A systematic review on outcome reporting in randomised controlled trials assessing treatment interventions in pregnant women with pregestational diabetes

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Background Pregestational diabetes mellitus (PGDM) is associated with adverse pregnancy outcomes. Studies assessing interventions to improve maternal and infant outcomes have increased exponentially over recent years. Several outcomes in this field of maternal diabetes are rare, making it difficult to synthesise evidence.

Objectives To collect outcomes reported in studies assessing treatment interventions in pregnant women with PGDM.

Search strategy CENTRAL, Web of Science, Medline, CINAHL, Embase and ClinicalTrials.gov from their inception until 27 January 2020.

Selection criteria Any randomised controlled trial assessing treatment interventions in pregnant women with PGDM reported in English.

Data collection and analysis Two independent reviewers assessed the suitability of articles and retrieved the data. Outcomes extracted from the literature were broadly categorised into maternal, fetal/infant or other outcomes by the study advisory group.

Main results Sixty-seven of the 1475 studies identified fulfilled the inclusion criteria. The median number of outcomes reported per study was 15 (range 1–46). The majority of studies were from North America and Europe. Insulin and metformin were the most commonly investigated pharmacological interventions. Glucose monitoring was the most assessed technological intervention. In all, 131 unique outcomes were extracted: maternal (n = 69), fetal/infant (n = 61) and other (n = 1).

Conclusions Outcome reporting in treatment interventions trials of pregnant women with PGDM is varied, making it difficult to synthesise evidence, especially for rare outcomes. Systems are needed to standardise outcome reporting in future clinical trials and so facilitate evidence synthesis in this area of maternal diabetes.

Registration The systematic review was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration number CRD42020173549).

Keywords Core outcome set, interventions, pregestational diabetes, pregnancy.

Tweetable abstract Outcome reporting is heterogeneous in intervention trials of pregnant women with diabetes existing before pregnancy.

Linked article This article is commented on by Naderpoor, pp. 1905–1906 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16841.

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Introduction

Diabetes is one of the most common pre-existing medical conditions complicating pregnancy. Women with pregestational diabetes mellitus (PGDM) and their babies are particularly vulnerable to adverse pregnancy outcomes compared with women with normal glucose tolerance. The St Vincent declaration (1989), stating that pregnancy
outcomes in women with diabetes should approximate those of women without diabetes, has not been achieved.\(^2\) PGDM is associated with increased morbidity to both mother and baby including preterm birth, small and large for gestational age, macrosomia, congenital malformations and pre-eclampsia.\(^3\)

In recent years, there has been a significant increase in treatment interventions to help alleviate morbidity and mortality in pregnant women with PGDM. These interventions include education programmes,\(^4,5\) pharmacological\(^6,7\) and technological interventions\(^8,9\) and pre-pregnancy care.\(^10\) In addition, organisations such as the Diabetic Pregnancy Study Group (DPSG) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG), have facilitated and disseminated research to improve outcomes in these high-risk pregnancies. Guidelines for the management of pregnant women with PGDM are also easily available globally to help clinicians care for these women.

It is important to monitor over time whether these interventions have had a positive impact on morbidity and mortality in pregnancies complicated by PGDM. There is evidence to suggest that many of these interventions have yielded positive results.\(^11,12\) However, robust evidence on how different interventions affect morbidity and mortality in pregnancies complicated by PGDM is inconsistent, in part due to the measurement and reporting of a variety of outcomes.\(^13,14\) One way to overcome the problem of variable outcome reporting is through the creation of Core Outcome Sets (COS), which measure a consensus-derived collection of outcomes to be reported on a particular healthcare topic. This work involves all relevant stakeholders including patients and patient representatives, healthcare workers, researchers and policy-makers. The CoRe Outcomes in WomeN’s health (CROWN) initiative, established to improve outcome reporting in maternal diabetes, made a call to researchers to produce, disseminate and implement COS to improve outcome reporting, build evidence synthesis and reduce research waste.\(^15\) The initial step in the COS development process was a systematic review to create a list of all unique outcomes reported in the literature.

The aim of this systematic review was to collate a list of outcomes reported in randomised controlled trials evaluating treatment interventions in pregnant women with PGDM. This systematic review formed the basis for an eDelphi process to create a COS in this topic.

**Methods**

The protocol for this systematic review has been published.\(^16\) This systematic review was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration number CRD42020173549). The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines.

Randomised controlled trials assessing any treatment interventions of pregnant women with PGDM were included in the study. Non-randomised controlled trials, longitudinal follow-up studies, secondary analyses, reviews, reports of conference proceedings or abstracts where there was no complete description of the trial methodology were excluded. Only studies reported in English were eligible for inclusion. Any comparator and any outcome were noted. Studies were restricted to interventions that occurred during pregnancy only.

The following databases were searched: CENTRAL (via the Cochrane Library), Web of Science (WOS), Medline (via OVID platform), Cumulative Index of Nursing and Allied Health Literature (CINAHL) (via EBSCO host platform) and Embase. In addition, ClinicalTrials.gov was searched for ongoing trials and references of relevant articles were reviewed for studies not captured in the search. There was no time restriction; however, the final database search was completed on 27 January 2020.

A search strategy was formulated with the assistance of the school librarian at the National University of Ireland, Galway (NUI Galway). A combination of keywords and Medical Subject Headings (MeSh) terms was used to search for specific concepts. These were then combined using Boolean operators to formulate the final search strategy. The full search strategy is shown in Appendix S1.

Studies deemed suitable for inclusion were identified from the search using the predetermined inclusion criteria. The reference management tools ZOTERO (https://www.zotero.org/) and RAYAN (https://www.rayyan.ai/) were used to manage and identify duplicate articles downloaded from the search results. Two independent reviewers (OK and DB) screened titles and abstracts of the selected studies to ensure eligibility. Full-text papers of selected studies were reviewed by both reviewers before the final decision regarding inclusion. Disagreements were resolved through discussion and recourse to a third author (FD) if necessary.

All reported outcomes were extracted from the Methods and Results sections of each paper. A data extraction template consisting of the following parameters was used to extract outcomes; authors, journal and year of publication, the condition of interest (type 1 diabetes mellitus, type 2 diabetes mellitus or both), outcome of interest and time-points or periods of outcome measurement. We also assessed how each outcome was defined and the instruments or indicators used to measure the outcome. Two independent reviewers (OK and DB) assessed the articles independently, reviewed outcomes together and ensured that all outcomes were identified and included.
Risk of bias in individual studies was not carried out because our study aimed to extract all outcomes reported in the literature regardless of reporting bias. In addition, some of the included studies were ongoing, making bias reporting not possible.

Outcomes extracted from the literature were broadly categorised into maternal, fetal/infant or other outcomes. The study advisory group (SAG) including women with PGDM, healthcare providers and researchers then carefully reviewed the outcomes and grouped them into the following domains: maternal (blood/urine parameters and monitoring, complications, life impact/psychological, miscellaneous), fetal/infant (laboratory measures, biometrics and anthropometrics, complications, miscellaneous) and other. Where clarification was needed for particular outcomes regarding suitability for grouping, advice was sought from the relevant experts.

**Results**

Of the 1475 potentially relevant studies, 67 \(^{4,9,11,17-76}\) fulfilled the inclusion criteria as shown on the PRISMA 2020 flowchart77 (Figure 1). The number of outcomes reported in each study is shown in Table S1. The median numbers of maternal and fetal/infant outcomes reported per article were seven and eight, respectively. On average, most studies reported a median of 15 outcomes. The number of overall reported outcomes ranged from one\(^5\) to 46.\(^{11}\) Twenty-four, 10 and 14 studies assessed interventions in women with pre-existing type 1 diabetes, type 2 diabetes and a combination of both, respectively. In some cases, the population was defined as women with PGDM \((n = 18)\) or with insulin-requiring diabetes \((n = 1)\).

Studies were carried out in North America \((n = 33)\), Europe \((n = 30)\), Asia \((n = 10)\), South America \((n = 7)\), Africa \((n = 6)\) and Australia/New Zealand \((n = 6)\). The earliest study was published in 1971\(^{58}\) with the most recent studies still ongoing. Interventions are shown in Table 1. The most researched pharmacological interventions were insulin \((n = 14)\) and metformin \((n = 9)\). Glucose monitoring \((n = 12)\) was the most assessed technological intervention, with continuous glucose monitoring \((n = 6)\) accounting for half of the studies.

Forty-one (61.2\%) studies specifically reported primary outcomes. Four studies (6.0\%) reported the primary outcome as a composite outcome. There were differences in items reported in composites. For example, two of the studies assessing metformin treatment included one

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Figure 1. PRISMA 2020 flowchart of selection of studies.
composite outcome; perinatal mortality, preterm birth, 
neonatal hypoglycaemia, hyperbilirubinemia, small and 
large for gestational age, low birthweight and birth 
trauma. The other study included the following in the 
large for gestational age, low birthweight and birth 
neonatal hypoglycaemia, hyperbilirubinemia, small and 
composite outcome; perinatal mortality, preterm birth, birth injury, moderate/severe respiratory distress, neonatal hypoglycaemia, neonatal intensive care unit admission and pregnancy loss. Thirty-six (53.7%) studies specifically reported sec-
ondary outcomes.

No studies specifically engaged Public and Patient Involvement (PPI). Wen et al. commented that although they did not actively seek patient engagement, physicians’ input was provided through a survey, suggesting that their patient population would be interested in the trial and their advice was sought on best practices to roll out the trial. However, no explicit PPI was sought.

Data extracted from the first ten studies are shown in Table S2. Before SAG review, a total of 210 outcomes were extracted from the literature (Table S3). The SAG then reviewed the outcomes, combining similar outcomes, removing duplicates and clarifying outcome terminology. Some examples of outcomes that were combined are as follows: vaginal birth and caesarean section birth were combined as ‘mode of birth’, sepsis and pyelonephritis were combined as ‘maternal infection’ and birthweight SD score, birthweight Z core, birthweight centile and customised birthweight centiles were combined as ‘birthweight’. Some outcomes that were not clearly defined were not listed as a unique outcome. For example, pregnancy loss was listed as miscarriage, stillbirth, ectopic pregnancy or pregnancy termination.

Differences in outcome definitions and time-point measurements were noted. Definitions were not specified for all outcomes. We used the most reported maternal and neonatal complications as examples, pre-eclampsia and neonatal hypoglycaemia, respectively (see Table 2). Some, but not all, studies assessing pre-eclampsia as an outcome (1) specified the blood pressure measurement used for diagnosis, (2) included HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome, pulmonary oedema or other organ failure in the definition, or (3) specified the time-point of 20 weeks gestation in the definition. There was significant variety in how neonatal hypoglycaemia was defined as shown in Table 2. A total of 17 definitions were given for neonatal hypoglycaemia. Time-points for measur-
ing neonatal hypoglycaemia ranged from ‘first glucose after birth’, ‘within 24 hours and/or 48 hours of birth’ to ‘thereafter’. For the most part, we did not consider the same outcome measured at different time-points as unique outcomes but rather grouped them. Some definitions of neonatal hypoglycaemia included need for treatment whereas others did not.

On completion of outcome review, the SAG identified 131 unique outcomes (69 maternal, 61 fetal/infant and one other) for presentation to the first eDelphi round of COS development. Extracted outcomes listed according to frequency of reporting across all studies are shown in Fig-
ure 2. The most commonly reported maternal outcomes (n ≥ 20) across all studies were; pre-eclampsia (n = 30), maternal hypoglycaemia (n = 28), trimester-specific glycated haemoglobin (n = 22), self-monitored blood glucose (n = 22), trimester-specific insulin dose (n = 20) and weight gain during pregnancy (n = 20). The most com-
monly reported fetal/infant outcomes were; birthweight (n = 41), gestational age at birth (n = 37), mode of birth (n = 35), neonatal hypoglycaemia (n = 34), neonatal intensive care unit admission (n = 27), large for gestational age (n = 24), congenital malformations (n = 24), for gesta-
tional age (n = 22) and macrosomia (n = 20).

Fifteen (22.4%) studies involved patients in low- to mid-
dle-income countries (LMIC). Of these, six studies included collaborations between high-income countries (HIC) and LMIC. Interventions used in LMIC were insulin (n = 6), metformin (n = 4), sulphonylurea (n = 1), diet (n = 1), aspirin (n = 1), folic acid (n = 1) and glucose monitoring (n = 1). The most reported maternal outcomes in studies involving LMIC were pre-eclampsia (n = 7), glu-
cose control (n = 7) and adverse events (n = 7). The most

Table 1. Types of interventions reported in each study

| Intervention                                      | Total number of studies |
|--------------------------------------------------|-------------------------|
| Pharmacology                                     |                         |
| Insulin                                          | 14                      |
| Metformin                                        | 9                       |
| Aspirin                                          | 3                       |
| Vitamin C and Vitamin E                          | 2                       |
| Eicosapentaenoic acid and docosahexaenoic acid   | 2                       |
| Sulphonylurea                                    | 1                       |
| Folic acid                                       | 1                       |
| Intravenous fluids                               | 1                       |
| Technology                                       |                         |
| Glucose monitoring                               | 12                      |
| Closed-loop insulin delivery system              | 4                       |
| Messaging and education systems                  | 3                       |
| Insulin pump                                     | 2                       |
| Other                                            |                         |
| Glycaemic targets                                | 3                       |
| Home care (versus hospital care)                 | 2                       |
| Induction of labour                              | 2                       |
| Diet                                             | 2                       |
| Insulin regimen                                  | 1                       |
| Early discharge (versus routine discharge)       | 1                       |
| Expressing milk in the antenatal period          | 1                       |
| Cognitive behavioural therapy                    | 1                       |
reported fetal/infant outcomes in LMIC studies were stillbirth \( (n = 10) \), preterm birth \( (n = 10) \), neonatal hypoglycaemia \( (n = 10) \) and birthweight \( (n = 8) \).

There were differences in what outcomes were reported for each intervention. To underscore this point, we assessed the three commonly reported outcomes (maternal and fetal/infant) for the most researched intervention: insulin.

| Outcome                  | Number of studies reporting outcome \( N \) (%) | Definitions and time-points | Number of studies reporting similar outcome definition and time-point \( N \) (%) |
|--------------------------|-----------------------------------------------|----------------------------|-----------------------------------------------------------------|
| Maternal                 |                                               |                            |                                                                  |
| Pre-eclampsia            | 30 (44.8)                                     | Blood pressure \( \geq 140/90 \) mmHg and proteinuria \( \geq 300 \) mg/24 h \( n = 34, 67 \) | 2 (6.7)                                                         |
|                          |                                               | Blood pressure \( \geq 140/90 \) mmHg on two occasions with significant proteinuria \( n = 3 \) | 1 (3.3)                                                         |
|                          |                                               | Blood pressure \( \geq 140/90 \) on two occasions at least 4 h apart with significant proteinuria \( \geq 300 \) mg/24 h developing after 20 weeks of gestation \( n = 22, 46, 47, 50, 71 \) | 5 (16.7)                                                        |
|                          |                                               | Diastolic blood pressure \( \geq 90 \) mmHg on two occasions \( \geq 4 \) h apart and proteinuria \( \geq 300 \) mg/24 h or urinary protein \( \geq 300 \) mg/24 h, or protein creatinine ratio \( \geq 30 \) mmol/mmol in women \( \geq 20 \) weeks of gestation or diagnosis of HELLP syndrome \( n = 59 \) | 1 (3.3)                                                         |
|                          |                                               | Development of HTN (Blood pressure \( \geq 140/90 \) mmHg on two occasions at least 4 h apart) plus one of: proteinuria \( \geq 300 \) mg/24 h or two dipstick-test \( \geq 2 + \) on dipstick, or urinary protein \( \geq 300 \) mg/24 h, or protein creatinine ratio \( \geq 30 \) mmol/mmol in women \( \geq 20 \) weeks of gestation or diagnosis of HELLP syndrome \( n = \geq 2 \) | 1 (3.3)                                                         |
|                          |                                               | New-onset HTN from gestational week 20 to delivery and simultaneous proteinuria or presence of eclampsia, HELLP syndrome or other severe organ involvement \( n = 22, 46, 47, 50, 71 \) | 1 (3.3)                                                         |
|                          |                                               | No specific definition \( n = 11, 17-19, 29, 30, 31, 38, 39, 43, 45, 52, 58, 60, 62, 64, 65, 66 \) | 18 (60.0)                                                        |
| Fetal/Infant             |                                               |                            |                                                                  |
| Neonatal hypoglycaemia   | 34 (50.7)                                     | Blood glucose \( \leq 2.6 \) mmol/l \( 47 \) mg/dl \( n = 34, 67 \) | 1 (2.9)                                                         |
|                          |                                               | Blood glucose \( \leq 2.5 \) mmol/l \( 45 \) mg/dl \( n = 31 \) | 1 (2.9)                                                         |
|                          |                                               | Two-hour plasma glucose \( < 2.5 \) mmol/l \( 45 \) mg/dl \( n = 24, 67 \) | 2 (5.9)                                                         |
|                          |                                               | Blood glucose \( < 2.2 \) mmol/l \( 40 \) mg/dl \( n = 36, 37 \) | 1 (2.9)                                                         |
|                          |                                               | Blood glucose \( < 1.9 \) mmol/l \( 35 \) mg/dl within the first 24 hours of life \( n = 65, 66 \) | 2 (5.9)                                                         |
|                          |                                               | Blood glucose \( < 1.9 \) mmol/l \( 35 \) mg/dl in term infants or \( < 1.4 \) mmol/l \( 25 \) mg/dl in preterm infants on at least two different occasions during first 48 h of life \( n = 65 \) | 1 (2.9)                                                         |
|                          |                                               | Blood glucose \( < 1.7 \) mmol/l \( 31 \) mg/dl \( n = 34, 47, 70 \) | 3 (8.8)                                                         |
|                          |                                               | Blood glucose \( < 2.6 \) mmol/l \( 47 \) mg/dl, measured before feeds \( n = 31 \) | 1 (2.9)                                                         |
|                          |                                               | Capillary blood glucose \( < 1.7 \) mmol/l \( 30 \) mg/dl on two or more occasions in the first 48 h of life \( n = 61 \) | 1 (2.9)                                                         |
|                          |                                               | Capillary blood glucose \( < 1.7 \) mmol/l \( 30 \) mg/dl in the first 24 hours of life and \( < 2.2 \) mmol/l \( 40 \) mg/dl thereafter \( n = 74 \) | 1 (2.9)                                                         |
|                          |                                               | Capillary blood glucose \( < 1.7 \) mmol/l \( 31 \) mg/dl or \( < 2.5 \) mmol/l \( 45 \) mg/dl within the first 24 h after birth \( n = 76 \) | 1 (2.9)                                                         |
|                          |                                               | Capillary blood glucose \( < 1.7 \) mmol/l \( 30 \) mg/dl during the first 24 h after birth or a Blood glucose \( < 2.5 \) mmol/l \( 45 \) mg/dl between 24 and 48 h after birth \( n = 79 \) | 1 (2.9)                                                         |
|                          |                                               | Hypoglycaemia requiring dextrose treatment \( n = 1, 63, 64, 69 \) | 4 (11.8)                                                        |
|                          |                                               | Blood glucose \( < 2.2 \) mmol/l \( 40 \) mg/dl in the first 24 h of life and \( < 2.8 \) mmol/l \( 50 \) mg/dl after or requiring medical therapy \( n = 17 \) | 1 (2.9)                                                         |
|                          |                                               | Capillary blood glucose \( < 2.2 \) mmol/l \( 40 \) mg/dl or any hypoglycaemia that requires IV fluid treatment \( n = 19 \) | 1 (2.9)                                                         |
|                          |                                               | Hypoglycaemia requiring intravenous dextrose therapy with Blood glucose \( < 1.4 \) mmol/l \( 25 \) mg/dl \( n = 6 \) | 1 (2.9)                                                         |
|                          |                                               | No specific definition \( n = 32, 34, 39, 44, 54, 58, 62, 65 \) | 9 (26.4)                                                        |

BGL, blood glucose levels; BP, blood pressure; CBG, capillary blood glucose; DBP, diastolic blood pressure; HELLP, haemolysis elevated liver enzymes low platelets; HTN, hypertension; PCR, protein creatinine ratio; PG, plasma glucose.

Overall, there were 14 published articles from 12 studies assessing insulin in pregnancy. With the exception of only two studies, \( n = 32, 65 \) most of the studies were performed in the first or second trimester. Of these, pre-eclampsia was reported in seven studies. Maternal hypoglycaemia was reported in 11 studies, with only five studies reporting on severe hypoglycaemia. Only four studies reported on
trimester-specific glycated haemoglobin. Neonatal birthweight was reported in eight trials. In one study,65 the intervention was during labour, so would not have been expected to have any effect on birthweight. Six studies reported gestational age at birth. Neonatal hypoglycaemia was reported in eight studies.

Discussion
Main findings
We identified significant heterogeneity in outcome reporting and a need to develop a COS in studies assessing treatment interventions in pregnant women with PGDM. The
differences are both in ‘what’ outcomes to report and ‘how’ to report these outcomes. The IADPSG has formulated a repository of definitions for outcomes commonly reported in the literature in order to help standardise the ‘how’ to report these outcomes. One of the common inconsistencies in outcome reporting in this study was related to variations in time-points at which each outcome was measured. This is not unique to this study. In addition, there were variations in some outcome definitions according to national guidelines.

**Strengths and limitations**

There are some limitations to this study. One limitation is that there is no consensus on how outcomes extracted from the literature should be classified. The Core Outcome Measures in Effectiveness Trials (COMET), an initiative that aims to bring together people interested in the development and application of COS, has endorsed the use of a 38-item scale to classify individual outcomes. Because our study involved two populations (mother and baby), we found this taxonomy unsuitable.

Another limitation is that studies from LMIC were under-represented. Therefore, it is not clear whether outcomes extracted from the current literature, mostly represented by HIC, would be clinically meaningful to these LMIC. Pre-eclampsia was the most reported maternal outcome in both LMIC and HIC. However, unlike in HIC, preterm birth and stillbirth were the most reported outcomes in LMIC.

In our study, a large number of outcomes were extracted (n = 210). As this systematic review was carried out in the context of a larger COS development study, it is important to recognise the risk of participant fatigue in the subsequent step (i.e. cDelphi survey) when such a large list of outcomes is generated. One way around this is grouping outcomes. There is currently no consensus on a reproducible method for developing a long list of unique outcomes for a COS with significant variation on how researchers extract, group and count trial outcomes. We maintained a systematic approach to outcome extraction and grouping.

**Interpretation**

In recent years, standardisation of outcome reporting in the area of diabetes in pregnancy in order to reduce research waste and synthesise evidence has been recognised. This systematic review employed rigorous methodology to capture all outcomes reported in the literature in this important topic of maternal diabetes. We also identified significant heterogeneity in both what outcomes are reported and how they are defined and measured.

Across all studies, outcomes in the maternal life impact/psychological effects domain were the least reported. This is even more so for studies based in LMIC. Only one outcome ‘patient satisfaction’ was reported in this domain in studies carried out in LMIC. Integration of patient-reported outcomes into studies assessing interventions in pregnant women with PGDM may be one way of improving outcome reporting in this domain. Another way of improving outcome reporting in this domain might be engaging with PPI. One such initiative is the James Lind Alliance (JLA). The JLA through the Diabetes and Pregnancy Priority Setting Partnership aims to improve research quality by ensuring that researchers and funders are aware of the issues that matter most to women with diabetes in pregnancy. We invited patients to participate as part of the SAG to ensure that their views and unique experiences are considered from study conception. Patients were actively involved in outcome review and finalising the list of unique outcomes. We hope that by involving women with diabetes in future studies this will translate into an increase in outcomes in the life impact and psychological effects domain.

The JLA has formulated a list of ten questions chosen by patients and clinicians to prioritise future research in diabetes and pregnancy to deliver maximum value and impact. Some of these questions include interventions in pregnant women with PGDM. This systematic review helps to inform what outcomes are reported in existing research in evaluating the effectiveness of interventions in pregnant women with PGDM. The planned COS derived from this work will help to prioritise a list of outcomes that are important to stakeholders, including women with PGDM, in this area of maternal diabetes.

Pre-pregnancy care has been shown to improve some pregnancy outcomes. Studies assessing pre-pregnancy care as an intervention were excluded from this review because a complimentary COS for studies evaluating the effectiveness of pre-pregnancy care for women with PGDM has already been developed. The planned COS will complement this previous work and provide stakeholders with guidance on outcome selection and reporting for studies conducted both before and during pregnancy in women with PGDM.

**Conclusions**

Outcome reporting in clinical trials evaluating treatment interventions in pregnant women with pregestational diabetes is varied both in ‘how’ and ‘what’ outcomes are measured and reported. A COS is needed to define what outcomes to report in future trials in this area of maternal diabetes. There is a need to prioritise and encourage LMIC participation and PPI in future studies evaluating treatment interventions in pregnant women to make research more applicable and impactful.

**Disclosure of interests**

OK has Sanofi through Royal college of Physicians Ireland (RCPI) (Fellowship grant); Astrazeneca (Meeting Chair). DB
has Wellcome Trust Irish Clinical Academic Training (ICAT) Programme fellow. All other authors have nothing to disclose.

**Contribution to authorship**
All authors were members for the SAG and participated in the formulation of the methodology for this review. OK and DB screened titles and abstracts and extracted all the outcomes from the literature. All authors reviewed the list of extracted outcomes. All authors revised the manuscript critically for important intellectual content and approved the final version to be published. OK co-ordinated the study and is responsible for the integrity of the work as a whole.

**Details of ethics approval**
Ethical approval for this study was granted by the Clinical Research Ethics Committee, Galway University Hospitals, Galway, Ireland (Ref: C.A 2293).

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**Data Availability Statement**
Template data collection forms and data extracted from included studies can be requested from authors.

**Supporting Information**
Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Appendix S1.** Full search strategy.

**Table S1.** Number of outcomes reported in each study. T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; PGDM, pregestational diabetes mellitus.

**Table S2.** Data extraction. T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; PIH, pregnancy-induced hypertension; PET, pre-eclampsia; NICU, neonatal intensive care unit; LGA, large for gestational age; SGA, small for gestational age; TTN, transient tachypnoea of the newborn; RDS, respiratory distress syndrome; BGL, blood glucose levels; BP, blood pressure; IV, intravenous; FBG, fasting plasma glucose; PPG, post-prandial glucose; GDM, gestational diabetes mellitus; SMBG, self-monitoring of blood glucose; HTN, hypertension; DM, diabetes mellitus; DKA, diabetic ketoacidosis; ICU, intensive care unit; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity; PGDM, pregestational diabetes mellitus; CSII, continuous subcutaneous insulin infusion; PPROM, preterm prelabour rupture of membranes; IUGR, intrauterine growth restriction; PPH, postpartum haemorrhage; HELLP, haemolysis elevated liver enzymes and low platelets.

**Table S3.** All outcomes extracted from the literature (n = 210). PET, pre-eclampsia; HELLP, haemolysis elevated liver enzymes and low platelets; ICU, intensive care unit; HbA1c, glycated haemoglobin; NICU, neonatal intensive care units; LGA, large for gestational age; SD, standard deviation; IGF-1, insulin growth factor 1.

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