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Adverse pregnancy outcomes in gestational diabetes mellitus – a systematic review and meta-analysis protocol

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Adverse pregnancy outcomes in gestational diabetes mellitus – a systematic review and meta-analysis protocol

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ABSTRACT

Introduction

Gestational Diabetes Mellitus (GDM) is associated with adverse pregnancy outcomes, including adverse outcomes for both the mother and the foetus. Different diagnostic criteria are used for GDM, and it is not clear how these affect the reported prevalence of adverse pregnancy outcomes. This protocol is for a systematic review to describe and compare the prevalence of adverse pregnancy outcomes in GDM using different diagnostic criteria across regions.

Methods and Analysis

A systematic review and meta-analysis will be carried out. A comprehensive search of observational studies that report the outcomes of interest to this review from 2010 to 2021 will be conducted. We will search the major electronic databases such as PubMed, Scopus, CINHAL, and Google scholar, and screen references of included studies for additional studies. Meta-analyses will be performed, if there is low heterogeneity, and pooled estimates per outcome reported. We will use the quality effects inverse heterogeneity model to pool prevalence estimates and do subgroup analyses by region, by age group, by diagnostic criteria, and by GDM screening method, if sufficient data are available. We will also compare prevalence of adverse outcomes by diagnostic method and report prevalence ratios. We will report 95% confidence estimates for all estimates.

Ethics and dissemination

Ethical approval is not required as the review utilises published data. Findings will be published in peer reviewed journals and presented at conferences.

PROSPERO Registration – CRD42020155061

Key words

Gestational diabetes (GDM), adverse outcomes, pregnancy, maternal and child health, prevalence, meta-analysis

Strengths and Limitation of this study

- This systematic review quantifies the effect of gestational diabetes on adverse pregnancy outcomes globally and provides the first analysis comparing the effects of different GDM definitions on adverse pregnancy outcomes.
- This study uses observational data and thus is likely to have confounded effects (such as the effect of maternal pre-pregnancy body mass index) which will may have to be minimized either through stratification or restriction.
- There may be a possibility of omitting certain publications that were not indexed properly under these terms as well as some unpublished data resulting in the identification of fewer studies.

INTRODUCTION

GDM is a metabolic disorder of pregnancy, defined as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy.(1)(2) Most women with GDM revert to normal glucose metabolism after delivery, however, they are at risk of developing type 2 diabetes and cardiovascular disease later in life as are their offspring.(3)(4)(5) (6)Notably, the diagnostic criteria for GDM and screening approaches vary widely internationally and this has also resulted in high heterogeneity in GDM prevalence estimates.(7)

GDM has been associated with adverse pregnancy outcomes such as macrosomia, shoulder dystocia, neonatal hypoglycaemia and perinatal mortality.(8) Recent results from the hyperglycaemia and adverse pregnancy outcome (HAPO) study showed that even milder levels of hyperglycaemia can have adverse effects on pregnancy outcomes.(9) This resulted in changes in many international GDM diagnosis guidelines, which either adopted or adapted the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations on the diagnosis and classification of hyperglycemia in pregnancy.(10) Examples of guidelines which became aligned to the IADPSG are the World Health Organization (WHO) which changed its GDM diagnosis criteria in 2013.(2) and the American Diabetes Association (ADA) which changed its guidelines to mirror the IADPSG since 2014 (11). However, there is still no consensus on diagnostic criteria for GDM, with more than 30

different guidelines in use at the moment.(11)(12)(6) The differences in these guidelines are not only in the maternal blood glucose cut-offs for the diagnosis of GDM, but also in screening approaches, screening methods and timing of screening for GDM during pregnancy

The continued lack of consensus on the diagnosis of GDM implies that the impact of GDM may differ in different settings depending on the diagnosis criteria used. This study, therefore, aims to describe and compare the prevalence of adverse pregnancy outcomes in GDM across different diagnostic criteria using a meta-analysis of existing data.

RESEARCH QUESTION

This systematic review will answer the following question:

What is the prevalence of adverse pregnancy outcomes in women diagnosed with GDM in studies during 2010-2020?

SPECIFIC OBJECTIVES

1. To estimate the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies using the IADPSG or similar criteria
2. To compare the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies between studies using the IADPSG or similar criteria and studies using different criteria
3. To estimate the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies by IDF region and per country.
4. To estimate the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies by the age-groups of 16-24 years, 25-34years, 35-44yrs, ≥45 years or 16-19 years, 20-29 years, 30-39 years, 40-49 years.

METHODS

Study design

A systematic review and meta-analysis will be carried out. The study protocol is registered on PROSPERO (CRD42020155061), the International prospective register

of systematic reviews and the findings will be reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (PRISMA 2020).

Patient and public involvement

No patient involved.

Search strategy for identification of studies

Data sources and electronic searches

We will search PubMed, Cochrane library, Scopus, Google Scholar and CINAHL for articles reporting on studies relevant to this study. An expert librarian will be consulted during the design of the search strategy. The search will use medical subject headings (MeSH terms) and keyword searches for GDM and pregnancy outcomes. The sample search strategy is attached as Supplementary Document S1. The reference lists of relevant citations for articles of interest will also be scanned for additional studies. Duplicates of articles will be identified and removed using Mendely, and the Rayyan systematic review management website (www.rayyan.ai) will be used to screen studies for inclusion. Four reviewers (TC, AG, KO, and SC) will independently screen the studies for inclusion within Rayyan, using title and abstract. The studies identified after the initial screening will then be assessed for inclusion using full text, following the pre-defined inclusion criteria.

Studies inclusion criteria

Types of studies

The systematic review will include observational studies (population-based reports, birth registers, cohort and cross-sectional studies) published from 2010 to 2021 that assessed the prevalence of adverse pregnancy outcomes in the mothers and offspring diagnosed with GDM, without language restriction.

Types of participants

Studies to be considered in this review would be those with participants who are women who had GDM during the period 2010-2020, and diagnosed using any criteria such as the WHO 2013 criteria (WHO, 2013)(2) or the International Association of Diabetes and Pregnancy Study Groups (IADPSG, 2010)(10) American Diabetes

Association 2014, and the National Institute for Health and Clinical Excellence (NICE) in the U.K (NICE 2014).

Exclusion criteria

Studies will be excluded if they were published before 2010, if they are review articles, contained animal studies, did not report on outcomes relevant to this study, included women with pre-existing diabetes or contained duplicate publications. For duplicate publications only the article containing the most information will be included in the review and all others excluded as duplicates.

Outcomes of interest

Pregnancy outcomes

These will include caesarean section (emergency and elective), any assisted delivery methods (for example, vacuum, and induced birth), preterm delivery (gestational age at delivery and deliveries before 37 weeks), peripartum infection, pregnancy induced hypertension and preeclampsia and eclampsia (13).

Maternal outcomes

Maternal outcomes will include post-partum depression, post-partum type 2 diabetes at 6 weeks, glucose control during pregnancy (including blood glucose measurements), pregnancy loss, hospitalisation, ICU and mortality within 6 weeks after delivery(14)(13).

Foetal outcomes

Foetal outcomes to be assessed in this study include the birthweight, large-for-gestational-age (LGA), small-for-gestational-age (SGA), macrosomia, neonatal mortality (within 28 days), stillbirth, congenital abnormalities, shoulder dystocia, neonatal hypoglycaemia, neonatal hospitalisation and intensive care admission (NICU), and respiratory distress syndrome. Macrosomia would be defined as birthweight above the 90th percentile for gestational age or birthweight greater than 4000 g. Perinatal mortality would be defined as any death around the time of delivery and include both foetal (of at least 20 weeks of gestation) and early infant (neonatal) deaths.

Data extraction and management

Data to be extracted from the articles will include study characteristics such as the design, sample size, GDM diagnostic criteria used, types of treatment given, GDM screening approach (one-step versus two-step; universal versus selective screening) and numbers of participants with the outcomes of interest. Data will be extracted into a pre-designed and piloted form in Microsoft Office Excel. For each study, two reviewers will independently extract data and compare thereafter. Disparity in data extracted will be resolved via discussion between all the reviewers.

Assessment of risk of bias

The risk of bias and external validity of the included studies will be assessed using the tool by Hoy et al. (15)Two reviewers will independently assess each included study, and any differences will be resolved by discussion and if no consensus is reached, a third party will be consulted.

Data synthesis and analysis

We will narratively describe study characteristics and other data where a meta-analysis is not possible and present these data in tables. For each of the adverse outcomes, we will calculate unadjusted prevalence estimates and their 95% confidence intervals for each study. We will pool the prevalence estimates if the heterogeneity between studies is low (less than 50%). We expect to find high heterogeneity between studies, and therefore we will pool studies by region, by country and by GDM diagnostic criteria, where sufficient data for each outcome exists. We will use the quality effects inverse variance heterogeneity model(16) to pool studies, as this method uses both study quality and sample size to weight studies into the pooled estimate. The quality weights will be derived from the score from the risk of bias assessment using Hoy et al. (15) Heterogeneity will be assessed using the I2 statistic and Cochran's Q p-values. We will also assess publication bias using either funnel plots if enough studies (more than 10) are available for the outcome or Doi plots if there are less than 10 studies available for each outcome. Causes of heterogeneity and publication bias will be explored using subgroup analyses according to region, country, types of screening approach used, diagnostic criteria, period that the study was carried out and age groups, if data are available. All analyses will be carried out using Stata version 15.

Dissemination Plan

The findings of this review will be published in a peer reviewed journal.

Funding

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

Contribution of authors

SC and KO conceptualised the study and contributed to the preparation of the protocol draft. TC and AG provided technical expertise and guidance to the protocol design and contributed to the preparation of the protocol draft.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	✓
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	✓
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓
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	✓
Sponsor	5b	Provide name for the review funder and/or sponsor	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	✓
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	✓
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	✓
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	✓
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	✓
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	✓
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	✓
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	✓
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓
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	✓
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	✓
	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 (such as I^2, Kendall's τ)	✓
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	✓
	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) (such as publication bias across studies, selective reporting within studies)	✓
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	✓

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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.

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Secondary Subject Heading:	Diabetes and endocrinology, Obstetrics and gynaecology
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ABSTRACT

Introduction

Gestational Diabetes Mellitus (GDM) is associated with adverse pregnancy outcomes, including adverse outcomes for both the mother and the foetus. Different diagnostic criteria are used for GDM, and it is not clear how these affect the reported prevalence of adverse pregnancy outcomes. This protocol is for a systematic review to describe and compare the prevalence of adverse pregnancy outcomes in GDM using the different diagnostic criteria applied in various countries/regions of the world.

Methods and Analysis

A systematic review and meta-analysis will be carried out. A comprehensive search of observational studies that report the outcomes of interest to this review from 2010 to 2021 will be conducted. We will search the major electronic databases such as PubMed, Scopus, CINHAL, and Google scholar, and screen references of included studies for additional studies. Meta-analyses will be performed, if there is low heterogeneity, and pooled estimates per outcome reported. We will use the quality effects inverse heterogeneity model to pool prevalence estimates and perform subgroup analyses by region, by age group, by diagnostic criteria, and by GDM screening method if sufficient data are available. We will also compare the prevalence of adverse outcomes by diagnostic method and report prevalence ratios. We will report 95% confidence estimates for all estimates.

Ethics and dissemination

Ethical approval is not required as the review utilises published data. Findings will be published in peer-reviewed journals and presented at conferences.

PROSPERO Registration – CRD42020155061

Key words

Gestational diabetes (GDM), adverse outcomes, pregnancy, maternal and child health, prevalence, meta-analysis

Strengths and Limitations of this study

- The review will be carried out rigorously following the PRISMA guidelines
- The review will incorporate global data, through a highly sensitive search strategy, to quantify the effect of different diagnostic criteria for gestational diabetes on adverse pregnancy outcomes.
- This study uses observational data and thus estimates of the prevalence of adverse pregnancy outcomes may be confounded.
- Studies before the year 2010 will be excluded, and therefore the review may exclude data from countries without recent (post-2010) data.

INTRODUCTION

GDM is a metabolic disorder of pregnancy, defined as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy.(1)(2) Most women with GDM revert to normal glucose metabolism after delivery, however, they are at risk of developing type 2 diabetes and cardiovascular disease later in life as are their offspring.(3)(4)(5)(6) Notably, the diagnostic criteria for GDM and screening approaches vary widely internationally and this has also contributed to high heterogeneity in GDM prevalence estimates.(7)

GDM has been associated with adverse pregnancy outcomes such as macrosomia, shoulder dystocia, neonatal hypoglycaemia and perinatal mortality.(8) Recent results from the hyperglycaemia and adverse pregnancy outcome (HAPO) study showed that even milder levels of hyperglycaemia can have adverse effects on pregnancy outcomes.(9) This resulted in changes in many international GDM diagnosis guidelines, with many guidelines being revised based on the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG).(10) Examples of organizations whose guidelines were changed to align with the IADPSG recommendations include the World Health Organization (WHO) which changed its GDM diagnosis criteria in 2013(2) and the American Diabetes Association (ADA) which changed its guidelines to mirror the IADPSG in 2014.(11) However, there is still no consensus on diagnostic criteria for GDM, with more than 30 different guidelines in use at the moment.(11)(12)(6) The differences in these guidelines are not only in the

maternal blood glucose cut-offs for the diagnosis of GDM, but also in screening approaches, screening methods and timing of screening for GDM during pregnancy, and resources for GDM screening and management.

The continued lack of consensus on the diagnosis of GDM implies that the measured impact of GDM may differ in different settings depending on the diagnosis criteria utilized. This study, therefore, aims to describe and compare the prevalence of adverse pregnancy outcomes in GDM across different diagnostic criteria using a meta-analysis of existing data.

RESEARCH QUESTION

This systematic review will answer the following question:

What is the prevalence of adverse pregnancy outcomes in women diagnosed using different GDM diagnostic criteria, based on studies carried out between 2010 and 2021?

SPECIFIC OBJECTIVES

1. To estimate the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies using the IADPSG or similar criteria.
2. To compare the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies between studies using the IADPSG or similar criteria and studies using different criteria.
3. To estimate the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies by IDF region and per country.
4. To estimate the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies across different age-groups.

METHODS

Study design

A systematic review and meta-analysis will be carried out with a planned start date of October 2021 and end date of December 2022. The study protocol is registered on PROSPERO (CRD42020155061), the International prospective register of systematic reviews and the findings will be reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (PRISMA 2020).

Patient and public involvement

No patients or members of the public would be involved in this study.

Search strategy for identification of studies

Data sources and electronic searches

We will search PubMed, Scopus, Google Scholar, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) for articles reporting on studies relevant to this study. An expert librarian will be consulted during the design of the search strategy. The search will use medical subject headings (MeSH terms) and keyword searches for GDM and pregnancy outcomes. The sample search strategy is attached as Supplementary Document S1. The reference lists of relevant citations for articles of interest will also be scanned for additional studies. Duplicates of articles will be identified and removed using Mendeley, and the Rayyan systematic review management website (www.rayyan.ai) will be used to screen studies for inclusion. Four reviewers (TC, AG, KO, and SC) will independently screen the studies for inclusion within Rayyan, using title and abstract. The studies identified after the initial screening will then be assessed for inclusion using full text, following the pre-defined inclusion criteria.

Studies inclusion criteria

Types of studies

The systematic review will include observational studies (population-based reports, birth registers, cohort, and cross-sectional studies) published from 2010 to 2021 that assessed the prevalence of adverse pregnancy outcomes in the mothers and offspring diagnosed with GDM, without language restriction.

Types of participants

Studies to be considered in this review would be those with participants who are women, aged 16 and above, who had GDM during the period 2010-2021, and diagnosed using any criteria such as the WHO 2013 criteria (WHO, 2013)(2) or the IADPSG (IADPSG, 2010),(10) American Diabetes Association 2014, and the National Institute for Health and Clinical Excellence (NICE) in the U.K (NICE 2014). Studies in which participants also presented with comorbidities would not be excluded.

Exclusion criteria

Studies will be excluded if they were published before 2010, if they are review articles, contained animal studies, did not report on outcomes relevant to this study, included women with pre-existing diabetes or contained duplicate/redundant publications.

Outcomes of interest

Pregnancy outcomes

These will include caesarean section (emergency and elective), any assisted delivery methods (for example, vacuum, and induced birth), preterm delivery (gestational age at delivery before 37 weeks), peripartum infection, pregnancy induced hypertension and preeclampsia and eclampsia.(13)

Maternal outcomes

Maternal outcomes will include post-partum depression, post-partum type 2 diabetes at 6 weeks, glucose control during pregnancy (including blood glucose measurements), pregnancy loss, hospitalisation, ICU and mortality within 6 weeks after delivery.(14)(13)

Foetal outcomes

Foetal outcomes to be assessed in this study include the birthweight, large-for-gestational-age (LGA), small-for-gestational-age (SGA), macrosomia, neonatal mortality (within 28 days), stillbirth, congenital abnormalities, shoulder dystocia, neonatal hypoglycaemia, neonatal hospitalisation and intensive care admission (NICU), and respiratory distress syndrome. Macrosomia would be defined as birthweight above the 90th percentile for gestational age or birthweight greater than 4000 g. Perinatal mortality would be defined as any death around the time of delivery and include both foetal (of at least 20 weeks of gestation) and early infant (neonatal) deaths.

Data extraction and management

For duplicate publications only the article containing the most information will be included in the review and all others excluded as duplicates. Data to be extracted from the articles will include study characteristics such as the year of publication, date of

study, age, region, country, study design, sample size, GDM diagnostic criteria used, types of treatment given, GDM screening approach (one-step versus two-step; universal versus selective screening), numbers of participants with the outcomes of interest and the effect size with their corresponding confidence intervals. Data will be extracted into a pre-designed and piloted form in Microsoft Office Excel. For each study, two reviewers will independently extract data and compare thereafter. Disparity in data extracted will be resolved via discussion between all the reviewers.

Assessment of risk of bias

The risk of bias and external validity of the included studies will be assessed using the tool by Hoy et al. (15)Two reviewers will independently assess each included study, and any differences will be resolved by discussion and if no consensus is reached, a third party will be consulted.

Data synthesis and analysis

We will narratively describe study characteristics and other data where a meta-analysis is not possible and present these data in tables. For each of the adverse outcomes, we will calculate unadjusted prevalence estimates and their 95% confidence intervals for each study. We will pool the prevalence estimates if the heterogeneity between studies is low (less than 50%). We expect to find high heterogeneity between studies, and therefore we will pool studies by region, by country and by GDM diagnostic criteria, where sufficient data for each outcome exists. Where meta-analysis is possible, we will use the quality effects inverse variance heterogeneity model(16) to pool studies, as this method uses both study quality and sample size to weight studies into the pooled estimate. The Freeman-Turkey transformation will be used to stabilize the variance of prevalence data during the meta-analysis. The quality weights will be derived from the score from the risk of bias assessment using Hoy et al. (15) Heterogeneity will be assessed using the I^2 statistic and Cochran's Q p-values. We will also assess publication bias using either funnel plots if enough studies (more than 10) are available for the outcome or Doi plots if there are less than 10 studies available for each outcome. Causes of heterogeneity and publication bias will be explored using subgroup analyses according to region, country, types of screening approach used, diagnostic criteria, pre-pregnancy obesity

status, period that the study was carried out and age groups, if data are available. All analyses will be carried out using Stata statistical software.

Dissemination Plan

The findings of this review will be published in a peer reviewed journal.

Funding

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

Contribution of authors

SC and KO conceptualised the study and contributed to the preparation of the protocol draft. TC and AG provided technical expertise and guidance to the protocol design and contributed to the preparation of the protocol draft.

Conflict of Interests

All authors declare no conflicts of interest

References

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16. Doi SAR, Barendregt JJ, Khan S, Thalib L, Williams GM. Advances in the meta-analysis of heterogeneous clinical trials I: The inverse variance heterogeneity model. Contemp Clin Trials. 2015 Nov;45(Pt A):130–8.

Table #: PubMed Search strategy, modified as needed for other electronic databases

Population:		
#1	MeSH terms:	Diabetes, Gestational
#2	Text Word:	Gestational Diabetes OR GDM OR Gestational Diabetes Mellitus OR Pregnancy-induced diabetes OR Diabetes in Pregnancy OR Hyperglycaemia in Pregnancy OR Hyperglycemia in Pregnancy
#3	#1 OR #2	
Outcomes		
#4	Text Word:	Fetal outcomes OR Foetal outcomes OR Macrosomia OR Large for Gestational Age OR Perinatal Mortality OR Shoulder Dystocia OR Congenital Malformation OR Miscarriage OR Spontaneous Abortion OR Neonatal Hypoglycaemia OR Neonatal Hypoglycemia OR Hyperbilirubinaemia OR Hyperbilirubinemia OR Birth Asphyxia OR Admission to the Neonatal Intensive Care Unit OR Overweight OR Obesity OR Offspring OR Child OR Childhood OR Children
#5	#3 AND #4	
#6	#5 NOT (review OR metaanalysis OR systematic review OR meta-analysis OR literature review)	

Filters

1. 2010-2021

2. Humans

Table #: Cochrane and other databases Search strategy

Population:		
#1	Key Word:	Gestational Diabetes OR GDM OR Gestational Diabetes Mellitus OR Pregnancy-induced diabetes OR Diabetes in Pregnancy OR Hyperglycaemia in Pregnancy OR Hyperglycemia in Pregnancy
#4	#1 OR #2 OR #3	
#5	Pregnancy	
Outcomes		
#6	Key Word:	Fetal Outcomes OR Foetal Outcomes OR Macrosomia OR Large for Gestational Age OR Perinatal Mortality OR Shoulder Dystocia OR Congenital Malformation OR Miscarriage OR Spontaneous Abortion OR Neonatal Hypoglycaemia OR Neonatal Hypoglycemia OR Hyperbilirubinaemia OR Hyperbilirubinemia OR Birth Asphyxia OR Admission to the Neonatal Intensive Care Unit OR Overweight OR Obesity OR Long Term Outcomes in Offsprings OR co-ordinated care OR coordinated integrated care OR co-ordinated integrated care OR multicare OR multiservice OR multiclinic
#10	#4 AND #5 AND #8 AND #9	

Table #: Scopus Search strategy

Population:		
#1	Key Word:	Gestational Diabetes OR GDM OR Gestational Diabetes Mellitus OR Pregnancy-induced diabetes OR Diabetes in Pregnancy OR Hyperglycaemia in Pregnancy OR Hyperglycemia in Pregnancy
Outcomes:		
#2	Key Word:	Macrosomia OR Mortality OR Shoulder Dystocia OR Congenital OR Malformation OR Miscarriage OR Abortion OR Hypoglycaemia OR Hypoglycemia OR Hyperbilirubinaemia OR Hyperbilirubinemia OR Birth Asphyxia OR Overweight OR Obesity
#3	#1 AND #2	

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item		
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	✓	**Page 1**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	✓	**Page 2**
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓	**Page 1**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓	**Page 8**
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	✓	
Sponsor	5b	Provide name for the review funder and/or sponsor	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	✓	**Pages 3-4**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)		✓ **Page 4**
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review		**Pages 5-6** ✓
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage		✓ **Page 5**
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		**Supplementary document S1** ✓
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review		**Pages 6-7** ✓

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 5 ✓
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 5 ✓
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 5 ✓
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 6 ✓
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 7 ✓
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	✓ Page 7
	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 (such as I^2, Kendall's τ) Describe any	✓
	15c	proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	✓ Page 7
	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) (such as publication bias across studies, selective reporting within studies)	Page 7 ✓
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	✓ Page 7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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.

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Adverse pregnancy outcomes in gestational diabetes mellitus – a systematic review and meta-analysis protocol

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Adverse pregnancy outcomes in gestational diabetes mellitus – a systematic review and meta-analysis protocol

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Number of references - 20

ABSTRACT

Introduction

Gestational Diabetes Mellitus (GDM) is associated with adverse pregnancy outcomes, including adverse outcomes for both the mother and the foetus. Different diagnostic criteria are used for GDM, and it is not clear how these affect the reported prevalence of adverse pregnancy outcomes. This protocol is for a systematic review to describe and compare the prevalence of adverse pregnancy outcomes in GDM using the different diagnostic criteria applied in various countries/regions of the world.

Methods and Analysis

A systematic review and meta-analysis will be carried out. A comprehensive search of observational studies that report the outcomes of interest to this review from 2010 to 2021 will be conducted. We will search the major electronic databases such as PubMed, Scopus, CINHAL, and Google scholar, and screen references of included studies for additional studies. Meta-analyses will be performed, if there is low heterogeneity, and pooled estimates per outcome reported. We will use the bias adjusted inverse variance heterogeneity model and random effects models, depending on the heterogeneity observed, to pool prevalence estimates and perform subgroup analyses by region, by age group, by diagnostic criteria, and by GDM screening method if sufficient data are available. We will also compare the prevalence of adverse outcomes by diagnostic method and report prevalence ratios. We will report 95% confidence estimates for all estimates.

Ethics and dissemination

Ethical approval is not required as the review utilises published data. Findings will be published in peer-reviewed journals and presented at conferences.

PROSPERO Registration – CRD42020155061

Key words

Gestational diabetes (GDM), adverse outcomes, pregnancy, maternal and child health, prevalence, meta-analysis

Strengths and limitations of this study

- The review will be carried out rigorously following the PRISMA guidelines
- The review will incorporate global data, through a highly sensitive search strategy, to quantify the effect of different diagnostic criteria for gestational diabetes on adverse pregnancy outcomes.
- This study uses observational data and thus estimates of the prevalence of adverse pregnancy outcomes may be confounded.
- Studies before the year 2010 will be excluded, and therefore the review may exclude data from countries without recent (post-2010) data.

INTRODUCTION

GDM is a metabolic disorder of pregnancy, defined as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy.(1) Most women with GDM revert to normal glucose metabolism after delivery, however, they are at risk of developing type 2 diabetes and cardiovascular disease later in life as are their offspring.(2, 3) Notably, the diagnostic criteria for GDM and screening approaches vary widely internationally and this has also contributed to high heterogeneity in GDM prevalence estimates.(4)

Apart from their impact on individuals, such as anxiety, excess morbidity, disability and mortality, adverse outcomes from pregnancy negatively affect health systems as they require mobilisation of scarce health resources in the care of affected individuals. (5, 6) GDM has been associated with adverse pregnancy outcomes in the short term such as macrosomia, shoulder dystocia, neonatal hypoglycaemia and perinatal mortality (7) and in the long term, with outcomes such as type 2 diabetes mellitus and cardiovascular disease in the mother and offspring. (2, 3, 8) Results from the landmark hyperglycaemia and adverse pregnancy outcome (HAPO) study showed that even milder levels of hyperglycaemia can have adverse effects on pregnancy outcomes.(7) This resulted in changes in many international GDM diagnosis guidelines, with many guidelines being revised based on the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) which were published in 2010.(9) Examples of organizations whose guidelines were changed to align with the IADPSG recommendations include the World Health Organization

(WHO) which changed its GDM diagnosis criteria in 2013 (1) and the American Diabetes Association (ADA). (10) However, there is still no consensus on diagnostic criteria for GDM, with more than 30 different guidelines, in different regions and countries currently in use. (11) The differences in these guidelines are not only in the maternal blood glucose cut-offs for the diagnosis of GDM, but also in screening approaches, screening methods and timing of screening for GDM during pregnancy, and resources for GDM screening and management.

Several studies (3, 12, 13, 14) have investigated the impact of GDM diagnosis criteria and different blood glucose cut-offs on adverse pregnancy outcomes but results remain unclear. In Denmark, for example, researchers have reported an increased prevalence of GDM to almost 40% when the HAPO cut-offs were used, and yet without significant differences in the prevalence of adverse pregnancy outcomes, when compared to women without GDM. (14) This raises the possibility that these criteria may not be universally applicable and that the measured impact of GDM may differ in different settings depending on the diagnosis criteria used. This study aims to describe and compare the prevalence of adverse pregnancy outcomes in GDM across different diagnostic criteria using a meta-analysis of existing data.

RESEARCH QUESTION

This systematic review will answer the following question:

What is the prevalence of adverse pregnancy outcomes in women diagnosed according to different GDM diagnostic criteria, based on studies carried out between 2010 and 2021?

SPECIFIC OBJECTIVES

This study has several objectives. The study's main objective is to estimate and compare the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies between studies using different criteria. The study will also. Further, the study seeks to estimate the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies by IDF region and by country using the IADPSG or similar criteria. Lastly, the study will estimate the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies across different age-groups.

METHODS

Study design

A systematic review and meta-analysis of eligible studies will be carried out. The study protocol follows the preferred reporting items for systematic reviews and meta-analyses (15) protocol extension (PRISMA-P) (Supplementary Doc S1) is registered on the International prospective register of systematic reviews (PROSPERO) (CRD42020155061).

Search strategy for identification of studies

Data sources and electronic searches

We will search PubMed, Scopus, Google Scholar, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) for articles reporting on studies relevant to this study. An expert librarian will be consulted during the design of the search strategy. The search will use medical subject headings (MeSH terms) and keyword searches for GDM and pregnancy outcomes. The sample search strategy is attached as Supplementary Document S2. The reference lists of relevant citations for articles of interest will also be scanned for additional studies. Duplicates of articles will be identified and removed using Mendeley, and the Rayyan systematic review management website (www.rayyan.ai) will be used to screen studies for inclusion. Four reviewers (TC, AG, KO, and SC) will independently screen the studies for inclusion within Rayyan, using title and abstract. The studies identified after the initial screening will then be assessed for inclusion using full text, following the pre-defined inclusion criteria.

Studies inclusion criteria

Inclusion criteria

The systematic review will include observational studies such as population-based reports, cohort studies, data from control arms of randomized controlled trials if selected randomly from the population, and cross-sectional studies published from 2010 to 2021 that assessed the prevalence of adverse pregnancy outcomes in the mothers and offspring diagnosed with GDM, without language restriction.

Studies to be considered in this review would be those with participants who are women, aged 16 and above, who had GDM and published during the period 2010-2021, and diagnosed using any criteria such as the WHO 2013 criteria (1) or the IADPSG, (9) American Diabetes Association 2014, (10) and the National Institute for Health and Clinical Excellence (NICE) in the U.K (11). Studies in which participants also presented with comorbidities would not be excluded, as GDM frequently co-presents with other comorbidities.

Exclusion criteria

Studies will be excluded if they were published before 2010, if they are review articles, contained animal studies, did not report on outcomes relevant to this study, or included women with pre-existing diabetes. Data from randomized controlled trial intervention arms will not be included. If the trials used some form of selective recruitment, they will also be excluded. Case control studies will also be excluded unless the cases represent all or a representative sample of GDM cases in the population. In the later cases, only data from cases will be used to estimate the prevalence of adverse outcomes.

Outcomes of interest

Pregnancy outcomes

These will include caesarean section (emergency and elective), any assisted delivery methods (for example, vacuum, and induced birth), preterm delivery (gestational age at delivery before 37 weeks), peripartum infection, pregnancy induced hypertension and preeclampsia and eclampsia. (13)

Maternal outcomes

Maternal outcomes will include post-partum depression, post-partum type 2 diabetes at 6 weeks, glucose control during pregnancy (including blood glucose measurements), pregnancy loss, hospitalisation, ICU and mortality within 6 weeks after delivery. (13)

Foetal outcomes

Foetal outcomes to be assessed in this study include the birthweight, large-for-gestational-age (LGA), small-for-gestational-age (SGA), macrosomia, neonatal

mortality (within 28 days), stillbirth, congenital abnormalities, shoulder dystocia, neonatal hypoglycaemia, neonatal hospitalisation, and intensive care admission (NICU), and respiratory distress syndrome. Macrosomia would be defined as birthweight above the 90th percentile for gestational age or birthweight greater than 4000 g. Perinatal mortality would be defined as any death around the time of delivery and include both foetal (of at least 20 weeks of gestation) and early infant (neonatal) deaths.

Data extraction and management

For duplicate publications only the article containing the most information will be included in the review and all others excluded as duplicates. Data to be extracted from the articles will include study characteristics such as the year of publication, date of study, age, region, country, study design, sample size, GDM diagnostic criteria used, types of treatment given, GDM screening approach (one-step versus two-step; universal versus selective screening), numbers of participants with the outcomes of interest and the effect size with their corresponding confidence intervals. Data will be extracted into a pre-designed and piloted form in Microsoft Office Excel. For each study, two reviewers will independently extract data and compare thereafter. Disparity in data extracted will be resolved via discussion between all the reviewers.

Assessment of risk of bias

The risk of bias and external validity of the included studies will be assessed using the tool by Hoy et al. (16) Two reviewers will independently assess each included study, and any differences will be resolved by discussion and if no consensus is reached, a third reviewer will be consulted.

Data synthesis and analysis

We will narratively describe study characteristics and other data where a meta-analysis is not possible and present these data in tables. For each of the adverse outcomes, we will calculate unadjusted prevalence estimates and their 95% confidence intervals for each study. We will pool the prevalence estimates if the heterogeneity between studies is low (less than 50%). We expect to find high heterogeneity between studies, and therefore we will pool studies by region, by country and by GDM diagnostic criteria, where sufficient data for each outcome exists.

Where meta-analysis is possible, we will use the quality effects inverse variance heterogeneity model (17) to pool studies, as this method uses both study quality and sample size to weight studies into the pooled estimate. The Freeman-Tukey transformation will be used to stabilize the variance of prevalence data during the meta-analysis. Random effects models (18) will also be used as sensitivity analysis to test robustness of the findings. The quality weights will be derived from the score from the risk of bias assessment using Hoy et al. (16) Heterogeneity will be assessed using the I^2 statistic and Cochran's Q p-values. (19) We will also assess publication bias using funnel plots. (20) Causes of heterogeneity and publication bias will be explored using subgroup analyses according to region, country, types of screening approach used, diagnostic criteria, pre-pregnancy obesity status, period that the study was carried out, comorbidity status and age groups, if data are available. All analyses will be carried out using Stata statistical software.

Dissemination Plan

The findings of this review will be published in a peer reviewed journal.

Patient and public involvement

No patients or members of the public would be involved in this study.

Funding

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

Contribution of authors

SC and KO conceptualised the study and contributed to the preparation of the protocol draft. TC and AG provided technical expertise and guidance to the protocol design and contributed to the preparation of the protocol draft.

Conflict of Interests

All authors declare no conflicts of interest

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page/ location in the manuscript
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4-5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
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	Supplementary document S2

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5-7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-7
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	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7-8
	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 (such as I^2, Kendall's τ)	7-8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7-8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7-8

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Table #: PubMed Search strategy, modified as needed for other electronic databases

Population:		
#1	MeSH terms:	Diabetes, Gestational
#2	Text Word:	Gestational Diabetes OR GDM OR Gestational Diabetes Mellitus OR Pregnancy-induced diabetes OR Diabetes in Pregnancy OR Hyperglycaemia in Pregnancy OR Hyperglycemia in Pregnancy
#3	#1 OR #2	
Outcomes		
#4	Text Word:	Fetal outcomes OR Foetal outcomes OR Macrosomia OR Large for Gestational Age OR Perinatal Mortality OR Shoulder Dystocia OR Congenital Malformation OR Miscarriage OR Spontaneous Abortion OR Neonatal Hypoglycaemia OR Neonatal Hypoglycemia OR Hyperbilirubinaemia OR Hyperbilirubinemia OR Birth Asphyxia OR Admission to the Neonatal Intensive Care Unit OR Overweight OR Obesity OR Offspring OR Child OR Childhood OR Children
#5	#3 AND #4	
#6	#5 NOT (review OR metaanalysis OR systematic review OR meta-analysis OR literature review)	

Filters

1. 2010-2021

2. Humans

Table #: Cochrane and other databases Search strategy

Population:		
#1	Key Word:	Gestational Diabetes OR GDM OR Gestational Diabetes Mellitus OR Pregnancy-induced diabetes OR Diabetes in Pregnancy OR Hyperglycaemia in Pregnancy OR Hyperglycemia in Pregnancy
#4	#1 OR #2 OR #3	
#5	Pregnancy	
Outcomes		
#6	Key Word:	Fetal Outcomes OR Foetal Outcomes OR Macrosomia OR Large for Gestational Age OR Perinatal Mortality OR Shoulder Dystocia OR Congenital Malformation OR Miscarriage OR Spontaneous Abortion OR Neonatal Hypoglycaemia OR Neonatal Hypoglycemia OR Hyperbilirubinaemia OR Hyperbilirubinemia OR Birth Asphyxia OR Admission to the Neonatal Intensive Care Unit OR Overweight OR Obesity OR Long Term Outcomes in Offsprings OR co-ordinated care OR coordinated integrated care OR co-ordinated integrated care OR multicare OR multiservice OR multiclinic
#10	#4 AND #5 AND #8 AND #9	

Table #: Scopus Search strategy

Population:		
#1	Key Word:	Gestational Diabetes OR GDM OR Gestational Diabetes Mellitus OR Pregnancy-induced diabetes OR Diabetes in Pregnancy OR Hyperglycaemia in Pregnancy OR Hyperglycemia in Pregnancy
Outcomes:		
#2	Key Word:	Macrosomia OR Mortality OR Shoulder Dystocia OR Congenital OR Malformation OR Miscarriage OR Abortion OR Hypoglycaemia OR Hypoglycemia OR Hyperbilirubinaemia OR Hyperbilirubinemia OR Birth Asphyxia OR Overweight OR Obesity
#3	#1 AND #2	

BMJ Open

Adverse pregnancy outcomes in gestational diabetes mellitus – a systematic review and meta-analysis protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058625.R3
Article Type:	Protocol
Date Submitted by the Author:	25-Jan-2023
Complete List of Authors:	Chukwuemeka, Scholarstica; University of the Western Cape, school of pharmacy Chivese, Tawanda; Qatar University Gopinath, Aswathy; Qatar University Obikeze, kenechukwu; University of the Western Cape, school of pharmacy
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Diabetes and endocrinology, Obstetrics and gynaecology
Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS, DIABETES & ENDOCRINOLOGY

Adverse pregnancy outcomes in gestational diabetes mellitus – a systematic review and meta-analysis protocol

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Manuscript word count – 1735
Abstract word count – 217
Number of references - 21

ABSTRACT

Introduction

Gestational Diabetes Mellitus (GDM) is associated with adverse pregnancy outcomes, including adverse outcomes for both the mother and the foetus. Different diagnostic criteria are used for GDM, and it is not clear how these affect the reported prevalence of adverse pregnancy outcomes. This protocol is for a systematic review to describe and compare the prevalence of adverse pregnancy outcomes in GDM using the different diagnostic criteria applied in various countries/regions of the world.

Methods and Analysis

A systematic review and meta-analysis will be carried out. A comprehensive search of observational studies that report the outcomes of interest to this review from 2010 to 2021 will be conducted. We will search the major electronic databases such as PubMed, Scopus, CINHAL, and Google scholar, and screen references of included studies for additional studies. Meta-analyses will be performed, if there is low heterogeneity, and pooled estimates per outcome reported. We will use the bias adjusted inverse variance heterogeneity model and random effects models, depending on the heterogeneity observed, to pool prevalence estimates and perform subgroup analyses by region, by age group, by diagnostic criteria, and by GDM screening method if sufficient data are available. We will also compare the prevalence of adverse outcomes by diagnostic method and report prevalence ratios. We will report 95% confidence estimates for all estimates.

Ethics and dissemination

Ethical approval is not required as the review utilises published data. Findings will be published in peer-reviewed journals and presented at conferences.

PROSPERO Registration – CRD42020155061

Key words

Gestational diabetes (GDM), adverse outcomes, pregnancy, maternal and child health, prevalence, meta-analysis

Strengths and limitations of this study

- The review will be carried out rigorously following the PRISMA guidelines
- The review will incorporate global data, through a highly sensitive search strategy, to quantify the effect of different diagnostic criteria for gestational diabetes on adverse pregnancy outcomes.
- Studies before the year 2010 will be excluded, and therefore the review may exclude data from countries without recent (post-2010) data.

INTRODUCTION

GDM is a metabolic disorder of pregnancy, defined as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy.(1) Most women with GDM revert to normal glucose metabolism after delivery, however, they are at risk of developing type 2 diabetes and cardiovascular disease later in life as are their offspring.(2, 3) Notably, the diagnostic criteria for GDM and screening approaches vary widely internationally and this has also contributed to high heterogeneity in GDM prevalence estimates.(4)

Apart from their impact on individuals, such as anxiety, excess morbidity, disability and mortality, adverse outcomes from pregnancy negatively affect health systems as they require mobilisation of scarce health resources in the care of affected individuals. (5, 6) GDM has been associated with adverse pregnancy outcomes in the short term such as macrosomia, shoulder dystocia, neonatal hypoglycaemia and perinatal mortality (7) and in the long term, with outcomes such as type 2 diabetes mellitus and cardiovascular disease in the mother and offspring. (2, 3, 8) Results from the landmark hyperglycaemia and adverse pregnancy outcome (HAPO) study showed that even milder levels of hyperglycaemia can have adverse effects on pregnancy outcomes.(7) This resulted in changes in many international GDM diagnosis guidelines, with many guidelines being revised based on the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) which were published in 2010.(9) Examples of organizations whose guidelines were changed to align with the IADPSG recommendations include the World Health Organization (WHO) which changed its GDM diagnosis criteria in 2013 (1) and the American Diabetes Association (ADA). (10) However, there is still no consensus on diagnostic

criteria for GDM, with more than 30 different guidelines, in different regions and countries currently in use. (11) The differences in these guidelines are not only in the maternal blood glucose cut-offs for the diagnosis of GDM, but also in screening approaches, screening methods and timing of screening for GDM during pregnancy, and resources for GDM screening and management.

Several studies (3, 12, 13, 14) have investigated the impact of GDM diagnosis criteria and different blood glucose cut-offs on adverse pregnancy outcomes but results remain unclear. In Denmark, for example, researchers have reported an increased prevalence of GDM to almost 40% when the HAPO cut-offs were used, and yet without significant differences in the prevalence of adverse pregnancy outcomes, when compared to women without GDM. (14) This raises the possibility that these criteria may not be universally applicable and that the measured impact of GDM may differ in different settings depending on the diagnosis criteria used. The prevalence of adverse pregnancy outcomes has also been shown to be associated with older age at childbearing (15) and will also be influenced by the criteria used to diagnose the adverse events. This study aims to describe and compare the prevalence of adverse pregnancy outcomes in GDM across different diagnostic criteria using a meta-analysis of existing data.

RESEARCH QUESTION

This systematic review will answer the following question:
What is the prevalence of adverse pregnancy outcomes in women diagnosed with GDM, according to different diagnostic criteria, in studies carried out between 2010 and 2021?".

SPECIFIC OBJECTIVES

This study has several objectives. The study's main objective is to estimate and compare the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies between studies using different criteria. Further, the study seeks to estimate the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies by the region where the study was carried out. In this study, we will use the International Diabetes Federation (IDF) regions, which are divided into seven regions, namely, Africa (AFR), Europe (EUR), Middle East and North Africa (MENA),

North America and Caribbean (NAC), South and Central America (SACA), Southeast Asia (SEA) and Western Pacific (WP). Lastly, the study will estimate the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies across different age-groups and different diagnostic criteria used for adverse events.

METHODS

Study design

A systematic review and meta-analysis of eligible studies will be carried out. The study protocol follows the preferred reporting items for systematic reviews and meta-analyses (16) protocol extension (PRISMA-P) (Supplementary Doc S1) is registered on the International prospective register of systematic reviews (PROSPERO) (CRD42020155061).

Search strategy for identification of studies

Data sources and electronic searches

We will search PubMed, Scopus, Google Scholar, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) for articles reporting on studies relevant to this study. An expert librarian will be consulted during the design of the search strategy. The search will use medical subject headings (MeSH terms) and keyword searches for GDM and pregnancy outcomes. The sample search strategy is attached as Supplementary Document S2. The reference lists of relevant citations for articles of interest will also be scanned for additional studies. Duplicates of articles will be identified and removed using Mendeley, and the Rayyan systematic review management website (www.rayyan.ai) will be used to screen studies for inclusion. Four reviewers (TC, AG, KO, and SC) will independently screen the studies for inclusion within Rayyan, using title and abstract. The studies identified after the initial screening will then be assessed for inclusion using full text, following the pre-defined inclusion criteria.

Studies inclusion criteria

Inclusion criteria

The systematic review will include observational studies such as population-based reports, cohort studies, data from control arms of randomized controlled trials if

selected randomly from the population, and cross-sectional studies published from 2010 to 2021 that assessed the prevalence of adverse pregnancy outcomes in the mothers and offspring diagnosed with GDM, without language restriction.

Studies to be considered in this review would be those with participants who are women, aged 16 and above, who had GDM and published during the period 2010-2021, and diagnosed using any criteria such as the WHO 2013 criteria (1) or the IADPSG, (9) American Diabetes Association 2014, (10) and the National Institute for Health and Clinical Excellence (NICE) in the U.K (11). Studies in which participants also presented with comorbidities would not be excluded, as GDM frequently co-presents with other comorbidities.

Exclusion criteria

Studies will be excluded if they were published before 2010, if they are review articles, contained animal studies, did not report on outcomes relevant to this study, or included women with pre-existing diabetes. Data from randomized controlled trial intervention arms will not be included. If the trials used some form of selective recruitment, they will also be excluded. Case control studies will also be excluded unless the cases represent all or a representative sample of GDM cases in the population. In the later cases, only data from cases will be used to estimate the prevalence of adverse outcomes.

Outcomes of interest

Pregnancy outcomes

These will include caesarean section (emergency and elective), any assisted delivery methods (for example, vacuum, and induced birth), preterm delivery (gestational age at delivery before 37 weeks), peripartum infection, pregnancy induced hypertension and preeclampsia and eclampsia. (13)

Maternal outcomes

Maternal outcomes will include post-partum depression, post-partum type 2 diabetes at 6 weeks, glucose control during pregnancy (including blood glucose measurements), pregnancy loss, hospitalisation, ICU and mortality within 6 weeks after delivery. (13)

Foetal outcomes

Foetal outcomes to be assessed in this study include the birthweight, large-for-gestational-age (LGA), small-for-gestational-age (SGA), macrosomia, neonatal mortality (within 28 days), stillbirth, congenital abnormalities, shoulder dystocia, neonatal hypoglycaemia, neonatal hospitalisation, and intensive care admission (NICU), and respiratory distress syndrome. Macrosomia would be defined as birthweight above the 90th percentile for gestational age or birthweight greater than 4000 g. Perinatal mortality would be defined as any death around the time of delivery and include both foetal (of at least 20 weeks of gestation) and early infant (neonatal) deaths.

Data extraction and management

For duplicate publications only the article containing the most information will be included in the review and all others excluded as duplicates. Data to be extracted from the articles will include study characteristics such as the year of publication, date of study, age, region, country, study design, sample size, GDM diagnostic criteria used, types of treatment given, GDM screening approach (one-step versus two-step; universal versus selective screening), numbers of participants with the outcomes of interest and the effect size with their corresponding confidence intervals. Data will be extracted into a pre-designed and piloted form in Microsoft Office Excel. For each study, two reviewers will independently extract data and compare thereafter. Disparity in data extracted will be resolved via discussion between all the reviewers.

Assessment of risk of bias

The risk of bias and external validity of the included studies will be assessed using the tool by Hoy et al. (17) Two reviewers will independently assess each included study, and any differences will be resolved by discussion and if no consensus is reached, a third reviewer will be consulted.

Data synthesis

We will narratively describe study characteristics and other data where a meta-analysis is not possible and present these data in tables. For each of the adverse outcomes, we will calculate unadjusted prevalence estimates and their 95%

confidence intervals for each study. We will pool the prevalence estimates if the heterogeneity between studies is low (less than 50%). We expect to find high heterogeneity between studies, and therefore we will pool studies by region, by country and by GDM diagnostic criteria, where sufficient data for each outcome exists. Where meta-analysis is possible, we will use the quality effects inverse variance heterogeneity model (18) to pool studies, as this method uses both study quality, sample size and heterogeneity to weight studies into the pooled estimate. The Freeman-Tukey transformation will be used to stabilize the variance of prevalence data during the meta-analysis. Random effects models (19) will also be used as sensitivity analysis to test robustness of the findings. The quality weights will be derived from the score from the risk of bias assessment using Hoy et al. (17) Heterogeneity will be assessed using the I^2 statistic and Cochran's Q p-values. (20) We will also assess publication bias using funnel plots. (21) Causes of heterogeneity will be explored using subgroup analyses according to region, country, types of screening approach used, GDM diagnostic criteria, diagnostic criteria for adverse events, pre-pregnancy obesity status, period that the study was carried out, comorbidity status and age groups, if data are available. All analyses will be carried out using Stata statistical software.

Dissemination Plan

The findings of this review will be published in a peer reviewed journal.

Patient and public involvement

No patients or members of the public would be involved in this study.

Funding

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

Contribution of authors

SC and KO conceptualised the study and contributed to the preparation of the protocol draft. TC and AG provided technical expertise and guidance to the protocol design and contributed to the preparation of the protocol draft.

Conflict of Interests

All authors declare no conflicts of interest

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page/ location in the manuscript
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
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	N/A
Support:			
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Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
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	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
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Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7-8

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#5	#3 AND #4	
#6	#5 NOT (review OR metaanalysis OR systematic review OR meta-analysis OR literature review)	

Filters

1. 2010-2021

2. Humans

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#5	Pregnancy	
Outcomes		
#6	Key Word:	Fetal Outcomes OR Foetal Outcomes OR Macrosomia OR Large for Gestational Age OR Perinatal Mortality OR Shoulder Dystocia OR Congenital Malformation OR Miscarriage OR Spontaneous Abortion OR Neonatal Hypoglycaemia OR Neonatal Hypoglycemia OR Hyperbilirubinaemia OR Hyperbilirubinemia OR Birth Asphyxia OR Admission to the Neonatal Intensive Care Unit OR Overweight OR Obesity OR Long Term Outcomes in Offsprings OR co-ordinated care OR coordinated integrated care OR co-ordinated integrated care OR multicare OR multiservice OR multiclinic
#10	#4 AND #5 AND #8 AND #9	

Table #: Scopus Search strategy

Population:		
#1	Key Word:	Gestational Diabetes OR GDM OR Gestational Diabetes Mellitus OR Pregnancy-induced diabetes OR Diabetes in Pregnancy OR Hyperglycaemia in Pregnancy OR Hyperglycemia in Pregnancy
Outcomes:		
#2	Key Word:	Macrosomia OR Mortality OR Shoulder Dystocia OR Congenital OR Malformation OR Miscarriage OR Abortion OR Hypoglycaemia OR Hypoglycemia OR Hyperbilirubinaemia OR Hyperbilirubinemia OR Birth Asphyxia OR Overweight OR Obesity
#3	#1 AND #2	

BMJ Open

Adverse pregnancy outcomes in gestational diabetes mellitus – a systematic review and meta-analysis protocol

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Adverse pregnancy outcomes in gestational diabetes mellitus – a systematic review and meta-analysis protocol

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Abstract word count – 217
Number of references - 21

ABSTRACT

Introduction

Gestational Diabetes Mellitus (GDM) is associated with adverse pregnancy outcomes, including adverse outcomes for both the mother and the foetus. Different diagnostic criteria are used for GDM, and it is not clear how these affect the reported prevalence of adverse pregnancy outcomes. This protocol is for a systematic review to describe and compare the prevalence of adverse pregnancy outcomes in GDM using the different diagnostic criteria applied in various countries/regions of the world.

Methods and Analysis

A systematic review and meta-analysis will be carried out. A comprehensive search of observational studies that report the outcomes of interest to this review from 2010 to 2021 will be conducted. We will search the major electronic databases such as PubMed, Scopus, CINHAL, and Google scholar, and screen references of included studies for additional studies. Meta-analyses will be performed, if there is low heterogeneity, and pooled estimates per outcome reported. We will use the bias adjusted inverse variance heterogeneity model and random effects models, depending on the heterogeneity observed, to pool prevalence estimates and perform subgroup analyses by region, by age group, by diagnostic criteria, and by GDM screening method if sufficient data are available. We will also compare the prevalence of adverse outcomes by diagnostic method and report prevalence ratios. We will report 95% confidence estimates for all estimates.

Ethics and dissemination

Ethical approval is not required as the review utilises published data. Findings will be published in peer-reviewed journals and presented at conferences.

PROSPERO Registration – CRD42020155061

Key words

Gestational diabetes (GDM), adverse outcomes, pregnancy, maternal and child health, prevalence, meta-analysis

Strengths and limitations of this study

- The review will be carried out rigorously following the PRISMA guidelines
- The review will incorporate global data, through a highly sensitive search strategy, to quantify the effect of different diagnostic criteria for gestational diabetes on adverse pregnancy outcomes.
- Studies before the year 2010 will be excluded, and therefore the review may exclude data from countries without recent (post-2010) data.

INTRODUCTION

GDM is a metabolic disorder of pregnancy, defined as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy.(1) Most women with GDM revert to normal glucose metabolism after delivery, however, they are at risk of developing type 2 diabetes and cardiovascular disease later in life as are their offspring.(2, 3) Notably, the diagnostic criteria for GDM and screening approaches vary widely internationally and this has also contributed to high heterogeneity in GDM prevalence estimates.(4)

Apart from their impact on individuals, such as anxiety, excess morbidity, disability and mortality, adverse outcomes from pregnancy negatively affect health systems as they require mobilisation of scarce health resources in the care of affected individuals. (5, 6) GDM has been associated with adverse pregnancy outcomes in the short term such as macrosomia, shoulder dystocia, neonatal hypoglycaemia and perinatal mortality (7) and in the long term, with outcomes such as type 2 diabetes mellitus and cardiovascular disease in the mother and offspring. (2, 3, 8) Results from the landmark hyperglycaemia and adverse pregnancy outcome (HAPO) study showed that even milder levels of hyperglycaemia can have adverse effects on pregnancy outcomes.(7) This resulted in changes in many international GDM diagnosis guidelines, with many guidelines being revised based on the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) which were published in 2010.(9) Examples of organizations whose guidelines were changed to align with the IADPSG recommendations include the World Health Organization (WHO) which changed its GDM diagnosis criteria in 2013 (1) and the American Diabetes Association (ADA). (10) However, there is still no consensus on diagnostic

criteria for GDM, with more than 30 different guidelines, in different regions and countries currently in use. (11) The differences in these guidelines are not only in the maternal blood glucose cut-offs for the diagnosis of GDM, but also in screening approaches, screening methods and timing of screening for GDM during pregnancy, and resources for GDM screening and management.

Several studies (3, 12, 13, 14) have investigated the impact of GDM diagnosis criteria and different blood glucose cut-offs on adverse pregnancy outcomes but results remain unclear. In Denmark, for example, researchers have reported an increased prevalence of GDM to almost 40% when the HAPO cut-offs were used, and yet without significant differences in the prevalence of adverse pregnancy outcomes, when compared to women without GDM. (14) This raises the possibility that these criteria may not be universally applicable and that the measured impact of GDM may differ in different settings depending on the diagnosis criteria used. The prevalence of adverse pregnancy outcomes has also been shown to be associated with older age at childbearing (15) and could be influenced by the criteria used to diagnose the adverse events. It is likely that the criteria that uses lower blood glucose cut-offs, such as those similar to the IADPSG, may result in a lower prevalence of adverse pregnancy outcomes. Conversely, the GDM diagnosis criteria that use higher blood glucose cut-offs, such as the National Institute for Health and Care Excellence (NICE) (11), may result in a higher prevalence of adverse pregnancy outcomes. However, it is still debatable whether the prevalence of adverse pregnancy outcomes differs when different criteria are used. This study aims to describe and compare the prevalence of adverse pregnancy outcomes in GDM across different diagnostic criteria using a meta-analysis of existing data.

RESEARCH QUESTION

This systematic review will answer the following question:

What is the prevalence of adverse pregnancy outcomes in women diagnosed with GDM, according to different diagnostic criteria, in studies carried out between 2010 and 2021?".

SPECIFIC OBJECTIVES

This study has several objectives. The study's main objective is to estimate and compare the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies between studies using different criteria. Further, the study seeks to estimate the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies by the region where the study was carried out. In this study, we will use the International Diabetes Federation (IDF) regions, which are divided into seven regions, namely, Africa (AFR), Europe (EUR), Middle East and North Africa (MENA), North America and Caribbean (NAC), South and Central America (SACA), Southeast Asia (SEA) and Western Pacific (WP). Lastly, the study will estimate the prevalence of adverse pregnancy outcomes from GDM complicated pregnancies across different age-groups and different diagnostic criteria used for adverse events.

METHODS

Study design

A systematic review and meta-analysis of eligible studies will be carried out. The study protocol follows the preferred reporting items for systematic reviews and meta-analyses (16) protocol extension (PRISMA-P) (Supplementary Doc S1) is registered on the International prospective register of systematic reviews (PROSPERO) (CRD42020155061).

Search strategy for identification of studies

Data sources and electronic searches

We will search PubMed, Scopus, Google Scholar, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) for articles reporting on studies relevant to this study. An expert librarian will be consulted during the design of the search strategy. The search will use medical subject headings (MeSH terms) and keyword searches for GDM and pregnancy outcomes. The sample search strategy is attached as Supplementary Document S2. The reference lists of relevant citations for articles of interest will also be scanned for additional studies. Duplicates of articles will be identified and removed using Mendeley, and the Rayyan systematic review management website (www.rayyan.ai) will be used to screen studies for inclusion. Four reviewers (TC, AG, KO, and SC) will independently screen the studies for inclusion within Rayyan, using title and abstract. The studies identified after the initial

screening will then be assessed for inclusion using full text, following the pre-defined inclusion criteria.

Studies inclusion criteria

Inclusion criteria

The systematic review will include observational studies such as population-based reports, cohort studies, data from control arms of randomized controlled trials if selected randomly from the population, and cross-sectional studies published from 2010 to 2021 that assessed the prevalence of adverse pregnancy outcomes in the mothers and offspring diagnosed with GDM, without language restriction.

Studies to be considered in this review would be those with participants who are women, aged 16 and above, who had GDM and published during the period 2010-2021, and diagnosed using any criteria such as the WHO 2013 criteria (1) or the IADPSG, (9) American Diabetes Association 2014, (10) and the National Institute for Health and Clinical Excellence (NICE) in the U.K (11). Studies in which participants also presented with comorbidities would not be excluded, as GDM frequently co-presents with other comorbidities.

Exclusion criteria

Studies will be excluded if they were published before 2010, if they are review articles, contained animal studies, did not report on outcomes relevant to this study, or included women with pre-existing diabetes. Data from randomized controlled trial intervention arms will not be included. If the trials used some form of selective recruitment, they will also be excluded. Case control studies will also be excluded unless the cases represent all or a representative sample of GDM cases in the population. In the later cases, only data from cases will be used to estimate the prevalence of adverse outcomes.

Outcomes of interest

Pregnancy outcomes

These will include caesarean section (emergency and elective), any assisted delivery methods (for example, vacuum, and induced birth), preterm delivery (gestational age

at delivery before 37 weeks), peripartum infection, pregnancy induced hypertension and preeclampsia and eclampsia. (13)

Maternal outcomes

Maternal outcomes will include post-partum depression, post-partum type 2 diabetes at 6 weeks, glucose control during pregnancy (including blood glucose measurements), pregnancy loss, hospitalisation, ICU and mortality within 6 weeks after delivery. (13)

Foetal outcomes

Foetal outcomes to be assessed in this study include the birthweight, large-for-gestational-age (LGA), small-for-gestational-age (SGA), macrosomia, neonatal mortality (within 28 days), stillbirth, congenital abnormalities, shoulder dystocia, neonatal hypoglycaemia, neonatal hospitalisation, and intensive care admission (NICU), and respiratory distress syndrome. Macrosomia would be defined as birthweight above the 90th percentile for gestational age or birthweight greater than 4000 g. Perinatal mortality would be defined as any death around the time of delivery and include both foetal (of at least 20 weeks of gestation) and early infant (neonatal) deaths.

Data extraction and management

For duplicate publications only the article containing the most information will be included in the review and all others excluded as duplicates. Data to be extracted from the articles will include study characteristics such as the year of publication, date of study, age, region, country, study design, sample size, GDM diagnostic criteria used, types of treatment given, GDM screening approach (one-step versus two-step; universal versus selective screening), numbers of participants with the outcomes of interest and the effect size with their corresponding confidence intervals. Data will be extracted into a pre-designed and piloted form in Microsoft Office Excel. For each study, two reviewers will independently extract data and compare thereafter. Disparity in data extracted will be resolved via discussion between all the reviewers.

Assessment of risk of bias

The risk of bias and external validity of the included studies will be assessed using the tool by Hoy et al. (17) Two reviewers will independently assess each included study, and any differences will be resolved by discussion and if no consensus is reached, a third reviewer will be consulted.

Data synthesis

We will narratively describe study characteristics and other data where a meta-analysis is not possible and present these data in tables. For each of the adverse outcomes, we will calculate unadjusted prevalence estimates and their 95% confidence intervals for each study. We will pool the prevalence estimates if the heterogeneity between studies is low (less than 50%). We expect to find high heterogeneity between studies, and therefore we will pool studies by region, by country and by GDM diagnostic criteria, where sufficient data for each outcome exists. Where meta-analysis is possible, we will use the quality effects inverse variance heterogeneity model (18) to pool studies, as this method uses both study quality, sample size and heterogeneity to weight studies into the pooled estimate. The Freeman-Tukey transformation will be used to stabilize the variance of prevalence data during the meta-analysis. Random effects models (19) will also be used as sensitivity analysis to test robustness of the findings. The quality weights will be derived from the score from the risk of bias assessment using Hoy et al. (17) Heterogeneity will be assessed using the I^2 statistic and Cochran's Q p-values. (20) We will also assess publication bias using funnel plots. (21) Causes of heterogeneity will be explored using subgroup analyses according to region, country, types of screening approach used, GDM diagnostic criteria, diagnostic criteria for adverse events, pre-pregnancy obesity status, period that the study was carried out, comorbidity status and age groups, if data are available. All analyses will be carried out using Stata statistical software.

Dissemination Plan

The findings of this review will be published in a peer reviewed journal.

Patient and public involvement

No patients or members of the public would be involved in this study.

Funding

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

Contribution of authors

SC and KO conceptualised the study and contributed to the preparation of the protocol draft. TC and AG provided technical expertise and guidance to the protocol design and contributed to the preparation of the protocol draft.

Conflict of Interests

All authors declare no conflicts of interest

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page/ location in the manuscript
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4-5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
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	Supplementary document S2

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5-7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-7
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	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7-8
	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 (such as I^2, Kendall's τ)	7-8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7-8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7-8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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.

Table #: PubMed Search strategy, modified as needed for other electronic databases

Population:		
#1	MeSH terms:	Diabetes, Gestational
#2	Text Word:	Gestational Diabetes OR GDM OR Gestational Diabetes Mellitus OR Pregnancy-induced diabetes OR Diabetes in Pregnancy OR Hyperglycaemia in Pregnancy OR Hyperglycemia in Pregnancy
#3	#1 OR #2	
Outcomes		
#4	Text Word:	Fetal outcomes OR Foetal outcomes OR Macrosomia OR Large for Gestational Age OR Perinatal Mortality OR Shoulder Dystocia OR Congenital Malformation OR Miscarriage OR Spontaneous Abortion OR Neonatal Hypoglycaemia OR Neonatal Hypoglycemia OR Hyperbilirubinaemia OR Hyperbilirubinemia OR Birth Asphyxia OR Admission to the Neonatal Intensive Care Unit OR Overweight OR Obesity OR Offspring OR Child OR Childhood OR Children
#5	#3 AND #4	
#6	#5 NOT (review OR metaanalysis OR systematic review OR meta-analysis OR literature review)	

Filters

1. 2010-2021

2. Humans

Table #: Cochrane and other databases Search strategy

Population:		
#1	Key Word:	Gestational Diabetes OR GDM OR Gestational Diabetes Mellitus OR Pregnancy-induced diabetes OR Diabetes in Pregnancy OR Hyperglycaemia in Pregnancy OR Hyperglycemia in Pregnancy
#4	#1 OR #2 OR #3	
#5	Pregnancy	
Outcomes		
#6	Key Word:	Fetal Outcomes OR Foetal Outcomes OR Macrosomia OR Large for Gestational Age OR Perinatal Mortality OR Shoulder Dystocia OR Congenital Malformation OR Miscarriage OR Spontaneous Abortion OR Neonatal Hypoglycaemia OR Neonatal Hypoglycemia OR Hyperbilirubinaemia OR Hyperbilirubinemia OR Birth Asphyxia OR Admission to the Neonatal Intensive Care Unit OR Overweight OR Obesity OR Long Term Outcomes in Offsprings OR co-ordinated care OR coordinated integrated care OR co-ordinated integrated care OR multicare OR multiservice OR multiclinic
#10	#4 AND #5 AND #8 AND #9	

Table #: Scopus Search strategy

Population:		
#1	Key Word:	Gestational Diabetes OR GDM OR Gestational Diabetes Mellitus OR Pregnancy-induced diabetes OR Diabetes in Pregnancy OR Hyperglycaemia in Pregnancy OR Hyperglycemia in Pregnancy
Outcomes:		
#2	Key Word:	Macrosomia OR Mortality OR Shoulder Dystocia OR Congenital OR Malformation OR Miscarriage OR Abortion OR Hypoglycaemia OR Hypoglycemia OR Hyperbilirubinaemia OR Hyperbilirubinemia OR Birth Asphyxia OR Overweight OR Obesity
#3	#1 AND #2	