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Research

Maternal and perinatal outcomes in women with chronic hypertension and risk factors of superimposed preeclampsia

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Abstract

Objective: The aim of this study is to evaluate obstetric outcomes among women with chronic hypertension, with and without superimposed preeclampsia, and identify risk factors of superimposed preeclampsia.

Material and Methods: This retrospective study included 198 Caucasian women with chronic hypertension (out of 14,424 singleton pregnancies) who delivered in a tertiary care center. Clinical findings, maternal and perinatal outcomes were compared between women with and without superimposed preeclampsia.

Results: Superimposed preeclampsia developed in 49.4% (98/198) of women studied. The mean gestational week at delivery and birth weight were significantly lower in women with superimposed preeclampsia ($p< 0.05$). Incidence of preterm delivery was higher in women with superimposed preeclampsia. Although there weren't significant differences in frequencies of intrauterine growth restriction, stillbirth, early and late neonatal deaths ($p > 0.05$), maternal near miss cases were significantly higher in women with superimposed preeclampsia ($p < 0.05$). Only mean arterial blood pressure [OR: 1,070 (1,008-1,135)] was independently associated with the occurrence of superimposed preeclampsia (p: 0.027).

Conclusions: Adverse maternal outcome was more likely to occur in women with suprerimposed preeclampsia. Chronic hypertension was associated with adverse perinatal outcome, regardless of superimposed preeclampsia.

Keywords: chronic hypertension; preeclampsia; maternal mortality; perinatal mortality

Introduction

Pregnancies in women with chronic hypertension are at an increased risk of adverse obstetric outcomes including superimposed preeclampsia, preterm birth, low birth weight, intrauterine growth restriction (IUGR), fetal death, HELLP (Hemolysis, elevated liver enzymes, and low platelets) syndrome and cesarean delivery [1, 2, 3]. Increased risk of adverse outcome was detected in women with superimposed preeclampsia compared to those without[3]. Increased risk of adverse outcome has been attributed to both underlying vascular abnormality and pathophysiology exclusive to the preeclampsia irrespective of underlying vascular abnormali-

ty[4,5]. This study was performed to evaluate obstetric outcomes among women with chronic hypertension, with and without superimposed preeclampsia, and identify risk factors of superimposed preeclampsia.

Materials and Methods

This retrospective study included 198 Caucasian women with chronic hypertension (out of 14,424 singleton pregnancies) who delivered in a tertiary care center, over a ten-year period. Clinical findings, maternal and perinatal outcomes were compared between women with and without superimposed preeclampsia. Risk factors of superimposed preeclampsia were identified.

Chronic hypertension was defined as systolic pressure ≥140 mmHg and/or diastolic pressure ≥ 90 mmHg that is present pre-pregnancy or before the 20th week of pregnancy (on at least two occasions) or persists longer than 12 weeks postpartum. Because of inadequate postpartum follow-up, women with chronic hypertension defined according to the persisting hypertension longer than 12 weeks postpartum were not enrolled in this study. Both primary and secondary hypertension were included. Superimposed preeclampsia was defined by the new onset of either proteinuria or end-organ dysfunction after 20 weeks of gestation in a woman with chronic hypertension. For women with chronic hypertension who have proteinuria prior to or in early pregnancy, superimposed preeclampsia was defined by worsening or resistant hypertension (especially acutely) in the last half of pregnancy or development of signs/symptoms of the severe spectrum of the disease. Diagnostic criteria for severe preeclampsia were:

1. **Hypertension:** systolic BP >160 mmHg or diastolic BP >110 mmHg on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time).
2. **Thrombocytopenia** (platelet count <100,000/microliter).
3. **Impaired liver function** (elevated blood levels of liver transaminases to twice the normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for alternative diagnosis, or both.
4. **New development of renal insufficiency** (elevated serum creatinine greater than 1.1 mg/dL, or doubling of serum creatinine in the absence of other renal disease).
5. **Pulmonary edema**.
6. **New-onset cerebral or visual disturbances**[6].

Gestational week was determined according to the last menstrual period and/or to the crown- rump length at first trimester ultrasound. IUGR was defined as a birth weight <10th percentile for gestational age. Perinatal mortality was defined as the number of stillbirth and death in the first week of life. Maternal deaths and maternal near- miss (MNM) cases were defined in respect of World Health Organization/ International Classification of Diseases-10 (WHO/ICD-10) definitions. The WHO defines a maternal near-miss case as "a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy." The flow chart recommended by Say et al. was used in the selection of MNM cases[7]. Only maternal deaths and MNM cases caused by hypertension were accepted as maternal deaths and MNM cases.

All women with severe symptoms were hospitalized. Women without severe symptoms were also hospitalized if they had fetal indication. Magnesium sulfate for eclamptic seizure prophylaxis and acute antihypertensive therapy were administered to women with severe superimposed preeclampsia when it is deemed within the indications. Besides acute antihypertensive therapy, only 35.3% of women had antihypertensive medication before or during pegnancy. Antenatal steroid was administered for fetal lung maturity to all pregnancies less than 34 weeks of gestation. Indications for delivery were severe symptoms, uncontrollable blood pressure, or nonreassuring fetal status according to cardiotocography and umbilical artery Doppler assesment with absent or reversed end-diastolic flow. Spontaneous labor was also an indication for delivery.

Following data were used: maternal age, gravidity, parity, previous history of immature-premature-term birth, previous history of stillbirth, previous history of abortion (before and/or after 12th gw), previous history of elective abortion, previous history of preeclampsia and/or eclampsia, systemic disease, antihypertensive medication, smoking, antenatal care, highest blood pressure (systolic-diastolic- mean arterial pressure) at admission, existence of HELLP syndrome, existence of eclampsia, existence of severe symptoms, gestational week at birth, gestational weight, birth percentile, gender of the fetus, maternal mortality, MNM, stillbirth, perinatal death, early neonatal death, neonatal death.

Statistical Package of the Social Sciences (SPSS) 17.0 software (SPSS Inc., Chicago, USA) was used for the statistical analyses. Data were expressed as n (%) and mean with standard deviation. Quantitative variables were tested for normal distribution (by Kolmogorov-Smirnov Test) and homogeneity (by One-Way Anova Test). For those variables not distributed normally, two groups were compared with Mann-Whitney U Test. Chi-square test for independence was used for the analysis of categorical variables. A p value < 0.05 was considered as significant.

A logistic model was also set up to describe the relationship between superimposed preeclampsia and variables associated with superimposed preeclampsia. Chi-square test for independence and univariate logistic regression analysis were used for the selection of variables ($p < 0.05$). Significant variables were included in the multivariate logistic regression analysis. Before multivariate logistic regression analysis, significant variables were analyzed by bivariate correlation test to determine whether the relationship between independent variables was significant. Backward stepwise elimination (likelihood ratio) was used in the logistic regression. Entry and removal significance levels for the backward selection were 0.05 and 0.1, respectively. Significance level of 0.05 was used for the assessment of model. Classification table and pseudo R2 statistics were applied to assess the adequacy of the model. Box-Tidwell test was used to determine the presence of linear correlation betweeen the continuous variables and the logit. Odds ratios were used in the interpretation of the last model. Likelihood ratio test was used for assessment of model. Likelihood ratio test and the Omnibus test were used for the assessment of variable coefficients. The goodness of fit of the model was performed by Hosmer-Lemeshow test.

This study was conducted according to the principles as have set forth by the Helsinki Declaration of 1975. An approval from the Human Ethics Committee of Institution was obtained.

Results

The mean maternal age was 32.42 ± 6.2, mean gestational week at delivery was 34.3 ± 4.2 weeks, mean birth weight was 2,139 ± 1,026 g. Ratios of antenatal, perinatal, neonatal mortality were, respectively as follows: 10.6%, 16.8%, 8.6%. Ratio of MNM was 14.1%. There were no any maternal deaths. 14.1% of cases didn't have antenatal care.

Among the 198 women 95 (48%) had severe symptoms, 1 (0.5%) had eclampsia, 16 (8.1%) had HELLP syndrome. Incidences of IUGR, delivery before 37 weeks, delivery before 34 weeks, and cesarean section were, 31.3%, 57.6%, 61.6%, and 66.2%, respectively. Superimposed preeclampsia developed in 98 (49.4%) women, 49% of it was early-onset.

Table 1 shows the association of some clinical characteristics with the occurrence of superimposed preeclampsia. Maternal age, nulliparity, previous history of term-premature-immature birth, history of stillbirth, history of abortion, history of preeclampsia-eclampsia, smoking, antihypertensive medication weren't significantly associated with preeclampsia ($p > 0.05$). Although the incidence of diabetes mellitus was significantly higher in women without preeclampsia ($p < 0.05$), there weren't significant differences in incidences of renal and rheumatic disease ($p > 0.05$). Male fetal gender, highest blood pressure (systolic-diastolic-mean arterial pressure), and severe symptoms were significantly associated with superimposed preeclampsia.

Table 2 shows obstetric outcomes among women with chronic hypertension, with and without super-

Table 1: Factors associated with development of superimposed preeclampsia by univariate analysis

	without superimposed preeclampsia *n*: 100 (%)	with superimposed preeclampsia *n*: 98 (%)
Maternal age	32.4 ± 6.2	32.09 ± 6.6
Nulliparity	47 (47)	35 (35.7)
Prior term delivery	48 (48)	56 (57.1)
History of preterm delivery	8 (8)	12 (12.2)
History of immature delivery	5 (5)	3 (3.1)
History of stillbirth	5 (5)	8 (8.2)
History of abortion	21 (21)	23 (23.5)
Before the 12th week of gestation	19 (19)	21 (21.4)
After the 12th week of gestation	4 (4)	2 (2)
History of elective abortion	13 (13)	19 (19.4)
History of preeclampsia/eclampsia	4 (4)	9 (9.2)
Smoking	12 (12)	5 (5.1)
Systemic disease		
Diabetes mellitus*	22 (22)	11 (11.2)
Renal disease	8 (8)	11 (11.2)
Romatologic disease	1 (1)	3 (3.1)
Antihipertansive therapy	37 (37)	33 (33.7)
Antenatal care	89 (89)	81 (82.7)
Gender of the fetus*		
Male	44 (44)	60 (61.2)
Female	56 (56)	38 (38.8)
Highest systolic pressure*	158.6 ± 28.8	172 ± 27.7
Highest diastolic pressure*	99 ± 16.6	106.5 ± 16
Mean arterial pressure*	119 ± 19.9	128.4 ± 19

**p < 0.05*

imposed preeclampsia. The mean gestational week at delivery and birth weight were significantly lower in women with superimposed preeclampsia ($p < 0.05$). Incidences of birth before the 34th and 37th weeks of gestation were higher in women with superimposed preeclampsia. Although there weren't significant differences in frequencies of IUGR, stillbirth, early and late neonatal death ($p > 0.05$), MNM cases were significantly higher in women with superimposed preeclampsia ($p < 0.05$).

In univariate analysis highest blood pressure (systolic-diastolic-mean arterial) at admission, fetal gender, severe symptoms and diabetes mellitus were significantly associated with superimposed preeclampsia ($p < 0.05$). The rate of superimposed preeclampsia substantially increased with high blood pressure at admisson. Because of positive correlation between three variables (systolic-diastolic-mean arterial pressure), we have chosen to include mean arterial blood pressure at multivariate analysis. In multivariate analysis only mean arterial blood pressure [OR: 1,070 (1,008-1,135)] was independently associated with the occurrence of superimposed preeclampsia (p: 0.027).

Table 2: Obstetric outcomes among women with chronic hypertension, with and without superimposed preeclampsia

	without superimposed preeclampsia *n*: 100 (%))	with superimposed preeclampsia *n*: 98 (%)
Gestational week at delivery *	34.3 ± 4.2	33.3 ± 4.2
Birth before the 34th week of gestation*	30 (30)	46 (46.9)
Birth before the 37th week of gestation*	44 (44)	70 (71.4)
Birth weight (g)*	2,139 ± 1,026	1,862 ± 935
Stillbirth	8 (8)	13 (13.3)
Early neonatal death	7 (7)	8 (8.2)
Perinatal mortality	13 (13.3)	20 (20.4)
Late neonatal death	1 (1)	1 (1)
Neonatal mortality	8 (8)	9 (9.2)
IUGR	28 (28)	34 (34.7)
Maternal mortality and MNM*	3 (3)	25 (25.5)
Eclampsia	0 (0)	1 (1)
HELLP syndrome*	0 (0)	16 (16.3)
Severe symptoms*	24 (24)	71 (72.4)
Cesarian section rate	70 (70)	61 (61.2)

* $p < 0.05$

Discussion

Although the proportion of women with superimposed preeclampsia (49.4%) was lower than that reported by some studies[1, 8], it was higher than that of other studies[9, 10]. The differences in results between these studies can be attributed to the population studied. They range from 5.2% to 25% in mild hypertension and from 52% to 100% in severe chronic hypertension[1]. In current study both mild and severe chronic hypertension were included. As interpreted by Chappell et al. nearly half of women with superimposed preeclampsia were early-onset[3].

In contrast to Lecarpentier et al., in univariate analysis we found that the rate of superimposed preeclampsia was not affected by nulliparity[11]. Similar to other studies, we did not find a significant association between maternal age and risk of superimposed preeclampsia[11, 12].

Although some studies stated that previous preeclampsia was independently associated with occurrence of superimposed preeclampsia, Sibai et al. did not find such association[3, 11, 12]. We didn't find such association either.

In contrast to Chappell et al., we found rate of superimposed preeclampsia was not affected by chronic renal disease. Although their sample size was larger than that of us, the incidence of chronic renal disease (9.59%) in our study was higher than those (4%)[3].

We didn't detect any relationship between antihypertensive therapy and risk of preeclampsia similar to study conducted by Lecarpentier et al.. Although their study included only women who received antihypertensive therapy prior to conception, our study also included women taking no medication[11]. These results were in contrast to results obtained by Chappell et al.. Chappell et al. stated that current antihypertensives increased the risk of preeclampsia[3].

There are conflicting reports in the literature concerning the relationship between smoking and risk

of preeclampsia in chronic hypertension. Chappell et al. found that smoking was an independent risk factor for superimposed preeclampsia, while others did not find any relation[3, 11, 12]. We didn't find such association either.

In current study women with superimposed preeclampsia were more likely to have higher blood pressures (systolic-diastolic-mean arterial), as compared to those without superimposed preeclampsia. Although these results were similar to other studies in some respects, there were some differences[3, 12, 13, 14]. In those studies systolic and diastolic blood pressures were obtained at first prenatal visit and/or prior to hospitalization, while in current study these variables were recorded at hospitalization. So, baseline values were higher in this study, whether with or without preeclampsia.

In the literature there are conflicting results regarding association between fetal gender and preeclampsia. Some studies concluded that male predominance was associated with higher incidence of preeclampsia[15, 16, 17, 18], while others not[19, 20]. However, we did not find any study investigated the association between fetal gender and superimposed preeclampsia. In univariate analysis we found that male predominance was significantly associated with superimposed preeclampsia, while in multivariate analysis only the mean arterial pressure was independently associated with the occurrence of superimposed preeclampsia.

Similar to several studies, irrespective of superimposed preeclampsia, adverse maternal and perinatal outcomes were increased in women with chronic hypertension. Rates of birth before 37th and 34th weeks of gestation were higher, but birth weight was lower in women with superimposed preeclampsia[3, 9]. Unlike these studies no statistically significant difference was shown in rates of cesarean section, IUGR, fetal and neonatal death between groups. In concordance with Srinivas et al. we concluded that pathogenesis of IUGR may differ in chronic hypertension from preeclampsia and/or superimposed preeclampsia[21]. It was suggested that circulating levels of angiogenic factors showed smaller increments when preeclampsia developed in women with chronic hypertension or diabetes mellitus, because there was already preexisting maternal endothelial cell dysfunction[22]. Underlying vascular pathologies may predispose fetal growth restriction in women with chronic hypertension.

Vigil-De Gracia et al. stated that eclampsia was not detected in women with superimposed preeclampsia suggesting different pathophysiological abnormalities leading to development of eclampsia in women with or without chronic hypertension[1]. We also detected only one women with eclampsia reinforcing this concept.

Conclusions

Adverse maternal outcome was more likely to occur in women with suprerimposed preeclampsia. Chronic hypertension was associated with adverse perinatal outcome, regardless of superimposed preeclampsia.

Limitations

Lack of blood pressures prior to hospitalization was limitation of this study because it precluded the prediction of preeclampsia prior to hospitalization. This study didn't included normotensive women. So, direct comparison of outcomes between women with chronic hypertension and normotensive women was not possible.

Conflict of interest

The authors declare that they have no conflict of interest.

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