



BMJ Open Risk for neonatal hypoglycaemia and bradycardia after beta-blocker use during pregnancy or lactation: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Beta-blockers are often used during pregnancy to treat diseases such as pre-existing hypertension, arrhythmias or pregnancy-related hypertension. Since beta-blockers are able to cross the placenta and can pass into breast milk, they could potentially harm the neonate. Known potential neonatal side effects of maternal beta-blocker use are hypoglycaemia and bradycardia. This systematic review and meta-analysis aims to investigate the risk for neonatal hypoglycaemia and bradycardia after exposure to beta-blockers in utero or through lactation.

Methods and analysis We will conduct a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A systematic electronic search will be conducted using EMBASE, Medline, Cochrane Central Register of Trials and Web of Science from initiation to April 2021. Our primary outcome will be the risk for hypoglycaemia or bradycardia in neonates exposed to beta-blockers in utero or through lactation in comparison with unexposed neonates. All articles will be screened by title and abstract twice by different independent review authors. Next, standardised methodological quality assessment will be conducted for each included article and finally a meta-analysis will be performed.

Ethics and dissemination Ethical approval is not required. The results of this study will help to assess the need for postnatal glucose and heart rate monitoring of the neonate after maternal beta-blocker exposure. Our findings will be communicated to the target audience through peer-reviewed publication.

PROSPERO registration number CRD42021264269.

INTRODUCTION

Antihypertensive medication is often used during pregnancy for maternal conditions such as pre-existing hypertension, pregnancy induced hypertension, pre-eclampsia or tachyarrhythmia. Beta-blockers are commonly prescribed antihypertensive agents, both used during pregnancy and during lactation.¹ Labetalol and metoprolol are the most

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ We will conduct both a systematic review and meta-analysis on the neonatal risk for hypoglycaemia and bradycardia after maternal beta-blocker use.
- ⇒ Both the neonatal effects of beta-blocker exposure in utero as well as through lactation will be studied.
- ⇒ We will use multiple databases for the identification of eligible studies.
- ⇒ Only articles published in English will be included, which could limit the inclusion of studies.
- ⇒ Confounding by indication could occur since the underlying disease of the mother could influence neonatal outcome.

commonly prescribed beta-blockers during pregnancy.²

As most beta-blockers are known to cross the placenta, their in utero exposure may affect the condition of the neonate after birth. In addition, some beta-blockers have been found in breast milk, although the degree of excretion into breast milk of different beta-blockers is dependent on their individual pharmacokinetic parameters.³ Beta-blockers such as labetalol and propranolol can pass into the breastmilk in low concentrations,^{4 5} while beta-blockers such as atenolol and sotalol reach relatively high concentrations.^{6 7}

Beta-blockers inhibit beta-1 and beta-2 receptors, which cause a decrease in heart rate and heart contractility.² The consequent decrease in cardiac output lowers the arterial blood pressure.² Even though the decrease in heart rate is one of the mechanisms of action of the beta-blocker, this can also be a dangerous side effect when the heart rate becomes too low. As neonates have a limited ability to increase cardiac output via an increase of their stroke volume, cardiac output is more dependent on heart rate than in adults. Therefore, exposure in utero and

through lactation to beta-blockers could potentially harm the neonate by a decrease in heart rate and as a consequence a decrease of cardiac output and organ perfusion.

Furthermore, beta-blocker use is associated with hypoglycaemia, since beta blockade inhibits glycogenolysis caused by activation of the sympathetic nervous system.² The question arises whether this also yields true for neonates after maternal use. Hypoglycaemia, and especially prolonged hypoglycaemia, can cause severe brain injury in neonates.^{8,9} Therefore, it is important to know whether exposure to beta-blockers in utero or through lactation substantially increases the risk for bradycardia and hypoglycaemia in neonates and to what extent.

Previous studies have shown that maternal use of beta-blockers is not associated with a large increase in the risk for overall malformations or cardiac malformations for the neonate.^{10,11} However, beta-blocker exposure during pregnancy has been associated with preterm birth and perinatal mortality.¹² Importantly, it is unknown whether exposure to beta-blockers in utero or through lactation considerably increases the risk for bradycardia or hypoglycaemia in neonates. In case of an increased risk postpartum, glucose monitoring and heart rate observation are needed in order to detect and treat those potential harmful side effects. On the other hand, if there is no increased risk for hypoglycaemia or bradycardia, then admission of the child for monitoring with possible separation from the parents and painful glucose tests are not needed.

Objectives

The aim of this systematic review and meta-analysis is to evaluate the incidence of hypoglycaemia and bradycardia in neonates exposed to beta-blockers in utero or through lactation in comparison with neonates without beta-blocker exposure. This will be investigated in order to assess the need of postnatal glucose monitoring and heart rate observation of the neonate.

METHODS

This protocol for a systematic review and meta-analysis has been written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for protocols (see online supplemental file 1).¹³ This study protocol has been submitted for registration in the PROSPERO database (registration number CRD42021264269).

Search strategy

A search strategy will be developed in consultation with a professional librarian, using the following electronic databases: EMBASE, Medline, Cochrane Central Register of Trials and Web of Science. Search terms on the following subjects will be included: (1) beta-blockers, (2) pregnancy or lactation and (3) the effect on the neonate in terms of hypoglycaemia and bradycardia. Search terms in MEDLINE will be included for instance ‘eta adrenergic

receptor blocking agent/exp’, ‘hypoglycaemia/de’, ‘bradycardia/exp’, ‘perinatal drug exposure’ and ‘lactation/de’ (see online supplemental file 2 for the search strategy. Only English-language human studies published between the start of the databases until 21 April 2021 will be included.

Eligibility criteria

The following inclusion criteria will be applied on the articles (including abstracts) resulting from the search:

1. Randomised controlled trials, case series, case reports and observational studies studying the adverse effects of beta-blockers exposure during pregnancy and lactation on the neonate.
2. The described effect on the neonate should focus on hypoglycaemia and/or bradycardia.

Articles will be excluded when they meet the following criteria:

1. Articles studying only the effect of the disease of the mother on the neonate.
2. Studies on the effect of beta-blockers on only the fetus and not the neonate.
3. Reviews and editorials.
4. Letters which are not case reports.
5. Animal studies.

Screening and data extraction

Two members of the study team will independently review the articles based on title and abstract using the above described inclusion and exclusion criteria (RdB and SF). Therewith, all articles will be evaluated twice by two different reviewers. After a selection based on title and abstract, two reviewers will read the full text of the selected articles (RdB and SvD). Any identified discrepancies between the independent reviewers will be resolved through evaluation and discussion by GEvdB and RBF when necessary. Extracted information will include the number of participants, participant demographics, study population, study design, outcome (hypoglycaemia and/or bradycardia), treatment indication and type and dosage of the beta-blocker. The number of articles meeting the inclusion criteria will be recorded and the reasons for exclusion will be documented in accordance with the PRISMA guidelines.

Outcomes

Our primary outcome is the occurrence of the short-term treatable neonatal adverse events hypoglycaemia and bradycardia. No additional outcomes will be included. Results in our systematic review will be presented as mean difference or standardised mean difference with 95% CI between exposed and unexposed neonates. If possible, based on the included articles, we will conduct a meta-analysis. We will calculate the relative risk for hypoglycaemia and bradycardia. Statistical analysis will be conducted according to the recommendations of the Cochrane Handbook and using the software of Cochrane Collaboration, RevMan V.5.3. We will use the χ^2 test and

I^2 statistic for the assessment of heterogeneity. A fixed effect model will be used if there is no obvious heterogeneity ($I^2 < 50\%$ and $p > 0.1$) and a random effects model will be used if significant heterogeneity is found to exist ($50\% < I^2 < 80\%$ or $p < 0.01$).

Assessment of risk of bias and quality of evidence

Qualitative assessment will be assessed by three reviewers (RdB, GEvdB and RBF) using an appropriate standardised risk of bias assessment tool for each study design. These tools include the Cochrane risk-of-bias assessment tool for randomised trials,¹⁴ the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies and the modified Newcastle-Ottawa scale for cross-sectional studies to assess cross-sectional studies.¹⁵ The quality of case reports will be evaluated using the Checklist for Case Reports by the JBI.¹⁶ Any discrepancies will be solved through further discussion between the reviewers (RdB, GEvdB and RBF). Grading of Recommendations Assessment, Development and Evaluations will be used to assess the quality of evidence and strength of recommendations.¹⁷

Implication of the systematic review

We aim to enhance our knowledge on the potential risk of using beta-blockers during pregnancy or lactation for the neonate. This may help to anticipate in a suited way when a neonate is born, with a monitoring protocol as minimal invasive as possible. Growing evidence suggest associations between beta-blocker exposure during pregnancy and hypoglycaemia and bradycardia in the neonate with potential harmful consequences. However, we do not know whether these potential side effects are rare or common in neonates. Therefore, this systematic review will present a comprehensive overview of the available information on the incidence of hypoglycaemia and bradycardia in the neonate after exposure to beta-blockers in utero or through lactation. The results of this review will be of interest to a broad audience (eg, neonatologists, paediatricians, gynaecologists, obstetricians, nurses, pharmacologists and researchers) as this will provide clinical guidance on the optimal policy of taking care of the exposed neonate. The methodological strengths of our review include a comprehensive search to locate all available evidence in the major electronic databases. Moreover, we will use a systematic approach. We foresee methodological weaknesses of the available literature, as we might include articles of lower evidence. Furthermore, there can be a confounding by indication in which bradycardia and hypoglycaemia occur as a consequence of the underlying disease of the mother or neonatal conditions related to the underlying disease of the mother such as prematurity.

ETHICS AND DISSEMINATION

There is no necessity for this study to acquire an ethical approval, since no private information of participants

will be involved. Results of this study will be disseminated in a peer-reviewed journal or conference presentation. Important protocol amendments will be documented and updated in PROSPERO.

Contributors RdB, SvD and SF drafted the protocol, which was revised by SHPS, RBF and GEvdB. RdB, SvD and SF will search, select, and identify studies included and extract data independently, while RBF and GEvdB will review the articles in case of discrepancies between RdB, SvD and SF. RdB, SvD and SF will outline the systematic review and will conduct the analysis. Both GEvdB, SHPS and RBF will provide a critical revision and the final approval of the article. SHPS will serve as an adviser for methodology. All authors have approved the publication of this protocol. GEvdB and RBF designed this study, and GEvdB is the guarantor for the article. Support for developing and updating the search strategy was obtained from the Erasmus MC medical library.

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