in the referred cohort. However, most large epidemiological studies report similar rates of long-term CVD after both preterm and severe preeclampsia compared to milder and term disease, making the risk of such bias low [7,25]. The relatively small cohort investigated increases the risk that the study overlooked other factors contributing to the development of postpartum hypertension. Although this may be the case, any such additional factors will inevitably have weaker odds ratios than observed in the study and are unlikely to help improve the identification of women with postpartum hypertension.

CONCLUSION

One out of five women present with new-onset chronic hypertension within three months postpartum in a cohort of predominantly preterm and/or severe pre-eclampsia. There was a weak association between advancing maternal age, multi-parity, and eclampsia with the diagnosis of postpartum chronic hypertension. Future studies assessing biochemical, hemodynamic or echocardiographic biomarkers are required to evaluate the risk postpartum chronic hypertension in women with pre-eclampsia.

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Contribution to Authorship: AK and BT conceived the study. All authors contributed to the design. AK, BV, DKM AAP carried out the data collection and guarantees data integrity. AK performed statistical analyses. BT, SSK, AAP, and DKM reviewed the analysis and AK & BT wrote the first draft. All authors contributed to revising and finalization of the manuscript. AK (corresponding author) guarantees all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Table 1: Maternal demographics and other characteristic in the antenatal period of the study population

	Normotensive (n=145)	**Hypertensive (n=32)**	**p value**
Age, years*	25.2 ±4.9	28.1 ±5.7	**0.004**
Parity**			
Nulliparous	101 (69.7%)	14(43.8%)	**0.005**
Multiparous	44 (30.3 %)	18(56.2%)	
Body Mass Index, kg/m^2*	25.5 ±3.8	25.9 ± 4.3	0.691
Co-morbidities**			
Diabetes Mellitus	12 (8.3 %)	5 (15.6 %)	0.202
Chronic Kidney Disease	0(0%)	2(6.3 %)	**0.002**
Pulse Rate, at admission, beats per minute*	86.6 ±11.3	84.7 ±12.1	0.396
Blood Pressure at admission, mm Hg*			
Systolic	146.3 ± 21.9	148.2 ± 17.9	0.645
Diastolic	93.2 ±13.3	95.4 ± 13.6	0.395
Highest BP value antenatal, mm Hg*			
Systolic	147.0 ± 16.3	149.3 ± 20.1	0.490
Diastolic	95.8 ± 9.5	95.4 ± 9.3	0.800
Small for gestational age**	58(40.0%)	15(46.8%)	0.479
Eclampsia**	28 (19.3%)	11 (34.3%)	**0.063**
HELLP syndrome**	19 (13.1%)	3 (9.4%)	0.564
Magnesium sulphate use**	114 (78.6%)	21 (65.6%)	0.204

*Mean ± Standard deviation

** n (%)

Table 2: Labour and delivery details and maternal characteristics

	Normotensive (n=145)	**Hypertensive (n=32)**	**p value**
Highest BP in labour, mm Hg*			
Systolic	133.4 ± 16.2	137.4 ±14.1	0.202
Diastolic	86.8 ± 9.8	90.4 ±9.1	**0.064**
Pulse Rate in labour, beats per minute*	91.1 ± 11.1	93.6 ±10.4	0.833
Gestation at birth**	34.2 ± 3.7	33.5 ± 4.2	0.376
Caesarean section**	82 (59.4%)	17(56.7%)	0.781
Birth weight, grams*	1892.9 ± 712.3	1608.1 ± 808.9	**0.065**
Stillbirth**	20 (13.9 %)	6(18.8 %)	0.707
Pulse Rate at discharge, beats per minute*	85.9 ± 10.7	87.7 ± 7.6	0.432
BP at discharge, mm Hg*			
Systolic	123.7 ±16.0	126.0 ± 7.7	0.434
Diastolic	82.1 ± 8.4	83.7 ± 7.0	0.322
Antihypertensive at 7 days**	80 (56.7 %)	23 (71.9%)	**0.081**

*Mean ± Standard deviation

** n (%)

Table 3 showing multivariate logistic regression assessing association of various risk factors associated with persistent of hypertension at 3 months

	Odds Ratio (OR)	**95% confidence interval**	**p value**
Age	1.10	1.01, 1.21	**0.047**
Parity**			
Nulliparous	1.0	1.0	**0.035**
Multiparous	2.79	1.07, 7.24	
Highest BP in labour, mm Hg*			
Systolic	0.99	0.96, 1.02	0.590
Diastolic	1.03	0.97, 1.10	0.270
Eclampsia**	3.07	1.03, 9.13	**0.044**
Gestation at birth**	1.02	0.85, 1.22	0.803
Birth weight, grams*	1.00	0.99, 1.01	0.524
Antihypertensive at 7 days**	1.38	0.50, 3.79	0.531

Table S1: Comparison of investigation among women who developed chronic hypertension compared to those who did not develop it.

	Normotensive (n=145	**Hypertensive (n=32)**	**p value**
Haemoglobin, gm/dl *	10.5 ± 2.3	10.1 ± 3.9	0.355
Platelet, lakhs per mm^3*	2.06 ± 0.92	2.00 ±0.90	0.762
Aspartate Transaminase, IU/L***	25.0 (4.0-775.0)	30.0(16.0-120.0)	0.723
Alanine Transaminase, IU/L***	20.0 (5.0-607.0)	23.0(8.0-130.0)	0.912
Urea, mg/dl*	18.0 (7.0-86.0)	21.0(7.0-47.0)	0.954
Creatine, mg/dl*	0.7 (0.4-4.92)	0.7 (0.3-9.1)	0.469
Total protein, gm/dl*	4.4 ±2.4	4.9 ±1.9	0.189
Albumin, gm/dl*	2.3 ± 1.1	2.6 ±0.9	0.164
Urine protein ≥2+, **	73 (50.3%)	16 (50.0%)	0.482

*Mean ± Standard deviation

** n (%)

*** Median, Range

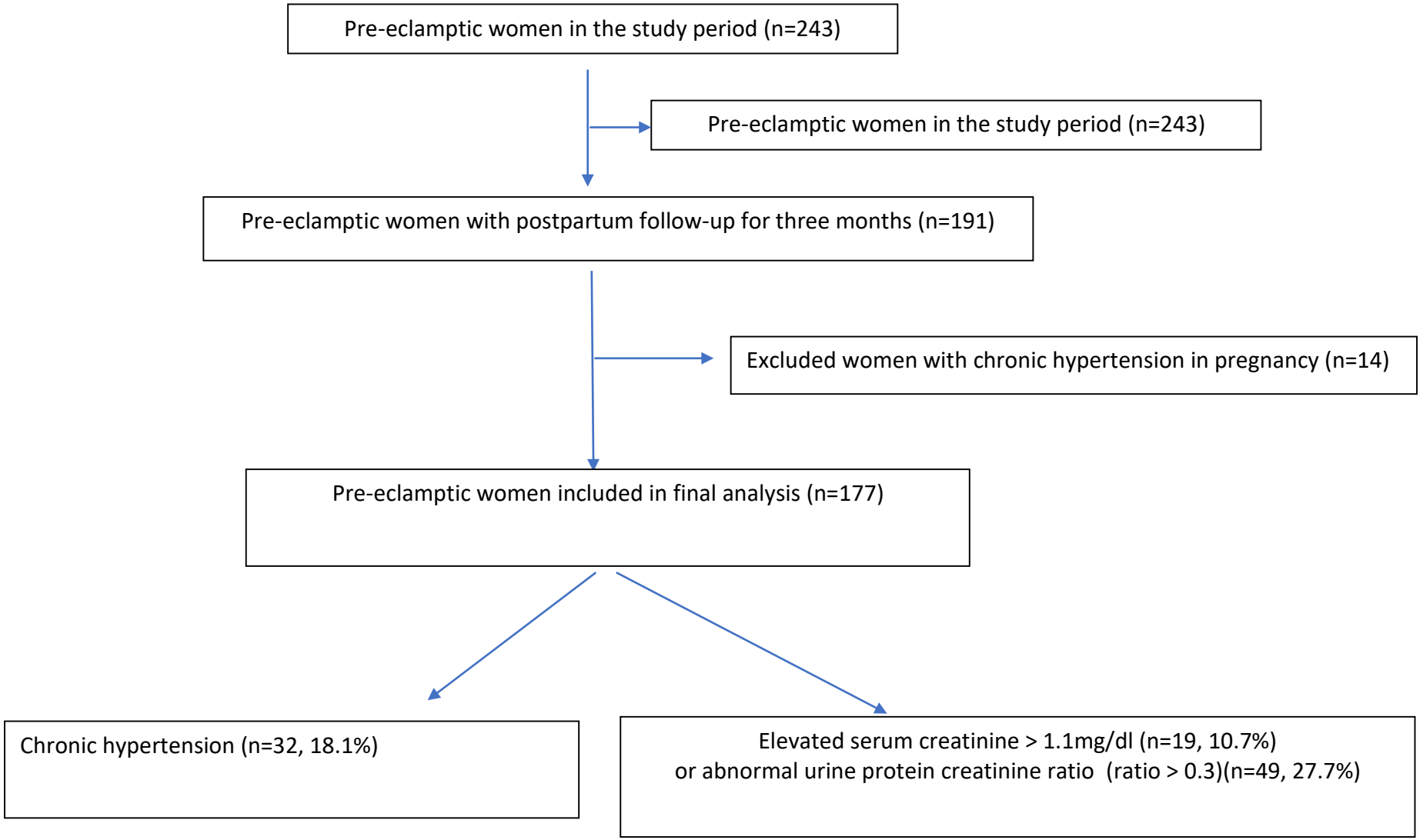

Figure 1: Study participant flow chart