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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 fetus. 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 uses published data. Findings will be published in peer-reviewed journals and presented at conferences.

PROSPERO registration number CRD42020155061.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The review will be carried out rigorously following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 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

Gestational diabetes mellitus (GDM) is a metabolic disorder of pregnancy, defined as carbohydrate intolerance resulting in hyperglycaemia 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 organisations whose guidelines were changed to align with the IADPSG

recommendations include 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 >30 different guidelines, in different regions and countries currently in use.[11] The differences in these guidelines are in the maternal blood glucose cut-offs for the diagnosis of GDM, and in screening approaches, screening methods and timing of screening for GDM during pregnancy, and resources for GDM screening and management.

Several studies[3 12–14] 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 with 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 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. Furthermore, 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 regions, which are divided into seven regions, namely, Africa, Europe, Middle East and North Africa, North America and Caribbean, South and Central America, Southeast Asia and Western Pacific. 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 Review and Meta-Analysis Protocols[16] (online supplemental document S1) and 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 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 and keyword searches for GDM and pregnancy outcomes. The sample search strategy is attached as online supplemental 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 predefined inclusion criteria.

INCLUSION CRITERIA

The systematic review will include observational studies such as population-based reports, cohort studies, data from control arms of randomised 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 years 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] ADA 2014[10] NICE in the UK.[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 randomised 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 (eg, vacuum and induced birth), preterm delivery (gestational age at delivery before 37 weeks), peripartum infection, pregnancy-induced hypertension and pre-eclampsia and eclampsia.[13]

Maternal outcomes

Maternal outcomes will include postpartum depression, postpartum type 2 diabetes at 6 weeks, glucose control during pregnancy (including blood glucose measurements), pregnancy loss, hospitalisation, intensive care unit and mortality within 6 weeks after delivery.[13]

Fetal outcomes

Fetal outcomes to be assessed in this study include the birth weight, large-for-gestational-age, small-for-gestational-age, macrosomia, neonatal mortality (within 28 days), stillbirth, congenital abnormalities, shoulder dystocia, neonatal hypoglycaemia, neonatal hospitalisation and intensive care admission (neonatal intensive care unit) and respiratory distress syndrome. Macrosomia would be defined as birth weight >90th percentile for gestational age or birth weight >4000 g. Perinatal mortality would be defined as any death around the time of delivery and include both fetal (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, with all others being 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 vs two-step; universal vs selective screening), number of participants with the outcomes of interest and the effect size with their corresponding CIs. Data will be extracted into a predesigned 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% CIs for each study. We will pool the prevalence estimates if the heterogeneity between studies is low (<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 exist. Where meta-analysis is possible, we will use the 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 stabilise 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, prepregnancy 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.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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