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Maternal Aritmi Tanısıyla Beta Bloker Tedavisi Alan Gebe Kadınlarda Obstetrik ve Fetal Sonuçlar

Obstetrics and Fetal Outcomes in Pregnant Women with Beta-blocker Treatment in Maternal Arrhythmia

BETÜL AKGÜN AKTAS [1] Orcid ID: 0000-0003-4523-011X
PETEK FERİHA UZUNER [1] Orcid ID: 0000-0002-9260-1780
ATAKAN TANACAN [1] Orcid ID: 0000-0001-8209-8248
DİLEK SAHİN [1] Orcid ID: 0000-0001-8567-9048

[1] Department of Obstetrics and Gynecology, Ministry of Health, Ankara City Hospital, Ankara, Turkey

ÖZ

Amaç: Bu çalışmanın amacı, maternal kardiyak aritmi tedavisi için beta-bloker kullanan hastaların gebelik prognozlarının incelemesidir.

Gereçler ve Yöntem: Bu çalışma, 1 Ocak 2020-1 Ocak 2022 arasında Ankara Şehir Hastanesi' ne başvuran 50 aritmi tanısı olan gebe ile 55 sağlıklı gebenin katıldığı retrospektif gözlemsel bir çalışmadır. Beta blokerler; metaprolol, propranolol ve bisoprolol olarak 3 gruba ayrılmıştır. Beta bloker kullanımı durumu yüksek doz ve düşük doz olarak iki grupta incelenmiştir. Gebelik prognozu için doğum haftası, doğum kilosu ve doğum kilosunun Z skoru, beta human koryo gonadotropik hormon (bHCG) MoM ve gebelikle ilişkili plazma protein-A (PAPP-A) MoM, yenidoğanların APGAR skoru ve yoğun bakıma gidiş oranları belirlendi.

Bulgular: Beta bloker alan hasta grubunun, beta bloker kullanmayan gruba göre istatistiksel olarak anlamlı bir erken doğum haftası vardı (p= <0.001). Primer sezaryen doğum oranı çalışma grubunda daha yüksekti (p=0,007). Doğum ağırlığı ve beşinci dakika APGAR skoru çalışma grubunda anlamlı olarak düşük, yoğun bakıma yatış oranı anlamlı olarak yüksekti (sırasıyla p=0.006, p=<0.001ve p=<0.001).

Sonuç: Maternal aritmiler için birinci basamak tedavi olan beta-blokerler, fetal gelişimi ve gebelik sonuçlarını etkileyebilir. Uygulanacak bu ilaçların, uygun alt gruplara ve en düşük etkili dozlara sahip olacak şekilde titizlikle seçilmesi önerilir.

Anahtar kelimeler: aritmi, beta-bloker, doğum ağırlığı, anne/fetal sonuçlar Obstetrics and fetal outcomes in pregnant women with beta-blocker treatment in maternal arrhythmia

ABSTRACT

Abstract

Aim: The aim of this study was to investigate the pregnancy outcome of patients taking beta-blockers for the treatment of maternal cardiac arrhythmias.

Materials and Method: This study was a retrospective observational study involving 50 pregnant women with cardiac arrhythmias and 55 healthy pregnant women, admitted between January 1, 2020 and January 1, 2022, to Ankara City Hospital. Beta-blockers were classified into three groups: metaprolol, propranolol, and bisoprolol. The use of beta-blockers was examined in two groups: high-dose and low-dose. For pregnancy outcome, birth week, birth weight and birth weight Z-score, beta human chorionic gonadotrophin (bHCG) MoM and pregnancy-associated plasma protein A (PAPP-A) MoM, neonatal APGAR score, and neonatal intensive care unit admission (NICU) rates were determined.

Results: The patient group taking beta-blockers had a statistically significant earlier delivery week than the group without beta-blocker use (p= <0.001). The rate of primary cesarean deliveries was higher in the study group (p= 0.007). Birth weight and APGAR score at the fifth minute was significantly lower in the study group, and NICU admission rate was significantly higher (p= 0.006, p= <0.001and p= <0.001, respectively).

Conclusion: Beta-blockers, a first-line therapy for maternal arrhythmias, may affect fetal development and pregnancy outcomes. İt is recommended that these drugs to be administered are meticulously selected for appropriate subgroups, with lowest effective doses.

Keywords: arrhythmia, beta-blocker, birth weight, maternal/fetal outcomes

Sorumlu Yazar/ Corresponding Author: Betul Akgun Aktas
Adres: Üniversiteler Mahallesi 1604. Cadde No: 9 Çankaya/Ankara/TURKEY
E-mail: drbetul07@gmail.com

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INTRODUCTION

Maternal arrhythmias in pregnancy are common, with or without structural abnormalities. We see maternal arrhythmias frequently for reasons such as maternal adaptation to pregnancy, pregnancies at advanced ages, and the increasing success of cardiac surgery in infancy (1). The heart conduction system mainly consists of the sinoatrial node, the atrioventricular node, and specialized myocytes (2). Conditions such as structural anomalies, inappropriate automaticity, abnormal electrolyte level in the blood, and thyroid dysfunction cause arrhythmia by affecting the conduction system. The 12-lead electrocardiogram (ECG) test is the primary step in diagnosing arrhythmia. Also, increased heart rate, left axis shift, and different P and QRS waveforms could be seen in the ECG during pregnancy (3).

Beta-blockers are used as first-line agents in treating cardiac arrhythmias, especially tachyarrhythmia, but there are studies suggesting cause pregnancy complications (4, 5). Beta-blockers affect the fetus by crossing the placental barrier and altering maternal cardiac output and uteroplacental flow (4). In addition, studies show that maternal arrhythmia is associated with poor obstetric outcomes (6). The aim of this study was to investigate the pregnancy outcome of patients taking beta-blockers for the treatment of cardiac arrhythmias.

MATERIALS AND METHOD

This study was a retrospective observational study involving 50 pregnant women with cardiac arrhythmias and 55 healthy pregnant women, admitted between January 1, 2020 and January 1, 2022, to Ankara City Hospital Department of Obstetrics and Gynaecology. The Ministry of Health of Republic of Turkey and the Medical Research Ethics Department of Ankara City Hospital approved the study protocol (ethics committee number: E2.23.3586). Participants who applied to the cardiology department with complaints such as heart palpitation, dizziness, and syncope were diagnosed with arrhythmia using the 12-lead ECG or 24-hour Holter monitor. The arrhythmia was defined as heart rates above 100 beats per minute (10–20 beats higher than resting during pregnancy) and abnormal P or QRS waves (7). Treatment was started with the beta-blocker diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, long QT syndrome, and ventricular arrhythmias. Patients diagnosed with cardiac arrhythmias, who had taken beta-blockers for at least six months before pregnancy and had no structural cardiac abnormalities were included in the study group. Multiple pregnancies, pregnant women with chronic hypertension, abnormal thyroid stimulating hormone (TSH) levels, anemia, structural heart abnormalities, smoking, and pregnant women with a body mass index (BMI) > 35 were not included in the study. Also, participants with comorbidities in the study group take no medication except beta blockers. Pregnant women with active comorbidity and using different drug groups were not included in the study to not affect the results.

The study recorded maternal age, pregestational BMI, gravidity, parity, additional maternal diseases, type and dose of beta-blocker used, and pregnancy outcomes. The gestational week was determined by last menstrual period or measurement of crown-rump length in the first trimester. Beta-blockers were classified into three groups: Metaprolol, propranolol, and bisoprolol. The use of beta-blockers was examined in two groups: high-dose and low-dose. The dosage of the drugs was calculated on the basis of expert opinions for pregnancy. High dosage was defined as > 75 mg/day for metoprolol, > 80 mg/day for propranolol, and > 10 mg/day for bisoprolol (4, 8). For pregnancy outcome, birth week, birth weight and birth weight Z-score, neonatal APGAR score, and neonatal intensive care unit (NICU) admission rates were determined (9, 10). In addition, beta human chorionic gonadotropin (bHCG) multiple of the median (MoM) and pregnancy associated plasma protein-A (PAPP-A) MoM levels were compared during the first-trimester screening tests of the pregnant women in the study and control groups.

Statistical analysis was performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). Shapiro-Wilk and Kolmogorov-Smirnov tests were both used to evaluate normality of variables. Groups were compared using the Student t-test and the Mann-Whitney U test. P-values < 0.05 were considered as statistically significant. With a confidence interval of 95%, power of 80%, and sample size of 1:1, samples of at least 40 patients per group were planned (5).

RESULTS

The study enrolled 105 subjects whose baseline characteristics are given in Table 1.

Table1. Demographic data of study [median (IQR)]

	Patient (n=50)	Control (n=55)	P Values
Maternal age (years)	29 (10)	30 (8)	0.535
Maternal body mass index before pregnancy (kg/m2)	27.6 (4.5)	27.5 (6.4)	0.434
Gravidity	3 (2)	3 (2)	0.267
Parity	1 (2)	1 (2)	0.278
Nulliparity (n,%)	16 (32)	11 (20)	0.253
Assisted reproductive techniques (n,%)	1 (2)	1 (1.8)	0.946

There was no significant difference between the two groups for demographic data. The vast majority (n=39, 78%) of pregnant women taking beta-blockers used metoprolol. The number of pregnant women taking propranolol was 6 (12%), and the number of pregnant women taking bisoprolol was 5 (10%). Seventy percent of patients in the study group were using high-dose medication. In the study group, thyroid disease, asthma, and rheumatological disease were observed as maternal comorbidities (10%, 10%, and 8%, respectively).

The pregnancy and birth outcomes of the two groups are shown in Table 2.

Table2. Pregnancy and birth outcomes

	Patient (n=50)	Control (n=55)	P Values
Gestational age at birth (week)	38 (2)	39 (2)	**<0.001**
Primary cesarean delivery (n,%)	21 (42)	11 (20)	**0.007**
Emergency cesarean delivery (n,%)	8 (16)	7 (12.7)	0.542
APGAR score, first minute	8 (1)	8 (1)	0.139
APGAR score, fifth minute	8 (1)	9 (0)	**<0.001**
Birth weight (g)	3190 (745)	3370 (682)	**0.006**
Birth weight Z score	-0.11 (1.07)	-0.3 (1.44)	0.965
Neonatal intensive care unit (n,%)	12 (24.0)	1 (1.8)	**<0.001**
PAPP-A MoM	1.15 (0.63)	0.96 (0.72)	0.673
bHCG MoM	1.09 (0.72)	1.24 (0.93)	0.725

The patient group taking beta-blockers had a statistically significant earlier delivery week than the group without beta-blocker use (p= <0.001). While the rate of emergency cesarean deliveries did not differ between the two groups, the rate of primary cesarean deliveries was significantly higher in the group taking beta-blockers (p=0.007). Although birth weight was significantly lower in the beta-blocker group, no difference was found in terms of the birth weight Z-score (p=0.006 and p=0.965, respectively). APGAR score at the fifth minute was significantly lower in the study group, and NICU admission rate was significantly higher (p= <0.001 and p= <0.001, respectively). When first-trimester biomarkers were examined in both groups, no difference was found for bHCG MoM, and PAPP-A MoM levels (p=0.752 and p=0.673, respectively).

Maternal and fetal complications in the group taking beta-blockers are given in Table 3.

Table3: Maternal and fetal complications

	Patient (n=50)
Preterm delivery (n,%)	6 (12)
Pre-eclampsia (n,%)	6 (12)
Hospitalization in intensive care (n,%)	6 (12)
Fetal growth restriction (n,%)	1 (2)
Oligohydramnios (n,%)	2 (4)
Embolism (n,%)	1 (2)

The most common pregnancy complications were preterm labor, preeclampsia, and postpartum maternal admission to the intensive care unit.

In this study, the patients taking beta-blockers were divided into two groups: low-dose and high-dose beta-blocker users. Participants taking low-dose and high-dose beta-blockers were compared in terms of pregnancy and birth outcomes (Table 4). The birth weeks of the two groups were similar. Almost half (n=17, 48.5%) of the high-dose beta-blocker users underwent primary cesarean section, and 1 in 5 underwent emergency cesarean section. However, the two groups did not differ significantly in the rate of primary and emergency cesarean sections (p=0.148 and p=0.241, respectively). The mean APGAR scores at the first and fifth minutes were similar in both groups. Although birth weight was lower in the group taking high-dose beta-blockers, this difference was not statistically significant (p=0.443). The birth weight Z-score in the high-dose beta-blocker user group was -0.18, while the Z-score in the low-dose beta-blocker user group was 0.09 (p=0.323). Rates of pregnancy complications and NICU admission were also higher with high-dose beta-blocker exposure (p=0.524 and p=0.674, respectively).

DISCUSSION

Cardiac adaptation to pregnancy is one of the most important causes of maternal arrhythmias. Already in the early stages of pregnancy, plasma volume increases under the influence of the renin-angiotensin-aldosterone system (11). Ion channels are stimulated by the increase in cardiac output and tension in the cardiac structure (12). In response to the increase in plasma, there is a decrease in systemic and pulmonary vascular resistance, and vascular remodeling occurs with vasodilation (11). Systemic vascular pressure tends to decrease in the first trimester of pregnancy (13). Consequently, mean arterial pressure also changes. In addition, hormonal changes and increased sympathetic activity during pregnancy also cause an increase in heart rate (14). All these maternal changes predispose pregnant women to cardiac arrhythmias or cause pre-existing cardiac arrhythmias to worsen and become symptomatic.

The most common arrhythmias in pregnancies without structural heart anomalies are atrial fibrillation, supraventricular tachycardia, and ventricular tachycardia (15). Beta-blockers are the most commonly used drugs in treating cardiac arrhythmias in pregnancy. These drugs are divided into selective and non-selective blockers of beta receptors. The mechanisms of beta blockers are on the sympathetic system, intracellular calcium release, and nitric oxide production (16). Fetal perfusion may be affected by reduced blood pressure and the negative inotropic/chronotropic effects of beta-blockers (17). The placental barrier is a priority in protecting the fetus, but the passage of beta-blockers through this barrier also affects the fetus.

A meta-analysis showed an increased risk of fetal heart anomalies, neural tube defects, and cleft palate-lip in pregnant women using beta blockers in the first trimester (18). However, our study detected no fetal structural anomalies in pregnant women using beta-blockers.

Previous studies pointed out an increase in the rate of small for gestational age (SGA) babies, low birth weight, preterm birth, and perinatal mortality in pregnancies with beta-blocker exposure (4, 17, 19). Other studies found that the risk of preeclampsia/eclampsia, neonatal bradycardia, and hypoglycemia was increased in pregnancies taking beta-blockers (17, 20). Similar to previous studies, pregnant women with a history of drug use were found to have significantly lower birth weight and gestational week in our study. In the study group, preterm births and preeclampsia were observed, as 12% and 12% , respectively. At the same time, a high number of NICU admissions, low APGAR scores, and a high rate of primary cesarean deliveries were observed in the group of newborns with beta-blocker exposure.

In a study examining maternal arrhythmia and pregnancy prognosis, although the number of patients was small, fetal growth restriction and placental abruption were more common in the study group (6). A previous study about treated and untreated maternal cardiac arrhythmias has shown lower preterm births and higher birth weight in the treated group (21). Untreated arrhythmia is also a significant risk factor for adverse obstetric outcomes. Therefore, treatments during pregnancy should be started by considering maternal and fetal benefits.

In a previous study that examined pregnancy outcomes as a function of beta-blocker dose, high-dose drug exposure was found to increase SGA rates (4). This result is comparable to that of our study. In addition, although more primary and emergency cesarean deliveries were observed in pregnant women with high-dose beta-blocker exposure in our study, this difference was not significant, which may be due to the small number of participants.

The limitations of this study are the insufficient number of participants and the inability to examine subgroups of beta-blockers.

CONCLUSION

Beta-blockers, a first-line therapy for maternal arrhythmias, may affect fetal development and pregnancy outcomes. For this reason, it is recommended that these drugs to be administered are meticulously selected for appropriate subgroups, with lowest effective doses.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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