# Detection and treatment of early gestational diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials

Apolonia García-Patterson, MD; Montserrat Balsells, MD; Ivan Solà, BSc; Rosa Corcoy, MD, PhD

**OBJECTIVE:** To estimate the impact of detection and treatment of early gestational diabetes mellitus on short-term maternal, fetal, and neonatal outcomes. We defined 2 maternal (gestational diabetes prevalence and cesarean section) and 2 neonatal (preterm birth and macrosomia) primary outcomes. We also defined 5 maternal and 12 fetal-neonatal secondary outcomes.

**DATA SOURCES:** Ovid Medline, Cochrane CENTRAL, and Embase since inception. The search was updated in November 2024.

**STUDY ELIGIBILITY CRITERIA:** Inclusion criteria: randomized controlled trials addressing detection and treatment of early gestational diabetes (diagnosed before 20 completed weeks). Exclusion criteria: pregestational diabetes or overt diabetes in pregnancy.

**STUDY APPRAISAL AND SYNTHESIS METHODS:** The Cochrane Handbook was used to guide data extraction and interpretation including risk of bias assessment (Risk of Bias 2 tool).

Aggregation and comparison of results were performed with Revman 5.4.1. Pooled relative risk and mean differences were calculated with 95% confidence intervals using random-effects models. The quality of the evidence for primary outcomes was summarized using Grading of Recommendations Assessment, Development and Evaluation criteria.

**RESULTS:** We identified 1221 unique references. Seven articles addressing early gestational diabetes met the eligibility criteria with a total of 30,791 participants. These studies used 2 strategies: (1) treatment vs usual care of women with a diagnosis of early gestational diabetes and (2) population-based approaches, either performing screening (vs not) or using different cutoffs for diagnosis.

In studies comparing treatment vs usual care, differences were observed only in secondary outcomes: more drug treatment, less maternal weight gain, lower birthweight, and less respiratory distress. In studies comparing different population-based strategies, primary outcomes differed for a higher rate of early and overall gestational diabetes (relative risk, 5.50; 95% confidence interval, 3.56—8.48 and 1.83; 95% confidence interval, 1.41—2.38, respectively) and a lower rate of primary cesarean section (relative risk, 0.88; 95% confidence interval, 0.84—0.93); as to secondary outcomes, differences were observed in terms of higher total pregnancy-induced hypertension and pre-eclampsia. The quality of evidence for most outcomes was low/very low.

**CONCLUSION:** Detection and treatment of early gestational diabetes mellitus do not offer indisputable benefits either in treated women or at the population level. More studies are required to elucidate this issue.

**Key words:** early gestational diabetes mellitus, screening, treatment

From the Institut d'Investigació Biomèdica Sant Pau (IIB SANT PAU), Barcelona, Spain (García-Patterson, Solà and Corcoy); Independent Investigator, Barcelona, Spain (Balsells); Iberoamerican Cochrane Centre, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (Solà); CIBER Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain (Solà); Servei d'Endocrinologia i Nutrició, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (Corcoy); Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain (Corcoy); and CIBER de Bioingeniería, Biomateriales y Nanotecnología (CIBER-BBN), Instituto de Salud Carlos III, Madrid, Spain (Corcoy).

Received Dec. 15, 2024; revised April 17, 2025; accepted April 25, 2025.

The authors report no conflict of interest.

There is no financial support to declare.

The findings of this study were presented at the Sociedad Española de Endocrinología (SEEN), Barcelona, October 18 to 20, 2023; Sociedad Española de Diabetes (SED), Granada, April 10 to 13, 2024; Diabetes and Pregnancy Study Group (DPSG), Örebro, September 5 to 7, 2024; and European Association for the Study of Diabetes (EASD), Madrid, September 9 to 13, 2024.

Prospero registration, date: April 9, 2023, number: PROSPERO CRD42023392060, url: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023392060

Data extracted from the included studies are available upon reasonable request to the corresponding author.

Corresponding author: Rosa Corcoy. rcorcoy@santpau.cat

0002-9378



https://doi.org/10.1016/j.ajog.2025.04.059

Click Supplemental Materials and Video under article title in Contents at ajog.org

## AJOG at a glance

### Why was this study conducted?

To assess the impact of detecting and treating early gestational diabetes mellitus (GDM) (before 20 completed weeks) on maternal and perinatal outcomes in randomized controlled trials.

We defined 2 maternal (GDM and cesarean section) and 2 neonatal (preterm birth and macrosomia) primary outcomes.

### Key findings

We identified 7 studies employing 2 strategies. The first compared treatment with usual care. The second focused on population-based approaches.

With the first approach, differences were observed in secondary outcomes. With the second approach, differences were observed in both primary (more GDM and less primary cesarean section) and secondary outcomes.

### What does this add to what is known?

This is the first meta-analysis to evaluate interventions targeting early GDM while accounting for study designs. Both benefits and risks were identified.

## Introduction

There is consensus in the benefit of diagnosis and treatment of gestational diabetes mellitus (GDM) at 24 to 28 weeks of pregnancy.[1–4] Similarly, most[2,5–7] but not all guidelines[4] consider screening for overt diabetes mellitus at booking. As to early hyperglycemia short of overt diabetes, it is associated with worse outcomes than hyperglycemia diagnosed at 24 to 28 weeks.[8] However, guidelines on this condition are heterogenous: they do not consider early screening;[4] when GDM is diagnosed following screening for overt diabetes, they vary in their emphasis on treatment;[2,5–7] or conclude that the current evidence is insufficient to assess the balance of benefits and harms.[1] In recent years, several randomized controlled trials (RCTs) have addressed detection and treatment of GDM diagnosed before the usual screening period at 24 to 28 weeks. However, no systematic review and meta-analysis have yet synthesized all relevant evidence to inform clinical practice.

## Objective

The aim of the current systematic review and meta-analysis was to summarize the impact of detection and treatment of early GDM on pregnancy outcomes.

## Methods

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023392060).[9] A specific protocol additional to PROSPERO is not available. We followed Cochrane guidance for conducting systematic reviews[10] and reported the findings according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.[11]

### Eligibility criteria, information sources, and search strategy

Inclusion criteria were articles reporting results from RCTs addressing detection and treatment of early GDM (diagnosed before 20 completed weeks) after any diagnostic criteria. Exclusion criteria were women with pregestational diabetes/overt diabetes in pregnancy.

We also excluded trials that were only reported as conference abstracts or proceedings.

One of the investigators (I.S.) searched Medline, Cochrane CENTRAL, and Embase from their inception using text terms and keywords such as "early," "screening," "hyperglycemia," "gestational diabetes," "trial," "randomized," and "clinical trial" (Supplemental Table 1). No restriction for language or geographic location was applied. References of selected publications and systematic reviews were checked. Protocol studies or conference abstracts were also tracked for further publication. The search was updated in November 2024.

### Study selection

Duplicate references were removed. Title and abstract screening were independently performed by 2 authors (A.G.P. and M.B.) and discrepancies were discussed with a third one (R.C.).

We defined 2 maternal (GDM and cesarean section) and 2 neonatal (preterm birth and macrosomia) primary outcomes. The rationale for selecting primary outcomes was to prioritize those that were relevant, not rare, and able to be measured objectively. Additionally, we defined 5 maternal and 12 fetal-neonatal as secondary outcomes (Supplemental Table 2). Outcome definitions used were those provided by the authors.

In a review of the registered protocol,[9] primary outcomes for the mother were restructured as follows. Early GDM and second/third trimester GDM, originally listed as secondary outcomes, were moved under the primary outcome GDM; GDM reversion in second/third trimester was added. Cesarean section was broken down into total, primary, and emergency. The rearrangement was performed to provide a more comprehensive evaluation of maternal impact, including Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment.

The protocol of this systematic review was prospectively registered in the PROSPERO (CRD42023392060) on April 9, 2023. While using publicly available data, ethics approval was not required.

### Data extraction

Data extraction was independently performed by 2 authors (A.G.P. and M.B.) using a previously designed form. Discrepancies were discussed with a third one (R.C.). We collected information of study characteristics such as country, year of publication, definition of

hyperglycemia, type of intervention, number of patients, maternal age, ethnicity, and baseline body mass index. No automation tool was used. No assumptions were made about missing data or unclear information.

Study characteristics and results were tabulated using a spreadsheet, inspected for patterns and pondered. As a result, we decided to categorize studies into 2 groups (those addressing treatment of women with GDM diagnosed early in pregnancy vs usual obstetric care and those addressing strategies of detection and treatment at population level). One of the studies used a cluster design and we checked if the cluster effect was addressed in the sample size estimation and analysis. Post-hoc, 2 comparisons were performed: (1) studies that used glycemia vs studies that used hemoglobin A1C ($HbA_{1c}$) as a diagnostic test for early GDM and (2) studies that addressed women with risk factors vs studies without this requirement. One of the studies[12] used both $HbA_{1c}$ and glycemia for diagnosis of early GDM; as 80% of diagnosis were performed with $HbA_{1c}$, the study was included in the group using this diagnostic test. Since one of the trials used a cluster noninferiority design, and introduced conceptual heterogeneity, we conducted a sensitivity analysis excluding it. In studies providing quantitative information as median and interquartile range, mean and standard deviation were calculated.

### Assessment of risk of bias

The version 2 of the Cochrane risk-of-bias tool for RCT (RoB2) was used to assess bias on included studies, using the specific tools for individual and cluster randomized trials.[13] Two researchers (A.G.P. and M.B.) assessed independently the risk of bias of included studies discussing discrepancies with a third investigator (R.C.) until a consensus was reached. We assessed an overall risk of bias at the study level through explicit judgments on randomization process, deviation from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported results. In a second step, we assessed the risk of bias at the outcome level to make judgments on its impact on the confidence of effect estimates for main outcomes. We performed a qualitative assessment comparing objectives, hypotheses, outcome measures, and noninferiority margins of the noninferiority cluster trial, first with those of the meta-analysis, and second with the individually randomized superiority trial whose results were pooled in the meta-analysis.

The Trustworthiness in RAndomized Controlled Trials (TRACT) checklist[14] was also applied.

No automation tools were used.

### Data synthesis

RevMan version 5.4.1 was used to pool summary statistics. We calculated relative risks (RRs) for dichotomous and mean differences (MDs) for continuous outcomes with their 95% confidence intervals (CIs). A random effects model was used because it gives more conservative effect estimations. We explored heterogeneity for all the analysis, considering $I^2$ values >50% as indicative of high heterogeneity and contemplating subgroup analysis. Funnel plots were not used to test for asymmetry because the number of studies was less than 10 in each category. Forest plots were used to plot and visualize the synthesis for all outcomes.

We classified the quality of the evidence for primary outcomes according to the GRADE approach[15] making explicit judgments on both internal (risk of bias, inconsistency, imprecision, and publication bias) and external validity. To facilitate judgments on imprecision, we set a definition of meaningful effect at an RR reduction of 25% for treatment vs usual care studies[16] and at 2.5% for population-based studies, taking into account that in the intervention arm of population-based studies, there was a ≈10% absolute increase in the prevalence of early GDM. We summarized the quality of evidence and estimates of the magnitude of the effect for each outcome in a table.

## Results

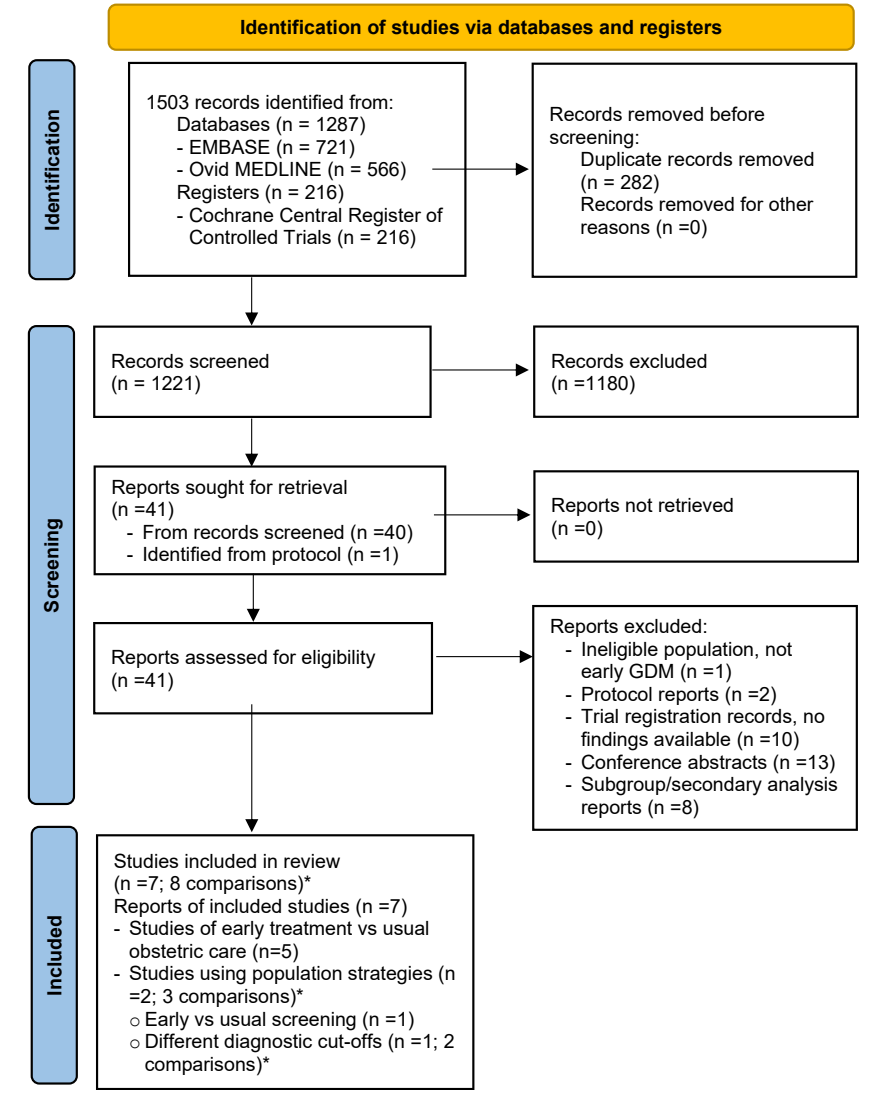
### Study selection

We identified 1221 unique references from the search and reviewed the full text of 41 articles for final inclusion (Figure 1). Seven met inclusion criteria and 1 of them was not identified by the search; the search identified the corresponding protocol[17] which lead us to the published article.[18] Five studies[12,19–22] compared treatment of women with a diagnosis of early GDM vs usual care at this point (either GDM treatment was deferred at 24–28 weeks or was initiated if second trimester screening led to a GDM diagnosis). Two studies[18,23] were population-based approaches where outcome information was not limited to women with hyperglycemia and were analyzed together. One study compared early screening with no screening in women with obesity[23] and the other[18] compared 2 sets of glycemic criteria (tight vs less tight) for early GDM diagnosis. This last study used a cluster design and provided 2 comparisons based on different diagnostic criteria used at 24 to 28 weeks.

### Study characteristics

Individual study characteristics including inclusion and exclusion criteria are shown in Table 1. Studies had been performed 1 in Australia;[19] 1 in Australia, India, Austria, and Sweden;[20] 3 in the United States;[12,21,23] 1 in New Zealand;[22] and 1 in Iran,[18] and overall, included a total of 30,372 pregnancies. The number of subjects in the individual studies ranged from 21 to 28,834. The test used for screening or diagnosis was $HbA_{1c}$ and/or plasma glucose. Baseline maternal characteristics are presented in Table 2. The characteristics of publications excluded after full text review, including reasons for exclusion (wrong population, study protocol, trial registration, conference abstract, and secondary analysis are described in Supplemental Table 3). All studies performed an intention to treat analysis, including the cluster randomized trial of Tehrani et al.[18] In this last study, the cluster effect was accounted for in both the sample size estimation and the analysis, and the reported results were

**FIGURE 1**
**Systematic review flow diagram**




*In the study of Tehrani et al,[18] 2 comparisons are made. In the first trimester, fasting blood glucose cutoffs of 5.1 mmol/l (groups A and D) and 5.6 mmol/l (groups C and E) are evaluated as diagnostic criteria. At 24 to 28 weeks, 2 different diagnostic criteria are used: the IADPSG criteria (groups A and C) and the Carpenter and Coustan criteria (groups D and E). Therefore, regarding first trimester cutoffs, 2 comparisons are provided: A vs C, D vs E.

*GDM*, gestational diabetes mellitus.

deemed suitable for inclusion in the meta-analysis.

### Risk of bias of included studies

The risk of bias assessment of the RCTs included in the meta-analysis was performed using Rob2 tool and was low for 3 comparisons, high for 5. All studies were included in a clinical trial registry; 4 of them registered several weeks after initiation of enrollment (Supplemental Table 4). The aim, hypotheses, outcomes, and marginal difference for noninferiority in the trial by Tehrani[18] aligned well with those of the meta-analysis that aimed to summarize the impact of early GDM detection and treatment on pregnancy outcomes. However, some variation was observed when comparing it with the other trial that evaluated strategies at the population level:[23] in the hyperglycemia approach (screening/nonscreening[23] vs universal screening and different diagnostic thresholds[18]), study hypotheses (superiority[23] vs noninferiority[18]), primary outcomes (primary cesarean section/macrosomia[23] vs composite outcome[18]), and a difficult comparison between an expected 50% reduction in primary outcome[23] vs a marginal difference of 0.03.[18]

The TRACT analysis showed that all studies had between 0 and 4 items rated as "moderate concerns" (Supplemental Table 5).

The quality of evidence for total cesarean section was high for the comparison treatment vs usual care (Table 3) and moderate for primary cesarean section in studies using population strategies (Table 4). For the rest of primary outcomes, the quality of evidence was low or very low primarily due to the inconsistency and imprecision of results.

### Synthesis of results

The summary statistics of maternal and fetal outcomes in RCTs addressing diagnosis and treatment of early GDM are shown in Table 5 including the effect estimates of the intervention and the corresponding confidence interval. In studies comparing treatment vs usual care, no difference was observed in primary outcomes. As to secondary outcomes, some differences were observed both in maternal and fetal outcomes: a higher rate of drug treatment (RR, 1.42; 95% CI, 1.26−1.60), less maternal weight gain (MD, −0.99 kg; 95% CI, −1.74 to −0.24), lower birthweight (MD, −101.5 g; 95% CI, −177.0 to −25.9), and less respiratory distress (RR, 0.57; 95% CI, 0.39−0.83). Heterogeneity measured with $I^2$ was low (0% −35%). The corresponding forest plots and risk of bias for primary outcomes are displayed in Supplemental Figure 1.

In studies comparing different strategies at the population level, differences were observed only in maternal outcomes. The intervention group displayed a higher rate of early and overall GDM (RR, 5.50; 95% CI, 3.56−8.48 and 1.83; 95% CI, 1.41−2.38, respectively) and a

**TABLE 1**
**Design of randomized controlled trials included in the meta-analysis**

| Reference | Study design | Primary outcome | Inclusion and exclusion criteria | Early pregnancy testing | Early pregnancy interventions | Second/third trimester testing | Second/third trimester interventions |
|---|---|---|---|---|---|---|---|
| Treatment vs usual care of women with early GDM | | | | | | | |
| Osmundson,[21] 2016, USA | Parallel RCT | −75 g OGTT at 26 28 wks | **Inclusion**<br>- GA <14+0 wks<br>**Exclusion**<br>- Pregestational DM<br>- Chronic corticoids<br>- Multiple pregnancy<br>- Age <18 y<br>- Prior shoulder distocia or injury attributable to DM/ macrosomia | - Universal screening<br>- $HbA_{1c}$ ≥5.7%−6.4% | **Intervention**<br>- Healthy WG and PA<br>- Diary of food intake<br>- SMBG 4x day<br>- Goal <92 mg/dl pre and <135 mg/dl 1 h pp<br>- If >20% values elevated, insulin Tx<br>- Control every 2 wks<br>**Control**<br>- Usual care<br>- Handout on healthy WG and PA | - GA 26−28 wks −2 h 75 g OGTT, IADPSG criteria | **Intervention**<br>- OGTT only if no insulin Tx<br>- Ongoing follow-up<br>**Control**<br>- OGTT in all women<br>- Tx if GDM dx |
| Hughes,[22] 2018, New Zealand | - Parallel RCT | - PE<br>- Emergency CS | **Inclusion**<br>- Age ≥18 y<br>**Exclusion**<br>- Preexisting DM<br>- Lethal congenital anomaly<br>- Multiple pregnancy | - Universal screening<br>- GA<14 wks<br>- $HbA_{1c}$ ≥5.9%−6.4% | **Intervention**<br>- Visits every 3−6 wks<br>- Lifestyle education<br>- BG monitoring before and after each meal<br>- Goal fasting <90, 1 h <133.3, 2 h<118 mg/dL<br>- Metformin and/or insulin<br>**Control** standard care | - GA 24 wks<br>- 2 h 75 g OGTT, NZ criteria | **Intervention**<br>- No OGTT<br>- Ongoing follow-up<br>**Control**<br>- OGTT in all women<br>Tx if GDM dx |
| Simmons,[19,24] 2018, Australia | - Parallel RCT | - To test the protocol for a larger RCT | **Inclusion**<br>- Age ≥18 y<br>- GA <19+6 wks<br>- Singleton<br>**Exclusion**<br>- Preexisting DM<br>- ODIP<br>- FPG 6.1−6.9 mmol/L<br>- Major active medical disorder | - Risk factor screening[a]<br>- GA<19+6 wks<br>- 2 h 75 g OGTT, IADPSG criteria | **Intervention**<br>- Notified of GDM dx<br>- Group education; dietitian consultation<br>- SMBG; goal fasting <5.3 mmol/L, 2 h pp <6.8<br>- Insulin or metformin if thresholds exceeded >2 occasions with no cause<br>**Control**<br>- Advised that they did not require referral to the clinic | - GA 24−28 wks<br>- 2 h 75 g OGTT, IADPSG criteria | **Intervention**<br>- No OGTT<br>- Ongoing follow-up<br>**Control**<br>- OGTT in all women<br>Tx if GDM dx |

*(continued)*

**TABLE 1**
**Design of randomized controlled trials included in the meta-analysis** *(continued)*

| Reference | Study design | Primary outcome | Inclusion and exclusion criteria | Early pregnancy testing | Early pregnancy interventions | Second/third trimester testing | Second/third trimester interventions |
|---|---|---|---|---|---|---|---|
| Roeder,[12] 2019, USA | - Parallel RCT | - Cord C-peptide >1.77 nmoL (90th percentile) | **Inclusion**<br>- GA ≤15 wks<br>- Age ≥18 y<br>- Singleton<br>- Planned care and delivery at the center<br>**Exclusion**<br>- GA >15 wks<br>- Prepregnancy DM<br>- Overt DM in first trimester<br>- Multiple pregnancy | - Universal screening<br>- GA <15 wks<br>- FPG and $HbA_{1c}$<br>- $HbA_{1c}$ 5.7%–6.4% and/or FPG 92–125 mg/dl | **Intervention** (unblinded)<br>- Education, monitoring, diet, and exercise<br>- FPG and 1 h PG 4 times daily, diet, and exercise; goal fasting <90/1 h <130 mg/dL<br>- If >40% high after 2 wks, drug treatment (NPH, metformin, glyburide)<br>**Control** (unblinded)<br>- Handout on balanced diet at enrollment<br>- Routine care until 28 wks<br>- After 28 wks Tx as in intervention group | - Blinded OGTT to dx GDM as secondary outcome unless gastric bypass<br>- GA 24–28 wks<br>- 2 h 75 g, IADPSG | **Intervention**<br>- OGTT in all women<br>- Ongoing follow-up<br>**Control**<br>- OGTT in all women<br>- Tx in all women (deferred) |
| Simmons,[20,24] 2023, Australia, India, Austria, Sweden | - Parallel RCT | - First: composite of adverse NN outcomes[b]<br>- Second: PIH<br>- Third: NN lean body mass | **Inclusion**<br>- ≥18 y<br>- 4 to 19+6 wks<br>- Singleton pregnancy<br>- 1 RF for hyperglycemia[a]<br>**Exclusion**<br>- Preexisting DM<br>- ODIP<br>- FPG 6.1 to 6.9 mmol/L<br>-Mmajor active medical disorder | - Risk factor screening[a]<br>- GA 4 to 19+6 wks<br>- 2 h 75 g OGTT, WHO criteria<br>- | **Intervention**<br>- Education, diet advice, and CBG<br>- Obstetrical management per local practice<br>- Fasting and 2 h pp glucose, targets <5.3 and <6.8 mmol/L, respectively<br>- Insulin or metformin if thresholds exceeded >2 occasions with no cause<br>**Control** (no Tx)<br>- Advised with identical letters to 'decoys' that referral not required<br>- Participant, healthcare, and research staff blinded to results | - GA 24 to 28 wks<br>- 2 h 75 g OGTT, IADPSG criteria | **Intervention**<br>- No OGTT<br>- Ongoing follow-up<br>**Control**<br>- OGTT in all women<br>Tx if GDM dx |

*(continued)*

**TABLE 1**
**Design of randomized controlled trials included in the meta-analysis** *(continued)*

| Reference | Study design | Primary outcome | Inclusion and exclusion criteria | Early pregnancy testing | Early pregnancy interventions | Second/third trimester testing | Second/third trimester interventions |
|---|---|---|---|---|---|---|---|
| Strategies at the population level | | | | | | | |
| Harper,[23] 2020, USA | - Parallel RCT | - Composite perinatal outcome[c] | **Inclusion**<br>- GA 14 to 20 wks<br>- BMI $\geq$30 kg/m$^2$ at inclusion<br>**Exclusion**<br>- Multiple pregnancy<br>- Prior cesarean<br>- Preexisting DM<br>- Bariatric surgery<br>- Major illness<br>- Fetal anomalies<br>- Chronic steroid use | - Risk factor screening (BMI $\geq$30 kg/m$^2$)<br>- GA 14 to 20 wks<br>- HbA$_{1c}$ <6.5% | **Intervention** (early screening and Tx)<br>- GCT with 50 g glucose; if $\geq$135 mg/dL, 3 h OGTT, CC criteria<br>- Diabetes education and SMBG; goal FBG <95 mg/dL and 2 h BG <120; oral agents and/or insulin if required<br>**Control** (routine care and Tx)<br>- If HbA$_{1c}$ 6.2% to 6.5%, GCT with 50 g glucose, follow-up as in intervention | - Screening at 24 to 28 wks<br>- GCT with 50 g glucose<br>- If $\geq$135 mg/dL, 3 h OGTT, CC criteria<br>- Tx if GDM dx | **Intervention**<br>- Rescreening if GDM not dx at 14 to 20 wks<br>**Control**<br>Screening in all women |
| Tehrani,[18] 2022, Iran<br>A vs C | - Cluster noninferiority RCT | - Primary CS<br>- Macrosomia | **Inclusion**<br>- All pregnant women <14 wks<br>**Exclusion**<br>- <18 years<br>- Preexisting DM<br>- Uncertain LMP and no available US at 6 to 14 wks<br>- Chronic HT<br>- Asthma<br>- Tx with corticoids, $\beta$-blockers, $\beta$-mimetics, phenytoin, and antiretroviral agents<br>- Bariatric surgery | - All pregnant women<br>- GA <14 wks<br>- FPG $\geq$5.1 and <7.0 mmol/L | **Intervention (group A)**<br>- Tx if FPG $\geq$5.1 mmol/L<br>- Lifestyle modification and BG monitoring; goals <95 mg/dL fasting, 140 1 h and 120 2 h pp<br>- If targets not achieved in 2 wks, drug Tx offered (insulin; if insulin declined, metformin offered)<br>- SMBG to achieve and maintain goals<br>- **Control (group C)**<br>- Tx if FPG $\geq$5.6 mmol/L (as described for the intervention group) | - 24 to 28 wks<br>- 2 h 75 g OGTT, IADPSG criteria<br>- Tx if GDM dx | **Intervention (group A)**<br>- Women not dx in the first trimester were rescreened<br>**Control (group C)** women not dx in first trimester rescreened |

*(continued)*

**TABLE 1**
**Design of randomized controlled trials included in the meta-analysis** *(continued)*

| Reference | Study design | Primary outcome | Inclusion and exclusion criteria | Early pregnancy testing | Early pregnancy interventions | Second/third trimester testing | Second/third trimester interventions |
|---|---|---|---|---|---|---|---|
| Tehrani,[18] 2022, Iran<br>D vs E | - As in A vs C comparison | As in A vs C comparison | **Inclusion** and **exclusion criteria** as in A vs C comparison | - All pregnant women<br>- GA <14 wks<br>- FPG ≥5.1 and <7.0 mmol/L | **Intervention (group D)**<br>- Tx if FPG ≥5.1 mmol/L<br>- Same as described for group A above<br>**Control (group E)**<br>- Tx if FPG ≥5.6 mmol/L same as described for group C above | - 24 to 28 wks<br>- 2 steps with 50 g GCT; 1 h ≥140 mg/dL followed by 3 h OGTT, CC criteria | **Intervention (group D)**<br>- Women not dx in first trimester, rescreened<br>**Control (group E)** women not dx in first trimester, rescreened |

*BG*, blood glucose; *BMI*, body mass index; *CC*, Carpenter & Coustan; *CBG*, capillary blood glucose; *CS*, cesarean section; *dx*, diagnosis; *DM*, diabetes mellitus; *FBG*, fasting blood glucose; *FPG*, fasting plasma glucose; *GA*, gestational age; *GCT*, glucose challenge test; *GDM*, gestational diabetes mellitus; *$HbA_{1C}$*, Hemoglobin A1C; *HT*, hypertension; *IADPSG*, International Association Diabetes and Pregnancy Study Groups; *LMP*, last menstrual period; *NN*, neonatal; *NZ*, New Zealand; *ODIP*, overt diabetes in pregnancy; *OGTT*, oral glucose tolerance test; *PA*, physical activity; *PE*, preeclampsia; *PG*, plasma glucose; *PIH*, pregnancy-induced hypertension; *pp*, postprandial; *RCT*, randomized controlled trial; *RF*, risk factor; *SMBG*, self-monitoring of blood glucose; *Tx*, treatment; *US*, ultrasound; *WG*, weight gain; *WHO*, World Health Organization.

[a] Previous hyperglycemia in pregnancy, previously elevated blood glucose level, maternal age ≥40 years, ethnicity: Asian, Indian subcontinent, Aboriginal, Torres Strait Islander, Pacific Islander, Maori, Middle Eastern, non-White African, family history DM (first degree relative with diabetes or a sister with hyperglycemia in pregnancy), prepregnancy body mass index >30 kg/$m^2$, previous macrosomia (baby with birth weight >4500 g or >90th centile), polycystic ovarian syndrome, medications: corticosteroids, antipsychotics; [b] birth at <37 weeks, birth weight of ≥4500 g, birth trauma, neonatal respiratory distress warranting treatment, phototherapy, stillbirth or neonatal death, or shoulder dystocia; [c] macrosomia, primary CS, PIH, shoulder dystocia, NN jaundice, or NN hypoglycemia (assessed within 48 h of birth).

lower rate of primary cesarean section (RR, 0.88; 95% CI, 0.84–0.93). As to secondary outcomes, differences were observed in total pregnancy-induced hypertension (PIH) (RR, 1.34; 95% CI, 1.08–1.68) and preeclampsia (RR, 1.33; 95% CI, 1.01–1.76). Heterogeneity measured with $I^2$ was high for all maternal outcomes (56%–98%) with the exception of primary cesarean section (0%). The corresponding forest plots and risk of bias for primary outcomes are displayed in Supplemental Figure 2.

The sensitivity analysis excluded the study of Tehrani, which employed a cluster noninferiority design and was 1 of the 2 trials comparing strategies at the population level (Supplemental Table 6). As a result, the findings for treatment vs usual care remained unchanged. With the sensitivity analysis, for strategies at the population level, 3 of the 5 outcomes that initially showed significant differences—total GDM (RR, 1.83; 95% CI, 1.41–2.38, $P<.001$), primary cesarean section (RR, 0.88; 95% CI, 0.84–0.93, $P<.001$), and preeclampsia (RR, 1.33; 95% CI, 1.01–1.76, $P=.04$)—became nonsignificant.

We performed 2 post-hoc analyses. The first analysis compared studies that used $HbA_{1c}$ or glycemia as a diagnostic test of early GDM (Supplemental Table 7). The second post-hoc analysis compared studies that used either universal screening or risk factors in the diagnostic approach (Supplemental Table 8). The study division in those post-hoc analysis coincided. In the treatment vs usual care studies, those using $HbA_{1c}$ for diagnosis adopted a universal screening approach, while those using glycemia relied on risk factor screening; however, in studies using population-level strategies, the correspondence was opposite; those using $HbA_{1c}$ for diagnosis relied on risk factor screening, while those using glycemia adopted universal screening.

In the comparison of $HbA_{1c}$ vs glycemia as diagnostic tests of early GDM (Supplemental Table 7), studies on treatment versus usual care showed no differences in primary or secondary

**TABLE 2**
**Characteristics of women in the randomized controlled trials included in the meta-analysis**

| Study | N, subjects | Age, y | BMI, kg/m$^2$ | Ethnicity, N | Gestational age,[a] wks | Diagnostic test results in first trimester |
|---|---|---|---|---|---|---|
| Treatment vs usual care of women with early GDM | | | | | | |
| Osmundson[21] | **Intervention**<br>50 (42 analyzed) | 32.4±5.1 | 27.2±6.2 | - Caucasian 7<br>- Asiatic 16 | No data | (%)<br>$HbA_{1c}$ 5.8±0.1 |
| | **Control**<br>45 (42 analyzed) | 34.3±5.2 | 27.4±7.5 | - African American<br>- Hispanic 17<br>- Caucasian 5<br>- Asiatic 15<br>- African American 1<br>- Hispanic 20 | No data | $HbA_{1c}$ 5.8±0.1 |
| Hughes[22] | **Intervention**<br>24 (23 analyzed) | 31.3±4.8 | 30.0±8.5 | - European 5<br>- Maori 0<br>- Pacific 4<br>- Asian 14<br>- Other 1 | 11.2±2.2 | (%)<br>$HbA_{1c}$ 6.1±0.09 |
| | **Control**<br>23 (21 analyzed) | 32.8±4.8 | 32.8±8.4 | - European 3<br>- Maori 2<br>- Pacific 3<br>- Asian 13<br>- Other 2 | 11.1±2.3 | $HbA_{1c}$ 6.1±0.09 |
| Simmons[19] | **Intervention**<br>11 | 29±5 | 32.3±7.8 | - Caucasian 7<br>- Other 4 | 18.5±1.2 | Fasting (mmol/L): 5.1±0.4<br>1 h: 8.0±1.7<br>2 h: 7.0±1.9 |
| | **Control**<br>10 | 30±7 | 33.0±7.0 | - Caucasian 5<br>- Other 5 | 17.5±1.8 | Fasting: 5.1±0.3<br>1 h: 8.4±1.6 |
| Roeder[12] | **Intervention**<br>82 | 32.7±5.1 | 28.1±8.7 | - Asian 8<br>- White 45<br>- African American 8<br>- Other 21 | 10.0±2.4 | No numeric data on FPG and $HbA_{1c}$; 80% diagnosed after $HbA_{1c}$ |
| | **Control**<br>75 | 33.0±4.1 | 27.2±6.3 | - Asian 11<br>- White 40<br>- African American 2<br>- Others 22 | 10.9±2.0 | |

*(continued)*

**TABLE 2**
**Characteristics of women in the randomized controlled trials included in the meta-analysis** *(continued)*

| Study | N, subjects | Age, y | BMI, kg/m$^2$ | Ethnicity, N | Gestational age,[a] wks | Diagnostic test results in first trimester |
|---|---|---|---|---|---|---|
| Simmons[20] | **Intervention** 400 | 32.1±4.8 | 32.1±7.7 | - White European 150<br>- South Asian 129<br>- East/Southeast Asia 51<br>- Middle Eastern 32<br>- Maori/Pacific Island 24<br>- Other 13 | 15.5±2.5 | Fasting (mmol/L): 5.1±0.4<br>1 h: 9.0±2.<br>2 h: 7.3±1.6 |
| | **Control** 393 | 32.6±4.9 | 32.9±8.4 | - White European 166<br>- South Asian 106<br>- East/Southeast Asia 60<br>- Middle Eastern 17<br>- Maori/Pacific Island 22<br>- Other 20 | 15.7±2.4 | Fasting: 5.0±0.5<br>1 h: 9.2±2.0<br>2 h: 7.4±1.6 |
| Strategies at the population level | | | | | | |
| Harper[23] | **Intervention** 459 | 27.2±5.9 | 37.2±6.6 | - White, non-Hispanic 52<br>- Black, non-Hispanic 280<br>- Native American 2<br>- Asian 1<br>- Hispanic 122<br>- Other 2 | 13.8±3.8 | (%)<br>$HbA_{1c}$ 5.3±0.44 |
| | **Control** 463 | 26.±5.9 | 37.0±6.5 | - White, non-Hispanic 35<br>- Black, non-Hispanic 299<br>- Native American 3<br>- Asian 2<br>- Hispanic 123<br>- Other 1 | 13.6±3.7 | $HbA_{1c}$ 5.3±0.44 |
| Tehrani[18] A vs C | **Intervention** 7117 | 30.0±5.9 | 26.2±4.6 | No data | 8.9±3.7 | No data |
| | **Control** 7494 | 29.8±5.7 | 25.6±4.9 | No data | 9.5±3.9 | No data |
| Tehrani[18] D vs E | **Intervention** 6412 | 29.2±5.9 | 25.2±4.8 | No data | 9.3±3.5 | No data |
| | **Control** 7748 | 29.6±6.0 | 25.4±4.8 | No data | 9.2±4.0 | No data |

*BMI*, body mass index; *FPG*, fasting plasma glucose; *GDM*, gestational diabetes mellitus; *$HbA_{1C}$*, Hemoglobin A1C.

[a] At booking or randomization.

**TABLE 3**
**Detection and treatment of early gestational diabetes mellitus—summary of findings (treatment compared to usual care of women with early gestational diabetes mellitus)**

| Outcomes | No. of participants (studies) | Certainty of the evidence[a] (GRADE) | Relative effect (95% CI) | Anticipated absolute effects[b] | |
|---|---|---|---|---|---|
| | | | | Risk with usual care | Risk difference with early diagnosis and treatment |
| GDM | | | | | |
| Total GDM | Not reported | | | | |
| Early GDM diagnosis | Not reported | | | | |
| Second/third trimester GDM diagnosis | Not reported | | | | |
| Second/third trimester GDM reversion | 204 participants from 2 trials | ⨁⨁◯◯ low[c,d] | **RR 1.12** (0.96–1.32) | 636 per 1.000 | **76 more per 1.000** 25 fewer to 204 more |
| Cesarean section | | | | | |
| Total cesarean section | 1040 participants from 5 trials | ⨁⨁⨁⨁ high | **RR 0.95** (0.81–1.11) | 382 per 1.000 | **19 fewer per 1.000** 73 fewer to 42 more |
| Primary cesarean section | 74 participants from 1 trial | ⨁◯◯◯ very low[c,e] | **RR 0.50** (0.19–1.32) | 270 per 1.000 | **135 fewer per 1.000** 219 fewer to 86 more |
| Emergency cesarean section | 809 participants from 3 trials | ⨁⨁◯◯ low[e] | **RR 0.93** (0.67–1.30) | 204 per 1.000 | **14 fewer per 1.000** 67 fewer to 61 more |
| Preterm birth | 790 participants from 2 trials | ⨁⨁◯◯ low[e] | **RR 0.88** (0.55–1.43) | 82 per 1.000 | **10 fewer per 1.000** 37 fewer to 35 more |
| Macrosomia | 868 participants from 2 trials | ⨁⨁◯◯ low[c,f] | **RR 0.32** (0.09–1.16) | 21 per 1.000 | **14 fewer per 1.000** 19 fewer to 3 more |

*CI*, confidence interval; *GDM*, gestational diabetes mellitus; *GRADE*, Grading of Recommendations, Assessment, Development and Evaluation; *RR*, relative risk.

[a] For judging imprecision, we set a threshold of a relative risk reduction or increase of 25% for appreciable benefit or harm.[16]; [b] Risks in the intervention group are based on the average assumed risk in the comparison group from the included studies and the relative effect of the intervention; [c] Downgrade by 1 level because of risk of bias; [d] Downgrade by 1 level because of imprecision (upper side of the 95% CI suggesting a meaningful effect); [e] Downgrade by 2 levels because of imprecision (both sides of the 95% CI suggesting a meaningful effect); [f] Downgrade by 1 level because of imprecision (lower side of the 95% CI suggesting a meaningful effect).

**TABLE 4**
**Detection and treatment of early gestational diabetes mellitus—summary of findings (strategies at population level)**

| Outcomes | No. of participants (studies) | Certainty of the evidence[a] (GRADE) | Relative effect (95% CI) | Anticipated absolute effects[b] | |
|---|---|---|---|---|---|
| | | | | Risk with usual care | Risk difference with early diagnosis and treatment/tight cutoffs |
| GDM | | | | | |
| Total GDM | 29,693 participants from 3 trials | ⨁◯◯◯ very low[c,d] | **RR 1.83** (1.41—2.38) | 101 per 1.000 | **84 more per 1.000** (41 more to 140 more) |
| Early GDM diagnosis | 29,693 participants from 3 trials | ⨁◯◯◯ very low[c,e] | **RR 5.50** (3.56—8.48) | 26 per 1.000 | **117 more per 1.000** (67 more to 194 more) |
| Second/third trimester GDM diagnosis | 29,693 participants from 3 trials | ⨁◯◯◯ very low[c,f,g] | **RR 0.96** (0.71—1.29) | 75 per 1.000 | **3 fewer per 1.000** (22 fewer to 22 more) |
| Second/third trimester GDM reversion | Not reported | | | | |
| Cesarean section | | | | | |
| Total cesarean section | 27,411 participants from 2 trials | ⨁◯◯◯ very low[c,h,i] | **RR 0.84** (0.71—1.01) | 432 per 1.000 | **69 fewer per 1.000** (125 fewer to 4 more) |
| Primary cesarean section | 28,333 participants from 3 trials | ⨁⨁⨁◯ moderate[c] | **RR 0.88** (0.84—0.93) | 170 per 1.000 | **20 fewer per 1.000** (27 fewer to 12 fewer) |
| Emergency cesarean section | Not reported | | | | |
| Preterm birth | 27,411 participants from 2 trials | ⨁⨁◯◯ low[c,j] | **RR 1.08** (0.98—1.18) | 61 per 1.000 | **5 more per 1.000** (1 fewer to 11 more) |
| Macrosomia | 28,333 participants from 3 trials | ⨁◯◯◯ very low[c,g] | **RR 0.93** (0.83—1.04) | 61 per 1.000 | **4 fewer per 1.000** (10 fewer to 2 more) |

*CI*, confidence interval; *GDM*, gestational diabetes mellitus; *GRADE*, Grading of Recommendations, Assessment, Development and Evaluation; *RR*, relative risk.

[a] For judging imprecision, we set a threshold of a relative risk reduction or increase of 25% for appreciable benefit or harm.[16] Moreover, for this comparison, we assumed that the effect could only be translated to the 10% prevalent population with hyperglycemia during the first trimester (candidates, in consequence, to treatment); [b] Risks in the intervention group are based on the average assumed risk in the comparison group from the included studies and the relative effect of the intervention; [c] Downgrade by 1 level because of risk of bias; [d] Downgrade by 2 levels because of very serious inconsistency ($I^2$=93%); [e] Downgrade by 2 levels because of very serious inconsistency ($I^2$=89%); [f] Downgrade by 2 levels because of very serious inconsistency ($I^2$=90%); [g] Downgrade by 2 levels because of imprecision (both sides of the 95% CI suggesting a meaningful effect); [h] Downgrade by 2 levels because of very serious inconsistency ($I^2$=97%); [i] Downgrade by 1 level because of imprecision (lower side of the 95% CI suggesting a meaningful effect); [j] Downgrade by 1 level because of imprecision (upper side of the 95% CI suggesting a meaningful effect).

**TABLE 5**
**Maternal and fetal outcomes in randomized controlled trials addressing detection and treatment of early gestational diabetes mellitus**

| Outcomes | N studies | N subjects | RR, CI 95% | MD, CI 95% | $I^2$, % |
|---|---|---|---|---|---|
| Treatment vs usual care of women with early GDM | | | | | |
| Maternal outcomes | | | | | |
| Primary outcomes | | | | | |
| Second/third trimester GDM reversion | 2 | 204 | 1.12 [0.96, 1.32] | | 0 |
| Total cesarean section | 5 | 1040 | 0.95 [0.81, 1.11] | | 0 |
| Primary cesarean section | 1 | 74 | 0.50 [0.19, 1.32] | | NA |
| Emergency cesarean section | 3 | 809 | 0.93 [0.67, 1.30] | | 3 |
| Secondary outcomes | | | | | |
| Weight gain | 3 | 730 | | **−0.99 [−1.74, −0.24]** | 0 |
| Drug treatment | 5 | 1044 | **1.42 [1.26, 1.60]** | | 0 |
| Total PIH | 3 | 844 | 1.09 [0.73, 1.64] | | 0 |
| Preeclampsia | 2 | 793 | 0.65 [0.07, 6.03] | | 59 |
| Shoulder dystocia | 2 | 785 | 0.98 [0.43, 2.24] | | NA |
| Fetal outcomes | | | | | |
| Primary outcomes | | | | | |
| Preterm birth | 2 | 790 | 0.88 [0.55, 1.43] | | 0 |
| Macrosomia | 2 | 868 | 0.32 [0.09, 1.16] | | 0 |
| Secondary outcomes | | | | | |
| Gestational age at birth | 4 | 997 | | −0.17 [−0.38, 0.04] | 0 |
| Birthweight | 4 | 962 | | **−101.5 [−177.0, −25.9]** | 0 |
| Large for gestational age | 4 | 881 | 0.81 [0.60, 1.09] | | 0 |
| Small for gestational age | 3 | 807 | 1.29 [0.87, 1.92] | | 0 |
| Neonatal hypoglycemia | 3 | 626 | 1.10 [0.51, 2.37] | | 31 |
| Neonatal hypoglycemia requiring IV glucose | 1 | 35 | 0.17 [0.01, 3.30] | | NA |
| Respiratory distress | 2 | 785 | **0.57 [0.39, 0.83]** | | 0 |
| Neonatal jaundice | 2 | 776 | 1.02 [0.69, 1.51] | | 0 |
| Birth trauma | 1 | 741 | 0.59 [0.14, 2.45] | | NA |
| NICU | 3 | 807 | 0.96 [0.46, 1.99] | | 15 |
| Stillbirth | 1 | 20 | 0.28 [0.01, 6.10] | | NA |
| Perinatal mortality | 1 | 748 | 1.47 [0.25, 8.74] | | NA |
| Strategies at the population level | | | | | |
| Maternal outcomes | | | | | |
| Primary outcomes | | | | | |
| Total GDM | 3 | 29,693 | **1.83 [1.41, 2.38]** | | 93 |
| Early GDM | 3 | 29,693 | **5.50 [3.56, 8.48]** | | 89 |
| Second/third trimester GDM diagnosis | 3 | 29,693 | 0.96 [0.71, 1.29] | | 90 |
| Total cesarean section | 2 | 27,411 | 0.84 [0.71, 1.01] | | 97 |
| Primary cesarean section | 3 | 28,333 | **0.88 [0.84, 0.93]** | | 0 |
| Emergency cesarean section | 0 | 0 | - | | - |

*(continued)*

**TABLE 5**
**Maternal and fetal outcomes in randomized controlled trials addressing detection and treatment of early gestational diabetes mellitus** *(continued)*

| Outcomes | N studies | N subjects | RR, CI 95% | MD, CI 95% | $I^2$, % |
|---|---|---|---|---|---|
| Secondary outcomes | | | | | |
| Weight gain | 2 | 28,771 | | −0.35 [−1.04, 0.34] | 98 |
| Drug treatment | 3 | 29,693 | 1.06 [0.87, 1.28] | | 56 |
| Total PIH | 1 | 922 | **1.34 [1.08, 1.68]** | | NA |
| Preeclampsia | 3 | 28,333 | **1.33 [1.01, 1.76]** | | 92 |
| Shoulder dystocia | 1 | 922 | 0.95 [0.58, 1.53] | | NA |
| Fetal outcomes | | | | | |
| Primary outcomes | | | | | |
| Preterm birth | 2 | 27,411 | 1.08 [0.98, 1.18] | | 0 |
| Macrosomia | 3 | 28,333 | 0.93 [0.83, 1.04] | | 21 |
| Secondary outcomes | | | | | |
| Gestational age at birth | 3 | 28,333 | | −0.06 [−0.15, 0.04] | 68 |
| Birthweight | 0 | 0 | - | | - |
| Large for gestational age | 3 | 28,333 | 0.92 [0.84, 1.01] | | 0 |
| Small for gestational age | 2 | 27,411 | 1.01 [0.92, 1.12] | | 39 |
| Neonatal hypoglycemia | 3 | 28,143 | 1.11 [0.88, 1.42] | | 0 |
| Neonatal hypoglycemia requiring IV glucose | 0 | 0 | - | | - |
| Respiratory distress | 0 | 0 | - | | - |
| Neonatal jaundice | 3 | 28,143 | 1.14 [0.48, 2.71] | | 99 |
| Birth trauma | 2 | 27,221 | 1.00 [0.67, 1.49] | | 34 |
| NICU | 2 | 27,221 | 1.00 [0.68, 1.48] | | 93 |
| Stillbirth | 2 | 27,411 | 0.95 [0.71, 1.26] | | 0 |
| Perinatal mortality | 0 | 0 | - | | - |

*CI*, confidential interval; *GDM*, gestational diabetes mellitus; *IV*, intravenous; *MD*, mean difference; *NA*, not applicable; *NICU*, neonatal intensive care unit; *PIH*, pregnancy-induced hypertension; *RR*, relative risk.

outcomes. However, in studies using different population-level strategies, a significant difference was noted in the primary outcome of total GDM that was higher when diagnosis was performed with glycemia: RR, 2.08; 95% CI, 1.58−2.73 vs 1.24; 95% CI, 0.90−1.73, *P*=.02).

In the comparison of universal screening vs risk factor approaches to diagnose early GDM (Supplemental Table 8), studies on treatment vs usual care showed no differences in primary or secondary outcomes. However, in studies using different population-level strategies, a significant difference was noted in the primary outcome of total GDM that was higher in studies using a universal screening strategy: RR, 2.08; 95% CI, 1.58−2.73 vs 1.24; 95% CI, 0.90−1.73, *P*=.02).

## Comment

### Principal findings

This systematic review and meta-analysis of RCTs addressing the detection and treatment of early GDM has not shown remarkable benefits either in the treated group or at the population level. In treatment vs usual care studies, the only beneficial effect was a decrease in neonatal respiratory distress, as lower maternal weight gain and birthweight could lead to either improved (ie, lower rate of macrosomia or large for gestational age) or worsened (ie, higher rate of small for gestational age) clinical outcomes. In studies using different strategies at the population level, both overall and early GDM diagnoses were increased without a net clinical benefit (lower rate of primary cesarean section but higher rate of total PIH and preeclampsia).

Larger effects can be expected in studies comparing treatment vs usual care in relation to those studies addressing different population-level strategies. In studies at the population level, the benefits of the intervention in women with early GDM diagnosis will be diluted within the general obstetric population, as the intervention is not expected to affect women without

hyperglycemia. This seemed to be the case for some outcomes, which showed a larger reduction in treatment vs usual care studies, even when statistical significance was not reached. Unfortunately, birthweight and respiratory distress, that displayed significant and clinically relevant reductions in the treatment vs usual care studies, were not addressed in population studies and the comparison between the 2 study designs is not possible.

Total PIH and preeclampsia deserve special attention. In the treatment vs usual care studies, the nonsignificant reduction of preeclampsia in the intervention group was in the expected direction, and its magnitude would be clinically relevant. However, in studies addressing population-level strategies, the effect not only went in the unexpected direction but also reached significance for both total PIH (3 studies: 2 in Iran and 1 in the United States) and preeclampsia (1 study in the United States). In observational studies, hyperglycemia in early pregnancy is associated with preeclampsia,[25,26] and the association does not disappear after adjustment for covariates.[25] In the current meta-analysis, the nonsignificant reduction in preeclampsia for treatment vs usual care studies could be attributed to insufficient statistical power. However, a significantly higher risk for both PIH and preeclampsia in studies using population-level strategies was totally unexpected. If the target population with hyperglycemia appears to benefit from the intervention, the rest of the women undergoing the screening apparently did not. It could be hypothesized that the higher rate of hypertensive complications in population strategies leading to higher rates of diagnosis of early GDM is connected with stress since both life and pregnancy stress have been associated with preeclampsia.[27] This aligns with the recent findings of the CDC4G study, which observed that lowering the diagnostic criteria for GDM in the second/third trimester did not lead to significant changes in hypertension at the population level but to an increased risk of gestational hypertension and preeclampsia in the subgroup that was discordant for GDM diagnosis and received treatment.[28] The authors suggest that this result could be due to surveillance bias warranting further evaluation but this implies that when treating maternal hyperglycemia, improvement cannot be taken for granted.

In the studies comparing strategies at the population level, heterogeneity was high for most maternal outcomes. As the number of included studies is small, the interpretation should be cautious.[29]

The sensitivity analysis did not alter the results of treatment vs usual care studies. However, in studies using strategies at the population level, the number of significant outcomes decreased, modifying the overall interpretation. In the single study within this group, a higher rate of early GDM diagnosis was only associated with an increase in total PIH, indicating potential harm. The concerns raised about this study based on this TRACT assessment are consistent with those identified in the RoB assessment. The study with the higher number of items scored as "some concerns" was also the one displaying the highest risk of bias according to RoB2, and that has been excluded in the sensitivity analysis.

The 2 post-hoc analysis provided little additional information. The only observed difference was a higher rate of total GDM in population-based studies that used glycemia as a diagnostic test for early GDM and it was driven by an increased rate of early GDM together while the rate of second/third trimester GDM remained unchanged. In turn, this was attributable to the clusters of Tehrani et al[18] using a 2-step approach in the second/third trimester; the clusters using stricter criteria for early GDM showed a significantly higher risk of GDM in second/third trimester (RR, 1.24, 95% CI, 1.08−1.43). We can only attribute this to chance.

In the second post-hoc analysis, the only observed difference was a higher rate of total GDM in population-based studies using a universal vs risk factor approach. As previously mentioned, the study division coincides with that of the first post-hoc analysis and the interpretation remains the same.

It is important to note that the study of Simmons et al[20] conducted exploratory subgroup analyses and suggested a more pronounced benefit of early treatment among women with oral glucose tolerance test values in the higher vs lower glycemic range and among those in whom hyperglycemia was identified before 14 weeks' gestation. These observations could modify our interpretation of early GDM treatment and warrant further investigation.

### Comparing with existing literature

A meta-analysis addressing detection and treatment of early GDM was published in 2022 by McLaren et al.[30] Their results and those of the present study cannot be compared. First, because their design was different (ie, conference abstracts were included; RCTs addressing treatment of women with early GDM and population-level strategies were combined). Second, we have been able to include RCTs that were published after McLaren meta-analysis.

### Strengths and limitations

A limitation of the evidence included in the review is the heterogeneity of the designs addressing the problem. Two categories of studies were identified (treatment vs usual obstetric care in the target population and studies addressing population-level strategies) that we circumvent through a separate analysis. However, the designs were heterogeneous within each of these categories including a cluster randomized trial in the last one. The impact of the cluster randomized trial was addressed with a sensitivity analysis.

A limitation of the review process is that we have only included reports published as full text excluding those in the gray literature. We are aware that this limits the range of information but we took that decision since the information presented in conference abstracts is frequently inconsistent with the results reported at full reports[31] and includes insufficient details regarding the study design limiting the possibility to properly assess some critical issues for systematic reviews such as risk of bias.[32] However, we kept in the meta-

analysis 4 articles that were registered several weeks after the initiation of enrollment. Given the entire recruitment period, we considered that any protocol modification that may have occurred prior to registration would likely not have had a relevant impact on the results.

## Conclusions and implications

We conclude that detection and treatment of early GDM does not offer indisputable benefits either in treated women or at the population level. More studies are required to elucidate this issue. ■

### REFERENCES


**1.** Davidson KW, Barry MJ, Mangione CM, et al. Screening for gestational diabetes: US preventive services task force recommendation statement. JAMA 2021;326:531–8.

**2.** American Diabetes Association Professional Practice Committee. 15. Management of diabetes in pregnancy: standards of care in diabetes-2024. Diabetes Care 2024;47:S282–94.

**3.** World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. Geneva: World Health Organization; 2013:1–63.

**4.** Diabetes in Pregnancy: Management from Preconception to the Postnatal Period. National Institute for Health and Care Excellence (NICE). 2020. http://www.ncbi.nlm.nih.gov/books/NBK555331/. Accessed April 27, 2024.

**5.** Metzger BE. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676–82.

**6.** ACOG Practice Bulletin No. 190: gestational diabetes mellitus. Obstet Gynecol 2018;131:e49–64.

**7.** Feig DS, Berger H, Donovan L, et al. Diabetes and pregnancy. Can J Diabetes 2018;42(Suppl 1):S255–82.

**8.** Immanuel J, Simmons D. Screening and treatment for early-onset gestational diabetes mellitus: a systematic review and meta-analysis. Curr Diab Rep 2017;17:115.

**9.** Prospero registration, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023392060. Accessed April 9, 2023.

**10.** Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane. 2024, Version 6.5. .

**11.** Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

**12.** Roeder H, Moore T, Wolfson M, Gamst A, Ramos G. Treating hyperglycemia in early pregnancy: a randomized controlled trial. Am J Obstet Gynecol MFM 2019;1:33–41.

**13.** Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

**14.** Mol BW, Lai S, Rahim A, et al. Checklist to assess Trustworthiness in RAndomised Controlled Trials (TRACT checklist): concept proposal and pilot. Res Integr Peer Rev 2023;8:6.

**15.** Alonso-Coello P, Schünemann HJ, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: introduction. BMJ 2016;353:i2016.

**16.** Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence–imprecision. J Clin Epidemiol 2011;64:1283–93.

**17.** Ramezani Tehrani F; Gulf Study Cooperative Research Group. Cost effectiveness of different screening strategies for gestational diabetes mellitus screening: study protocol of a randomized community non-inferiority trial. Diabetol Metab Syndr 2019;11:106.

**18.** Ramezani Tehrani F, Behboudi-Gandevani S, Farzadfar F, et al. A cluster randomized noninferiority field trial of gestational diabetes mellitus screening. J Clin Endocrinol Metab 2022;107:e2906–20.

**19.** Simmons D, Nema J, Parton C, et al. The treatment of booking gestational diabetes mellitus (TOBOGM) pilot randomised controlled trial. BMC Pregnancy Childbirth 2018;18:151.

**20.** Simmons D, Immanuel J, Hague WM, et al. Treatment of gestational diabetes mellitus diagnosed early in pregnancy. N Engl J Med 2023;388:2132–44.

**21.** Osmundson S, Norton M, El-Sayed Y, Carter S, Faig J, Kitzmiller J. Early screening and treatment of women with prediabetes: a randomized controlled trial. Am J Perinatol 2016;33:172–9.

**22.** Hughes RCE, Rowan J, Williman J. Prediabetes in pregnancy, can early intervention improve outcomes? A feasibility study for a parallel randomised clinical trial. BMJ Open 2018;8:e018493.

**23.** Harper LM, Jauk V, Longo S, Biggio JR, Szychowski JM, Tita AT. Early gestational diabetes screening in obese women: a randomized controlled trial. Am J Obstet Gynecol 2020;222:495.e1–8.

**24.** Simmons D, Hague W, Teede H, et al. Hyperglycaemia in early pregnancy: the Treatment of Booking Gestational diabetes Mellitus (TOBOGM) study. A randomised controlled trial. Med J Aust 2018;209:405–6.

**25.** Kattini R, Hummelen R, Kelly L. Early gestational diabetes mellitus screening with glycated hemoglobin: a systematic review. J Obstet Gynaecol Can JOGC 2020;42:1379–84.

**26.** Mane L, Flores-Le Roux JA, Benaiges D, et al. Role of first-trimester HbA1c as a predictor of adverse obstetric outcomes in a multiethnic cohort. J Clin Endocrinol Metab 2017;102:390–7.

**27.** Yu Y, Zhang S, Wang G, et al. The combined association of psychosocial stress and chronic hypertension with preeclampsia. Am J Obstet Gynecol 2013;209:438.e1–12.

**28.** de Brun M, Magnuson A, Montgomery S, et al. Changing diagnostic criteria for gestational diabetes (CDC4G) in Sweden: a stepped wedge cluster randomised trial. PLoS Med 2024;21:e1004420.

**29.** von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. BMC Med Res Methodol 2015;15:35.

**30.** McLaren RA, Ruymann KR, Ramos GA, Osmundson SS, Jauk V, Berghella V. Early screening for gestational diabetes mellitus: a meta-analysis of randomized controlled trials. Am J Obstet Gynecol MFM 2022;4:100737.

**31.** Li G, Abbade LPF, Nwosu I, et al. A scoping review of comparisons between abstracts and full reports in primary biomedical research. BMC Med Res Methodol 2017;17:181.

**32.** Li T, Higgins J, Deeks J. Chapter 5: collecting data. In: Higgins JPT, Thomas J, Chandler J, et al, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 6.4. 2023. Available from, www.training.cochrane.org/handbook. Accessed August 20, 2024.