

Gestational Outcomes of Beta Blocker Therapy as a Treatment of Palpitations

Miri Secagoi¹, Michele Thomson², Mouhamed Amr Sabouni^{2*}, Amine Hila³ and Alon Yarkoni²

¹Kaplan Medical Center, Rehovot, Israel

²Department of Cardiology, United Health Services 33-57 Harrison St, Johnson City, New York, USA

³Department of Gastroenterology, United Health Services 33-57 Harrison St, Johnson City, New York, USA

*Corresponding Author: Mouhamed Amr Sabouni, Department of Cardiology, United Health Services, Wilson Medical Center, Johnson City, New York, USA, Tel: 0016107301384; Email: Mouhamed.a.sabouni@hotmail.com

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Abstract

Introduction: Beta blocker therapy is considered the primary treatment for palpitations caused by supraventricular or ventricular ectopy. The safety of beta blocker therapy during pregnancy is somewhat controversial and not well studied.

Objective: Examine the outcomes of beta blocker therapy for heart palpitations in pregnant women.

Methods: We conducted a retrospective review of 3778 pregnant patients between January 2014 and January 2016. The patients' ages ranged between 18 to 40 years old. 227 patients had complaints of palpitation. 52 patients were eligible for inclusion and were dichotomized into two groups based on their treatment status, Eight patients received treatment with a non-selective beta blocker. The second group did not receive beta blocker therapy. Primary and secondary outcomes based on data collected from the patients' electronic medical records were compared between the two groups

Results: Beta-blocker exposure during pregnancy was found to be associated with increased risk of small for gestational age (SGA) (OR 7.663, p-value 0.033) as well as a tendency towards increased risk of pregnancy induced hypertension (PIH) (OR 10.87, p-value 0.052). There was no statistical difference in the rates of preterm birth, stillbirth, postpartum haemorrhage, gestational diabetes, need for blood transfusion or the method of delivery between the two groups.

Conclusion: The data indicates that exposure to beta-blockers during pregnancy was associated with a significant increase in the risk of both SGA and PIH. This Finding should be explored further with a large randomized controlled trial.

Keywords: Pregnancy; Palpitation; Beta-blockers; Adverse pregnancy outcomes; Arrhythmias

Introduction

Heart palpitations are one of the most common reasons for referral to the internist and cardiologist, both in the general population and during pregnancy [1]. Although beta blocker (b-Blocker) therapy (BBT) can alleviate palpitations; in the absence of hemodynamically significant arrhythmia, medical treatment for the symptomatic relief of palpitations is not generally recommended [2]. For benign arrhythmias, a conservative approach is preferred including abstinence from aggravating factors such as caffeine, smoking, and alcohol [3]. Arrhythmias most frequently treated with BBT include isolated ventricular and atrial ectopy, and supraventricular tachycardias [4].

The main concern with BBT is interference with the fetal growth and development during the second and third trimesters [5]. There have been reports of BBT use during pregnancy causing adverse neonatal effects such as bradycardia, apnea, hypoglycemia and metabolic abnormalities [6]. The adverse effects of BBT on woman

during pregnancy and fetal development has not been well studied. There is data suggesting an association between BBT and preterm birth, small for gestational age, and perinatal mortality [6]. In these studies, however, complications were not adjusted for confounding factors such as high-risk pregnancy, treatment indication, and severity of maternal disease. In this retrospective study, we seek to examine if the use of BBT for the treatment of heart palpitations, during uncomplicated pregnancy in healthy women, was associated with adverse effect on maternal and fetal outcomes

Methods

This retrospective study received ethics approval from the UHS Institutional Review board (IRB) committee. Charts of 3778 pregnant women who received prenatal care in the United Health Services (UHS) outpatient clinics, located in Broome County, New York were reviewed. All pregnant women who presented to the UHS outpatient clinics for evaluation of heart palpitations between January 1st 2014 and January 1st 2016 were eligible for enrollment. The study population was obtained from UHS Wilson hospital electronic medical record (EMR) according to ICD 9 and ICD 10 codes. We identified the

diagnosis of heart palpitations in women with ICD 9 and ICD 10 - 785.1 and R00.2, respectively. Codes for pregnancy according to ICD 9 were V22.0, V22.1, V23.42, V23.85, V23.87 and V72.42. The codes for pregnancy according to ICD 10 were O09-O09, O10-O16, O20-O29, O30-O48, O60-O77, O80-O82.

Women between the ages of 18-40 who were pregnant with a single foetus and presented to UHS outpatient clinics experiencing new onset heart palpitations were eligible for inclusion. Out of 3778 patients, 228 were evaluated for palpitations and therefore eligible for further evaluation in this retrospective study. Exclusion criteria included women with a history of heart palpitations and known structural or functional heart disorder, history or current use of antiarrhythmic drugs, known medical causes for palpitations (such as thyrotoxicosis, severe anemia, psychological disorder).

We also excluded pregnant women who were at risk for adverse pregnancy outcomes such as preterm delivery, preeclampsia, and intrauterine growth retardation (IUGR). Pregnant women were considered to be at risk for adverse pregnancy outcomes if they had one of the following: history of previous adverse pregnancy outcome, pre-gestational diabetes mellitus, chronic hypertension, or congenital anomalies.

Data collection

A password protected encrypted file which contained a randomized generated unique identifier, medical record number, and patient initials was obtained from the hospital Electronic Health Record (EHR). The data was obtained then reviewed from two EHR systems: NextGen® (NextGen Healthcare), Soarian® Cerner Corporation. A second file which contains a unique identifier and non-identifiable medical information was created. Data concerning the baseline demographic data, outpatient clinics, and medical and cardiac evaluation was obtained.

The baseline data included patient age, gravida, nicotine exposure, vital signs measured during encounter (blood pressure, heart rate, weight, height), hemoglobin level (up to one month prior or after encounter), glucose level (up to one month prior or after encounter), and gestational age (at time of first medical encounter). The gestational age at the time of the first medical encounter was calculated according to the date of the patient's last menstrual period and the date of the medical encounter. Cardiac baseline data included cardiac rhythm, atrial ectopy, ventricular ectopy, ejection fraction, pulmonary artery pressure, and mitral valve prolapse. The type and dosage of b-blocker (if administered) was obtained from EHR as well.

The patient population was dichotomized into two groups: Those treated with b-blockers and those who were not. Primary and secondary outcomes were compared between the two groups.

Definition of outcome

The primary outcome of the study was major adverse events of pregnancy which included preterm birth (PTB), small for gestational age (SGA), and stillbirth. Preterm birth was defined as delivery prior to 37+0 weeks of gestation, where gestational age is calculated from last menstrual period and date of delivery. SGA was defined as having birth weight below the 10th percentile for the corresponding gestational age. The percentile for the corresponding gestational age was calculated by the world health organization (WHO) fetal growth

percentile calculator. Stillbirth was defined as death occurring at ≥ 20 weeks of gestation until delivery.

Secondary outcomes included method of delivery, clinical diagnosis of postpartum hemorrhage (PPH), gestational diabetes (GDM), pregnancy induced hypertension (PIH), and blood transfusion. Clinical diagnosis of PPH was considered to be positive if a definite diagnosis was made by health care provider or if there was a 10 point decrease in hematocrit after delivery from antepartum level, or an estimated blood loss of ≥ 500 mL during normal vaginal delivery (NVD) and ≥ 1000 mL during caesarean delivery (CD). Clinical diagnosis of GDM was considered to be positive if (1) a definite diagnosis was made by health care provider; (2) a random glucose challenge test (GCT) of >200 mg/dL; (3) two elevated glucose values during a 100 g three-hour oral GTT (as proposed by Carpenter and Coustan); or (4) one elevated glucose value during a 75 gram two-hour oral GTT (as proposed by International Association of Diabetes and Pregnancy Study group -IADPSG).

Clinical diagnosis of PIH was considered to be positive if a definite diagnosis was made by a healthcare provider or by new onset of hypertension (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg) at ≥ 20 weeks of gestation as documented on at least two occasions on prenatal flow chart.

Sample size

Sample size was calculated using WinPepi software, based on the BMJ study published by Meidahl Petersen et al. (2012). In order to find an odd ratio (OR) of at least 2.26 (in pregnant women using beta-blockers for cardiac symptoms compared to pregnant women not taking beta-blocker), and assuming preterm birth is about 12.01% in the unexposed pregnant population, the study groups will have to include at least 188 women in each group to show significant results and differences in the primary outcome of the study (significance level 5%, Power 80%). We assumed that this sample size will also be sufficient in order to see significant results in the other primary and secondary outcomes of the study.

Statistical analysis

Data was imported for analysis to SPSS 17 software. Data processing included descriptive analysis and uni and multi-variate analysis using appropriate statistical tests. Categorical variables were described using frequencies and percentages. Continuous variables were described using mean, standard deviation, median and range. Univariate analyses were performed using chi-square and t-tests or mann-whitney nonparametric tests accordingly. Association between the use of b-blockers for various cardiac complaints and adverse pregnancy outcomes was tested by logistic regression, while adjusting for maternal age. In all cases OR was calculated with 95% confidence interval (confidence interval, CI). All analyses with p-value <0.05 were considered statistically significant (Tables 1 and 2).

Results

A total of 3778 pregnant women presented to UHS outpatient clinics between January 1st 2014 and January 1st 2016. 228 of those women (6%) were treated for heart palpitations (Figure 1).

Total of 176 pregnancies (77.1%) were excluded from enrolment; 66 women (37.5%) for loss of follow up, 57 women (32.4%) for pre-pregnancy palpitations (most of whom had an underlying condition

either thyroid, psychiatric or functional/structural heart disease), 10 women (5.7%) due to post-pregnancy palpitations, 7 pregnant women (3.9%) were older than age 40 or younger than age 18 and 2 pregnant women (1.1%) had multiple gestation pregnancy.

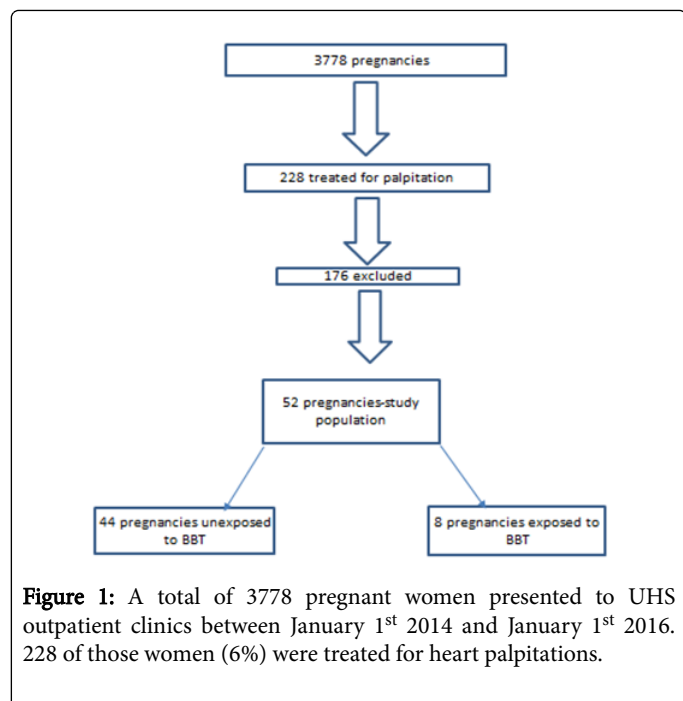


Figure 1: A total of 3778 pregnant women presented to UHS outpatient clinics between January 1st 2014 and January 1st 2016. 228 of those women (6%) were treated for heart palpitations.

Five women (2.8%) had previously known structural or functional heart disorder, 9 women (5.1%) had known medical causes for palpitations, of whom 6 (3.4%) had thyroid disorder, and 3 (1.7%) had psychological disorder. We also excluded 20 (11.4%) pregnant women who were considered to be at risk for adverse pregnancy outcomes, 11 had history of previous adverse pregnancy outcome (Preterm delivery (PTD), PIH, perinatal mortality or stillbirth), 1 had pre-gestational diabetes mellitus, 6 had chronic hypertension, 2 had congenital anomalies. We identified 8 pregnancies exposed to BBT (15%) of the pregnant women with palpitations and 44 pregnant women in the unexposed group (85%). All of pregnancies exposed to b-Blockers were exposed to a single agent. We found six pregnancies exposed to labetalol and two pregnancies exposed to propranolol.

Basic demographic and clinical characteristics for pregnancies exposed to BBT for the treatment of new onset palpitation during pregnancy compared with unexposed pregnancies are shown in Table 1 (number and percentages of pregnancies).

There was no statistically significant difference in any of these characteristics, although the BBT exposed group tend to be with less nicotine exposure, lower heart rate at admission, higher BMI at admission and higher haemoglobin. Primary and secondary outcomes for pregnancies exposed to BBT due to palpitations compared with unexposed pregnancies are shown in Table 3. No of cases of preterm delivery occurred in the BBT exposed group (0%) while 5 women had PTD in the unexposed group (11.6%). The mean fetal weight was lower by about 100 g in the BBT exposed group, this was a small difference and not statistically significant.

Characteristics	b-blocker exposed	b-blocker unexposed	p-value
Patients' age (years)			0.517
Mean +/- SD	26.13 +/- 4.79	27.86 +/- 5.32	
Median	27	27	
Range	21-34	19-40	
Nicotine exposure			0.153
Yes	12.5% (1)	38.6% (17)	
No	87.5% (7)	61.4% (27)	
Gestational age at time of first medical interaction			0.917
1 st trimester<14 weeks	25.0% (2)	25.0% (11)	
2 nd trimester>14 weeks and <28 weeks	50.0% (4)	43.2% (19)	
3 rd trimester>28 weeks to delivery	25.0% (2)	31.8%(14)	
Gravida			0.622
1 to 2	50.0% (4)	52.3% (23)	
3 to 4	50.0% (4)	38.6% (17)	
>5	0.0% (0)	9.1% (4)	
Vital signs measured during encounter (1 st medical interaction)			
Systolic blood pressure			0.388

Mean +/- SD	123.88 +/- 19.54	116.82 +/- 10.78	
Median	116.5	116	
Range	103-167	97-151	
Diastolic blood pressure			0.829
Mean +/- SD	73.5 +/- 4.78	72.41 +/- 9.09	
Median	73	72.5	
Range	69-84	57-92	
Heart rate			0.522
Mean +/- SD	88.43 +/- 8.36	93.38 +/- 18.34	
Median	80	90	
Range	80-104	59-130	
BMI			0.897
Mean +/- SD	34.24 +/- 14.09	31.44 +/- 6.62	
Median	29.16	31.12	
Range	19.10-60.66	18.99-45.18	
Haemoglobin level			0.069
Mean +/- SD	12.3 +/- 0.44	11.66 +/- 1.09	
Median	12.3	11.6	
Range	11.6-12.9	9.2-14.6	
Glucose level			0.069
Mean +/- SD	98.8 +/- 14.13	87.44 +/- 10.46	
Median	96	85	
Range	86-123	71-109	

Table 1: Basic demographic and clinical characteristics for pregnancies exposed to b-blockers due to palpitations compared with unexposed pregnancies.

Characteristics	b-blocker exposed	b-blocker unexposed	p-value
Cardiac rhythm			
Sinus rhythm	5 (100%)	33 (100%)	
Not Sinus rhythm	0 (0.0%)	0 (0.0%)	
	mis=3	mis=11	
Atrial Ectopy			0.459
Yes	1 (20.0%)	3 (9.1%)	
No	4 (80.0%)	30 (90.9%)	
	mis=3	mis=11	
Ventricular ectopy			0.357
Yes	2 (40.0%)	7 (21.2%)	

No	3 (60.0%)	26 (78.8%)	
	mis=3	mis=11	
Ejection fraction %			0.899
<50	0 (0.0%)	0 (0.0%)	
50-54	0 (0.0%)	1 (5.9%)	
55-59	1 (33.3%)	7 (41.2%)	
60-64	2 (66.7%)	8 (47.1%)	
>/=65	0 (0.0%)	1 (5.9%)	
	mis=5	mis=26	
Pulmonary artery pressure			
Normal	3 (100%)	18 (100%)	
Abnormal	0 (0.0%)	0 (0.0%)	
	mis=5	mis=26	
Mitral valve prolapse			0.676
Yes	3 (100%)	1 (5.9%)	
No	0 (0.0%)	17 (94.4%)	
	mis=5	mis=26	

Table 2: Basic cardiac characteristic for pregnancies exposed to b-blockers due to palpitations compared with unexposed pregnancies.

Pregnancy outcome	b-blocker exposed	b-blocker unexposed	p-value
Gestational age at delivery			0.6
<37.0 weeks	0 (0.0%)	5 (11.6%)	
>/=37.0 weeks	8 (100%)	38 (88.4%)	
		mis=1	
Fetal weight (grams)			0.917
Mean +/- SD	3.263.13 +/- 656.64	3379.67 +/- 520.34	
Median	3429.5	3316	
Range	2296-3968	2097-4762	
		mis=1	
Percentile SGA			0.014
<10	3 (37.5%)	3 (7.0%)	
>/=10	5 (62.5%)	40 (93.0%)	
		mis=1	
Stillbirth			
Yes	0 (0.0%)	0 (0.0%)	
No	8 (100%)	43 (100%)	

		miss=1	
Delivery method			0.058
CS	0 (0.0%)	21 (48.8%)	
Normal vaginal delivery (NVD)	8 (100%)	21 (48.8%)	
VE	0 (0.0%)	mis=1	
Post-partum haemorrhage (PMH)			0.441
Yes	0 (0.0%)	3 (7.0%)	
No	8 (100%)	40 (93.0%)	
		mis=1	
Gestational diabetes mellitus			0.313
Yes	2 (25.0%)	5 (11.6%)	
No	6 (75.0%)	38 (88.4%)	
		mis=1	
Pregnancy induced hypertension			0.049
Yes	2 (25.0%)	2 (4.7%)	
No	6 (75.0%)	41 (95.3%)	
		mis=1	
Blood transfusion			0.534
Yes	0 (0.0%)	2 (4.7%)	
No	8 (100%)	41 (95.3%)	
		mis=1	

Table 3: Pregnancy outcomes for pregnancies exposed to b-blockers with unexposed pregnancies.

Logistic regression was conducted for estimating the risk of SGA and PIH while adjusting for maternal age (as possible confounder). The BBT exposed group were found to have statistically significant

higher risk for SGA foetus (OR 7.663, p-value 0.033). Those exposed to BBT during pregnancy also had higher risk (OR 10.87, p-value 0.052) than unexposed women for PIH (Table 4).

Outcome	OR (95% CI)	p-value
SGA		
b-blocker unexposed	Reference	Reference
b-blocker exposed	7.663	0.033
Pregnancy induced hypertension (PIH)		
b-blocker unexposed	Reference	Reference
b-blocker exposed	10.87	0.052

Table 4: Pregnancy outcomes after exposure to b-blockers during pregnancy (Logistic regression).

Delivery of foetus below the 10th percentile for gestational age, which was documented in 37.5% of women exposed to BBT compared to 7% only in the unexposed group (Figure 2). No event of stillbirth occurred during the pregnancy of women analysed.

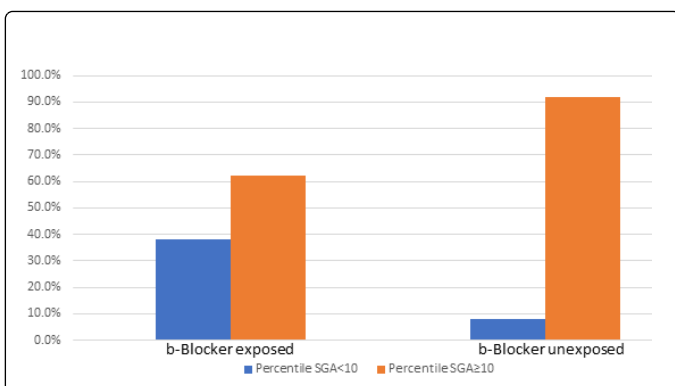


Figure 2: Percentile SGA for pregnancies exposed to beta-blocker due to palpitations compared with unexposed pregnancies.

All pregnant women exposed to BBT had normal vaginal delivery, in the unexposed group the percentages of NVD and CD were equal (48.8%). PPH severe enough to be resulted in blood transfusions occurred in two out of three cases of PPH, all of them in the BBT unexposed group (both during CD). The unexposed group to BBT had higher tendency to have GDM diagnosis but this wasn't statistically significant (p-value 0.313).

Discussion

Palpitations are the perceived sensation of rapid, strong, irregular heartbeat or unusual awareness of one's heartbeat. [7,8] Palpitations are one of the most common reasons for referral to outpatient internist and cardiologist, accounting for 16% of complaints in the general population [9]. Although a common reason for referral, the true incidence of palpitations during pregnancy remains unknown. One study by Author et al., in which an interview of postpartum women was conducted within 3 days after delivery, 11.5% experienced palpitations during their pregnancy [1]. In our study, 228 out of 3778 (6%) women had heart palpitations during their pregnancy. This lower observed incidence may be a result of not including emergency room visits in our analysis. In addition, women may not have perceived their palpitations as a serious concern which may have attributed to underreporting and under referring for their symptoms.

There are multiple physiological changes that occur throughout pregnancy which may lead to palpitations. Normally pregnancy is known to be associated with profound alterations in the maternal cardiovascular system. The physiologic hemodynamic changes induced by pregnancy include sodium and water retention which results in a 6-8 liter increase in total body water which leads to blood volume expansion. Initial decrease in peripheral resistance causes an increase in maternal heart rate from as early as 5 weeks of gestation. An increase in cardiac output starts at approximately 10 weeks of gestation and plateaus near the end of the second trimester at a level 30 to 50% above non-pregnant values. Heart rate increase during pregnancy ranges in the literature from 10 to 30% (or 10 to 15 beats per minutes above baseline). There is a reduction in blood pressure due to peripheral vasodilatation that is maximal in the second trimester. A rise in stroke volume ranges between 10 and 50%, reaching a peak early in the third trimester, and is achieved mainly through the increase in blood volume [10].

The changes in the maternal cardiovascular system during pregnancy contribute to optimal growth and development of the foetus and help to protect the mother from the risks of delivery, such as hemodynamic or conduction instability. However, these changes can also aggravate underlying cardiac disease which may be associated with increased maternal morbidity and mortality [11].

For these reasons, palpitations are a common complaint during pregnancy requiring immediate medical attention. A thorough history, physical examination, 12-lead electrocardiography and targeted laboratory testing, are sufficient to making a definitive diagnosis. Weber et al. studied 190 patients presenting with a chief complaint of palpitations, an etiology was determined in 84% of patients [12]. In some cases the etiology remains unknown. In our study about 71 women had a definitive etiology for their palpitations (31%), this difference can be a result of a high percentage of loss to follow up in patients who had an underlying condition which required referral to a higher level of care. Non-cardiac causes of palpitations include anemia, alterations in thyroid function, and medication-induced. Psychiatric disorders such as panic attacks, generalized anxiety disorder or stress induced have also been implicated in up to nearly one-third of all patients [13].

Cardiac causes of palpitation in pregnancy included arrhythmias, valvular heart disease (e.g., mitral or aortic insufficiency, mitral valve prolapse), and cardiomyopathy. Ectopic beats and nonsustained arrhythmias were objectively encountered in more than 50% of pregnant women investigated for palpitations, while sustained tachycardia were less common, at around 2-3/1000.14 out of 52 pregnancies in the study 9.1-20% had atrial ectopic beats and 21-40% had ventricular ectopic beats. No episodes of sustained tachycardia occurred. Although Shotan and colleagues found no correlation between the high incidence of arrhythmias in pregnancy and symptoms. Only 10% of symptomatic episodes of palpitation were accompanied by the presence of arrhythmias [14,15]. In our study ectopic beats occurred more often in the BBT exposed group, arising the possibility that women undergoing treatment were indeed more symptomatic.

In a large population based cohort study by Meidahl Petersen et al., it was found that exposure to b-blocker during pregnancy increased the risk of SGA, preterm birth and perinatal mortality with adjusted OR 1.97, 2.26, 1.89 respectively [7]. However the results were not adjusted for treatment indication and severity of maternal disease. We found a strong association between BBT exposure and being born SGA (OR 7.663, p-value 0.033). Most b-blockers are known to cross the placenta [16]. A mechanism has been proposed of diminished placental blood flow due to selective vasoconstriction of placental vessels by b-blockers [17,18]. This effect on placental hemodynamics could explain children being born SGA when exposed to BBT during pregnancy.

Exposure to BBT was not associated with preterm delivery. We found a tendency in the unexposed group for preterm delivery, but the percentage was not higher than what accounted for the general population in the USA. In the United States in 2013, 11.4% of births were <37 weeks [19]. No stillbirth occurred in both groups. The prevalence of gestational diabetes as traditionally defined is about 6 to 7% in the United States (range 1 to 25%) [20]. In our study we found 11.6% in the unexposed group and 25% in the BBT exposed group. This was not statistically significant.

In the BBT exposed group there was a statistically significance increase in PIH (OR 10.87, p-value 0.052), This might be a confounder, the pregnant women who have mildly elevated blood pressure will more easily get treatment with BBT than those with normal to low blood pressure. The percentage of United States cesarean births was 31.1% in 2006. In our study, the percentages of caesarean delivery in the unexposed group to BBT approached 50% compared to no operations in the exposed group. This is true in spite the fact that both groups had approximately the same percentages of primigravida. This difference between the two groups was not statistically significant (p-value 0.058).

The age is known to be an independent predictor of poor outcomes in pregnancy. However, this analysis adjusted for maternal age as a possible confounder and there was no age difference between the two study groups, therefore should not impact results.

The largest research which investigated the association between exposure to BBT during pregnancy and the risk of small for gestational age and preterm birth was unable to adjust for treatment indications nor rule out confounding by indication for treatment (as information regarding diagnosis of essential hypertension was not available) [7,21]. The unique aspect of the study was the ability to eliminate any possible confounding factors related to b-Blocker use. This was accomplished by excluding high risk features such as structural heart disease, high risk pregnancy and previous use of b-Blocker agents. We focused on the population of pregnant women without any other etiology for palpitations (thyroid, severe anemia or psychiatric disorder). Palpitations due to these conditions would prompt treatment of the underlying disease.

Limitations of our study include the high percentage of loss to follow up, single center and small study sample. The study population may have had adverse pregnancy outcomes or admitted for treatment at an outside facility. We were unable to adjust for the treatment indication of pregnancy-induced hypertension. Exposure to therapy was derived from data available on EMR chart review.

Overestimation of exposure is therefore a possibility since we can't adjust for potential lack of compliance. Although the statistical analysis is not significant, there is a trend toward higher HG, and higher glucose. These were not adjusted for as possible confounding factors. It is therefore unclear to what extent this may have affected our results.

In conclusion, there is uncertainty of benefit and possible harm with the use of b-blocker for the symptomatic relief of palpitations during pregnancy. This finding justifies the current approach of applying therapy only in the presence of hemodynamically significant arrhythmia. Large scale randomized prospective studies should be performed to further elucidate this finding.

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