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Metformin in Pregnancy Study (MiPS): Protocol for a Systematic Review with Individual Patient Data Meta-analysis

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Running Title: Protocol for the Metformin in Pregnancy Study (MiPS) international network

Metformin in Pregnancy Study (MiPS): Protocol for a Systematic Review with Individual Patient Data Meta-analysis

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ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) is a common disorder of pregnancy and contributes to adverse pregnancy outcomes. Metformin is often used as a therapeutic option for the prevention and management of GDM; however, its efficacy and safety in pregnancy continues to be debated.

Objective: The Metformin in Pregnancy Study (MiPS) aims to utilise individual patient data (IPD) meta-analysis to clarify the efficacy and safety of metformin use in pregnancy and to identify relevant knowledge gaps.

Methods and Analysis: Medline, EMBASE, and all EBM will be systematically searched for randomised controlled trials (RCTs) comparing metformin with placebo, usual care, or other pharmacological or non-pharmacological interventions in pregnant women. Two independent reviewers will assess eligibility using pre-specified criteria and will conduct data extraction and quality appraisal of all eligible studies. Study authors of included trials will be contacted and asked to contribute IPD. Primary outcomes include maternal glycaemic parameters and GDM, as well as neonatal hypoglycaemia, anthropometry, and gestational age at delivery. Other adverse maternal, birth, and neonatal outcomes will be assessed as secondary outcomes. IPD will be harmonised and a two-step meta-analytic approach will be utilised with *a priori* adjustment for covariates and subgroups to examine effect moderators of treatment outcomes. Sensitivity analyses will assess heterogeneity, risk of bias, and the impact of trials which have not provided IPD.

Ethics and Dissemination: All IPD will be de-identified and studies contributing IPD will have ethical approval from their respective local ethics committees. This study will provide robust evidence regarding the efficacy and safety of metformin use in pregnancy, and may identify subgroups of patients who may benefit most from this treatment modality. Findings will be published in peer-reviewed journals and disseminated at scientific meetings, and will provide much needed evidence to inform clinical and public health actions in this area.

Trial Registration Number: International Prospective Register of Systematic Reviews (PROSPERO): CRD## (to be confirmed)

Strengths and Limitations:

- Important area of research which will inform clinical practice and public health actions in this area;
- Protocol is for the first individual patient data meta-analysis investigating metformin use in pregnancy;
- Employs rigorous methodology and a comprehensive search strategy to provide the most robust evidence to date;
- Limitations include potential for publication bias or data availability bias if IPD is not available for some studies or outcomes.

Keywords: metformin, insulin, oral hypoglycaemic drugs, gestational diabetes, pregnancy, maternal outcomes, neonatal outcomes.

1. INTRODUCTION

Pregnancy is a period of major anatomic and physiological changes, with heightened metabolic demands on both mother and fetus. Gestational diabetes mellitus (GDM) is a common metabolic disorder of pregnancy with global prevalence estimates varying by country, from <1% in Croatia to 28% in India [1]. The incidence of GDM is increasing in line with obesity and advanced maternal age [2]. Elevated maternal glucose concentrations and GDM increase the risk for adverse pregnancy outcomes including pre-eclampsia, macrosomia and fetal abnormalities, and GDM itself is the strongest population predictor of type 2 diabetes (T2D) [3]. Increasing evidence suggests that fetal exposure to hyperglycaemia *in utero* increases the risk of obesity and T2D in adulthood [4]. Effective strategies for the prevention and/or treatment of GDM and its associated complications are therefore of paramount importance.

Metformin, a biguanide compound and first-line treatment for T2D, offers opportunities for preventing and treating GDM, although its role in pregnancy is debated due to the known placental transfer of metformin to the fetus [5,6]. Metformin exerts its clinical effects by reducing hepatic glucose output and increasing insulin sensitivity, leading to lower glucose concentrations without an increased risk of hypoglycaemia or weight gain [3]. Although metformin crosses the placenta, to date it has been shown to be safe, generally well-tolerated and preferred by women over insulin [7,8]. In the UK and New Zealand, clinical guidelines recommend the use of metformin as initial glucose-lowering treatment in women with GDM if lifestyle interventions are unsuccessful in maintaining glycaemic targets [9]. However, in Australia and the US, lifestyle and insulin remain the mainstay for GDM therapy and metformin is used on a case-by-case basis at the clinician's discretion [5,6]. Concerns around the use of metformin in pregnancy include a lack of conclusive evidence regarding its efficacy and safety for preventing or treating GDM. Despite many published studies over the last four decades, there have been no placebo-controlled trials with GDM or glucose regulation as the

primary endpoint. This is an important gap in the evidence given that introducing a medication or treatment in pregnancy can have a powerful placebo effect. Also more recently, a number of follow up studies have suggested potential longer term adverse child health implications of metformin use in pregnancy, although confirmation of these effects requires further study [10].

Regarding the use of metformin for the treatment of GDM, early observational studies by Coetzee and colleagues [5,11,12] in South Africa showed that metformin improved glycaemic control in women with GDM and subsequently reduced fetal anomalies and perinatal mortality. However, controversies regarding whether metformin was a safe and viable option for the treatment of GDM continued. This was particularly relevant in the context of poorly-resourced countries where low health literacy and high costs of insulin are problematic [5,6]. In 2008, Rowan et al. [13] published the landmark MiG (Metformin in GDM) trial and found that, in 751 women randomised to metformin or insulin, there were no differences in the primary outcome - a composite of neonatal hypoglycaemia, respiratory distress, need for phototherapy, Apgar score <7 at 5 min and preterm birth. Secondary outcomes including neonatal anthropometry also did not differ between groups; however, severe neonatal hypoglycaemia (<1.6 mmol/L) was reduced with metformin compared with insulin [13]. It should be noted that 46.3% of women in the metformin group required supplemental insulin treatment to maintain glycaemic control [13]. A large number of RCTs and meta-analyses have since been published, with many showing that particularly in cases of mild GDM, metformin is as effective as insulin in controlling GDM and preventing fetal, maternal and neonatal complications [7,14-27]. Yet, some have reported that metformin increased the risk of preterm birth compared with insulin [7], while others found a decreased risk of pregnancy-induced hypertension [20,27], neonatal death, or serious comorbidity [14] with metformin compared with insulin or other oral hypoglycaemic drugs.

In addition to treating GDM, the potential role of metformin as a GDM prevention strategy has also been proposed. Evidence regarding metformin exposure in early pregnancy and its

role in GDM prevention began developing when metformin use became more common in the treatment of polycystic ovary syndrome (PCOS). However, observational studies (primarily retrospective), RCTs and meta-analyses in women with PCOS have produced conflicting findings. Some report that metformin reduced the risk of GDM, early pregnancy loss, preterm delivery and pre-eclampsia [28-33], and others report no effects on some or all of these outcomes [28,34,35]. Most of these studies were designed to assess metformin use for ovulation, pregnancy rates and live births rather than for pregnancy complications, and existing meta-analyses have been of variable quality. A recent study which combined three RCTs totalling 800 women with PCOS randomized to metformin or placebo during pregnancy did not show any improvement in glucose homeostasis or reduction in GDM or need for insulin therapy, despite the lower gestational weight gain in the metformin group [36]. Notably, exposure to metformin in early pregnancy was not associated with teratogenic effects or increased risk of miscarriage in any of these studies to date, or in a recent case-control study of >50,000 babies with congenital anomalies [8].

Use of metformin for preventing GDM has also been explored in recent RCTs of overweight or obese non-diabetic pregnancies [37-39]. Two trials in the UK [37,39] examined metformin versus placebo in obese pregnancies, while the GRoW trial in Australia [38] examined whether the use of metformin as an adjunct therapy to dietary and lifestyle advice in overweight or obese pregnancies was effective in improving maternal, fetal and infant health outcomes. All three trials reported that metformin had no effect on the primary outcome of neonatal birthweight compared with placebo [37-39], despite reduced gestational weight gain with metformin in two trials [38,39]. No effects on glycaemic outcomes including incidence of GDM were found; however, all trials were not powered to detect differences in these outcomes [37,39]. Another RCT in non-diabetic women with pregestational insulin resistance reported no effect of metformin in the prevention of GDM compared with placebo [40]. The relatively small sample size (n=111) and high drop out rate (23%) may have influenced these results [40].

Overall, there is substantial heterogeneity in the designs, participant characteristics and methodological rigour of existing studies, precluding firm conclusions regarding the efficacy and safety of metformin use in pregnancy. Although several meta-analyses have been conducted, most have targeted women with PCOS and all have used aggregate data, which may be subject to ecological bias and study-level confounding. Here, we aim to address these knowledge gaps by conducting a comprehensive systematic review incorporating meta-analyses of individual patient data (IPD). Using these data, we will test the hypothesis that metformin in pregnancy is a safe and effective strategy for improving maternal and neonatal glycaemic outcomes. Use of IPD will allow adjustment for differences in participant characteristics including maternal demographics, baseline glucose concentrations and use of supplemental insulin, and it can also identify subgroups of women who may benefit from metformin treatment in pregnancy.

2. SYSTEMATIC REVIEW QUESTION

Is metformin use in pregnancy effective and safe versus placebo, usual care, or other pharmacological or non-pharmacological interventions in:

a) women with GDM for improving glycaemic, maternal and/or neonatal adverse outcomes?

b) women without GDM for improving glycaemic, maternal and/or neonatal adverse outcomes?

3. METHODS/ DESIGN

This review will adopt rigorous international gold standard methodology as outlined in the Cochrane Library and Centre for Evidence-based Medicine guidelines [41,42], and will conform to the standards of the Preferred Reporting Items for Systematic Reviews and Meta-analyses of IPD Statement (PRISMA-IPD) [43]. The protocol for this systematic review has been registered on PROSPERO under the identification code: CRD####.

3.1. Eligibility Criteria

Selection criteria established *a priori* using the PICO (Population, Intervention, Comparison, Outcomes) framework in **Table 1** will be used to determine eligibility of articles.

3.2. Search Strategy

A systematic search will be developed using relevant search terms (Supplementary Material) in accordance with the selection criteria (Table 1), and the following electronic databases will be searched:

- MEDLINE via OVID
- Medline in-process and other non-indexed citations via OVID
- EMBASE via OVID
- All Evidence Based Medicine (EBM) Reviews via OVID incorporating: The Cochrane Library; Cochrane Database of Systematic Reviews (Cochrane Reviews); Database of Abstracts of Reviews of Effects (Other Reviews); Cochrane Central Register of Controlled Trials (Clinical Trials); Cochrane Database of Methodology Reviews (Methods Reviews); The Cochrane Methodology Register (Methods Studies); Health Technology Assessment Database (Technology Assessments); NHS Economic Evaluation Database (Economic Evaluations); and ACP Journal Club.

Table 1. PICO for study inclusion

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)
Inclusion	Pregnant women of any age, ethnicity, socio-economic status, geographic area, co-morbidity, or gestational age	Metformin administered in any form and route, alone or combined with other intervention/s, of any dosage and for any duration	Placebo, usual care and/or other pharmacological or non-pharmacological interventions including insulin, lifestyle intervention/s, or other oral hypoglycaemic agents (sulfonylureas, acarbose, glibenclamide/ glyburide)	**Primary Maternal Outcomes:** Glycaemic control (glucose, insulin, HbA1c); incidence of GDM* or hyper/hypoglycaemia* **Primary Neonatal Outcomes:** hypoglycaemia*, birthweight, birth length, head circumference and gestational age at delivery **Secondary Outcomes:** Other maternal, birth and neonatal outcomes including miscarriage, birth defects, GWG, pre-eclampsia/ eclampsia, LGA/ macrosomia, SGA and PTB (see full list in Supplementary Material)
Exclusion	Studies in non-pregnant populations	Studies without a metformin therapy arm	Studies without a control or comparison arm	Studies without clinical outcomes (mechanistic studies)
Study type	Systematic reviews of RCTs and RCTs			
Language	No limit			
Year of publication	No limit			

*as defined by authors and using the criteria selected in individual studies. **GDM**, gestational diabetes mellitus; **GWG**, gestational weight gain; **HbA1c**, haemoglobin A1c, **LGA/SGA**, large/small for gestational age; **LBW**, low birthweight; **PTB**, preterm birth; **RCTs**, randomized controlled trials.

Bibliographies and citations of all relevant studies identified by the search strategy and relevant reviews/ meta-analyses will be examined for identification of additional studies. Google will be used to manually search for grey literature (ie, material not published in recognized or indexed scientific journals). Unpublished or ongoing studies will be identified via manual searching of the National Institute of Health Clinical Trials Registry (https://clinicaltrials.gov/) and the Australian New Zealand Clinical Trials Registry (ANZCTR) (https://www.anzctr.org.au).

3.3. Study Selection

To determine eligible studies, one reviewer will scan the titles, abstracts and keywords of every record retrieved by the search strategy using the selection criteria outlined in Table 1 and in consultation with a second reviewer. Disagreement will be resolved by discussion and consensus, otherwise referred to a third reviewer. All articles which appear to meet the selection criteria will be retrieved for full text assessment, and articles with insufficient information in the titles and abstracts will also be retrieved in full text to clarify eligibility. Studies excluded based on full text will be recorded with reasons for their exclusion.

3.4. Data Extraction

Using a specifically developed data extraction form, two independent reviewers will extract data from all included studies. Pilot testing of the extraction form will be conducted using 3-4 studies to ensure all required data is captured. Computed data entries will be cross-checked for meta-analyses where required. Pre-specified data will be extracted in aggregate format from all published studies (**Table 2**). Relevant data will also be requested in IPD format from all authors along with any study or treatment protocol details not reported in published studies (Table 2).

- ***Aggregate Data Extraction:***

For each treatment group, extracted data will include sample sizes, aggregate point estimates and measures of variability, frequency counts for dichotomous variables, and intention-to-treat analysis. For outcomes reported as continuous variables, the aggregate mean values with standard deviations (SD) or confidence intervals will be extracted and used to measure the effects. Where standard errors (SE) are reported, these will be converted to SD using the formula: $SE \times \sqrt{n}$. For outcomes reported as dichotomous variables, relative measures of risk (risk ratio or odds ratio along with confidence intervals), or absolute numbers of patients experiencing at least one episode of the outcome of interest will be extracted and used in the analyses.

Table 2. Data to be extracted in aggregate and IPD format from included studies

Study	Participants	Intervention/ Control	Primary Outcomes†	Secondary Outcomes
First author and Journal/ Source	Maternal age, parity, ethnicity, and gestational age at enrolment	Metformin treatment protocols (dose, including graded dosing, frequency, duration)	Maternal glycaemic control (fasting and postprandial/post-challenge glucose; insulin; and HbA1c) at any/ all timepoints	All other maternal, birth and neonatal outcomes reported in individual studies (Supplementary Material)
Country and year of publication	Maternal anthropometry (BMI, weight, GWG)	Regimens for each control or comparator group.	Incidence of GDM* and/or maternal hyper/hypoglycaemia*	Long term infant/child outcomes
Study design, setting and sample size	Smoking status and use of medications, supplements, or substances	Use of supplemental insulin	Incidence of neonatal hypoglycaemia*	Development of T2D (in pregnancy or postpartum)
Follow up duration	Disease status (pre-existing T2D, GDM, PCOS, etc)	Use of other pharmacological or non-pharmacological co-interventions	Birthweight, birth length and head circumference, and gestational age at delivery*	Patient satisfaction with experience/ treatment
Inclusion/ exclusion and diagnostic criteria	Comorbidities, history of GDM or family history of diabetes	Number analysed per group and ITT analysis		Adverse events/ side effects occurring during the study
Primary outcome*				

*as defined by authors of individual studies which may be based on clinical diagnosis (separate analyses will be performed for different GDM diagnostic criteria) or in the case of gestational age, this may be based on ultrasound measurements, last menstrual cycle, self report, etc.
†baseline, follow up and delta values will be collected for all continuous primary maternal outcomes.
BMI, body mass index; **GDM**, gestational diabetes mellitus; **GWG**, gestational weight gain; **HbA1c**, haemoglobin A1c; **ITT**, intention to treat; **PCOS**, polycystic ovary syndrome, **T2D**, type 2 diabetes.

- ***Individual Patient Data Collection:***

Corresponding and/or lead authors will be contacted and asked to provide fully anonymised data for IPD meta-analyses. Data for participant characteristics and primary and secondary outcomes (as specified in Table 2 and Supplementary Material) will be requested for each patient, in addition to data on supplemental insulin use (or other co-interventions) if individual-level data for these parameters were recorded. These data will be used to conduct stratified and subgroup analyses at the patient level, in particular by baseline body mass index (BMI) and baseline glucose concentrations, as well as by maternal age, parity, ethnicity, previous history of GDM, gestational weight gain and supplemental insulin use.

A formatted template detailing the requested data and recommended coding will be created and sent to authors; however, data will be accepted in any suitable electronic format. All data will be checked to ensure correct coding, consistency with published results and accuracy of extreme values and to identify missing data, and any issues will be queried and rectified as necessary. A single database will be created by the study investigators to incorporate data from all trials in consistent fields and standardised formats (as much as possible). Studies which are excluded or where IPD is not available will be tabulated with reasons, and aggregate data will be used where appropriate.

3.5. Quality appraisal of the evidence

Risk of bias of included studies will be assessed at the study-level by two independent reviewers. Using a critical appraisal template [44] (adapted from the Cochrane risk of bias tool [45]) with predetermined criteria, each study will be allocated a high, moderate, or low risk of bias rating. Individual quality items will be assessed using a descriptive component approach that includes items such as conflict of interest of authors, presence of pre-specified selection criteria, methods of randomisation and allocation of participants to study groups, blinding of participants, carers, investigators or outcome assessors, methods of outcome

assessment and reporting, and statistical issues such as powering and methods of data analysis. Disagreement will be resolved by consensus.

3.6. Data analysis & synthesis

Our IPD analysis will follow a two-step meta-analytical approach where possible to automatically account for clustering of participants within studies [46]. In this approach, IPD analyses will be conducted to generate estimates of the intervention effect for each study separately. These effect estimates will then be pooled and analysed using conventional meta-analyses with inverse-variance weighted models (DerSimonian and Laird random-effects models) to account for between-study variability [46]. Where IPD is derived from a small number of studies or for binary outcome data where the event risk is low or the sample size is small, a one-step IPD approach will be used (IPD from all studies are modelled simultaneously). Stratified analysis by study will be performed to account for participant clustering in the one-step approach [46,47]. If IPD is only available for some studies, we will combine aggregate data with the available IPD to compare results from analyses including and excluding IPD [48,49]. This approach will allow the effect of non-IPD studies on meta-analysis conclusions to be quantified and displayed transparently. For outcomes with no IPD available, aggregate effect measures and random-effects models will be used for meta-analyses where appropriate, provided that data are derived from clinically homogeneous groups (where participants, interventions and outcome measures are sufficiently similar).

Dichotomous outcomes will be presented as relative risks/ risk ratios with 95% confidence intervals and continuous outcomes will be presented as weighted mean differences (WMD) with 95% confidence intervals. Where outcome measures or study methods differ substantially, data will be analysed in line with Cochrane guidelines [41], using random-effects models and Cohen *d* to calculate the standardised mean difference (SMD). All meta-analyses will be conducted on Review Manager 5.3 and IPD data will be initially analysed in Stata V.15 and then imported into Review Manager. Comprehensive

Meta-analysis V.3 software will be used for meta-regression (if applicable) and assessment of publication bias. *P*-values <0.05 will indicate statistical significance. Statistical heterogeneity will be assessed using the I^2 test, where I^2 values over 50% will be considered as moderate to high heterogeneity. Descriptive analyses will be conducted for those studies which are deemed clinically heterogeneous or present insufficient IPD or aggregate data for pooling.

- ***Subgroup and sensitivity analyses:***

Subgroup analyses and, where applicable, multivariable meta-analyses or meta-regression will be performed for factors presumed to cause heterogeneity or variations in outcomes. Pre-specified variables to be accounted for will include maternal age, ethnicity, comorbidity/ disease status, baseline BMI and glucose concentrations, previous history of GDM or other relevant pregnancy complication/s, dose and duration of metformin therapy, use of supplemental insulin, and gestational age at commencement of therapy. These variables were selected on the basis of evidence showing that the benefits of metformin therapy may vary by these factors [50-52]. Diagnostic criteria for GDM will also be explored for studies measuring incidence of GDM as an outcome. The exact variables to be explored will be selected after data collation but prior to any analyses and will be justified by biological reasoning. Caution will be used in interpretation of subgroup results and adjustment for multiple testing will be considered as necessary. IPD meta-analyses generally have increased power to detect genuine subgroup effects; however, we will assess whether subgroup effects are consistent within individual studies, if deemed necessary. Any post-hoc subgroup analyses will be considered hypothesis-generating for the purpose of planning and designing future studies. Meta-regression and/or multivariable meta-analyses using linear or logistic regression estimates will be used where appropriate to adjust for the above covariates and to synthesise multiple interaction estimates from each study, accounting for their correlations.

Sensitivity analyses will be conducted and factors to be included will be determined during the review process. Heterogeneity (I^2 >50%) will be explored through sensitivity analysis using risk of bias and IPD availability. For IPD and aggregate meta-analyses incorporating more than three studies, funnel plot asymmetry and Egger [53] and Begg [54] statistical tests will be used to determine small study effects and potential publication bias [55,56].

3.7. Grading the body of evidence

Quality of the evidence will be assessed at the outcome-level by two independent reviewers and rated as high, moderate, low, or very low using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [57]. These ratings will be based on risk of bias, imprecision, heterogeneity, indirectness, and suspicion of publication bias. Availability of IPD and presence of selection or publication bias for IPD studies will also be incorporated into quality assessments in line with PRISMA-IPD guidelines [43]. Disagreements will be resolved by discussion and consultation with a third reviewer where needed.

3.8. Ethics

Ethical approval is not required for aggregate data meta-analyses. Individual trials contributing primary data for IPD meta-analyses will have ethical approval from their respective Human Research Ethics Committees in the countries where the studies took place. All data from primary trials will be fully anonymised prior to being imported into our database.

3.9. Data availability statement

No data has been generated or analysed in this manuscript.

3.10. Patient and public involvement statement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

4. RESULTS

Data will be presented in summary tables and in narrative format to describe the populations, interventions and outcomes of the included studies. Forest plots and funnel plots will be used to present results from meta-analyses and publication bias assessments, respectively. Where necessary, results with and without IPD will be presented for comparison. Both aggregate and IPD meta-analyses processes, including results, will be reported according to PRISMA [58] and PRISMA-IPD [43] guidelines.

5. DISCUSSION

GDM is one of the most common complications of pregnancy and contributes to adverse perinatal outcomes, as well as long-term risk of obesity and T2D in the offspring [59]. Although metformin is often prescribed (in addition to lifestyle intervention) in the clinical treatment of GDM, its efficacy and safety in pregnancy continues to be debated [9,60]. Recent RCTs have provided much-needed evidence in this field; however, heterogeneity in study designs, participant characteristics and methodological quality have made it difficult to draw firm conclusions from the available evidence. Moreover, whether metformin may be beneficial in women without GDM for the prevention of glycaemic and other adverse outcomes remains uncertain.

To the best of our knowledge, this will be the most comprehensive systematic review investigating the use of metformin for preventing or treating GDM and other pregnancy complications. It is also the only review in this area to incorporate an IPD meta-analysis examining whether the effects of metformin, if any, are independent of potential confounders and whether they may be specific to certain subgroups of women. Our systematic review process will have several strengths, including the use of rigorous methodology, pre-specified criteria and pre-determined primary and secondary outcomes in order to establish the efficacy

and safety of metformin in a variety of population groups. The IPD component of this study will involve acquiring, cleaning, standardising and synthesizing raw data from existing studies. Although this is an intensive process, it is more feasible and less costly than large-scale RCTs and avoids the ethical problem of research waste [61], thus it is considered the gold-standard approach to evidence synthesis [43]. This approach is particularly important in reviewing controversial therapeutic areas and can provide level 1 evidence to guide clinical practice [43].

In contrast to standard aggregate data meta-analysis, using individual-level data enables a more detailed assessment of risk of bias and, more importantly for this study, it provides more power to detect subgroups of interest and to examine effect modifiers at the individual level, which would otherwise require a very large and costly study [62]. Aggregate data, while useful, are often reported poorly, inconsistently (ie. using different measures), or selectively according to which results are significant, further amplifying the problems of publication bias and selective reporting [63]. Here, the use of IPD will allow us to: standardise the data (e.g. of timepoints, units, analysis methods, etc.); use consistent exclusion and inclusion criteria; directly extract data in the required format and deal with missing data appropriately; adjust for baseline (prognostic) factors and individual risk status consistently across studies to increase power and account for potential confounders; and examine complex relationships, multiple timepoints and multiple individual-level factors and their interactions [63].

Potential limitations should be noted. First, IPD meta-analyses are no panacea against poorly designed and conducted primary research. Thus, the strength of the evidence and conclusions drawn from this meta-analysis will depend on the quality of included trials and their data availability. Second, although we will endeavour to identify grey literature and unpublished data as part of the search strategy, publication bias cannot be ruled out. Finally, there is potential for data availability bias if IPD are unavailable for some studies and this

influences our results. To counter this and ensure transparency, we will report findings from meta-analyses with and without IPD and we will contact authors to initiate collaboration and to seek data-sharing agreements to access anonymised data from major trials.

6. CONCLUSIONS

Given the impact of GDM on adverse pregnancy outcomes and the long-term health of both mother and offspring, putting in place simple and effective strategies for prevention and management is crucial. This IPD meta-analysis will provide the most robust evidence to date as to whether metformin is an effective and safe therapy for use in pregnancy and may identify specific subgroups of patients whom may benefit most from this treatment modality. Findings from this meta-analysis will provide much needed evidence to inform appropriate evidence-based clinical and public health actions in this area.

7. ACKNOWLEDGEMENTS

7.1. Author Contributions

We would like to thank Dr Marie Misso for providing expert input into the systematic review methods and for her assistance in refining the search strategy.

AM is project lead, conceptualised and designed the protocol, wrote the first draft of the manuscript and will coordinate the MiPS project. TL, IH, LEM, SMC, LM-P, JST, KT, TR, AS, HS, KN, CB, JEN, JR, JD and WH are key collaborators on the project and members of the MiPS steering committee, contributed to writing and editing the manuscript, and will contribute IPD for the meta-analysis. EV and HT are chair and deputy chair of the MiPS steering committee, respectively, and co-designed the protocol, contributed to writing and editing the manuscript, and will co-lead the project with AM. HT is the study guarantor and will oversee data collection, analysis, and interpretation. All authors meet ICMJE criteria for authorship and have approved the final version for publication.

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7.3. Competing Interests

None declared.

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Supplementary Material

Supplementary Table 1. Primary & secondary outcomes to be extracted/ requested for included studies

- Maternal / birth outcomes
  - **Primary:** maternal glycaemic control (glucose, insulin, and glycosylated haemoglobin [HbA1c], and incidence of hyper/hypoglycaemia) + incidence of GDM in women without GDM
  - gestational weight gain
  - preterm birth (iatrogenic or spontaneous)
  - pregnancy-induced hypertension, pre-eclampsia, and eclampsia
  - mode of birth (spontaneous vaginal, instrumental, caesarean section)
  - maternal satisfaction with experience of pregnancy and birth
  - maternal death
  - maternal obstetric complications (haemorrhage, infection, thrombosis, admission to intensive care unit, incontinence, perineal trauma)
  - maternal adverse events or side effects (gastrointestinal disturbance, vomiting)
  - maternal diabetic complications: diabetic ketoacidosis (DKA), retinopathy, nephropathy, macrovascular disease
  - development of type 2 diabetes during pregnancy or postpartum
- Neonatal outcomes
  - **Primary:** hypoglycaemia, birthweight (and birthweight centile), birth length, head circumference, and gestational age at delivery
  - cord-blood insulin, glucose, and C-peptide
  - miscarriage, stillbirth, neonatal or infant death
  - congenital malformation
  - macrosomia, small for gestational age (SGA), low birthweight
  - shoulder dystocia, birth trauma (bone fracture, nerve palsy)
  - admission and length of stay at different levels of care including neonatal intensive care unit, high-dependency unit, special care unit or transitional care unit
  - Apgar score <7 at 5 min
  - respiratory distress, sepsis, transient heart failure, resuscitation, jaundice, hypocalcaemia, polycythaemia, hypoxic ischaemic encephalopathy, impairment of neurodevelopment.
  - long term infant child outcomes (neurodevelopment/ cognitive, anthropometric, etc)

Supplementary Table 2. Sample search strategy for OVID Medline

1. metformin/	51. randomly.ti,ab.
2. metformin.mp.	52. trial.ti.
3. metformin hydrochloride.mp.	53. or/46-52
4. metformin HCL.mp.	54. exp animals/ not exp humans/
5. hypoglycemic?.mp.	55. 53 not 54
6. hypoglycaemic?.mp.	56. Meta-Analysis as Topic/
7. anti?diabetic?.mp.	57. meta analy$.tw.
8. antihyperglycemic?.mp.	58. metaanaly$.tw.
9. antihyperglycaemic?.mp.	59. Meta-Analysis/
10. glucose?lowering.mp.	60. (systematic adj (review$1 or overview$1)).tw.
11. dimethylbiguanidine.mp.	61. exp Review Literature as Topic/
12. dimethylguanylguanidine.mp.	62. or/56-61
13. glucophage.mp.	63. cochrane.ab.
14. biguanide?.mp.	64. embase.ab.
15. buformin.mp.	65. (psychlit or psyclit).ab.
16. phenformin.mp.	66. (psychinfo or psycinfo).ab.
17. sitagliptin.mp.	67. (cinahl or cinhal).ab.
18. glumetza.mp.	68. science citation index.ab.
19. carbophage.mp.	69. bids.ab.
20. obimet.mp.	70. cancerlit.ab.
21. gluformin.mp.	71. or/63-70
22. dianben.mp.	72. reference list$.ab.
23. diabex.mp.	73. bibliograph$.ab.
24. diaformin.mp.	74. hand-search$.ab.
25. siofor.mp.	75. relevant journals.ab.
26. metfogamma.mp.	76. manual search$.ab.
27. glifor.mp.	77. or/72-76
28. riomet.mp.	78. selection criteria.ab.
29. janumet.mp.	79. data extraction.ab.
30. fortamet.mp.	80. 78 or 79
31. obimet.mp.	81. Review/
32. pregnancy.mp.	82. 80 and 81
33. pregnan?.mp.	83. Comment/
34. reproductive.mp.	84. Letter/
35. maternal.mp.	85. Editorial/
36. neonatal.mp.	86. animal/
37. gestation?.mp.	87. human/
38. infant.mp.	88. 86 not (86 and 87)
39. offspring.mp.	89. or/83-85,88
40. f?etal.mp.	90. 62 or 71 or 77 or 82
41. neonat?.mp.	91. 90 not 89
42. ?natal.mp.	92. 53 or 91
43. gestational diabetes.mp.	93. 45 and 92
44. GDM.mp.	94. limit 93 to humans
45. or/1-44	95. or/1-31
46. randomi?ed controlled trial.pt.	96. or/32-44
47. controlled clinical trial.pt.	97. 95 and 96
48. randomi?ed.ti,ab.	98. 92 and 97
49. placebo.ti,ab.	99. limit 98 to humans
50. clinical trials as topic.sh.	

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
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	NA
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	17
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list	NA

		changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	18
Sponsor	#5b	Provide name for the review funder and / or sponsor	18
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	4-7
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
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	8-9
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	8-9

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	8-9, Suppl Table
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-11
Study records - 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)	9
Study records - 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	10-12
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	10-12, Table 2
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-13, Table 1 and 2
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	11 and 14

Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	12-13
Data synthesis	#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 I2, Kendall's τ)	12-13
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
Data synthesis	#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)	12-13
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14

BMJ Open

Metformin in Pregnancy Study (MiPS): Protocol for a Systematic Review with Individual Patient Data Meta-analysis

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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Diabetes and endocrinology, Pharmacology and therapeutics, Reproductive medicine

Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, OBSTETRICS, PREVENTIVE MEDICINE, REPRODUCTIVE MEDICINE

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Running Title: Protocol for the Metformin in Pregnancy Study (MiPS) international network

Metformin in Pregnancy Study (MiPS): Protocol for a Systematic Review with Individual Patient Data Meta-analysis

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ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) is a common disorder of pregnancy and contributes to adverse pregnancy outcomes. Metformin is often used for the prevention and management of GDM; however, its use in pregnancy continues to be debated. The Metformin in Pregnancy Study (MiPS) aims to utilise individual patient data (IPD) meta-analysis to clarify the efficacy and safety of metformin use in pregnancy and to identify relevant knowledge gaps.

Methods and Analysis: Medline, EMBASE, and all EBM will be systematically searched for randomised controlled trials (RCTs) testing the efficacy of metformin compared with placebo, usual care, or other interventions in pregnant women. Two independent reviewers will assess eligibility using pre-specified criteria and will conduct data extraction and quality appraisal of eligible studies. Authors of included trials will be contacted and asked to contribute IPD. Primary outcomes include maternal glycaemic parameters and GDM, as well as neonatal hypoglycaemia, anthropometry, and gestational age at delivery. Other adverse maternal, birth, and neonatal outcomes will be assessed as secondary outcomes. IPD from these RCTs will be harmonised and a two-step meta-analytic approach will be utilised to determine the efficacy and safety of metformin in pregnancy, with *a priori* adjustment for covariates and subgroups to examine effect-moderators of treatment outcomes. Sensitivity analyses will assess heterogeneity, risk of bias, and the impact of trials which have not provided IPD.

Ethics and Dissemination: All IPD will be de-identified and studies contributing IPD will have ethical approval from their respective local ethics committees. This study will provide robust evidence regarding the efficacy and safety of metformin use in pregnancy, and may identify subgroups of patients who may benefit most from this treatment modality. Findings will be published in peer-reviewed journals and disseminated at scientific meetings, providing much needed evidence to inform clinical and public health actions in this area.

Registration Details: International Prospective Register of Systematic Reviews (PROSPERO) under ID number: 175498.

Strengths and Limitations:

- Important area of research which will inform clinical practice and public health actions in this area;
- Protocol is for the first individual patient data meta-analysis investigating metformin use in pregnancy;
- Employs rigorous methodology and a comprehensive search strategy to provide the most robust evidence to date;
- Limitations include potential for publication bias or data availability bias if IPD is not available for some studies or outcomes.

Keywords: metformin, insulin, oral hypoglycaemic drugs, gestational diabetes, pregnancy, maternal outcomes, neonatal outcomes.

1. INTRODUCTION

Pregnancy is a period of major anatomic and physiological changes, with heightened metabolic demands on both mother and fetus. Gestational diabetes mellitus (GDM) is a common metabolic disorder of pregnancy with global prevalence estimates varying by country, from <1% in Croatia to 28% in India [1]. The incidence of GDM is increasing in line with obesity and advanced maternal age [2]. Elevated maternal glucose concentrations and GDM increase the risk for adverse pregnancy outcomes including pre-eclampsia, macrosomia and fetal abnormalities, and GDM itself is the strongest population predictor of type 2 diabetes (T2D) [3]. Increasing evidence suggests that fetal exposure to hyperglycaemia *in utero* increases the risk of obesity and T2D in adulthood [4]. Effective strategies for the prevention and/or treatment of GDM and its associated complications are therefore of paramount importance.

Metformin, a biguanide compound and first-line treatment for T2D, offers opportunities for preventing and treating GDM, although its role in pregnancy is debated due to the known placental transfer of metformin to the fetus [5,6]. Metformin exerts its clinical effects by reducing hepatic glucose output and increasing insulin sensitivity, leading to lower glucose concentrations without an increased risk of hypoglycaemia or weight gain [3]. Although metformin crosses the placenta, to date it has been shown to be safe, generally well-tolerated and preferred by women over insulin [7,8]. In the UK and New Zealand, clinical guidelines recommend the use of metformin as initial glucose-lowering treatment in women with GDM if lifestyle interventions are unsuccessful in maintaining glycaemic targets [9]. However, in Australia and the US, lifestyle and insulin remain the mainstay for GDM therapy and metformin is used on a case-by-case basis at the clinician's discretion [5,6]. Concerns around the use of metformin in pregnancy include a lack of conclusive evidence regarding its efficacy and safety for preventing or treating GDM. Despite many published studies over the last four decades, there have been no placebo-controlled trials with GDM or glucose regulation as the

primary endpoint. This is an important gap in the evidence given that introducing a medication or treatment in pregnancy can have a powerful placebo effect. Also more recently, a number of follow up studies have suggested potential longer term adverse child health implications of metformin use in pregnancy, although confirmation of these effects requires further study [10].

Regarding the use of metformin for the treatment of GDM, early observational studies by Coetzee and colleagues [5,11,12] in South Africa showed that metformin improved glycaemic control in women with GDM and subsequently reduced fetal anomalies and perinatal mortality. However, controversies regarding whether metformin was a safe and viable option for the treatment of GDM continued. This was particularly relevant in the context of poorly-resourced countries where low health literacy and high costs of insulin are problematic [5,6]. In 2008, Rowan et al. [13] published the landmark MiG (Metformin in GDM) trial and found that, in 751 women randomised to metformin or insulin, there were no differences in the primary outcome - a composite of neonatal hypoglycaemia, respiratory distress, need for phototherapy, Apgar score <7 at 5 min and preterm birth. Secondary outcomes including neonatal anthropometry also did not differ between groups; however, severe neonatal hypoglycaemia (<1.6 mmol/L) was reduced with metformin compared with insulin [13]. It should be noted that 46.3% of women in the metformin group required supplemental insulin treatment to maintain glycaemic control [13]. A large number of RCTs and meta-analyses have since been published, with many showing that particularly in cases of mild GDM, metformin is as effective as insulin in controlling GDM and preventing fetal, maternal and neonatal complications [7,14-27]. Yet, some have reported that metformin increased the risk of preterm birth compared with insulin [7], while others found a decreased risk of pregnancy-induced hypertension [20,27], neonatal death, or serious comorbidity [14] with metformin compared with insulin or other oral hypoglycaemic drugs. Ongoing trials which are sufficiently powered, such as the SUGAR-DIP trial [28] which aims to recruit 810 women with GDM, should be able to shed some light on the impact of metformin on some of these pregnancy outcomes.

In addition to treating GDM, the potential role of metformin as a GDM prevention strategy has also been proposed. Evidence regarding metformin exposure in early pregnancy and its role in GDM prevention began developing when metformin use became more common in the treatment of polycystic ovary syndrome (PCOS). However, observational studies (primarily retrospective), RCTs and meta-analyses in women with PCOS have produced conflicting findings. Some report that metformin reduced the risk of GDM, early pregnancy loss, preterm delivery and pre-eclampsia [29-34], and others report no effects on some or all of these outcomes [29,35,36]. Most of these studies were designed to assess metformin use for ovulation, pregnancy rates and live births rather than for pregnancy complications, and existing meta-analyses have been of variable quality. A recent study which combined three RCTs totalling 800 women with PCOS randomized to metformin or placebo during pregnancy did not show any improvement in glucose homeostasis or reduction in GDM or need for insulin therapy, despite the lower gestational weight gain in the metformin group [37]. Notably, exposure to metformin in early pregnancy was not associated with teratogenic effects or increased risk of miscarriage in any of these studies to date, or in a recent case-control study of >50,000 babies with congenital anomalies [8].

Use of metformin for preventing GDM has also been explored in recent RCTs of overweight or obese non-diabetic pregnancies [38-40]. Two trials in the UK [38,40] examined metformin versus placebo in obese pregnancies, while the GRoW trial in Australia [39] examined whether the use of metformin as an adjunct therapy to dietary and lifestyle advice in overweight or obese pregnancies was effective in improving maternal, fetal and infant health outcomes. All three trials reported that metformin had no effect on the primary outcome of neonatal birthweight compared with placebo [38-40], despite reduced gestational weight gain with metformin in two trials [39,40]. No effects on glycaemic outcomes including incidence of GDM were found; however, all trials were not powered to detect differences in these outcomes [38,40]. Another RCT in non-diabetic women with pregestational insulin resistance reported

no effect of metformin in the prevention of GDM compared with placebo [41]. The relatively small sample size (n=111) and high drop out rate (23%) may have influenced these results [41].

Overall, there is substantial heterogeneity in the designs, participant characteristics and methodological rigour of existing studies, precluding firm conclusions regarding the efficacy and safety of metformin use in pregnancy. Although several meta-analyses have been conducted, most have targeted women with PCOS and all have used aggregate data, which may be subject to ecological bias and study-level confounding. Here, we aim to address these knowledge gaps by conducting a comprehensive systematic review incorporating meta-analyses of individual patient data (IPD). Using these data, we will test the hypothesis that metformin in pregnancy is a safe and effective strategy for improving maternal and neonatal glycaemic outcomes. Use of IPD will allow adjustment for differences in participant characteristics including maternal demographics, baseline glucose concentrations and use of supplemental insulin, and it can also identify subgroups of women who may benefit from metformin treatment in pregnancy.

2. SYSTEMATIC REVIEW QUESTION

Is metformin use in pregnancy effective and safe versus placebo, usual care, or other pharmacological or non-pharmacological interventions in:

a) women with GDM for improving glycaemic, maternal and/or neonatal adverse outcomes?

b) women without GDM for improving glycaemic, maternal and/or neonatal adverse outcomes?

3. METHODS AND ANALYSIS

This review will adopt rigorous international gold standard methodology as outlined in the Cochrane Library and Centre for Evidence-based Medicine guidelines [42,43], and will conform to the standards of the Preferred Reporting Items for Systematic Reviews and Meta-

analyses of IPD Statement (PRISMA-IPD) [44]. The protocol for this systematic review has been submitted for registration on PROSPERO under the ID number: 175498.

3.1. Eligibility Criteria

Selection criteria established *a priori* using the PICO (Population, Intervention, Comparison, Outcomes) framework in **Table 1** will be used to determine eligibility of articles.

3.2. Search Strategy

A systematic search will be developed using relevant search terms (Supplementary Material) in accordance with the selection criteria (Table 1), and the following electronic databases will be searched:

- MEDLINE via OVID
- Medline in-process and other non-indexed citations via OVID
- EMBASE via OVID
- All Evidence Based Medicine (EBM) Reviews via OVID incorporating: The Cochrane Library; Cochrane Database of Systematic Reviews (Cochrane Reviews); Database of Abstracts of Reviews of Effects (Other Reviews); Cochrane Central Register of Controlled Trials (Clinical Trials); Cochrane Database of Methodology Reviews (Methods Reviews); The Cochrane Methodology Register (Methods Studies); Health Technology Assessment Database (Technology Assessments); NHS Economic Evaluation Database (Economic Evaluations); and ACP Journal Club.

Table 1. PICO for study inclusion

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)
Inclusion	Pregnant women of any age, ethnicity, socio-economic status, geographic area, co-morbidity, or gestational age	Metformin administered in any form and route, alone or combined with other intervention/s, of any dosage and for any duration	Placebo, usual care and/or other pharmacological or non-pharmacological interventions including insulin, lifestyle intervention/s, or other oral hypoglycaemic agents (sulfonylureas, acarbose, glibenclamide/ glyburide)	**Primary Maternal Outcomes:** Glycaemic control (glucose, insulin, HbA1c); incidence of GDM* or hyper/hypoglycaemia* **Primary Neonatal Outcomes:** hypoglycaemia*, birthweight, birth length, head circumference and gestational age at delivery **Secondary Outcomes:** Other maternal, birth and neonatal outcomes including miscarriage, birth defects, GWG, pre-eclampsia/ eclampsia, LGA/ macrosomia, SGA and PTB (see full list in Supplementary Material)

Exclusion	Studies in non-pregnant populations	Studies without a metformin therapy arm	Studies without a control or comparison arm	Studies without clinical outcomes (mechanistic studies)
Study type	Systematic reviews of RCTs and RCTs			
Language	No limit			
Year of publication	No limit			

*as defined by authors and using the criteria selected in individual studies. **GDM**, gestational diabetes mellitus; **GWG**, gestational weight gain; **HbA1c**, haemoglobin A1c, **LGA/SGA**, large/small for gestational age; **LBW**, low birthweight; **PTB**, preterm birth; **RCTs**, randomized controlled trials.

Bibliographies and citations of all relevant studies identified by the search strategy and relevant reviews/ meta-analyses will be examined for identification of additional studies. Google will be used to manually search for grey literature (ie, material not published in recognized or indexed scientific journals). Unpublished or ongoing studies will be identified via manual searching of the National Institute of Health Clinical Trials Registry (https://clinicaltrials.gov/) and the Australian New Zealand Clinical Trials Registry (ANZCTR) (https://www.anzctr.org.au).

3.3. Study Selection

To determine eligible studies, one reviewer will scan the titles, abstracts and keywords of every record retrieved by the search strategy using the selection criteria outlined in Table 1 and in consultation with a second reviewer. Disagreement will be resolved by discussion and consensus, otherwise referred to a third reviewer. All articles which appear to meet the selection criteria will be retrieved for full text assessment, and articles with insufficient information in the titles and abstracts will also be retrieved in full text to clarify eligibility. Studies excluded based on full text will be recorded with reasons for their exclusion.

3.4. Data Extraction

Using a specifically developed data extraction form, two independent reviewers will extract data from all included studies. Pilot testing of the extraction form will be conducted using 3-4 studies to ensure all required data is captured. Computed data entries will be cross-checked for meta-analyses where required. Pre-specified data will be extracted in aggregate

format from all published studies (**Table 2**). Relevant data will also be requested in IPD format from all authors along with any study or treatment protocol details not reported in published studies (Table 2).

- ***Aggregate Data Extraction:***

For each treatment group, extracted data will include sample sizes, aggregate point estimates and measures of variability, frequency counts for dichotomous variables, and intention-to-treat analysis. For outcomes reported as continuous variables, the aggregate mean values with standard deviations (SD) or confidence intervals will be extracted and used to measure the effects. Where standard errors (SE) are reported, these will be converted to SD using the formula: $SE \times \sqrt{n}$. For outcomes reported as dichotomous variables, relative measures of risk (risk ratio or odds ratio along with confidence intervals), or absolute numbers of patients experiencing at least one episode of the outcome of interest will be extracted and used in the analyses.

Table 2. Data to be extracted in aggregate and IPD format from included studies

Study	Participants	Intervention/ Control	Primary Outcomes†	Secondary Outcomes
First author and Journal/ Source	Maternal age, parity, ethnicity, and gestational age at enrolment	Metformin treatment protocols (dose, including graded dosing, frequency, duration)	Maternal glycaemic control (fasting and postprandial/post-challenge glucose; insulin; and HbA1c) at any/ all timepoints	All other maternal, birth and neonatal outcomes reported in individual studies (Supplementary Material)
Country and year of publication	Maternal anthropometry (BMI, weight, GWG)	Regimens for each control or comparator group.	Incidence of GDM* and/or maternal hyper/hypoglycaemia*	Long term infant/child outcomes
Study design, setting and sample size	Smoking status and use of medications, supplements, or substances	Use of supplemental insulin	Incidence of neonatal hypoglycaemia*	Development of T2D (in pregnancy or postpartum)
Follow up duration	Disease status (pre-existing T2D, GDM, PCOS, etc)	Use of other pharmacological or non-pharmacological co-interventions	Birthweight, birth length and head circumference, and gestational age at delivery*	Patient satisfaction with experience/ treatment
Inclusion/ exclusion and diagnostic criteria	Comorbidities, history of GDM or family history of diabetes	Number analysed per group and ITT analysis		Adverse events/ side effects occurring during the study

Primary outcome*				

*as defined by authors of individual studies which may be based on clinical diagnosis (separate analyses will be performed for different GDM diagnostic criteria) or in the case of gestational age, this may be based on ultrasound measurements, last menstrual cycle, self report, etc.
†baseline, follow up and delta values will be collected for all continuous primary maternal outcomes.
BMI, body mass index; **GDM**, gestational diabetes mellitus; **GWG**, gestational weight gain; **HbA1c**, haemoglobin A1c; **ITT**, intention to treat; **PCOS**, polycystic ovary syndrome, **T2D**, type 2 diabetes.

- ***Individual Patient Data Collection:***

Corresponding and/or lead authors will be contacted and asked to provide fully anonymised data for IPD meta-analyses. Data for participant characteristics and primary and secondary outcomes (as specified in Table 2 and Supplementary Material) will be requested for each patient, in addition to data on supplemental insulin use (or other co-interventions) if individual-level data for these parameters were recorded. These data will be used to conduct stratified and subgroup analyses at the patient level, in particular by baseline body mass index (BMI) and baseline glucose concentrations, as well as by maternal age, parity, ethnicity, previous history of GDM, gestational weight gain and supplemental insulin use.

A formatted template detailing the requested data and recommended coding will be created and sent to authors; however, data will be accepted in any suitable electronic format. All data will be checked to ensure correct coding, consistency with published results and accuracy of extreme values and to identify missing data, and any issues will be queried and rectified as necessary. A single database will be created by the study investigators to incorporate data from all trials in consistent fields and standardised formats (as much as possible). Studies which are excluded or where IPD is not available will be tabulated with reasons, and aggregate data will be used where appropriate.

3.5. Quality appraisal of the evidence

Risk of bias of included studies will be assessed at the study-level by two independent reviewers. Using a critical appraisal template [45] (adapted from the Cochrane risk of bias tool [46]) with predetermined criteria, each study will be allocated a high, moderate, or low

risk of bias rating. Individual quality items will be assessed using a descriptive component approach that includes items such as conflict of interest of authors, presence of pre-specified selection criteria, methods of randomisation and allocation of participants to study groups, blinding of participants, carers, investigators or outcome assessors, methods of outcome assessment and reporting, and statistical issues such as powering and methods of data analysis. Disagreement will be resolved by consensus.

3.6. Data analysis & synthesis

Our IPD analysis will follow a two-step meta-analytical approach where possible to automatically account for clustering of participants within studies [47]. In this approach, IPD analyses will be conducted to generate estimates of the intervention effect for each study separately. These effect estimates will then be pooled and analysed using conventional meta-analyses with inverse-variance weighted models (DerSimonian and Laird random-effects models) to account for between-study variability [47]. Where IPD is derived from a small number of studies or for binary outcome data where the event risk is low or the sample size is small, a one-step IPD approach will be used (IPD from all studies are modelled simultaneously). Stratified analysis by study will be performed to account for participant clustering in the one-step approach [47,48]. If IPD is only available for some studies, we will combine aggregate data with the available IPD to compare results from analyses including and excluding IPD [49,50]. This approach will allow the effect of non-IPD studies on meta-analysis conclusions to be quantified and displayed transparently. For outcomes with no IPD available, aggregate effect measures and random-effects models will be used for meta-analyses where appropriate, provided that data are derived from clinically homogeneous groups (where participants, interventions and outcome measures are sufficiently similar).

Dichotomous outcomes will be presented as relative risks/ risk ratios with 95% confidence intervals and continuous outcomes will be presented as weighted mean differences (WMD) with 95% confidence intervals. Where outcome measures or study

methods differ substantially, data will be analysed in line with Cochrane guidelines [42], using random-effects models and Cohen *d* to calculate the standardised mean difference (SMD). All meta-analyses will be conducted on Review Manager 5.3 and IPD data will be initially analysed in Stata V.15 and then imported into Review Manager. Comprehensive Meta-analysis V.3 software will be used for meta-regression (if applicable) and assessment of publication bias. *P*-values <0.05 will indicate statistical significance. Statistical heterogeneity will be assessed using the I^2 test, where I^2 values over 50% will be considered as moderate to high heterogeneity. Descriptive analyses will be conducted for those studies which are deemed clinically heterogeneous or present insufficient IPD or aggregate data for pooling.

- ***Subgroup and sensitivity analyses:***

Subgroup analyses and, where applicable, multivariable meta-analyses or meta-regression will be performed for factors presumed to cause heterogeneity or variations in outcomes. Pre-specified variables to be accounted for will include maternal age, ethnicity, comorbidity/ disease status, baseline BMI and glucose concentrations, previous history of GDM or other relevant pregnancy complication/s, dose and duration of metformin therapy, use of supplemental insulin, and gestational age at commencement of therapy. These variables were selected on the basis of evidence showing that the benefits of metformin therapy may vary by these factors [51-53]. Diagnostic criteria for GDM will also be explored for studies measuring incidence of GDM as an outcome. The exact variables to be explored will be selected after data collation but prior to any analyses and will be justified by biological reasoning. Caution will be used in interpretation of subgroup results and adjustment for multiple testing will be considered as necessary. IPD meta-analyses generally have increased power to detect genuine subgroup effects; however, we will assess whether subgroup effects are consistent within individual studies, if deemed necessary. Any post-hoc subgroup analyses will be considered hypothesis-generating for the purpose of planning and designing future studies. Meta-regression and/or multivariable meta-analyses using linear or

logistic regression estimates will be used where appropriate to adjust for the above covariates and to synthesise multiple interaction estimates from each study, accounting for their correlations.

Sensitivity analyses will be conducted and factors to be included will be determined during the review process. Heterogeneity (I^2 >50%) will be explored through sensitivity analysis using risk of bias and IPD availability. For IPD and aggregate meta-analyses incorporating more than three studies, funnel plot asymmetry and Egger [54] and Begg [55] statistical tests will be used to determine small study effects and potential publication bias [56,57].

3.7. Grading the body of evidence

Quality of the evidence will be assessed at the outcome-level by two independent reviewers and rated as high, moderate, low, or very low using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [58]. These ratings will be based on risk of bias, imprecision, heterogeneity, indirectness, and suspicion of publication bias. Availability of IPD and presence of selection or publication bias for IPD studies will also be incorporated into quality assessments in line with PRISMA-IPD guidelines [44]. Disagreements will be resolved by discussion and consultation with a third reviewer where needed.

3.8. Presentation of Findings

Data will be presented in summary tables and in narrative format to describe the populations, interventions and outcomes of the included studies. Forest plots and funnel plots will be used to present results from meta-analyses and publication bias assessments, respectively. Where necessary, results with and without IPD will be presented for comparison. Both aggregate and IPD meta-analyses processes, including results, will be reported according to PRISMA [59] and PRISMA-IPD [44] guidelines.

4.0. ETHICS AND DISSEMINATION

Ethical approval is not required for aggregate data meta-analyses. Individual trials contributing primary data for IPD meta-analyses will have ethical approval from their respective Human Research Ethics Committees in the countries where the studies took place. All data from primary trials will be fully anonymised prior to being imported into our database.

Findings will be disseminated via publications in peer-reviewed journals and presentations at scientific meetings. If deemed appropriate, findings will also be communicated at meetings and forums to relevant stakeholders to guide clinical practice and public health actions in this area.

4.1. Data availability statement

No data has been generated or analysed in this manuscript.

4.2. Patient and public involvement statement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

5. DISCUSSION

GDM is one of the most common complications of pregnancy and contributes to adverse perinatal outcomes, as well as long-term risk of obesity and T2D in the offspring [60]. Although metformin is often prescribed (in addition to lifestyle intervention) in the clinical treatment of GDM, its efficacy and safety in pregnancy continues to be debated [9,61]. Recent RCTs have provided much-needed evidence in this field; however, heterogeneity in study designs, participant characteristics and methodological quality have made it difficult to draw firm conclusions from the available evidence. Moreover, whether metformin may be beneficial in women without GDM for the prevention of glycaemic and other adverse outcomes remains uncertain.

To the best of our knowledge, this will be the most comprehensive systematic review investigating the use of metformin for preventing or treating GDM and other pregnancy complications. It is also the only review in this area to incorporate an IPD meta-analysis examining whether the effects of metformin, if any, are independent of potential confounders and whether they may be specific to certain subgroups of women. Our systematic review process will have several strengths, including the use of rigorous methodology, pre-specified criteria and pre-determined primary and secondary outcomes in order to establish the efficacy and safety of metformin in a variety of population groups. The IPD component of this study will involve acquiring, cleaning, standardising and synthesizing raw data from existing studies. Although this is an intensive process, it is more feasible and less costly than large-scale RCTs and avoids the ethical problem of research waste [62], thus it is considered the gold-standard approach to evidence synthesis [44]. This approach is particularly important in reviewing controversial therapeutic areas and can provide level 1 evidence to guide clinical practice [44].

In contrast to standard aggregate data meta-analysis, using individual-level data enables a more detailed assessment of risk of bias and, more importantly for this study, it provides more power to detect subgroups of interest and to examine effect modifiers at the individual level, which would otherwise require a very large and costly study [63]. Aggregate data, while useful, are often reported poorly, inconsistently (ie. using different measures), or selectively according to which results are significant, further amplifying the problems of publication bias and selective reporting [64]. Here, the use of IPD will allow us to: standardise the data (e.g. of timepoints, units, analysis methods, etc.); use consistent exclusion and inclusion criteria; directly extract data in the required format and deal with missing data appropriately; adjust for baseline (prognostic) factors and individual risk status consistently across studies to increase power and account for potential confounders; and

examine complex relationships, multiple timepoints and multiple individual-level factors and their interactions [64].

Potential limitations should be noted. First, IPD meta-analyses are no panacea against poorly designed and conducted primary research. Thus, the strength of the evidence and conclusions drawn from this meta-analysis will depend on the quality of included trials and their data availability. Second, although we will endeavour to identify grey literature and unpublished data as part of the search strategy, publication bias cannot be ruled out. Finally, there is potential for data availability bias if IPD are unavailable for some studies and this influences our results. To counter this and ensure transparency, we will report findings from meta-analyses with and without IPD and we will contact authors to initiate collaboration and to seek data-sharing agreements to access anonymised data from major trials.

6. CONCLUSIONS

Given the impact of GDM on adverse pregnancy outcomes and the long-term health of both mother and offspring, putting in place simple and effective strategies for prevention and management is crucial. This IPD meta-analysis will provide the most robust evidence to date as to whether metformin is an effective and safe therapy for use in pregnancy and may identify specific subgroups of patients whom may benefit most from this treatment modality. Findings from this meta-analysis will provide much needed evidence to inform appropriate evidence-based clinical and public health actions in this area.

7. ACKNOWLEDGEMENTS

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7.1. Author Contributions

AM is project lead, conceptualised and designed the protocol, wrote the first draft of the manuscript and will coordinate the MiPS project. TL, IH, SMC, LM-P, KT, TR, AS, KN, HS,

CB, JEN, JR, JD and WH are key collaborators on the project and members of the MiPS steering committee, contributed to writing and editing the manuscript, and will contribute IPD for the meta-analysis. EV and HT are chair and deputy chair of the MiPS steering committee, respectively, and co-designed the protocol, contributed to writing and editing the manuscript, and will co-lead the project with AM. HT is the study guarantor and will oversee data collection, analysis, and interpretation. All authors meet ICMJE criteria for authorship and have approved the final version for publication.

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7.3. Competing Interests

None declared.

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Supplementary Material

Supplementary Table 1. Primary & secondary outcomes to be extracted/ requested for included studies

- Maternal / birth outcomes
  - **Primary:** maternal glycaemic control (glucose, insulin, and glycosylated haemoglobin [HbA1c], and incidence of hyper/hypoglycaemia) + incidence of GDM in women without GDM
  - gestational weight gain
  - preterm birth (iatrogenic or spontaneous)
  - pregnancy-induced hypertension, pre-eclampsia, and eclampsia
  - mode of birth (spontaneous vaginal, instrumental, caesarean section)
  - maternal satisfaction with experience of pregnancy and birth
  - maternal death
  - maternal obstetric complications (haemorrhage, infection, thrombosis, admission to intensive care unit, incontinence, perineal trauma)
  - maternal adverse events or side effects (gastrointestinal disturbance, vomiting)
  - maternal diabetic complications: diabetic ketoacidosis (DKA), retinopathy, nephropathy, macrovascular disease
  - development of type 2 diabetes during pregnancy or postpartum
- Neonatal outcomes
  - **Primary:** hypoglycaemia, birthweight (and birthweight centile), birth length, head circumference, and gestational age at delivery
  - cord-blood insulin, glucose, and C-peptide
  - miscarriage, stillbirth, neonatal or infant death
  - congenital malformation
  - macrosomia, small for gestational age (SGA), low birthweight
  - shoulder dystocia, birth trauma (bone fracture, nerve palsy)
  - admission and length of stay at different levels of care including neonatal intensive care unit, high-dependency unit, special care unit or transitional care unit
  - Apgar score <7 at 5 min
  - respiratory distress, sepsis, transient heart failure, resuscitation, jaundice, hypocalcaemia, polycythaemia, hypoxic ischaemic encephalopathy, impairment of neurodevelopment.
  - long term infant child outcomes (neurodevelopment/ cognitive, anthropometric, etc)

Supplementary Table 2. Sample search strategy for OVID Medline

1. metformin/	51. randomly.ti,ab.
2. metformin.mp.	52. trial.ti.
3. metformin hydrochloride.mp.	53. or/46-52
4. metformin HCL.mp.	54. exp animals/ not exp humans/
5. hypoglycemic?.mp.	55. 53 not 54
6. hypoglycaemic?.mp.	56. Meta-Analysis as Topic/
7. anti?diabetic?.mp.	57. meta analy$.tw.
8. antihyperglycemic?.mp.	58. metaanaly$.tw.
9. antihyperglycaemic?.mp.	59. Meta-Analysis/
10. glucose?lowering.mp.	60. (systematic adj (review$1 or overview$1)).tw.
11. dimethylbiguanidine.mp.	61. exp Review Literature as Topic/
12. dimethylguanylguanidine.mp.	62. or/56-61
13. glucophage.mp.	63. cochrane.ab.
14. biguanide?.mp.	64. embase.ab.
15. buformin.mp.	65. (psychlit or psyclit).ab.
16. phenformin.mp.	66. (psychinfo or psycinfo).ab.
17. sitagliptin.mp.	67. (cinahl or cinhal).ab.
18. glumetza.mp.	68. science citation index.ab.
19. carbophage.mp.	69. bids.ab.
20. obimet.mp.	70. cancerlit.ab.
21. gluformin.mp.	71. or/63-70
22. dianben.mp.	72. reference list$.ab.
23. diabex.mp.	73. bibliograph$.ab.
24. diaformin.mp.	74. hand-search$.ab.
25. siofor.mp.	75. relevant journals.ab.
26. metfogamma.mp.	76. manual search$.ab.
27. glifor.mp.	77. or/72-76
28. riomet.mp.	78. selection criteria.ab.
29. janumet.mp.	79. data extraction.ab.
30. fortamet.mp.	80. 78 or 79
31. obimet.mp.	81. Review/
32. pregnancy.mp.	82. 80 and 81
33. pregnan?.mp.	83. Comment/
34. reproductive.mp.	84. Letter/
35. maternal.mp.	85. Editorial/
36. neonatal.mp.	86. animal/
37. gestation?.mp.	87. human/
38. infant.mp.	88. 86 not (86 and 87)
39. offspring.mp.	89. or/83-85,88
40. f?etal.mp.	90. 62 or 71 or 77 or 82
41. neonat?.mp.	91. 90 not 89
42. ?natal.mp.	92. 53 or 91
43. gestational diabetes.mp.	93. 45 and 92
44. GDM.mp.	94. limit 93 to humans
45. or/1-44	95. or/1-31
46. randomi?ed controlled trial.pt.	96. or/32-44
47. controlled clinical trial.pt.	97. 95 and 96
48. randomi?ed.ti,ab.	98. 92 and 97
49. placebo.ti,ab.	99. limit 98 to humans
50. clinical trials as topic.sh.	

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
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	NA
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	17
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list	NA

		changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	18
Sponsor	#5b	Provide name for the review funder and / or sponsor	18
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	4-7
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
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	8-9
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	8-9

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	8-9, Suppl Table
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-11
Study records - 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)	9
Study records - 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	10-12
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	10-12, Table 2
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-13, Table 1 and 2
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	11 and 14

Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	12-13
Data synthesis	#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 I2, Kendall's τ)	12-13
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
Data synthesis	#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)	12-13
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14

BMJ Open

Metformin in Pregnancy Study (MiPS): Protocol for a Systematic Review with Individual Patient Data Meta-analysis

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Running Title: Protocol for the Metformin in Pregnancy Study (MiPS) international network

Metformin in Pregnancy Study (MiPS): Protocol for a Systematic Review with Individual Patient Data Meta-analysis

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ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) is a common disorder of pregnancy and contributes to adverse pregnancy outcomes. Metformin is often used for the prevention and management of GDM; however, its use in pregnancy continues to be debated. The Metformin in Pregnancy Study (MiPS) aims to utilise individual patient data (IPD) meta-analysis to clarify the efficacy and safety of metformin use in pregnancy and to identify relevant knowledge gaps.

Methods and Analysis: Medline, EMBASE, and all EBM will be systematically searched for randomised controlled trials (RCTs) testing the efficacy of metformin compared with placebo, usual care, or other interventions in pregnant women. Two independent reviewers will assess eligibility using pre-specified criteria and will conduct data extraction and quality appraisal of eligible studies. Authors of included trials will be contacted and asked to contribute IPD. Primary outcomes include maternal glycaemic parameters and GDM, as well as neonatal hypoglycaemia, anthropometry, and gestational age at delivery. Other adverse maternal, birth, and neonatal outcomes will be assessed as secondary outcomes. IPD from these RCTs will be harmonised and a two-step meta-analytic approach will be utilised to determine the efficacy and safety of metformin in pregnancy, with *a priori* adjustment for covariates and subgroups to examine effect-moderators of treatment outcomes. Sensitivity analyses will assess heterogeneity, risk of bias, and the impact of trials which have not provided IPD.

Ethics and Dissemination: All IPD will be de-identified and studies contributing IPD will have ethical approval from their respective local ethics committees. This study will provide robust evidence regarding the efficacy and safety of metformin use in pregnancy, and may identify subgroups of patients who may benefit most from this treatment modality. Findings will be published in peer-reviewed journals and disseminated at scientific meetings, providing much needed evidence to inform clinical and public health actions in this area.

Strengths and limitations of this study:

- Important area of research which will inform clinical practice and public health actions in this field;
- Protocol is for the first individual patient data meta-analysis investigating metformin use in pregnancy;
- Employs rigorous methodology and a comprehensive search strategy to provide the most robust evidence to date;
- Limitations include potential for publication bias or data availability bias if IPD is not available for some studies or outcomes.

Keywords: metformin, insulin, oral hypoglycaemic drugs, gestational diabetes, pregnancy, maternal outcomes, neonatal outcomes.

1. INTRODUCTION

Pregnancy is a period of major anatomic and physiological changes, with heightened metabolic demands on both mother and fetus. Gestational diabetes mellitus (GDM) is a common metabolic disorder of pregnancy with global prevalence estimates varying by country, from <1% in Croatia to 28% in India [1]. The incidence of GDM is increasing in line with obesity and advanced maternal age [2]. Elevated maternal glucose concentrations and GDM increase the risk for adverse pregnancy outcomes including pre-eclampsia, macrosomia and fetal abnormalities, and GDM itself is the strongest population predictor of type 2 diabetes (T2D) [3]. Increasing evidence suggests that fetal exposure to hyperglycaemia *in utero* increases the risk of obesity and T2D in adulthood [4]. Effective strategies for the prevention and/or treatment of GDM and its associated complications are therefore of paramount importance.

Metformin, a biguanide compound and first-line treatment for T2D, offers opportunities for preventing and treating GDM, although its role in pregnancy is debated due to the known placental transfer of metformin to the fetus [5,6]. Metformin exerts its clinical effects by reducing hepatic glucose output and increasing insulin sensitivity, leading to lower glucose concentrations without an increased risk of hypoglycaemia or weight gain [3]. Although metformin crosses the placenta, to date it has been shown to be safe, generally well-tolerated and preferred by women over insulin [7,8]. In the UK and New Zealand, clinical guidelines recommend the use of metformin as initial glucose-lowering treatment in women with GDM if lifestyle interventions are unsuccessful in maintaining glycaemic targets [9]. However, in Australia and the US, lifestyle and insulin remain the mainstay for GDM therapy and metformin is used on a case-by-case basis at the clinician's discretion [5,6]. Concerns around the use of metformin in pregnancy include a lack of conclusive evidence regarding its efficacy and safety for preventing or treating GDM. Despite many published studies over the last four decades, there have been no placebo-controlled trials with GDM or glucose regulation as the

primary endpoint. This is an important gap in the evidence given that introducing a medication or treatment in pregnancy can have a powerful placebo effect. Also more recently, a number of follow up studies have suggested potential longer term adverse child health implications of metformin use in pregnancy, although confirmation of these effects requires further study [10].

Regarding the use of metformin for the treatment of GDM, early observational studies by Coetzee and colleagues [5,11,12] in South Africa showed that metformin improved glycaemic control in women with GDM and subsequently reduced fetal anomalies and perinatal mortality. However, controversies regarding whether metformin was a safe and viable option for the treatment of GDM continued. This was particularly relevant in the context of poorly-resourced countries where low health literacy and high costs of insulin are problematic [5,6]. In 2008, Rowan et al. [13] published the landmark MiG (Metformin in GDM) trial and found that, in 751 women randomised to metformin or insulin, there were no differences in the primary outcome - a composite of neonatal hypoglycaemia, respiratory distress, need for phototherapy, Apgar score <7 at 5 min and preterm birth. Secondary outcomes including neonatal anthropometry also did not differ between groups; however, severe neonatal hypoglycaemia (<1.6 mmol/L) was reduced with metformin compared with insulin [13]. It should be noted that 46.3% of women in the metformin group required supplemental insulin treatment to maintain glycaemic control [13]. A large number of RCTs and meta-analyses have since been published, with many showing that particularly in cases of mild GDM, metformin is as effective as insulin in controlling GDM and preventing fetal, maternal and neonatal complications [7,14-27]. Yet, some have reported that metformin increased the risk of preterm birth compared with insulin [7], while others found a decreased risk of pregnancy-induced hypertension [20,27], neonatal death, or serious comorbidity [14] with metformin compared with insulin or other oral hypoglycaemic drugs. Ongoing trials which are sufficiently powered, such as the SUGAR-DIP trial [28] which aims to recruit 810 women with GDM, should be able to shed some light on the impact of metformin on some of these pregnancy outcomes.

In addition to treating GDM, the potential role of metformin as a GDM prevention strategy has also been proposed. Evidence regarding metformin exposure in early pregnancy and its role in GDM prevention began developing when metformin use became more common in the treatment of polycystic ovary syndrome (PCOS). However, observational studies (primarily retrospective), RCTs and meta-analyses in women with PCOS have produced conflicting findings. Some report that metformin reduced the risk of GDM, early pregnancy loss, preterm delivery and pre-eclampsia [29-34], and others report no effects on some or all of these outcomes [29,35,36]. Most of these studies were designed to assess metformin use for ovulation, pregnancy rates and live births rather than for pregnancy complications, and existing meta-analyses have been of variable quality. A recent study which combined three RCTs totalling 800 women with PCOS randomized to metformin or placebo during pregnancy did not show any improvement in glucose homeostasis or reduction in GDM or need for insulin therapy, despite the lower gestational weight gain in the metformin group [37]. Notably, exposure to metformin in early pregnancy was not associated with teratogenic effects or increased risk of miscarriage in any of these studies to date, or in a recent case-control study of >50,000 babies with congenital anomalies [8].

Use of metformin for preventing GDM has also been explored in recent RCTs of overweight or obese non-diabetic pregnancies [38-40]. Two trials in the UK [38,40] examined metformin versus placebo in obese pregnancies, while the GRoW trial in Australia [39] examined whether the use of metformin as an adjunct therapy to dietary and lifestyle advice in overweight or obese pregnancies was effective in improving maternal, fetal and infant health outcomes. All three trials reported that metformin had no effect on the primary outcome of neonatal birthweight compared with placebo [38-40], despite reduced gestational weight gain with metformin in two trials [39,40]. No effects on glycaemic outcomes including incidence of GDM were found; however, all trials were not powered to detect differences in these outcomes [38,40]. Another RCT in non-diabetic women with pregestational insulin resistance reported

no effect of metformin in the prevention of GDM compared with placebo [41]. The relatively small sample size (n=111) and high drop out rate (23%) may have influenced these results [41].

Overall, there is substantial heterogeneity in the designs, participant characteristics and methodological rigour of existing studies, precluding firm conclusions regarding the efficacy and safety of metformin use in pregnancy. Although several meta-analyses have been conducted, most have targeted women with PCOS and all have used aggregate data, which may be subject to ecological bias and study-level confounding. Here, we aim to address these knowledge gaps by conducting a comprehensive systematic review incorporating meta-analyses of individual patient data (IPD). Using these data, we will test the hypothesis that metformin in pregnancy is a safe and effective strategy for improving maternal and neonatal glycaemic outcomes. Use of IPD will allow adjustment for differences in participant characteristics including maternal demographics, baseline glucose concentrations and use of supplemental insulin, and it can also identify subgroups of women who may benefit from metformin treatment in pregnancy.

2. METHODS AND ANALYSIS

This review will adopt rigorous international gold standard methodology as outlined in the Cochrane Library and Centre for Evidence-based Medicine guidelines [42,43], and will conform to the standards of the Preferred Reporting Items for Systematic Reviews and Meta-analyses of IPD Statement (PRISMA-IPD) [44]. The protocol for this systematic review will be registered on PROSPERO prior to commencing the data analysis. The specific research question addressed by this review is as follows:

- Is metformin use in pregnancy effective and safe versus placebo, usual care, or other pharmacological or non-pharmacological interventions in:

a) women with GDM for improving glycaemic, maternal and/or neonatal adverse outcomes?

b) women without GDM for improving glycaemic, maternal and/or neonatal adverse outcomes?

2.1. Eligibility Criteria

Selection criteria established *a priori* using the PICO (Population, Intervention, Comparison, Outcomes) framework in **Table 1** will be used to determine eligibility of articles.

2.2. Search Strategy

A systematic search will be developed using relevant search terms (Supplementary Material) in accordance with the selection criteria (Table 1), and the following electronic databases will be searched:

- MEDLINE via OVID
- Medline in-process and other non-indexed citations via OVID
- EMBASE via OVID
- All Evidence Based Medicine (EBM) Reviews via OVID incorporating: The Cochrane Library; Cochrane Database of Systematic Reviews (Cochrane Reviews); Database of Abstracts of Reviews of Effects (Other Reviews); Cochrane Central Register of Controlled Trials (Clinical Trials); Cochrane Database of Methodology Reviews (Methods Reviews); The Cochrane Methodology Register (Methods Studies); Health Technology Assessment Database (Technology Assessments); NHS Economic Evaluation Database (Economic Evaluations); and ACP Journal Club.

Table 1. PICO for study inclusion

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)
Inclusion	Pregnant women of any age, ethnicity, socio-economic status, geographic area, co-morbidity, or gestational age	Metformin administered in any form and route, alone or combined with other intervention/s, of any dosage and for any duration	Placebo, usual care and/or other pharmacological or non-pharmacological interventions including insulin, lifestyle intervention/s, or other oral hypoglycaemic agents (sulfonylureas, acarbose, glibenclamide/ glyburide)	**Primary Maternal Outcomes:** Glycaemic control (glucose, insulin, HbA1c); incidence of GDM* or hyper/hypoglycaemia* **Primary Neonatal Outcomes:** hypoglycaemia*, birthweight, birth length, head circumference and gestational age at delivery **Secondary Outcomes:** Other maternal, birth and neonatal outcomes including miscarriage, birth defects, GWG, pre-eclampsia/ eclampsia, LGA/ macrosomia, SGA and PTB (see full list in Supplementary Material)

Exclusion	Studies in non-pregnant populations	Studies without a metformin therapy arm	Studies without a control or comparison arm	Studies without clinical outcomes (mechanistic studies)
Study type	Systematic reviews of RCTs and RCTs			
Language	No limit			
Year of publication	No limit			

*as defined by authors and using the criteria selected in individual studies. **GDM**, gestational diabetes mellitus; **GWG**, gestational weight gain; **HbA1c**, haemoglobin A1c, **LGA/SGA**, large/small for gestational age; **LBW**, low birthweight; **PTB**, preterm birth; **RCTs**, randomized controlled trials.

Bibliographies and citations of all relevant studies identified by the search strategy and relevant reviews/ meta-analyses will be examined for identification of additional studies. Google will be used to manually search for grey literature (ie, material not published in recognized or indexed scientific journals). Unpublished or ongoing studies will be identified via manual searching of the National Institute of Health Clinical Trials Registry (https://clinicaltrials.gov/) and the Australian New Zealand Clinical Trials Registry (ANZCTR) (https://www.anzctr.org.au).

2.3. Study Selection

To determine eligible studies, one reviewer will scan the titles, abstracts and keywords of every record retrieved by the search strategy using the selection criteria outlined in Table 1 and in consultation with a second reviewer. Disagreement will be resolved by discussion and consensus, otherwise referred to a third reviewer. All articles which appear to meet the selection criteria will be retrieved for full text assessment, and articles with insufficient information in the titles and abstracts will also be retrieved in full text to clarify eligibility. Studies excluded based on full text will be recorded with reasons for their exclusion.

2.4. Data Extraction

Using a specifically developed data extraction form, two independent reviewers will extract data from all included studies. Pilot testing of the extraction form will be conducted using 3-4 studies to ensure all required data is captured. Computed data entries will be cross-checked for meta-analyses where required. Pre-specified data will be extracted in aggregate

format from all published studies (**Table 2**). Relevant data will also be requested in IPD format from all authors along with any study or treatment protocol details not reported in published studies (Table 2).

- ***Aggregate Data Extraction:***

For each treatment group, extracted data will include sample sizes, aggregate point estimates and measures of variability, frequency counts for dichotomous variables, and intention-to-treat analysis. For outcomes reported as continuous variables, the aggregate mean values with standard deviations (SD) or confidence intervals will be extracted and used to measure the effects. Where standard errors (SE) are reported, these will be converted to SD using the formula: $SE \times \sqrt{n}$. For outcomes reported as dichotomous variables, relative measures of risk (risk ratio or odds ratio along with confidence intervals), or absolute numbers of patients experiencing at least one episode of the outcome of interest will be extracted and used in the analyses.

Table 2. Data to be extracted in aggregate and IPD format from included studies

Study	Participants	Intervention/ Control	Primary Outcomes†	Secondary Outcomes
First author and Journal/ Source	Maternal age, parity, ethnicity, and gestational age at enrolment	Metformin treatment protocols (dose, including graded dosing, frequency, duration)	Maternal glycaemic control (fasting and postprandial/post-challenge glucose; insulin; and HbA1c) at any/ all timepoints	All other maternal, birth and neonatal outcomes reported in individual studies (Supplementary Material)
Country and year of publication	Maternal anthropometry (BMI, weight, GWG)	Regimens for each control or comparator group.	Incidence of GDM* and/or maternal hyper/hypoglycaemia*	Long term infant/child outcomes
Study design, setting and sample size	Smoking status and use of medications, supplements, or substances	Use of supplemental insulin	Incidence of neonatal hypoglycaemia*	Development of T2D (in pregnancy or postpartum)
Follow up duration	Disease status (pre-existing T2D, GDM, PCOS, etc)	Use of other pharmacological or non-pharmacological co-interventions	Birthweight, birth length and head circumference, and gestational age at delivery*	Patient satisfaction with experience/ treatment
Inclusion/ exclusion and diagnostic criteria	Comorbidities, history of GDM or family history of diabetes	Number analysed per group and ITT analysis		Adverse events/ side effects occurring during the study

Primary outcome*				

*as defined by authors of individual studies which may be based on clinical diagnosis (separate analyses will be performed for different GDM diagnostic criteria) or in the case of gestational age, this may be based on ultrasound measurements, last menstrual cycle, self report, etc.
†baseline, follow up and delta values will be collected for all continuous primary maternal outcomes.
BMI, body mass index; **GDM**, gestational diabetes mellitus; **GWG**, gestational weight gain; **HbA1c**, haemoglobin A1c; **ITT**, intention to treat; **PCOS**, polycystic ovary syndrome, **T2D**, type 2 diabetes.

- ***Individual Patient Data Collection:***

Corresponding and/or lead authors will be contacted and asked to provide fully anonymised data for IPD meta-analyses. Data for participant characteristics and primary and secondary outcomes (as specified in Table 2 and Supplementary Material) will be requested for each patient, in addition to data on supplemental insulin use (or other co-interventions) if individual-level data for these parameters were recorded. These data will be used to conduct stratified and subgroup analyses at the patient level, in particular by baseline body mass index (BMI) and baseline glucose concentrations, as well as by maternal age, parity, ethnicity, previous history of GDM, gestational weight gain and supplemental insulin use.

A formatted template detailing the requested data and recommended coding will be created and sent to authors; however, data will be accepted in any suitable electronic format. All data will be checked to ensure correct coding, consistency with published results and accuracy of extreme values and to identify missing data, and any issues will be queried and rectified as necessary. A single database will be created by the study investigators to incorporate data from all trials in consistent fields and standardised formats (as much as possible). Studies which are excluded or where IPD is not available will be tabulated with reasons, and aggregate data will be used where appropriate.

2.5. Quality appraisal of the evidence

Risk of bias of included studies will be assessed at the study-level by two independent reviewers. Using a critical appraisal template [45] (adapted from the Cochrane risk of bias tool [46]) with predetermined criteria, each study will be allocated a high, moderate, or low

risk of bias rating. Individual quality items will be assessed using a descriptive component approach that includes items such as conflict of interest of authors, presence of pre-specified selection criteria, methods of randomisation and allocation of participants to study groups, blinding of participants, carers, investigators or outcome assessors, methods of outcome assessment and reporting, and statistical issues such as powering and methods of data analysis. Disagreement will be resolved by consensus.

2.6. Data analysis & synthesis

Our IPD analysis will follow a two-step meta-analytical approach where possible to automatically account for clustering of participants within studies [47]. In this approach, IPD analyses will be conducted to generate estimates of the intervention effect for each study separately. These effect estimates will then be pooled and analysed using conventional meta-analyses with inverse-variance weighted models (DerSimonian and Laird random-effects models) to account for between-study variability [47]. Where IPD is derived from a small number of studies or for binary outcome data where the event risk is low or the sample size is small, a one-step IPD approach will be used (IPD from all studies are modelled simultaneously). Stratified analysis by study will be performed to account for participant clustering in the one-step approach [47,48]. If IPD is only available for some studies, we will combine aggregate data with the available IPD to compare results from analyses including and excluding IPD [49,50]. This approach will allow the effect of non-IPD studies on meta-analysis conclusions to be quantified and displayed transparently. For outcomes with no IPD available, aggregate effect measures and random-effects models will be used for meta-analyses where appropriate, provided that data are derived from clinically homogeneous groups (where participants, interventions and outcome measures are sufficiently similar).

Dichotomous outcomes will be presented as relative risks/ risk ratios with 95% confidence intervals and continuous outcomes will be presented as weighted mean differences (WMD) with 95% confidence intervals. Where outcome measures or study

methods differ substantially, data will be analysed in line with Cochrane guidelines [42], using random-effects models and Cohen *d* to calculate the standardised mean difference (SMD). All meta-analyses will be conducted on Review Manager 5.3 and IPD data will be initially analysed in Stata V.15 and then imported into Review Manager. Comprehensive Meta-analysis V.3 software will be used for meta-regression (if applicable) and assessment of publication bias. *P*-values <0.05 will indicate statistical significance. Statistical heterogeneity will be assessed using the I^2 test, where I^2 values over 50% will be considered as moderate to high heterogeneity. Descriptive analyses will be conducted for those studies which are deemed clinically heterogeneous or present insufficient IPD or aggregate data for pooling.

- ***Subgroup and sensitivity analyses:***

Subgroup analyses and, where applicable, multivariable meta-analyses or meta-regression will be performed for factors presumed to cause heterogeneity or variations in outcomes. Pre-specified variables to be accounted for will include maternal age, ethnicity, comorbidity/ disease status, baseline BMI and glucose concentrations, previous history of GDM or other relevant pregnancy complication/s, dose and duration of metformin therapy, use of supplemental insulin, and gestational age at commencement of therapy. These variables were selected on the basis of evidence showing that the benefits of metformin therapy may vary by these factors [51-53]. Diagnostic criteria for GDM will also be explored for studies measuring incidence of GDM as an outcome. The exact variables to be explored will be selected after data collation but prior to any analyses and will be justified by biological reasoning. Caution will be used in interpretation of subgroup results and adjustment for multiple testing will be considered as necessary. IPD meta-analyses generally have increased power to detect genuine subgroup effects; however, we will assess whether subgroup effects are consistent within individual studies, if deemed necessary. Any post-hoc subgroup analyses will be considered hypothesis-generating for the purpose of planning and designing future studies. Meta-regression and/or multivariable meta-analyses using linear or

logistic regression estimates will be used where appropriate to adjust for the above covariates and to synthesise multiple interaction estimates from each study, accounting for their correlations.

Sensitivity analyses will be conducted and factors to be included will be determined during the review process. Heterogeneity (I^2 >50%) will be explored through sensitivity analysis using risk of bias and IPD availability. For IPD and aggregate meta-analyses incorporating more than three studies, funnel plot asymmetry and Egger [54] and Begg [55] statistical tests will be used to determine small study effects and potential publication bias [56,57].

2.7. Grading the body of evidence

Quality of the evidence will be assessed at the outcome-level by two independent reviewers and rated as high, moderate, low, or very low using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [58]. These ratings will be based on risk of bias, imprecision, heterogeneity, indirectness, and suspicion of publication bias. Availability of IPD and presence of selection or publication bias for IPD studies will also be incorporated into quality assessments in line with PRISMA-IPD guidelines [44]. Disagreements will be resolved by discussion and consultation with a third reviewer where needed.

2.8. Presentation of Findings

Data will be presented in summary tables and in narrative format to describe the populations, interventions and outcomes of the included studies. Forest plots and funnel plots will be used to present results from meta-analyses and publication bias assessments, respectively. Where necessary, results with and without IPD will be presented for comparison. Both aggregate and IPD meta-analyses processes, including results, will be reported according to PRISMA [59] and PRISMA-IPD [44] guidelines.

3.0. ETHICS AND DISSEMINATION

Ethical approval is not required for aggregate data meta-analyses. Individual trials contributing primary data for IPD meta-analyses will have ethical approval from their respective Human Research Ethics Committees in the countries where the studies took place. All data from primary trials will be fully anonymised prior to being imported into our database.

Findings will be disseminated via publications in peer-reviewed journals and presentations at scientific meetings. If deemed appropriate, findings will also be communicated at meetings and forums to relevant stakeholders to guide clinical practice and public health actions in this area.

3.1. Data availability statement

No data has been generated or analysed in this manuscript.

3.2. Patient and public involvement statement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

4. DISCUSSION

GDM is one of the most common complications of pregnancy and contributes to adverse perinatal outcomes, as well as long-term risk of obesity and T2D in the offspring [60]. Although metformin is often prescribed (in addition to lifestyle intervention) in the clinical treatment of GDM, its efficacy and safety in pregnancy continues to be debated [9,61]. Recent RCTs have provided much-needed evidence in this field; however, heterogeneity in study designs, participant characteristics and methodological quality have made it difficult to draw firm conclusions from the available evidence. Moreover, whether metformin may be beneficial in women without GDM for the prevention of glycaemic and other adverse outcomes remains uncertain.

To the best of our knowledge, this will be the most comprehensive systematic review investigating the use of metformin for preventing or treating GDM and other pregnancy complications. It is also the only review in this area to incorporate an IPD meta-analysis examining whether the effects of metformin, if any, are independent of potential confounders and whether they may be specific to certain subgroups of women. Our systematic review process will have several strengths, including the use of rigorous methodology, pre-specified criteria and pre-determined primary and secondary outcomes in order to establish the efficacy and safety of metformin in a variety of population groups. The IPD component of this study will involve acquiring, cleaning, standardising and synthesizing raw data from existing studies. Although this is an intensive process, it is more feasible and less costly than large-scale RCTs and avoids the ethical problem of research waste [62], thus it is considered the gold-standard approach to evidence synthesis [44]. This approach is particularly important in reviewing controversial therapeutic areas and can provide level 1 evidence to guide clinical practice [44].

In contrast to standard aggregate data meta-analysis, using individual-level data enables a more detailed assessment of risk of bias and, more importantly for this study, it provides more power to detect subgroups of interest and to examine effect modifiers at the individual level, which would otherwise require a very large and costly study [63]. Aggregate data, while useful, are often reported poorly, inconsistently (ie. using different measures), or selectively according to which results are significant, further amplifying the problems of publication bias and selective reporting [64]. Here, the use of IPD will allow us to: standardise the data (e.g. of timepoints, units, analysis methods, etc.); use consistent exclusion and inclusion criteria; directly extract data in the required format and deal with missing data appropriately; adjust for baseline (prognostic) factors and individual risk status consistently across studies to increase power and account for potential confounders; and

examine complex relationships, multiple timepoints and multiple individual-level factors and their interactions [64].

Potential limitations should be noted. First, IPD meta-analyses are no panacea against poorly designed and conducted primary research. Thus, the strength of the evidence and conclusions drawn from this meta-analysis will depend on the quality of included trials and their data availability. Second, although we will endeavour to identify grey literature and unpublished data as part of the search strategy, publication bias cannot be ruled out. Finally, there is potential for data availability bias if IPD are unavailable for some studies and this influences our results. To counter this and ensure transparency, we will report findings from meta-analyses with and without IPD and we will contact authors to initiate collaboration and to seek data-sharing agreements to access anonymised data from major trials.

Given the impact of GDM on adverse pregnancy outcomes and the long-term health of both mother and offspring, putting in place simple and effective strategies for prevention and management is crucial. This IPD meta-analysis will provide the most robust evidence to date as to whether metformin is an effective and safe therapy for use in pregnancy and may identify specific subgroups of patients whom may benefit most from this treatment modality. Findings from this meta-analysis will provide much needed evidence to inform appropriate evidence-based clinical and public health actions in this area.

5. ACKNOWLEDGEMENTS

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5.1. Author Contributions

AM is project lead, conceptualised and designed the protocol, wrote the first draft of the manuscript and will coordinate the MiPS project. TL, IH, SMC, LM-P, KT, TR, AS, KN, HS, CB, JEN, JR, JD and WH are key collaborators on the project and members of the MiPS steering committee, contributed to writing and editing the manuscript, and will contribute IPD

for the meta-analysis. EV and HT are chair and deputy chair of the MiPS steering committee, respectively, and co-designed the protocol, contributed to writing and editing the manuscript, and will co-lead the project with AM. HT is the study guarantor and will oversee data collection, analysis, and interpretation. All authors meet ICMJE criteria for authorship and have approved the final version for publication.

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5.3. Competing Interests Statement

None declared.

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Supplementary Material

Supplementary Table 1. Primary & secondary outcomes to be extracted/ requested for included studies

- Maternal / birth outcomes
  - **Primary:** maternal glycaemic control (glucose, insulin, and glycosylated haemoglobin [HbA1c], and incidence of hyper/hypoglycaemia) + incidence of GDM in women without GDM
  - gestational weight gain
  - preterm birth (iatrogenic or spontaneous)
  - pregnancy-induced hypertension, pre-eclampsia, and eclampsia
  - mode of birth (spontaneous vaginal, instrumental, caesarean section)
  - maternal satisfaction with experience of pregnancy and birth
  - maternal death
  - maternal obstetric complications (haemorrhage, infection, thrombosis, admission to intensive care unit, incontinence, perineal trauma)
  - maternal adverse events or side effects (gastrointestinal disturbance, vomiting)
  - maternal diabetic complications: diabetic ketoacidosis (DKA), retinopathy, nephropathy, macrovascular disease
  - development of type 2 diabetes during pregnancy or postpartum
- Neonatal outcomes
  - **Primary:** hypoglycaemia, birthweight (and birthweight centile), birth length, head circumference, and gestational age at delivery
  - cord-blood insulin, glucose, and C-peptide
  - miscarriage, stillbirth, neonatal or infant death
  - congenital malformation
  - macrosomia, small for gestational age (SGA), low birthweight
  - shoulder dystocia, birth trauma (bone fracture, nerve palsy)
  - admission and length of stay at different levels of care including neonatal intensive care unit, high-dependency unit, special care unit or transitional care unit
  - Apgar score <7 at 5 min
  - respiratory distress, sepsis, transient heart failure, resuscitation, jaundice, hypocalcaemia, polycythaemia, hypoxic ischaemic encephalopathy, impairment of neurodevelopment.
  - long term infant child outcomes (neurodevelopment/ cognitive, anthropometric, etc)

Supplementary Table 2. Sample search strategy for OVID Medline

1. metformin/	51. randomly.ti,ab.
2. metformin.mp.	52. trial.ti.
3. metformin hydrochloride.mp.	53. or/46-52
4. metformin HCL.mp.	54. exp animals/ not exp humans/
5. hypoglycemic?.mp.	55. 53 not 54
6. hypoglycaemic?.mp.	56. Meta-Analysis as Topic/
7. anti?diabetic?.mp.	57. meta analy$.tw.
8. antihyperglycemic?.mp.	58. metaanaly$.tw.
9. antihyperglycaemic?.mp.	59. Meta-Analysis/
10. glucose?lowering.mp.	60. (systematic adj (review$1 or overview$1)).tw.
11. dimethylbiguanidine.mp.	61. exp Review Literature as Topic/
12. dimethylguanylguanidine.mp.	62. or/56-61
13. glucophage.mp.	63. cochrane.ab.
14. biguanide?.mp.	64. embase.ab.
15. buformin.mp.	65. (psychlit or psyclit).ab.
16. phenformin.mp.	66. (psychinfo or psycinfo).ab.
17. sitagliptin.mp.	67. (cinahl or cinhal).ab.
18. glumetza.mp.	68. science citation index.ab.
19. carbophage.mp.	69. bids.ab.
20. obimet.mp.	70. cancerlit.ab.
21. gluformin.mp.	71. or/63-70
22. dianben.mp.	72. reference list$.ab.
23. diabex.mp.	73. bibliograph$.ab.
24. diaformin.mp.	74. hand-search$.ab.
25. siofor.mp.	75. relevant journals.ab.
26. metfogamma.mp.	76. manual search$.ab.
27. glifor.mp.	77. or/72-76
28. riomet.mp.	78. selection criteria.ab.
29. janumet.mp.	79. data extraction.ab.
30. fortamet.mp.	80. 78 or 79
31. obimet.mp.	81. Review/
32. pregnancy.mp.	82. 80 and 81
33. pregnan?.mp.	83. Comment/
34. reproductive.mp.	84. Letter/
35. maternal.mp.	85. Editorial/
36. neonatal.mp.	86. animal/
37. gestation?.mp.	87. human/
38. infant.mp.	88. 86 not (86 and 87)
39. offspring.mp.	89. or/83-85,88
40. f?etal.mp.	90. 62 or 71 or 77 or 82
41. neonat?.mp.	91. 90 not 89
42. ?natal.mp.	92. 53 or 91
43. gestational diabetes.mp.	93. 45 and 92
44. GDM.mp.	94. limit 93 to humans
45. or/1-44	95. or/1-31
46. randomi?ed controlled trial.pt.	96. or/32-44
47. controlled clinical trial.pt.	97. 95 and 96
48. randomi?ed.ti,ab.	98. 92 and 97
49. placebo.ti,ab.	99. limit 98 to humans
50. clinical trials as topic.sh.	

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
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	NA
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	17
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list	NA

		changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	18
Sponsor	#5b	Provide name for the review funder and / or sponsor	18
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	4-7
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
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	8-9
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	8-9

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	8-9, Suppl Table
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-11
Study records - 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)	9
Study records - 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	10-12
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	10-12, Table 2
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-13, Table 1 and 2
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	11 and 14

Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	12-13
Data synthesis	#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 I2, Kendall's τ)	12-13
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
Data synthesis	#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)	12-13
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14