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ORIGINAL RESEARCH

Metoprolol Use in Hypertensive Pregnancy Disorder – a Single-center Study

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ABSTRACT

Hypertensive pregnancy disorder is among the leading causes of maternal and fetal mortality, affecting 5–7% of pregnant women. Beta-blockers are known to improve endothelial dysfunction and may be beneficial in the treatment of this condition. We carried out a retrospective observational study involving 80 pregnant women with hypertension, admitted to the Alexandru Simionescu County Hospital, Hunedoara, Romania, from May 1, 2021 to December 31, 2023. Systolic blood pressure, diastolic blood pressure, and hypertension treatment were compared between patients receiving metoprolol and patients receiving other antihypertensive medication. Preeclampsia and premature delivery occurred in a significantly higher proportion among those who received other antihypertensive medication ($p = 0.006$ and $p = 0.021$, respectively). Low Apgar score (Apgar 6) was encountered in 2.5% of cases. Intrauterine growth restriction did not occur in either study group, and the neonatal and maternal mortality rates were zero in both groups. Metoprolol had demonstrated its benefits in treating hypertensive pregnancy disorders. The final goal is improving maternal and fetal outcomes.

Keywords: hypertensive pregnancy disorder, preeclampsia, metoprolol

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INTRODUCTION

Hypertensive pregnancy disorder is associated with significant fetal and maternal complications such as eclampsia, intrauterine growth restriction (IUGR), premature birth, intrauterine fetal death, and maternal cardiovascular diseases. It affects 5–7% of pregnant women and is a leading cause of maternal mortality.[1,2]

Gestational hypertension represents a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg on two separate occasions at least 4 h apart, in a previously normotensive pregnant woman after 20 weeks of pregnancy, according to the guidelines of the American College of Obstetricians and Gynecologists. In severe cases, gestational hypertension may pose a risk to the life of the mother and fetus.[1] A normal pregnancy is characterized by a series of complex temporary processes, such as decidualization, placentation, and parturition. Any alteration to this chronological progression can have significant effects on the mother and the fetus.[3,4] Brosens *et al.* were the first to demonstrate that preeclampsia is associated with a failure in the remodeling of the spiral arteries within the placental bed.[4] This abnormal placentation, together with endothelial dysfunction, has a crucial role in the development of this condition.[2] An important feature of preeclampsia is the incomplete remodeling of spiral arteries, leading to utero-placental malperfusion, which can be visualized through perfusion studies using Doppler ultrasound and magnetic resonance imaging.[5] This malperfusion results in vasoconstriction, ischemia-reperfusion injury, and oxidative stress. Abnormal placentation also disrupts the balance of angiogenic factors. Elevated lev-

els of circulating anti-angiogenic factors, such as soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng), reduce the availability of pro-angiogenic factors such as placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), leading to the development of hypertension and glomerulopathy, followed by the installation of hypertensive disorder during pregnancy.[5]

Beta-blockers are known to improve endothelial dysfunction and may also be beneficial in the treatment of preeclampsia.[6,7] These agents have been shown to increase the expression of pro-angiogenic factors, such as PlGF and VEGF, while having a moderate effect on the levels of anti-angiogenic factors, such as sFlt-1 and sEng. This is particularly important because endothelial dysfunction is a hallmark feature of preeclampsia and a key contributor to the multiorgan injury associated with the condition.[6]

The aim of our study was to assess the benefits of metoprolol in the treatment of hypertensive pregnancy disorders.

MATERIAL AND METHOD

We carried out a retrospective observational study involving 80 pregnant women with hypertension admitted to the Alexandru Simionescu County Hospital, Hunedoara, Romania from May 1, 2021 to December 31, 2023, with termination of pregnancy and postpartum stay in the same hospital.

Inclusion criteria were the following: pregnant women with high blood pressure according to World Health Organization criteria.[8] High blood pressure was defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg on at least two measurements performed at least 4 h apart. Patients with multiple pregnancies, infections, heart or kidney diseases were excluded.

Systolic and diastolic blood pressure values, as well as the antihypertensive treatment were compared between patients receiving metoprolol and patients receiving other treatments such as nifedipine and methyl-dopa. Demographic information, clinical symptoms, information about maternal age and parity were obtained from their medical records, together with information about previous chronic diseases such as chronic hypertension or diabetes mellitus. Laboratory parameters such as platelet count, creatinine, aspartate transaminase, alanine transaminase, proteinuria, and uric acid levels were recorded.

We also collected data about the most important obstetric complications observed during pregnancy, such as preterm birth, preeclampsia, and IUGR. We recorded the birth date, sex, weight, and Apgar score of the newborn, and complications at birth, such as fetal hypoxia, maternal or neonatal death. The benefits of the treatments were quantified depending on the evolution of the pathology, the presence of obstetric complications, and the number of days of hospitalization.

STATISTICAL ANALYSIS

Continuous and normally distributed baseline characteristics are presented as mean ± s.d. with minimum and maximum. Non-normally distributed variables are presented as median with 25th percentile (Q1) and 75th percentile (Q3). Categorical variables, presented as frequency and percentages, were compared between groups using the chi-squared test or Fisher's exact test. Normal distribution was assessed with the Shapiro–Wilk test. In the analysis of the difference between the numerical data of the two groups, the independent samples t test was used when the data were distributed in a normal distribution, and the Mann–Whitney U test was used when the data were not normally distributed. The effect size of studied dependencies was then quantified by the odds ratio and 95% confidence interval. The statistical analyses were performed using SPSS v.25.0 (IBM Corp). A p value of <0.05 was considered statistically significant.

RESULTS

In total, 80 patients have fulfilled the predefined criteria of hypertensive pregnancy disorder in the studied period, and 83.8% of these patients had preeclampsia. Demographic data and maternal and fetal outcomes of the study population are presented in Table 1.

Mean age was 25.9 years among the patients receiving metoprolol and 27.8 years among the patients receiving other antihypertensive medication. In total, 42.5% of the included patients had a high body mass index, an important risk factor for hypertensive pregnancy disorder. Notably, the proportion of patients with high body mass index was significantly higher among those receiving metoprolol ($p = 0.041$). Additionally, a higher proportion of patients receiving metoprolol were from urban environments ($p = 0.083$). Preeclampsia and premature delivery occurred in a significantly higher proportion among those receiving other antihypertensive medication ($p = 0.006$ and $p = 0.021$, respectively), suggesting that metoprolol may be able to prevent these adverse outcomes. The most common adverse fetal outcomes were the requirement of neonatal intensive care in one case (1.25%) and an Apgar score of 6 in two cases (2.5%). The mean birth

TABLE 1. Pro-atherogenic and prothrombotic mechanisms of Lp(a)[4]

Variables	All patients (*n* = 80)	With metoprolol (*n* = 40)	Without metoprolol (*n* = 40)	p value
Age (years), mean ± s.d.	26.8 ± 4.54	25.90 ± 4.67	27.80 ± 4.25	0.67
Gestational week at delivery, mean ± s.d.	37.61 ± 1.17	37.20 ± 1.41	38.03 ± 0.66	0.06
Birth weight, mean ± s.d.	2,787.87 ± 356.09	2,746.50 ± 379.99	2,829.25 ± 330.06	0.30
Body mass index, *n* (%)	34 (42.5)	12 (30.0)	22 (55.0)	0.041
Urban environment, *n* (%)	65 (81.2)	36 (90.0)	29 (72.5)	0.083
Preeclampsia, *n* (%)	67 (83.8)	38 (95.0)	29 (72.5)	0.006
Prematurity, *n* (%)	5 (6.2)	5 (12.5)	0 (0.0)	0.021
IUGR, *n* (%)	8 (10.0)	4 (10.0)	4 (10.0)	0.98
Cesarean section	72 (90.0)	37 (92.5)	35 (87.5)	0.71
Doppler changes in the 3rd trimester	35 (43.8)	18 (45.0)	17 (42.5)	0.82
Oligoamnios	6 (7.5)	4 (10.0)	2 (5.0)	0.39
CTG affected before birth	27 (33.8)	17 (42.5)	10 (25.0)	0.15
Male sex, *n* (%)	21 (26.2)	11 (27.5)	10 (25.0)	0.79
G1, *n* (%)	53 (66.2)	27 (67.5)	26 (65.0)	0.96
G2, *n* (%)	23 (28.7)	11 (27.5)	12 (30.0)	
G2, *n* (%)	4 (5.0)	5 (5.0)	2 (5.0)	
P1, *n* (%)	70 (87.5)	34 (85.0)	36 (90.0)	0.73
P2, *n* (%)	10 (12.5)	6 (15.0)	4 (10.0)	
Prophylaxis with acetylsalicilic acid, *n* (%)	29 (36.2)	10 (25.0)	19 (47.5)	0.062

CTG, cardiotocography; G, gestation; P, parity

weight was 2,829.25 g for the newborns of mothers receiving other antihypertensive medication and 2,746.50 g for the newborns of mothers receiving metoprolol (p = 0.30). IUGR was found in 10% of patients who received metoprolol and 10% of patients who received other antihypertensive medication. Neonatal and maternal mortality rates were zero in both groups. Aspartate transaminase, alanine transaminase, uric acid, and proteinuria were not modified, and the duration of hospital stay was similar in both groups. We found that 87.5% of the included patients were primiparous, which suggests that primiparity plays an important role in the development of hypertensive disorder. Preeclampsia has been associated with poor perinatal outcomes such as IUGR, low Apgar score at 5 min, and an increased need for neonatal intensive care. In our study, 36.2% of the entire cohort received preventive treatment with acetylsalicylic acid (25.0% of patients receiving metoprolol and 47.5% of patients receiving other antihypertensive medication). Both metoprolol and acetylsalicylic acid had a protective effect on pregnant women with hypertensive disorder, preventing the occurrence of preeclampsia (Table 2).

TABLE 2. The relationship between preeclampsia and treatment with metoprolol and acetylsalicylic acid

Variables	Odds ratio	95% confidence interval	p value
Treatment with metoprolol	0.0886	0.0171 to 0.4600	0.0039
Prophylaxis with acetylsalicylic acid	0.1456	0.0274 to 0.7736	0.0237

DISCUSSION

Hypertension appears in various pathologies associated with pregnancy, such as antiphospholipid syndrome, thrombophilia, lupus, thrombotic microangiopathies, diabetes mellitus, SARS-CoV-2 infection, and dislipidemia.[2,3,9] At the same time, although hypercoagulability is a normal feature of pregnancy, coagulability is further increased in preeclampsia. This is attributed to increased fibrinogen levels, thrombin generation, low protein S and activated protein C resistance, and fibrinolysis.[5]

The prevalence of chronic hypertension has risen in the United States, and its treatment follows the 2017 guidelines of the American Heart Association and the American College of Cardiology. The most important change in these guidelines is the replacement of methyldopa with labetalol for managing hypertension during pregnancy.[10] Other beta-blockers, such as metoprolol, are considered safe during pregnancy.[11–14]

Our study highlights that IUGR is a consequence of hypertensive disorder rather than the use of metoprolol during pregnancy. Additionally, metoprolol was not associated with prematurity or other adverse maternal or fetal outcomes. On the contrary, it contributed to prolonging the gestation period under safe conditions.

Similar findings have been reported in other studies. Ghafarzadeh *et al.* conducted a study involving 300 pregnant women with hypertension and showed that those receiving methyldopa had a relative risk of preeclampsia, whereas the risk of IUGR was not significantly higher among those who received metoprolol. Metoprolol, alone or in association with methyldopa, labetalol, or nifedipine, is recommended for treating hypertension in pregnancy.[15] However, Redman *et al.* found beta-blockers to be associated with a major risk of severe growth retardation.[16] Similarly, Kubota *et al.* identified a significant risk of hypoglycemia and IUGR in fetuses exposed to beta-blockers.[17] In contrast, Aktas *et al.* reported a higher risk of premature delivery and lower Apgar scores among patients receiving beta-blockers compared to the control group.[18] Kayser *et al.* observed that long-term intrauterine exposure to metoprolol may increase the risk of IUGR, although serious neonatal complications were rare. According to their study, metoprolol can be well tolerated when used in carefully selected cases with close neonatal monitoring.[19] Furthermore, first-trimester oral beta-blocker use has been shown to be safe, with no major congenital anomalies reported.11 Sandström compared metoprolol with hydralazine and found a higher rate of perinatal mortality and IUGR in the hydralazine group. Beta-blockers, on the other hand, showed no abnormal effects on the fetus.[20]

Certain beta-blockers have a protective effect on the endothelium and are useful for managing hypertension during pregnancy.[21,22] However, recent research has raised concerns regarding their safety in relation to neonatal and obstetrical outcomes. Significant improvements in pregnancy outcomes can be achieved through the careful selection and monitoring of beta-blockers in pregnant women with hypertension.[21] Sanchez-Pardo *et al.* demonstrated notable improvements in outcomes, although combined medication was required in most cases.[23] Beta-blockers are particularly recommended in severe preeclampsia, in which they have been shown to improve both maternal and fetal outcomes.[24]

Women with hypertensive pregnancy disorder have an increased risk of immediate and long-term cardiovascular complications.[10] In their 2024 review, Leonard *et al.* highlighted the effectiveness of beta-blockers in preventing episodes of severe hypertension in women with preeclampsia, showing that they are more effective than methyldopa. They also found no significant differences in the risks of preeclampsia, IUGR, neonatal death, or preterm birth associated with beta-blocker use.[10] Beta-blockers can be successfully used when monotherapy is insufficient for adequate blood pressure control.[25,26]

Preeclampsia-associated endothelial dysfunction has been shown to persist postpartum, along with altered cerebrovascular autoregulation, which may increase the risk of postpartum hypertension.[5] Long-term maternal health consequences include an elevated risk of hypertension, ischemic heart disease, and stroke.[27] A more aggressive approach to treating hypertension during pregnancy can prevent the development of severe hypertension.[2,5] Additionally, treating non-severe hypertension during pregnancy has been shown to prolong gestation in women who might otherwise require early delivery. Lowering treatment thresholds could reduce premature deliveries, thereby avoiding complications associated with prematurity. There is substantial evidence linking hypertension pregnancy disorders to an increased risk of immediate postpartum complications and future maternal vascular diseases.[5,28] However, there is no definitive evidence favoring one antihypertensive drug over another, including beta-blockers, when considering all treatment options.[5]

Anticoagulation is an important approach in preventing severe preeclampsia and its complications, as demonstrated in our study and supported by the literature.[2,3,9] In our study, the use of low-dose acetylsalicylic acid as prophylaxis had a beneficial effect on pregnant women with hypertensive disorder, preventing the occurrence of preeclampsia.

The exploration of novel adjuvant therapies holds promise for extending the duration of pregnancy and improve perinatal and maternal outcomes.[29] Potential future treatments include therapeutic plasma exchange, which may be beneficial in early-onset preeclampsia, purpura, or lupus, associated with methyldopa and metoprolol. However, further research is needed to validate these approaches. Pravastatin also shows promise as an alternative therapy.

Efforts to prevent fetal hypoxia are essential, and medications such as allopurinol have shown potential in this regard.[2,9,27,30,31] Additionally, novel animal models could have an important role in the development of targeted therapies, not only for preeclampsia but also for cardiovascular diseases that follow preeclampsia.[32]

In a 2016 study, the sFlt-1/PlGF ratio has been found to be inversely corelated with prolongation of pregnancy and adverse outcomes.[33] These innovative biomarkers identi-

fied in humans should be evaluated for their potential in predicting and diagnosing preeclampsia.[32,34]

Hypertensive pregnancy disorder is a heterogenous, complex condition, and overly generalized approaches may overlook the interplay and varying contributions of maternal and placental preeclampsia. The effective management of hypertension should remain a cornerstone of preeclampsia prevention. This not only mitigates immediate maternal complications, but also reduces the risk of long-term cardiovascular injury.[5,12,35]

A limitation of our study is its observational retrospective design, conducted in a single center with a small study group.

CONCLUSION

The optimal choice of therapy must remain a matter of carefully analyzing the risk/benefit ratio for each individual patient. Metoprolol use showed its benefits in treating hypertensive pregnancy disorders. The final goal is improving maternal and fetal outcomes.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS APPROVAL

The study was approved by the local ethics committee where it was conducted (approval no. 16552/04.11.2024).

CONSENT TO PARTICIPATE

Informed consent was obtained from all subjects involved in the study. All methods were carried out in accordance with the Declaration of Helsinki.

DATA AVAILABILITY

Further data is available from the corresponding author upon reasonable request.

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This research received no external funding.

AUTHOR CONTRIBUTIONS

C.F.B. contributed to conceptualization. M.I.M. contributed to methodology. S.V. contributed to software analysis. M.C. contributed to validation. M.I.M. and C.F.B. contributed to investigation. M.I.M. prepared the original draft. C.F.B. contributed to review and editing. M.C. contributed to supervision.

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