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Review Article

The effects on fetal outcome of the use of beta-blockers during pregnancy: a systematic review and meta-analysis

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Abstract: Background: Beta-blockers are widely used in pregnancy-induced hypertension and heart disease because of their good efficacy. The effects of β-blockers on fetal outcomes are controversial. In order to find out more about the relationship between β-blockers and fetal outcomes, we conducted a meta-analysis. Methods: We searched PubMed, Embase, and The Cochrane Library database for cohort studies or RCT on beta-blockers and pregnancy-related conditions. We used an odds ratio (OR) with a 95% confidence interval (CI) and pooled it with random- or fixed-effect models when appropriate. Results: This meta-analysis included 13 cohort studies with a total of 3,281,239 participants, including 14,010 cases of pregnant women which were exposed to beta-blockers and 3,267,229 cases which were unexposed. It turned out that those who were exposed to beta-blockers were associated with a relatively higher risk of SGA (OR: 1.72 95% CI 1.59-1.86, P<0.001), fetal mortality (OR: 2.59 95% CI 1.94-3.45, P<0.001), and neonatal hypoglycemia (OR: 2.60 95% CI 1.55-4.38, P<0.001). Conclusions: The use of beta-blockers during pregnancy increases the risk of SGA, perinatal mortality, and neonatal hypoglycemia.

Keywords: SGA, neonatal hypoglycemia, perinatal mortality, preterm delivery, perinatal outcome, meta-analysis, fetal outcome

Introduction

At present, there is a growing trend in pregnant women who use anti-hypertension drugs, and beta-blockers are the most common choice. Beta-blockers are also used in the treatment of heart diseases and thyroid diseases, and good outcomes have been demonstrated. However, there are some adverse effects of beta-blockers on pregnancy as well, which we pay less attention to. Beta-blockers have been classified by the US Food and Drug Administration as Class C, indicating that the effects of beta-blockers on pregnancy are still uncertain. Some studies show that beta-blockers can pass through the placenta and affect its blood flow, and the effect of beta-blockers on insulin may cause a rise in blood sugar during pregnancy. A large European cohort study shows that the use of beta-blockers in the first trimester can lead to cleft lip and harm the fetus' heart and nervous system [1]. Other studies show that the use of beta-blockers during pregnancy increases the risk of small for gestational age, premature birth, perinatal mortality, and neonatal hypoglycemia [2-5], but some studies have reached the opposite conclusion [6, 7]. Therefore, a systemic analysis of the relationship between β-blockers and pregnancy outcomes is necessary.

Magee did a meta-analysis on this relationship in 2003 [8], and, as time goes on and as new data is generated from new studies, some of the original conclusions have been questioned. Thus, we undertook a systematic review and meta-analysis to evaluate fetal outcomes in women with beta-blocker exposure.

Methods

Based on the PRISMA standards and procedures, we used the following method for this meta-analysis. We searched PubMed, Embase, The Cochrane The Library database for related

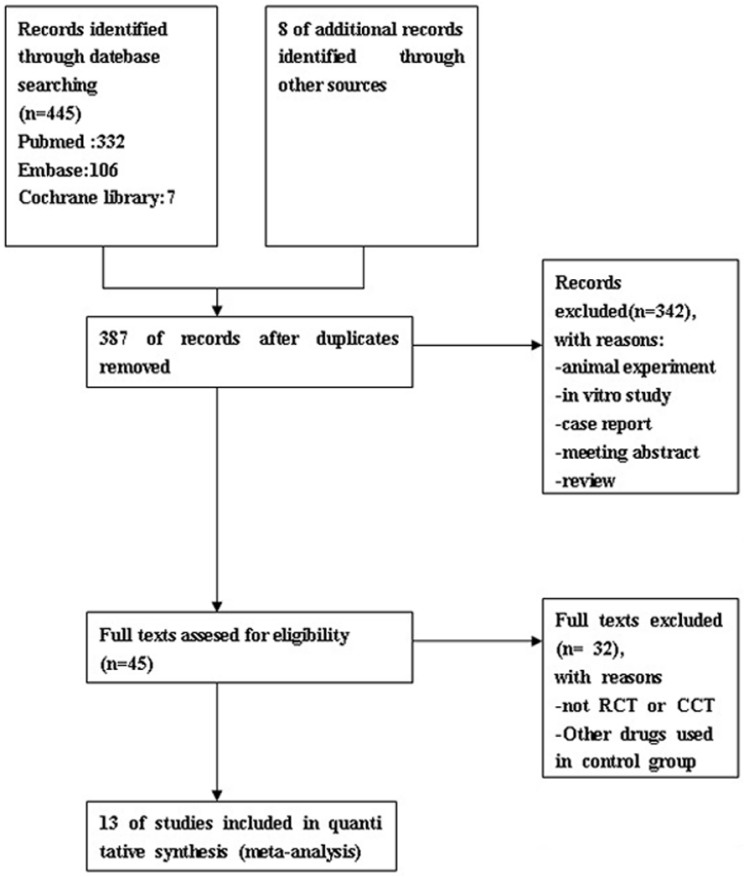

Figure 1. Process for identifying studies eligible for the meta-analysis.

cohort studies, and RCT. The retrieval time was from the establishment of the database till May 2018. Our search used a combination of controlled vocabulary and natural language terms, and the references included in the related studies were also been reviewed. The search terms included: Beta blocker/pregnant women/sga/Neonatal hypoglycemia/Perinatal Mortality/preterm delivery/perinatal outcome. Cross-sectional, descriptive or case series/reported studies were excluded. Studies on thyroid disease treated with beta blocks were also not included, because thyroid disease may affect fetal outcomes.

Data extraction and quality assessment

The content mainly includes: 1. Basic information included in the research: the author's name, year of publication, country. 2. The basic characteristics of the study subjects: sample size, beta-blocker type, time of administration, frequency, indications. 3. The main data of the clinical outcomes and confounding factors which need to be adjusted. Two researchers (LQ and LGJ) screened the literature independently, extracted the data, and cross-checked. In case of a disagreement, we would resolve it by discussion or submit it to the third researcher (ZSQ) to make a final decision. We assessed the authenticity and quality of the included studies using the Newcastle-Ottawa scales (NOS) [9], and 6 points or more was defined as high quality research.

Statistical analysis

The meta-analysis was performed using RevMan 5.3 and Stata 12.0 software. The effect index of dichotomous data was the risk ratio (OR), and the effect index of the continuous data was the mean difference (MD), and there was also a 95% confidence interval (95% CI). We used an X^2 test (test level α=0.1) to assess the heterogeneity of the included studies, and the quantitative analysis was done combined with I^2 [10]. If there is no statistical heterogeneity across the studies, a fixed effect model was used for the meta-analysis, but if there is statistical heterogeneity, the source of heterogeneity would be further analyzed. When the obvious clinical heterogeneity was excluded, a random effects model was used for the meta-analysis. If there was significant clinical heterogeneity, a subgroup analysis or sensitivity analysis, or only a descriptive analysis was used. The level of the meta-analysis was set to α=0.05 [11, 12].

Results

Study characteristics

13 studies were identified among the 453 articles which resulted from the literature search, according to the inclusion criteria (**Figure 1**) [2, 3, 5, 6, 13-21]. **Tables 1**, **2** contain the charac-

Table 1. Characteristics of the included studies

Author, Year	Study Design	Country	Specific β-Blocker	Beta blocker usage	Period of Pregnancy of Drug Use	Indication of Drug Use	Major clinical outcomes	Quality score
Ersbøll 2014	RC	Denmark	labetalol, carvedilol, sotalol, propranolol, pindolol, atenolol, and metoprolol	Labetalol was started at a dose of 100 mg twice daily	1 mo preconception through the 7 month of pregnancy	cv	SGA, Neonatal hypoglycemia	6
Meidahl Petersen 2012	RC	Denmark	Labetalol, metoprolol, atenolol, propranolol, pindolol, sotalol	No description	First 6 months	HTN	SGA, Perinatal mortality, Preterm delivery	6
Davis 2011	RC	USA	No description	No description	First 3 months	HTN	SGA, neonatal Hypoglycemia	7
Heida 2012	RC	Holland	labetalol	>600 mg oral maternal labetalol daily	No description	HTN	SGA, neonatal Hypoglycemia, Perinatal mortality, Preterm delivery	6
Bayliss 2002	RC	England	atenolol	No description	No description	HTN	SGA	4
Sibai 1990	RCT	USA	labetalol	labetalol was started at 300 mg/day	First 3 months	HTN	SGA, Preterm delivery, Perinatal mortality	7
Pickles 1992	PC	England	labetalol	The initial dose was one tablet (100 mg) three times daily	5 mo preconception through the 9 month of pregnancy	HTN	SGA, Preterm delivery, Perinatal mortality, Neonatal hypoglycemia	6
Plouin 1990	RCT	France	oxprenolol	160 mg in two daily doses	First 7 months	HTN	SGA, Perinatal mortality, Apgar score less than 7 at 5 minutes	6
Butters 1990	RCT	England	atenolol	starting dose of atenolol was 50 mg daily and the number of tablets was increased at each visit until	between 12 and 24 weeks	HTN	SGA, Perinatal mortality	7
Cruickshank 1992	RCT	England	labetalol	Labetalol was started at a dose of 100 mg twice a day	between 24 to 39 weeks	HTN	SGA	6
Darcie 2004	PC	Brazil	atenolol	No description	No description	HTN	Neonatal hypoglycemia	5
Bateman 2016	RC	USA	Labetalol, Metoprolol, Atenolol	50 mg twice a day	5 months after	HTN	Neonatal hypoglycemia, Neonatal bradycardia	6
Ishibashi 2017	RC	Japan	No description	No description	No description	cv	Preterm delivery	5

Table 2. Characteristics of the included studies

Author, Year	Sample size of patients without beta blockers	Sample size of patients with beta blockers	Patients with diabetes excluded/adjusted	Patients with Congenital heart disease excluded/adjusted	Other confounding factors adjusted
Ersbøll 2014	124	51	Not clear	Yes	Yes
Meidahl Petersen 2012	919685	2459	Yes	Not clear	Yes
Davis 2011	49648	188	Not clear	Not clear	Yes
Heida 2012	54	55	Not clear	Not clear	Yes
Bayliss 2002	189	29	Not clear	Not clear	Yes
Sibai 1990	90	86	Yes	Yes	Yes
Pickles 1992	74	70	Yes	Yes	Yes
Plouin 1990	77	78	Yes	Yes	Yes
Butters 1990	14	15	Yes	Yes	Yes
Cruickshank 1992	45	31	Yes	Yes	Yes
Darcie 2004	14	40	Yes	Yes	Yes
Bateman 2016	2281531	10585	Yes	Not clear	Yes
Ishibashi 2017	94	21	Not clear	Not clear	Yes

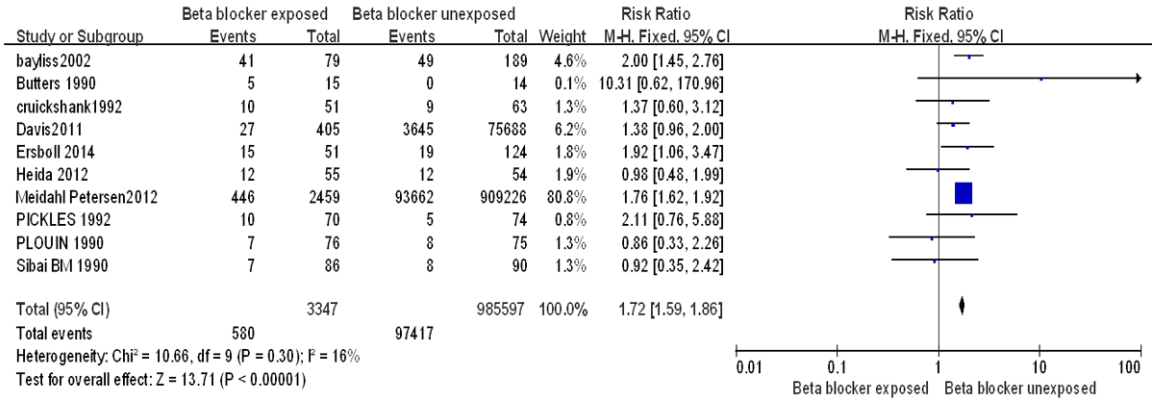

Figure 2. Comparison of SGA in pregnant women exposed and unexposed to β-blockers.

teristics of these studies. With sample sizes ranging from 29 to 911,685, these studies were performed from 1990 to 2014. The study-design types were as follows: 4 single-center studies [3, 15, 18, 20], 7 retrospective studies [2, 5, 6, 13, 14, 19, 21], and 2 prospective studies [16, 17]. Beta blockers were used for heart disease in 2 studies [5, 21] and in the remaining studies for hypertension [2, 3, 6, 13-20]. Beta-blockers were given in the first trimester in 2 studies [19, 20], and were given in the third trimester in 7 studies [2, 3, 5, 13, 15, 17, 18], but in the other 4 studies, the medication time was not mentioned [6, 14, 16, 21]. The dose of beta-blockers was >600 mg/day in one study [6], >200 mg/day in 6 studies [3, 5, 15, 17, 18, 20], but in 5 studies the dose of beta-blocker was not stated [2, 13, 14, 19, 21]. There were ten high-quality studies with scores ≥6 and three low-quality studies with scores <6.

Fetal outcome

10 studies reported 580 cases of SGA in 3,347 Pregnant women with beta blocker exposure and 97,417 cases of SGA of the 985,597 pregnant women with no beta blocker exposure, producing a 1.72 fold (95% CI 1.59 to 1.86, P<0.001) higher likelihood risk in pregnant women with beta blocker exposure [2, 3, 5, 6, 14, 15, 17-19, 20], with a very low evidence of heterogeneity (I^2=16%, P=0.30, **Figure 2**). 6 studies reported 51 cases of stillbirth in 2765 pregnant women with beta-blocker exposed, and 6,051 cases of stillbirth among the

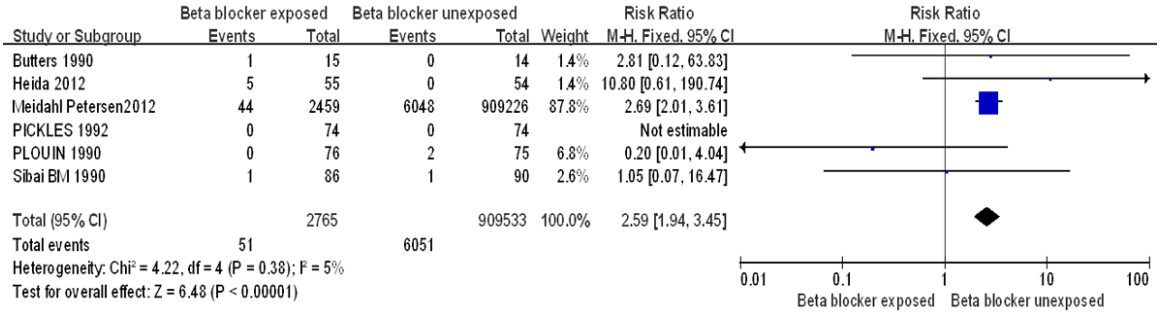

Figure 3. Comparison of SGA in pregnant women exposed and unexposed to β-blockers.

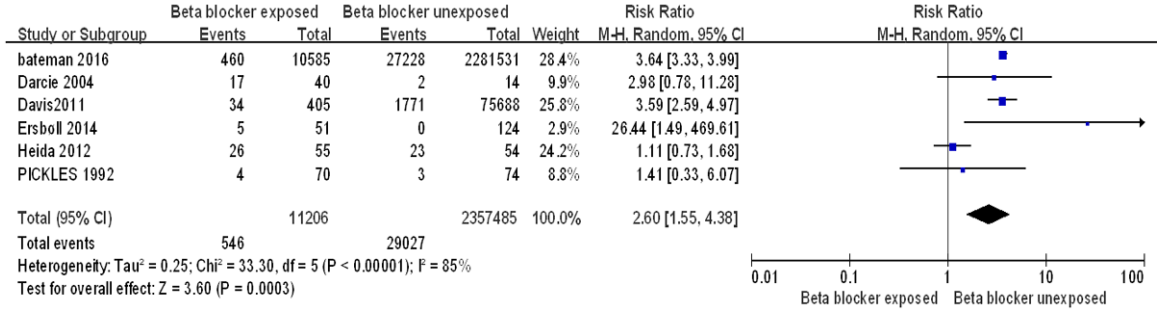

Figure 4. Comparison of neonatal hypoglycemia in pregnant women exposed and unexposed to β-blockers.

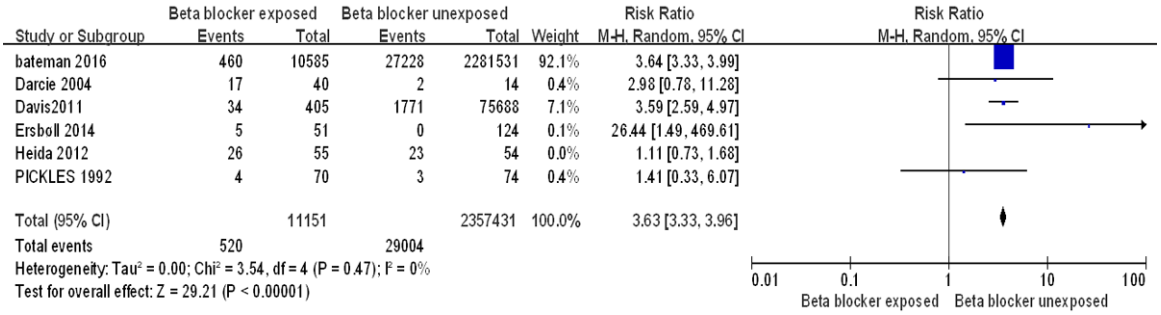

Figure 5. Comparison of preterm delivery in pregnant women exposed and unexposed to β-blockers.

909,533 pregnant women with no beta blocker exposure, producing a 2.59 fold (95% CI 1.94 to 3.45, P<0.001) higher likelihood in pregnant women with beta blocker exposure [2, 3, 6, 17, 18, 20], with very low evidence of heterogeneity (I^2=5%, P=0.38, **Figure 3**). Results from 6 studies showed that Beta blocker exposure is associated with an increased risk of neonatal hypoglycemia, with high heterogeneity (OR, 2.60, 95% CI 1.55 to 4.38, I^2=85.0%, P<0.001, **Figure 4**) [5, 6, 13, 16, 17, 19]. We further studied the heterogeneity of neonatal hypoglycemia and found that the heterogeneity came from a study in the Netherlands (accounting for 24.2% of the weight) [6]. In this study, the daily dose of B-blockers for pregnant women was >600 mg/d, but it was <600 mg/d in the other 5 studies. The difference in the daily dose of B blockers explains the cause of heterogeneity. The higher risk of neonatal hypoglycemia (OR, 3.63; 95% CI 3.33 to 3.96; P<0.001) was not eliminated when this study was excluded, but the heterogeneity dropped to 0% (I^2=0%, P= 0.47) (**Figure 5**). 5 studies examined the relationship between beta-blockers and preterm delivery [2, 6, 17, 20, 21]. There was not enough evidence that exposure to β-blockers during pregnancy is associated with an increased incidence of preterm birth (OR, 1.51; 95% CI 0.88 to 2.59; P=0.13) (**Figure 6**). When a single

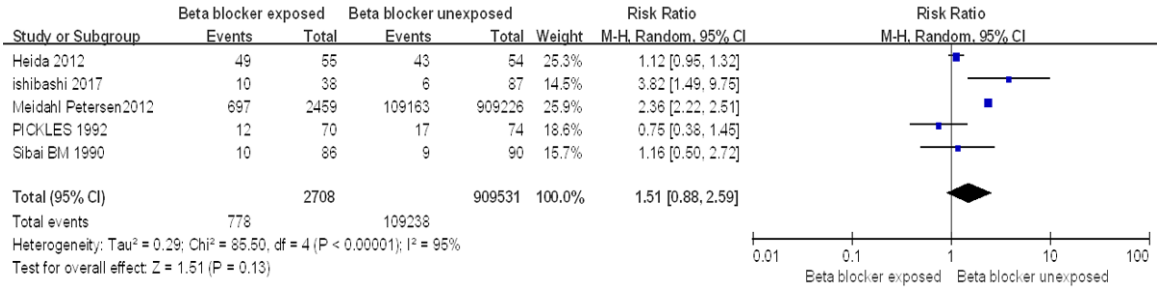

Figure 6. Comparison of preterm delivery in pregnant women exposed and unexposed to β-blockers.

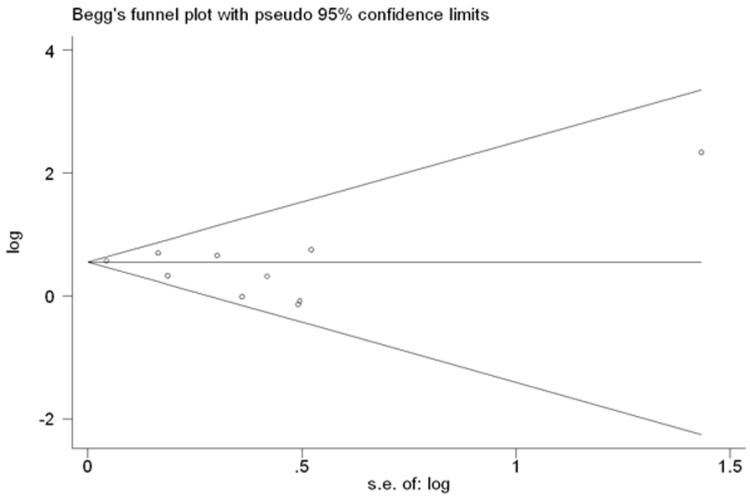

Figure 7. Funnel plot with pseudo 95% confidence limits of SGA among the included studies.

study was removed in sequence, the heterogeneity did not decrease significantly, and the conclusion did not change.

Publication bias

The Newcastle-Ottawa scales (NOS) evaluation indicated that the incidence rate of SGA had low-quality evidence (**Table 1**). There may be biases in the studies included, but the symmetry of the funnel plot was further evaluated using Begg's test, and no publication bias was found (Begg's test, P=0.335) (**Figure 7**).

Discussion

Main findings

At present, beta-blockers have been widely used for pregnant women to treat heart disease and hypertension. 1 in 200 pregnant women will use them to treat hypertension [22, 23]. Beta-blockers can reduce the complications of pregnancy-induced hypertension. Beta-blocker exposure has some adverse effects on fetal outcomes, which we haven't paid much attention to. In our study, an extensive data analysis showed a direct relationship between beta receptor exposure and pregnancy. It was confirmed that exposure to beta-blockers during pregnancy is associated with a higher risk of SGA (1.72 fold), stillbirth (2.59 fold), and Neonatal hypoglycemia (2.60 fold). The incidence of SGA in pregnant women with beta-blocker exposure in our study is similar to the conclusion reported by Magee et al. (1.36 fold) [8], and while with the data is from some new research, we reached the opposite conclusion regarding the incidence of stillbirth and neonatal hypoglycemia.

Possible mechanism

Although beta-blocker exposure may increase the risk of SGA, stillbirth, and neonatal hypoglycemia, the reason remains unclear and may be explained as follows: currently, most beta-blockers are considered to cross the placenta [24], which is associated with various adverse effects, including intra-uterine growth retardation, neonatal respiratory depression, bradycardia and hypoglycemia [20, 25]. The effects of beta-blockers on placental hemodynamics have been observed in both human and animal studies. A mechanism has been proposed, suggesting that the decrease of placental blood flow is due to the selective vasoconstriction of

placental vessels caused by the effect of beta-blockers, which also lead to no intrinsic sympathomimetic activity. This effect on placental hemodynamics could explain growth retardation of fetuses and might result in infants being born SGA and preterm [6, 24]. The reduction in uteroplacental circulation may lead to fetal hypoxemia, and then the effects of hormones and the circulatory system are stimulated, the blood flow of the fetus would be redistributed, and glycolysis (the Pasteur effect) may happen, and all this may result in hypoglycemia and an increase in triphosphate adenosine (ATP) and lactic acid [16]. Atenolol and metoprolol are the commonly used beta blockers in pregnancy. Butters' study shows that women with hypertensive disorders during pregnancy treated with atenolol are associated with a significant and progressive fall in human placental lactogen concentration [3]. Lydakis' research [26] found that atenolol have adverse effects on uteroplacental and fetal hemodynamics. Woods [27] thinks that labetalol may interfere with catecholamine-mediated circulatory responses, which are harmful to acidotic asphyxiated infants. These studies suggest that exposure to beta-blockers during pregnancy interferes with placental hemodynamics and disturbs placental metabolism and endocrine function, leading to various fetal complications.

Clinical implications and limitations

The strength of this systematic review and meta-analysis lies in the instruction significance for clinical questions, as a large volume of data was included and a rigorous methodology used. However, there are several limitations to our study. The first is that there are retrospective studies and low-quality literature in this study, and there are potential biases among the studies. This is followed by individual studies that have different definitions of SGA and neonatal hypoglycemia, leading us to miss some SGA and pregnant women with hypoglycemia. Finally, there are different indications of beta blockers in the study, and there are factors that cannot be adjusted.

Conclusion

Beta-blockers lead to an increased incidence of SGA, fetal death, and neonatal hypoglycemia. Although some conclusions still require more research to support them, this study resolves the dispute.

Disclosure of conflict of interest

None.

Abbreviations

RC, retrospective cohort; PC, prospective cohort; CV, cardiovascular; HTN, hypertension; SGA, small for gestational age; PB, Preterm birth was defined as birth before the 37th gestational week; Perinatal mortality was defined as either death occurring within the first 28 days of life or stillbirth; RCT, randomized clinical trial; NH, Neonatal hypoglycemia is defined as glucose less than 2.7 mmol/L.

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