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The 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 (PRISMA) guidelines. A systematic electronic search will be conducted in EMBASE, Medline, Cochrane Central Register of Trials and Web of Science from initiation up till April 2021. Our primary outcome will be the risk of 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, standardized 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 heartrate 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 The protocol for this systematic review is submitted for registration to the international database of prospectively registered systematic reviews (PROSPERO, awaiting registration number).

Strengths and limitations of this study

- To our knowledge this study is the first systematic review and meta-analysis on the risk of hypoglycaemia and bradycardia for the neonate after exposure to beta-blockers in utero or through lactation.
- The present study will provide evidence for clinical management for neonates after beta-blocker exposure in utero as well as through lactation.
- We will only include articles published in English in our systematic electronic search which could limit the inclusion of studies.
- Confounding by indication could be a limitation of our study since the underlying disease of the mother could influence the neonatal outcomes.

Keywords

Beta-blockers, pregnancy, lactation, neonatal hypoglycaemia, neonatal bradycardia

Wordcount

1571 words

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 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 propanolol 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 heartrate and heart contractility (2). The consequent decrease in cardiac output lowers the arterial blood pressure (2). Even though the decrease in heartrate is one of the mechanisms of action of the beta-blocker, this can also be a dangerous side effect when the heartrate 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). 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 can cause hypoglycaemia in neonates.

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 increases the risk for bradycardia or hypoglycaemia in neonates. In case of an increased risk postpartum, glucose monitoring and heartrate 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 heartrate 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-P) guidelines for protocols (see supplemental file 1) (13). This study protocol has been submitted for registration in the PROSPERO database.

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

Eligibility criteria

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

1. Randomized 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

Each of three members of the study team will independently review two-third of the articles based on title and abstract using the above described inclusion and exclusion criteria (RB, SD and SF). Therewith, all articles will be evaluated twice by two different persons. After a selection based on title and abstract, the three reviewers will all read the full text of the selected articles. Any identified discrepancies between the independent reviewers will be resolved through evaluation and discussion by GB and RF 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. This will be done 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 standardized mean difference with 95% confidence interval 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 5.3. We will use the $\chi 2$ 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 ($50\% <I2<80\%$ or $p<0.01$).

Assessment of risk of bias and quality of evidence

Qualitative assessment will be assessed by three reviewers (RB, SD, SF) using an appropriate standardized risk of bias assessment tool for each study design. These tools include the Cochrane risk-of-bias assessment tool for randomized 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 two other reviewers (GB and RF). Grading of Recommendations Assessment, Development and Evaluations (GRADE) will be used to assess the quality of evidence and strength of recommendations (17).

Implication of the systematic review

We aspire to enhance our knowledge about 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 prevalence of hypoglycaemia and bradycardia in the neonate with potential harmful consequences. 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 (e.g. 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 the 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 the present study will be disseminated in a peer-reviewed journal or conference presentation. Important protocol amendments will be documented and updated in PROSPERO.

Authors' contributions

RB, SD and SF drafted the protocol, which was revised by SS, RF and GB.
RB, SD and SF will search, select, and identify studies included and extract data independently, while RF and GB will review the articles in case of discrepancies between RB, SD and SF. RB, SD and SF will outline the systematic review and will conduct the analysis. Both GB and RF will provide a critical revision and the final approval of the article. The final approval will also be granted by SS. SS will serve as an adviser for methodology. All authors have approved the publication of this protocol. GB and RF designed this study, and GB is the guarantor for the article.

Support for developing and updating the search strategy was obtained from the Erasmus MC medical library.

Funding

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Competing interests

None declared.

Patients and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

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Supplemental file 1

PRISMA Protocol Checklist

Section and topic	Item No	Checklist	Reporting. Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number	PROSPERO (awaiting registration number)
Authors:			
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 4
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 5
Sponsor	5b	Provide name for the review funder and/or sponsor Role of sponsor/ funder	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 2

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 2
METHODS			
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years	Page 3

		considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	Page 3
Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplemental file 2
Study Records			
	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 3
	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta- analysis)	Page 3
	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 3-4
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 4
Data synthesis			

	15a	Describe criteria under which study data will be quantitatively synthesized	Page 3
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I 2 , Kendall's tau)	Page 3
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	Page 3
	15d	If quantitative synthesis is not appropriate, describe the type	NA
		of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	Page 4
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	Page 4

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplemental file 2

Search strategy

embase.com

('beta adrenergic receptor blocking agent'/exp OR (((beta* OR β OR β1 OR β2 OR β3) NEAR/3 (block* OR antagonist*)) OR adaprolol* OR afurolol* OR alprenolol* OR befunolol* OR bfe-55* OR bopindolol* OR bornaprolol* OR bromoacetylalprenololmenthane* OR bucindolol* OR bucumolol* OR bufetolol* OR bufuralol* OR bunitrolol* OR bunolol* OR bupranolol* OR butofilolol* OR carazolol* OR carpindolol* OR carteolol* OR carvedilol* OR cloranolol* OR deacetylmetipranolol* OR dexpropranolol* OR diacetolol* OR dichlorisoprenaline* OR dihydroalprenolol* OR dilevalol* OR diprafenone* OR ersentilide* OR exaprolol* OR falintolol* OR flestolol* OR hydroxybenzylpindolol* OR indenolol* OR iodopindolol* OR iprocrolol* OR isamoltane* OR isoxaprolol* OR labetalol* OR levobunolol* OR levomoprolol* OR mepindolol* OR mercuderamide* OR metipranolol* OR moprolol* OR nadolol* OR nifenalol* OR oberadilol* OR oxprenolol* OR pafenolol* OR pamatolol* OR penbutolol* OR pindolol* OR primidolol* OR prizidilol* OR procinolol* OR pronetalol* OR propranolol* OR proxodolol* OR ridazolol* OR soquinolol* OR sotalol* OR spirendolol* OR tazolol* OR tertatolol* OR tienoxolol* OR tilisolol* OR timolol* OR tolamolol* OR toliprolol* OR trasitensin* OR trepress* OR tribendilol* OR viskaldix* OR xibenolol* OR zoleprodolol* OR acebutolol* OR alpha-hydroxymetoprolol* OR atenolol* OR bendacalol* OR betaxolol* OR bevantolol* OR bisoprolol* OR celiprolol* OR cetamolol* OR cyanoiodopindolol* OR cyanopindolol* OR dramedilol* OR epanolol* OR esmolol* OR flusoxolol* OR landiolol* OR metoprolol* OR nebivolol* OR practolol* OR ritodrine* OR salcardolol* OR sandoz-204545* OR talinolol* OR vortioxetine* OR bendacalol* OR butoxamine* OR cicloprolol* OR arotinolol*):Ab,ti) AND (pregnancy/exp OR 'pregnant woman'/de OR 'prenatal exposure'/de OR 'breast feeding'/exp OR 'breast milk'/de OR lactation/de OR 'maternal exposure'/de OR 'maternal treatment'/de OR 'prenatal drug exposure'/de OR 'prenatal period'/de OR 'maternal hypertension'/de OR 'intrauterine growth retardation'/de OR 'pregnancy disorder'/de OR 'pregnancy outcome'/exp OR 'drug milk level'/de OR 'placental transfer'/de OR 'perinatal drug exposure'/de OR (pregnan* OR prenatal* OR (breast NEXT/1 (feed* OR fed OR milk)) OR human-milk OR lactat* OR intra-uterin* OR intrauterin* OR ((fetus* OR foetus* OR fetal* OR foetal*) NEAR/3 expos*) OR mother OR maternal OR placenta* OR perinatal* OR peri-natal*):Ab,ti) AND (bradycardia/exp OR 'adverse event'/de OR 'side effect'/de OR 'intrauterine growth retardation'/de OR 'low birth weight'/exp OR hypoglycemia/de OR 'pregnancy outcome'/de OR stillbirth/exp OR 'Apgar score'/de OR hemodynamics/de OR 'toxicity and intoxication'/exp OR complication/de OR 'birth weight'/de OR prematurity/exp OR (adverse* OR bradycard* OR effect* OR ((intrauterin* OR intra-uterin*) NEAR/3 growth) OR birth-weight* OR birthweight* OR (small NEXT/2 (date OR gestation*)) OR hypoglycemi* OR hypoglycaemia OR ((pregnan* OR deliver* OR obstetr* OR childbirth OR labour OR labor) NEAR/3 outcome*) OR stillbirth OR stillborn OR still-birth OR still-born OR Apgar OR harm* OR toxic* OR intoxic* OR hemodynamic* OR haemodynamic* OR complication* OR (prematur* NEAR/3 (birth)) OR prematurity):ab,ti) AND (newborn/exp OR 'low birth weight'/exp OR stillbirth/exp OR 'Apgar score'/de OR 'birth weight'/de OR (newborn* OR new-born* OR neonat* OR postnatal* OR birth-weight* OR birthweight* OR (small NEXT/2 (date OR gestation*)) OR stillbirth OR stillborn OR still-birth OR still-born OR Apgar):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([conference abstract]/lim AND [2000-2018]/py) AND [english]/lim

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The 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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The 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 (PRISMA) guidelines. A systematic electronic search will be conducted using EMBASE, Medline, Cochrane Central Register of Trials and Web of Science from initiation up till 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, standardized 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 heartrate 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 The protocol for this systematic review is registered in the international database of prospectively registered systematic reviews (PROSPERO registration number CRD42021264269).

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.

Keywords

Beta-blockers, pregnancy, lactation, neonatal hypoglycaemia, neonatal bradycardia

Wordcount

1619 words

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 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 heartrate and heart contractility (2). The consequent decrease in cardiac output lowers the arterial blood pressure (2). Even though the decrease in heartrate is one of the mechanisms of action of the beta-blocker, this can also be a dangerous side effect when the heartrate 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 heartrate 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 heartrate 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-P) guidelines for protocols (see 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 'beta adrenergic receptor blocking agent/exp', 'hypoglycaemia/de', 'bradycardia/exp', 'perinatal drug exposure' and 'lactation/de' (see supplemental file 2 for the search strategy). Only English-language human studies published between the start of the databases until April 21st 2021 will be included.

Eligibility criteria

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

1. Randomized 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 (RB 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 (RB and SD). Any identified discrepancies between the independent reviewers will be resolved through evaluation and discussion by GB and RF 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 standardized mean difference with 95% confidence interval 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 5.3. We will use the $\chi 2$ 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% <I2<80% or p<0.01).

Assessment of risk of bias and quality of evidence

Qualitative assessment will be assessed by three reviewers (RB, GB, RF) using an appropriate standardized risk of bias assessment tool for each study design. These tools include the Cochrane risk-of-bias assessment tool for randomized 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 (RB, GB and RF). Grading of Recommendations Assessment, Development and Evaluations (GRADE) 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 (e.g. 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 the present study will be disseminated in a peer-reviewed journal or conference presentation. Important protocol amendments will be documented and updated in PROSPERO.

Authors' contributions

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

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Patients and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

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Supplemental file 1

PRISMA Protocol Checklist

Section and topic	Item No	Checklist	Reporting. Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number	PROSPERO (awaiting registration number)
Authors:			
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 4
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 5
Sponsor	5b	Provide name for the review funder and/or sponsor Role of sponsor/ funder	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 2

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 2
METHODS			
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years	Page 3

		considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	Page 3
Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplemental file 2
Study Records			
	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 3
	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta- analysis)	Page 3
	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 3-4
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 4
Data synthesis			

	15a	Describe criteria under which study data will be quantitatively synthesized	Page 3
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I 2 , Kendall's tau)	Page 3
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	Page 3
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	Page 4
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	Page 4

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplemental file 2

Search strategy

embase.com

('beta adrenergic receptor blocking agent'/exp OR (((beta* OR β OR β1 OR β2 OR β3) NEAR/3 (block* OR antagonist*)) OR adaprolol* OR afurolol* OR alprenolol* OR befunolol* OR bfe-55* OR bopindolol* OR bornaprolol* OR bromoacetylalprenololmenthane* OR bucindolol* OR bucumolol* OR bufetolol* OR bufuralol* OR bunitrolol* OR bunolol* OR bupranolol* OR butofilolol* OR carazolol* OR carpindolol* OR carteolol* OR carvedilol* OR cloranolol* OR deacetylmetipranolol* OR dexpropranolol* OR diacetolol* OR dichlorisoprenaline* OR dihydroalprenolol* OR dilevalol* OR diprafenone* OR ersentilide* OR exaprolol* OR falintolol* OR flestolol* OR hydroxybenzylpindolol* OR indenolol* OR iodopindolol* OR iprocrolol* OR isamoltane* OR isoxaprolol* OR labetalol* OR levobunolol* OR levomoprolol* OR mepindolol* OR mercuderamide* OR metipranolol* OR moprolol* OR nadolol* OR nifenalol* OR oberadilol* OR oxprenolol* OR pafenolol* OR pamatolol* OR penbutolol* OR pindolol* OR primidolol* OR prizidilol* OR procinolol* OR pronetalol* OR propranolol* OR proxodolol* OR ridazolol* OR soquinolol* OR sotalol* OR spirendolol* OR tazolol* OR tertatolol* OR tienoxolol* OR tilisolol* OR timolol* OR tolamolol* OR toliprolol* OR trasitensin* OR trepress* OR tribendilol* OR viskaldix* OR xibenolol* OR zoleprodolol* OR acebutolol* OR alpha-hydroxymetoprolol* OR atenolol* OR bendacalol* OR betaxolol* OR bevantolol* OR bisoprolol* OR celiprolol* OR cetamolol* OR cyanoiodopindolol* OR cyanopindolol* OR dramedilol* OR epanolol* OR esmolol* OR flusoxolol* OR landiolol* OR metoprolol* OR nebivolol* OR practolol* OR ritodrine* OR salcardolol* OR sandoz-204545* OR talinolol* OR vortioxetine* OR bendacalol* OR butoxamine* OR cicloprolol* OR arotinolol*):Ab,ti) AND (pregnancy/exp OR 'pregnant woman'/de OR 'prenatal exposure'/de OR 'breast feeding'/exp OR 'breast milk'/de OR lactation/de OR 'maternal exposure'/de OR 'maternal treatment'/de OR 'prenatal drug exposure'/de OR 'prenatal period'/de OR 'maternal hypertension'/de OR 'intrauterine growth retardation'/de OR 'pregnancy disorder'/de OR 'pregnancy outcome'/exp OR 'drug milk level'/de OR 'placental transfer'/de OR 'perinatal drug exposure'/de OR (pregnan* OR prenatal* OR (breast NEXT/1 (feed* OR fed OR milk)) OR human-milk OR lactat* OR intra-uterin* OR intrauterin* OR ((fetus* OR foetus* OR fetal* OR foetal*) NEAR/3 expos*) OR mother OR maternal OR placenta* OR perinatal* OR peri-natal*):Ab,ti) AND (bradycardia/exp OR 'adverse event'/de OR 'side effect'/de OR 'intrauterine growth retardation'/de OR 'low birth weight'/exp OR hypoglycemia/de OR 'pregnancy outcome'/de OR stillbirth/exp OR 'Apgar score'/de OR hemodynamics/de OR 'toxicity and intoxication'/exp OR complication/de OR 'birth weight'/de OR prematurity/exp OR (adverse* OR bradycard* OR effect* OR ((intrauterin* OR intra-uterin*) NEAR/3 growth) OR birth-weight* OR birthweight* OR (small NEXT/2 (date OR gestation*)) OR hypoglycemi* OR hypoglycaemia OR ((pregnan* OR deliver* OR obstetr* OR childbirth OR labour OR labor) NEAR/3 outcome*) OR stillbirth OR stillborn OR still-birth OR still-born OR Apgar OR harm* OR toxic* OR intoxic* OR hemodynamic* OR haemodynamic* OR complication* OR (prematur* NEAR/3 (birth)) OR prematurity):ab,ti) AND (newborn/exp OR 'low birth weight'/exp OR stillbirth/exp OR 'Apgar score'/de OR 'birth weight'/de OR (newborn* OR new-born* OR neonat* OR postnatal* OR birth-weight* OR birthweight* OR (small NEXT/2 (date OR gestation*)) OR stillbirth OR stillborn OR still-birth OR still-born OR Apgar):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([conference abstract]/lim AND [2000-2018]/py) AND [english]/lim

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(exp Adrenergic beta-Antagonists/ OR (((beta*) ADJ3 (block* OR antagonist*)) OR adaprolol* OR afurolol* OR alprenolol* OR befunolol* OR bfe-55* OR bopindolol* OR bornaprolol* OR bromoacetylalprenololmenthane* OR bucindolol* OR bucumolol* OR bufetolol* OR bufuralol* OR bunitrolol* OR bunolol* OR bupranolol* OR butofilolol* OR carazolol* OR carpindolol* OR carteolol* OR carvedilol* OR cloranolol* OR deacetylmetipranolol* OR dexpropranolol* OR diacetolol* OR dichlorisoprenaline* OR dihydroalprenolol* OR dilevalol* OR diprafenone* OR ersentilide* OR exaprolol* OR falintolol* OR flestolol* OR hydroxybenzylpindolol* OR indenolol* OR iodopindolol* OR iprocrolol* OR isamoltane* OR isoxaprolol* OR labetalol* OR levobunolol* OR levomoprolol* OR mepindolol* OR mercuderamide* OR metipranolol* OR moprolol* OR nadolol* OR nifenalol* OR oberadilol* OR oxprenolol* OR pafenolol* OR pamatolol* OR penbutolol* OR pindolol* OR primidolol* OR prizidilol* OR procinolol* OR pronetalol* OR propranolol* OR proxodolol* OR ridazolol* OR soquinolol* OR sotalol* OR spirendolol* OR tazolol* OR tertatolol* OR tienoxolol* OR tilisolol* OR timolol* OR tolamolol* OR toliprolol* OR trasitensin* OR trepress* OR tribendilol* OR viskaldix* OR xibenolol* OR zoleprodolol* OR acebutolol* OR alpha-hydroxymetoprolol* OR atenolol* OR bendacalol* OR betaxolol* OR bevantolol* OR bisoprolol* OR celiprolol* OR cetamolol* OR cyanoiodopindolol* OR cyanopindolol* OR dramedilol* OR epanolol* OR esmolol* OR flusoxolol* OR landiolol* OR metoprolol* OR nebivolol* OR practolol* OR ritodrine* OR salcardolol* OR sandoz-204545* OR talinolol* OR vortioxetine* OR bendacalol* OR butoxamine* OR cicloprolol* OR arotinolol*).ab,ti.) AND (exp Pregnancy/ OR Pregnant Women/ OR Breast Feeding/ OR Milk, Human/ OR Lactation/ OR Maternal Exposure/ OR Maternal-Fetal Exchange/ OR Prenatal Exposure Delayed Effects/ OR Fetal Growth Retardation/ OR exp Pregnancy Outcome/ OR (pregnan* OR prenatal* OR (breast ADJ (feed* OR fed OR milk)) OR human-milk OR lactat* OR intra-uterin* OR intrauterin* OR ((fetus* OR foetus* OR fetal* OR foetal*) ADJ3 expos*) OR mother OR maternal OR placenta* OR perinatal* OR peri-natal*).ab,ti.) AND (Bradycardia/ OR Drug-Related Side Effects and Adverse Reactions/ OR Fetal Growth Retardation/ OR Infant, Low Birth Weight/ OR Hypoglycemia/ OR Pregnancy Outcome/ OR Stillbirth/ OR Apgar Score/ OR Hemodynamics/ OR toxicity.xs. OR complication.xs. OR exp Birth Weight/ OR exp Infant, Premature/ OR (adverse* OR bradycard* OR effect* OR ((intrauterin* OR intra-uterin*) ADJ3 growth) OR birth-weight* OR birthweight* OR (small ADJ2 (date OR gestation*)) OR hypoglycemi* OR hypoglycaemia OR ((pregnan* OR deliver* OR obstetr* OR childbirth OR labour OR labor) ADJ3 outcome*) OR stillbirth OR stillborn OR still-birth OR still-born OR Apgar OR harm* OR toxic* OR intoxic* OR hemodynamic* OR haemodynamic* OR complication* OR (prematur* ADJ3 (birth)) OR prematurity).ab,ti.) AND (Infant, Newborn/ OR Infant, Low Birth Weight/ OR Stillbirth/ OR Apgar Score/ OR exp Birth Weight/ OR (newborn* OR new-born* OR neonat* OR postnatal* OR birth-weight* OR birthweight* OR (small ADJ2 (date OR gestation*)) OR stillbirth OR stillborn OR still-birth OR still-born OR Apgar).ab,ti.) NOT (exp animals/ NOT humans/) AND english.la.

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TS=(((((beta* OR β OR β1 OR β2 OR β3) NEAR/2 (block* OR antagonist*)) OR adaprolol* OR afurolol* OR alprenolol* OR befunolol* OR bfe-55* OR bopindolol* OR bornaprolol* OR bromoacetylalprenololmenthane* OR bucindolol* OR bucumolol* OR bufetolol* OR bufuralol* OR bunitrolol* OR bunolol* OR bupranolol* OR butofilolol* OR carazolol* OR carpindolol* OR carteolol* OR carvedilol* OR cloranolol* OR deacetylmetipranolol* OR dexpropranolol* OR diacetolol* OR dichlorisoprenaline* OR dihydroalprenolol* OR dilevalol* OR diprafenone* OR ersentilide* OR exaprolol* OR falintolol* OR flestolol* OR hydroxybenzylpindolol* OR indenolol* OR iodopindolol* OR iprocrolol* OR isamoltane* OR isoxaprolol* OR labetalol* OR levobunolol* OR levomoprolol* OR mepindolol* OR mercuderamide* OR metipranolol* OR moprolol* OR nadolol* OR nifenalol* OR oberadilol* OR oxprenolol* OR pafenolol* OR pamatolol* OR penbutolol* OR pindolol* OR primidolol* OR prizidilol* OR procinolol* OR pronetalol* OR propranolol* OR proxodolol* OR ridazolol* OR soquinolol* OR sotalol* OR spirendolol* OR tazolol* OR tertatolol* OR tienoxolol* OR tilisolol* OR timolol* OR tolamolol* OR toliprolol* OR trasitensin* OR trepress* OR tribendilol* OR viskaldix* OR xibenolol* OR zoleprodolol* OR acebutolol* OR alpha-hydroxymetoprolol* OR atenolol* OR bendacalol* OR betaxolol* OR bevantolol* OR bisoprolol* OR celiprolol* OR cetamolol* OR cyanoiodopindolol* OR cyanopindolol* OR dramedilol* OR epanolol* OR esmolol* OR flusoxolol* OR landiolol* OR metoprolol* OR nebivolol* OR practolol* OR ritodrine* OR salcardolol* OR sandoz-204545* OR talinolol* OR vortioxetine* OR bendacalol* OR butoxamine* OR cicloprolol* OR arotinolol*)) AND ((pregnan* OR prenatal* OR (breast NEAR/1 (feed* OR fed OR milk)) OR human-milk OR lactat* OR intra-uterin* OR intrauterin* OR ((fetus* OR foetus* OR fetal* OR foetal*) NEAR/2 expos*) OR mother OR maternal OR placenta* OR perinatal* OR peri-natal*)) AND ((adverse* OR bradycard* OR effect* OR ((intrauterin* OR intra-uterin*) NEAR/2 growth) OR birth-weight* OR birthweight* OR (small NEAR/2 (date OR gestation*)) OR hypoglycemi* OR hypoglycaemia OR ((pregnan* OR deliver* OR obstetr* OR childbirth OR labour OR labor) NEAR/2 outcome*) OR stillbirth OR stillborn OR still-birth OR still-born OR Apgar OR harm* OR toxic* OR intoxic* OR hemodynamic* OR haemodynamic* OR complication* OR (prematur* NEAR/2 (birth)) OR prematurity)) AND ((newborn* OR new-born* OR neonat* OR postnatal* OR birth-weight* OR birthweight* OR (small NEAR/2 (date OR gestation*)) OR stillbirth OR stillborn OR still-birth OR still-born OR Apgar))) AND DT=(article) AND LA=(english)

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((((beta* OR β OR β1 OR β2 OR β3) NEAR/3 (block* OR antagonist*)) OR adaprolol* OR afurolol* OR alprenolol* OR befunolol* OR bfe NEXT 55* OR bopindolol* OR bornaprolol* OR bromoacetylalprenololmenthane* OR bucindolol* OR bucumolol* OR bufetolol* OR bufuralol* OR bunitrolol* OR bunolol* OR bupranolol* OR butofilolol* OR carazolol* OR carpindolol* OR carteolol* OR carvedilol* OR cloranolol* OR deacetylmetipranolol* OR dexpropranolol* OR diacetolol* OR dichlorisoprenaline* OR dihydroalprenolol* OR dilevalol* OR diprafenone* OR ersentilide* OR exaprolol* OR falintolol* OR flestolol* OR hydroxybenzylpindolol* OR indenolol* OR iodopindolol* OR iprocrolol* OR isamoltane* OR isoxaprolol* OR labetalol* OR levobunolol* OR levomoprolol* OR mepindolol* OR mercuderamide* OR metipranolol* OR moprolol* OR nadolol* OR nifenalol* OR oberadilol* OR oxprenolol* OR pafenolol* OR pamatolol* OR penbutolol* OR pindolol* OR primidolol* OR prizidilol* OR procinolol* OR pronetalol* OR propranolol* OR proxodolol* OR ridazolol* OR soquinolol* OR sotalol* OR spirendolol* OR tazolol* OR tertatolol* OR tienoxolol* OR tilisolol* OR timolol* OR tolamolol* OR toliprolol* OR trasitensin* OR trepress* OR tribendilol* OR viskaldix* OR xibenolol* OR zoleprodolol* OR acebutolol* OR alpha NEXT hydroxymetoprolol* OR atenolol* OR bendacalol* OR betaxolol* OR bevantolol* OR bisoprolol* OR celiprolol* OR cetamolol* OR cyanoiodopindolol* OR cyanopindolol* OR dramedilol* OR epanolol* OR esmolol* OR flusoxolol* OR landiolol* OR metoprolol* OR nebivolol* OR practolol* OR ritodrine* OR salcardolol* OR sandoz NEXT 204545* OR talinolol* OR vortioxetine* OR bendacalol* OR butoxamine* OR cicloprolol* OR arotinolol*):Ab,ti) AND ((pregnan* OR prenatal* OR (breast NEXT/1 (feed* OR fed OR milk)) OR human NEXT milk OR lactat* OR intra NEXT uterin* OR intrauterin* OR ((fetus* OR foetus* OR fetal* OR foetal*) NEAR/3 expos*) OR mother OR maternal OR placenta* OR perinatal* OR peri NEXT natal*):Ab,ti) AND ((adverse* OR bradycard* OR effect* OR ((intrauterin* OR intra NEXT uterin*) NEAR/3 growth) OR birth NEXT weight* OR birthweight* OR (small NEXT/2 (date OR gestation*)) OR hypoglycemi* OR hypoglycaemia OR ((pregnan* OR deliver* OR obstetr* OR childbirth OR labour OR labor) NEAR/3 outcome*) OR stillbirth OR stillborn OR still NEXT birth OR still NEXT born OR Apgar OR harm* OR toxic* OR intoxic* OR hemodynamic* OR haemodynamic* OR complication* OR (prematur* NEAR/3 (birth)) OR prematurity):ab,ti) AND ((newborn* OR new NEXT born* OR neonat* OR postnatal* OR birth NEXT weight* OR birthweight* OR (small NEXT/2 (date OR gestation*)) OR stillbirth OR stillborn OR still NEXT birth OR still NEXT born OR Apgar):ab,ti)