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Can we predict the need for antihypertensive treatment during the early postpartum period for women with preeclampsia or gestational hypertension?

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ABSTRACT

Objectives: To determine factors that predict the need for antihypertensive treatment during early postpartum period among women with preeclampsia or gestational hypertension.
Study design: Retrospective cohort of 358 women.
Main outcome measures: Demographic, clinical and laboratory data of 63 women diagnosed with preeclampsia or gestational hypertension during a singleton pregnancy and who needed antihypertensive agents during early postpartum period were compared to 295 who did not.
Results: No difference was found between groups regarding age, parity, body mass index, or weight gain ($p = 0.95$, 0.19, 0.56, and 0.078, respectively). Early onset preeclampsia or gestational hypertension was diagnosed among 28.6% of the women who subsequently needed antihypertensive treatment, as compared to 4.1% who did not ($p < 0.001$). Antepartum, mean maximum blood pressure in the treated vs. untreated group was 165/109 mmHg vs. 150/100 mmHg, respectively ($p = 0.001$).

Groups did not differ regarding symptoms of preeclampsia (38.7% vs. 31.5%, $p = 0.273$) or laboratory abnormalities. The group that received antihypertensive treatment during early postpartum period, had more preterm deliveries ($p < 0.001$) and Cesarean deliveries ($p < 0.001$), and more received magnesium sulfate during labor ($p < 0.001$). During the early postpartum period, mean maximum blood pressure was higher among the treated group (167/106 vs. 143/92, $p = 0.001$), as were symptoms of preeclampsia ($p = 0.001$). The groups were similar regarding laboratory abnormalities that define preeclampsia.
Conclusions: Early onset preeclampsia or gestational hypertension, severe antepartum hypertension, magnesium sulfate during labor, preterm, and Cesarean delivery might be good predictors of the need for antihypertensive treatment during early postpartum period.

1. Introduction

Hypertension is one of the most common complications of pregnancy, estimated to affect approximately 5%–15% of all pregnancies [1], of which preeclampsia and gestational hypertension occur most often [2]. Preeclampsia refers to the new onset of hypertension and proteinuria or hypertension and significant end-organ dysfunction with or without proteinuria, after 20 weeks of gestation, in a previously normotensive woman. Gestational hypertension is defined as hypertension without proteinuria or other signs/symptoms of preeclampsia-related to end-organ dysfunction, which develops after 20 weeks of gestation [3].

A subset of preeclampsia is classified as preeclampsia with severe features, which include systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg and proteinuria, or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (with or without proteinuria) and one or more of the signs and symptoms of significant end-organ dysfunction. These include new-onset cerebral or visual disturbances, persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by an alternative

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; WHO, World Health Organization

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diagnosis or serum transaminase concentration ≥2 times upper limit of normal, thrombocytopenia (< 100,000 platelets/μL) or progressive renal insufficiency (serum creatinine > 1.1 mg/dl) [3].

Hypertension can persist from the antepartum to the postpartum periods or present *de novo* postpartum and continue to pose a risk to maternal well-being. Although a large proportion of complications associated with preeclampsia occurs in the postpartum period (44% of eclamptic seizures and 10% of maternal deaths) [4], medical literature covering this topic focused on antenatal and intrapartum management, and little information is available regarding the postpartum period.

Current management schemes designed to prevent eclampsia are based on early detection of gestational hypertension or preeclampsia and subsequent preventive therapy [5–7]. Several risk factors are associated with hypertension postpartum, including pre-existing chronic hypertension, obesity and hypertensive disorders of pregnancy [8]. Yet, it is still difficult to forecast the need for antihypertensive treatment postpartum in patients with preeclampsia or gestational hypertension.

A case-control study [9], which investigated possible antepartum predictors of the need for postpartum antihypertensive treatment in women with severe preeclampsia, found that patients with chronic hypertension and those who needed intrapartum hydralazine were more likely to require antihypertensive medications at discharge. Another study [10] found that preeclamptic women who received prophylactic magnesium sulfate and those who had higher peak antenatal systolic blood pressure were more likely to need postpartum antihypertensive treatment. These studies included women with preeclampsia only; cases of gestational hypertension were not evaluated.

It is important to identify women who need antihypertensive treatment in the early postpartum period in order to prevent complications secondary to hypertension, such as stroke, pulmonary edema or renal failure. The objective of current study was to determine factors that could predict the need for antihypertensive treatment during the early postpartum period among women with pre-eclampsia or gestational hypertension.

2. Material and methods

The study included an historical cohort of 358 women diagnosed with preeclampsia or gestational hypertension during a singleton pregnancy, who were admitted to the Department of Obstetrics & Gynecology at Meir Medical Center, from 2/2014 to 10/2016. Women were identified by querying electronic medical records. Preeclampsia was defined as new onset of hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on two occasions at least four hours apart) and proteinuria (≥0.3 g in a 24-hour urine specimen or > 0.3 protein to creatinine ratio) after 20 weeks of gestation. In the absence of proteinuria, the condition was diagnosed when new-onset hypertension was accompanied by signs or symptoms of significant end-organ dysfunction. Gestational hypertension was defined as new onset hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) without proteinuria or other signs/symptoms of preeclampsia-related end-organ dysfunction that developed after 20 weeks of gestation [3]. Early-onset preeclampsia/gestational hypertension was defined when diagnosed < 34 weeks of gestation [11]. Symptoms of preeclampsia were defined as new-onset cerebral or visual disturbance, or severe, persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by an alternative diagnosis [3].

Inclusion criteria were singleton pregnancy and clinical diagnosis of gestational hypertension or preeclampsia. Exclusion criteria were twin pregnancy, use of aspirin during pregnancy, and comorbid conditions of chronic hypertension, pregestational/gestational diabetes, autoimmune disease or renal disease or who were given antihypertensive medications antepartum. Indication for antihypertensive treatment postpartum, before hospital discharge was blood pressure ≥150/100 mmHg [3].

Data were collected from electronic medical records and included information on maternal demographics; medical, obstetric and prenatal history; and information about the symptoms and signs of preeclampsia (symptoms of preeclampsia, blood pressure measurements, proteinuria, blood biochemistry, and the use and quantity of antihypertensive and other medications) in the early postpartum period (before discharge).

The cutoff value for body mass index (BMI) was 27, according to a study suggesting BMI > 27 as overweight [12]. The cutoff for weight gain was 12 kg according to the recommendations of the Institute of Medicine concerning weight gain during pregnancy [13].

Information regarding the mode of delivery, 5-minute Apgar scores and birth weight percentile, based on sex and gestational age according to Dollberg curves [14] were collected, as well.

The data regarding the 63 women who received antihypertensive medication postpartum were compared to those of the 295 women who did not receive treatment. Antihypertensives used for treatment included oral calcium channel blockers, oral or IV beta-blockers and oral angiotensin converting enzyme inhibitors. All women continued PO treatment for at least one week after discharge and stopped according to the recommendations of their family physician.

Antepartum, intrapartum and early postpartum variables were analyzed separately to determine how each period affected the outcomes.

2.1. Ethical approval

The study was approved by the Institutional Ethics Committee on 04/12/2016. Approval number 0267-16-MMC.

2.2. Statistical analysis

Statistical analysis was performed using SPSS -25 software (IBM, Armonk, NY, USA). Categorical variables were analyzed with the chi-squared test or Fisher's exact test. Continuous variables were analyzed by *t*-test. Multiple comparisons were done using Bonferroni correction when appropriate. Because of possible influence of confounders, stratification on severe features were done with Mantel-Haenzel risk ratio.

Multifactorial regression was conducted to estimate each relevant parameter and its independent effect on the outcomes. A p-value < 0.05 was considered statistically significant. All statistical tests were two-tailed.

3. Results

The case records of 358 women diagnosed with preeclampsia or gestational hypertension during a singleton pregnancy were analyzed. Among them, 63 ((17.5% had received antihypertensives postpartum (the treated group) and 295 (82.4%(had not (untreated group).

In the treated group, 42 (67%) women were diagnosed with preeclampsia in the early postpartum period and 21 (33%) with gestational hypertension.

Average maternal ages in the treated and the untreated groups were similar (30.8 ± 7.3 years vs. 30.2 ± 6 years, respectively). No significant difference was found between groups regarding parity, BMI > 27 at diagnosis or weight gain > 12 kg (Table 1).

3.1. Antepartum characteristics

Mean maximum blood pressures in the treated vs. untreated group were 165/109 mmHg and 150/100 mmHg, respectively ($p = 0.001$). No significant difference was found between groups regarding symptoms of preeclampsia (38.7% vs. 31.5%, $p = 0.273$).

Maximum aspartate aminotransferase (AST) and creatinine levels were significantly higher among the treated as compared to the untreated group (both $p = 0.003$). No significant differences were found regarding maximum alanine aminotransferase (ALT) ($p = 0.308$) or

Table 1
Baseline maternal characteristics according to antihypertensive treatment.

Parameter	Antihypertensives in early postpartum period	
	Yes N = 63	No N = 295
Age, years (mean ± SD)	30.8 ± 7.3	30.2 ± 6
Primipara, n (%)	47 (74.6%)	195 (66.1%)
BMI > 27, n (%)	20 (31.7%)	108 (36.6%)
Weight gain > 12 kg, n (%)	44/60* (73.3%)	165/294* (56.1%)

SD: standard deviation, BMI: body mass index.
* Missing data for some cases.

minimum platelet ($p = 0.117$) levels.

No significant differences were found between groups regarding laboratory abnormalities that define preeclampsia with severe features, including thrombocytopenia < 100 K (1.6% vs. 2.7%, $p = 1$) and liver enzymes ≥2 times upper limit of normal (AST 6.9% vs. 5.1%, $p = 0.529$ and ALT 3.5% vs. 4.4%, $p = 1$), respectively. Serum creatinine > 1.1 mg/dl was higher in the treated group (8.6% vs. 3.3%, p = 0.065); however, this did not reach statistical significance.

Among the group who received antihypertensive treatment postpartum, 18 women (28.6%) were diagnosed with early onset preeclampsia or gestational hypertension as compared to 12 women (4.1%) in the untreated group ($p < 0.001$). See Table 2.

3.2. Intrapartum characteristics

The mean gestational age at delivery among the group that received antihypertensive treatment was 36 weeks ± 3.3 days as compared to 38 weeks ± 1.7 days among the untreated group ($p < 0.001$).

No difference was found between the groups regarding epidural analgesia (58.7% vs. 70.2%, $p = 0.07$). In the treated group, 33 women (52.6%) received antihypertensives intrapartum, as compared to 36 women (12.2%) in the untreated group (p = 0.001). In the treated group, 22 women were delivered preterm. All had induction of labor; 18 (81.8%) because of preeclampsia with severe features, 2 (9.1%) because of intrauterine growth restriction and 2 (9.1%) due to preterm premature rupture of membranes.

More women in the treated group received magnesium sulfate during labor than in the untreated group (54% vs. 12.2%, respectively; $p < 0.001$). They also had a significantly higher rate of Cesarean deliveries as compared to the untreated group (50.8% vs. 22%, $p < 0.001$).

Regarding neonatal outcomes, the weight percentile at delivery was significantly lower in the treated group as compared to the untreated group (34th percentile vs. 45th percentile, respectively; $p = 0.007$). 5-minute Apgar scores were similar in both groups ($p = 0.39$; Table 3).

Table 3
Intrapartum characteristics according to antihypertensive treatment.

Parameter	Antihypertensives in early postpartum period		*p*-value
	Yes N = 63	No N = 295	
Epidural analgesia, n (%)	37 (58.7%)	207 (70.2%)	0.07
Antihypertensives intrapartum	33 (52.3%)	36 (12.2%)	0.001
Gestational age at delivery < 37 weeks, n (%)	40 (63.5%)	69 (23.4%)	< 0.001
Cesarean delivery, n (%)	32 (50.8%)	65 (22.0%)	< 0.001
Magnesium sulfate during labor, n (%)	34 (54.0%)	36 (12.2%)	< 0.001
Birth weight percentile (mean ± SD)	34.05 ± 27.5	44.9 ± 28.9	0.007
5-minute Apgar ≤ 8, n (%)	3 (4.8%)	7 (2.4%)	0.39

SD: standard deviation.

3.3. Postpartum characteristics

The mean maximum blood pressure was higher in the treated group than it was in the untreated group (167/106 vs. 143/92, $p = 0.001$). Women in this group also had more symptoms of preeclampsia, particularly headache (OR = 6.1, 95% CI 2.37–15.77).

No significant differences were found between groups regarding laboratory abnormalities, such as minimum platelets, maximum AST, ALT or creatinine ($p = 0.091$, $p = 0.078$, $p = 0.173$, and $p = 0.113$, respectively). Also, no significant differences were found between the groups regarding laboratory abnormalities that define preeclampsia (Table 4).

Regarding treatment for hypertension, 66.7% of the women in the treated group received one drug, labetalol PO/IV, during hospitalization. A combined 2-drug therapy of labetalol and calcium channel blockers or angiotensin converting enzyme inhibitors was given to 33.3% of the women in the treated group.

4. Discussion

In this historical cohort study of 358 pregnant women with antepartum preeclampsia or gestational hypertension, 63 (17.5%) required antihypertensive treatment in the early postpartum period, before

Table 2
Antepartum characteristics according to antihypertensive treatment.

Parameter	Antihypertensives in early postpartum period		*p*-value
	Yes N = 63	No N = 295	
Maximum mean blood pressure, mmHg	165/109	150/100	0.001
Symptoms of preeclampsia, n (%)	24/62* (38.7%)	93 (31.5%)	0.273
Epigastric/Right upper quadrant pain	14 (58.3%)	50 (53.8%)	
Headache			
Blurred vision	8 (33.3%)	35 (37.6%)	
	2 (8.3%)	8 (8.6%)	
Platelet count < 100 K, n (%)	1 (1.6(%	8 (2.7%)	1
AST > 74, n (%)	4/58* (6.9%)	15 (5.1%)	0.529
ALT > 80, n (%)	2/58* (3.5%)	13 (4.4%)	1
Creatinine > 1.1 mg/dl, n (%)	5/58* (8.6%)	10 (3.3%)	0.065
Minimum platelet count (mean ± SD)	188 K ± 67 K	200 K ± 65 K	0.117
Maximum AST, U/L (mean ± SD)	31 ± 29	30 ± 60	0.003
Maximum ALT, U/L (mean ± SD)	21 ± 27	22 ± 51	0.308
Maximum creatinine, mg/dl (mean ± SD)	0.8 ± 0.2	0.7 ± 0.2	0.003
Gestational age at diagnosis < 34 weeks, n (%)	18 (28.6%)	12 (4.1%)	< 0.001

* Missing data, SD: standard deviation.

Table 4
Postpartum characteristics according to receipt of antihypertensives.

Parameter	Antihypertensives in early postpartum period		*p*-value
	Yes N = 63	No N = 295	
Maximum mean blood pressure, mmHg	167/106	143/92	< 0.001
Symptoms of preeclampsia, n (%)	10/62* (16.1%)	9 (3.1%)	< 0.001
Epigastric/Right upper quadrant pain	3 (30%)	6 (66.67%)	
Headache			
Blurred vision	6 (60%)	2 (22.2%)	
	1 (10%)	1 (11.1%)	
Platelet count < 100 K, n (%)	4/62* (6.5%)	27 (9.1%)	0.793
AST > 74, n (%)	10/62* (16.1%)	32 (10.8%)	0.307
ALT > 80, n (%)	8 (12.7%)	33 (11.2%)	0.762
Creatinine > 1.1 mg/dl, n (%)	4/62* (6.5%)	28 (9.4%)	0.786
Minimum platelet count (mean ± SD)	177 K ± 62 K	190 K ± 66 K	0.091
Maximum AST, U/L (mean ± SD)	48 ± 52	60 ± 15	0.078
Maximum ALT, U/L (mean ± SD)	33 ± 28	42 ± 10	0.173
Maximum creatinine, mg/dL (mean ± SD)	0.8 ± 0.2	0.8 ± 0.2	0.113

SD: standard deviation.
* Missing data.

hospital discharge, to maintain blood pressure < 150/100 mmHg. The exact incidence of postpartum hypertensive treatment during early postpartum period is not cited clearly in the literature [3]. Usually, blood pressure will decrease 48 h after delivery and will peak at 3–6 days postpartum, after hospital discharge [15]. In two previous case-control studies, the incidence of antihypertensive treatment during that period was 51.3% (in a cohort of women with severe preeclampsia, including women with chronic hypertension) [9], and 32.7% in a cohort similar to that of the current study [10].

We identified several risk factors that could help stratify patients who are more likely to require antihypertensive treatment in the early postpartum period before hospital discharge when no differences were found between groups regarding age, primiparity, BMI and maternal weight gain.

During the antepartum and the intrapartum periods, the risk factors were higher mean maximum blood pressure, early onset preeclampsia or gestational hypertension (before the 34th week), induced preterm labor, prophylactic magnesium sulfate treatment during labor and Cesarean delivery. Laboratory results (AST, ALT, creatinine, platelet count), in themselves, were poor predictors for the need of antihypertensive treatment postpartum.

The risk factor in the early postpartum period was symptoms of preeclampsia, mainly headache. Some of these risk factors (higher antenatal systolic blood pressure, prophylactic treatment with magnesium sulfate and Cesarean section) were described previously in a small, retrospective case control study [10].

4.1. Antepartum and the intrapartum periods

No significant difference was found between the groups regarding symptoms of preeclampsia or laboratory findings in the range of severe features. The finding that the laboratory results in the severe range do not predict the need for antihypertensive treatment was described previously [9,10].

There were more preterm deliveries in the treated as compared to the untreated group (63.5% vs. 23.4%, $p < 0.001$). All preterm deliveries in the treated group were induced. The main indication was preeclampsia with severe features, mainly elevated blood pressure.

Early-onset preeclampsia has a poor prognosis, usually requires delivery before the 34th week of gestation, and is commonly associated with adverse maternal and neonatal outcomes. By contrast, late-onset preeclampsia, is mostly associated with mild maternal disease and a low rate of fetal involvement [16]. Thus, early onset preeclampsia and the need for induction of a preterm birth are indicators of the severity of the disease. The weight percentile at delivery was significantly lower in the treated group as compared to the untreated group, which may reflect disease severity.

Our results show that more women in the treated group received magnesium sulfate during labor compared to the untreated group (54% vs. 12.2%, $p < 0.001$). This is another feature of the severity of the preeclampsia.

The treated group had a significantly higher rate of Cesarean deliveries compared to the untreated group (50.8% vs. 22%, $p < 0.001$), which may reflect disease severity and the need for immediate intervention and stabilization.

4.2. Postpartum characteristics

During the early postpartum period, more symptoms of preeclampsia, mainly headache, were seen in the treated group. Headache is indeed considered a feature of severity of preeclampsia [17].

Our results show that the need for antihypertensive treatment in early postpartum period relates to the severity of preeclampsia. Early onset preeclampsia, higher mean blood pressure, induced preterm labor, the need for prophylactic magnesium sulfate and Cesarean section are all risk-factors for persistent postpartum hypertension. Women's healthcare providers should be aware of these risk factors and increase surveillance of these patients. Early initiation of antihypertensive treatment in high-risk patients may decrease postpartum complications and shorten hospital stays [9].

The strengths of this study are that the cohort included the entire spectrum of pregnancy-induced hypertensive disease, from gestational hypertension to preeclampsia, excluding women with chronic hypertension who are more likely to need antihypertensive treatment postpartum. The current study includes the largest case series evaluated for predictors of postpartum antihypertensive treatment before hospital discharge. The strict criteria used by our institution to initiate antihypertensive treatment (blood pressure ≥150/100) is another strength. The most significant limitation of the study is its retrospective design. Another limitation is that this is a retrospective study; thus, we cannot establish causality.

5. Conclusion

Early onset preeclampsia and gestational hypertension, severe hypertension in the antepartum period, preterm delivery, Cesarean delivery and the need for magnesium sulphate treatment during labor, might be good predictors of the need for anti-hypertensive treatment during the postpartum period.

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Internal.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.05.020.

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