Gestational diabetes mellitus and adverse maternal and perinatal outcomes in twin and singleton pregnancies: a systematic review and meta-analysis

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OBJECTIVE: This study aimed to assess the risk of adverse maternal and perinatal complications between twin and singleton pregnancies affected by gestational diabetes mellitus and the respective group without gestational diabetes mellitus (controls).

DATA SOURCES: A literature search was performed using MEDLINE, Embase, and Cochrane from January 1980 to May 2023.

STUDY ELIGIBILITY CRITERIA: Observational studies reporting maternal and perinatal outcomes in singleton and/or twin pregnancies with gestational diabetes mellitus vs controls were included.

METHODS: This was a systematic review and meta-analysis. Pooled estimate risk ratios with 95% confidence intervals were generated to determine the likelihood of adverse pregnancy outcomes between twin and singleton pregnancies with and without gestational diabetes mellitus. Heterogeneity among studies was evaluated in the model and expressed using the I^2 statistic. A P value of $<.05$ was considered statistically significant. The meta-analyses were performed using Review Manager (RevMan Web). Version 5.4. The Cochrane Collaboration, 2020. Meta-regression was used to compare relative risks between singleton and twin pregnancies. The addition of multiple covariates into the models was used to address the lack of adjustments.

RESULTS: Overall, 85 studies in singleton pregnancies and 27 in twin pregnancies were included. In singleton pregnancies with gestational diabetes mellitus, compared with controls, there were increased risks of hypertensive disorders of pregnancy (relative risk, 1.85; 95% confidence interval, 1.69—2.01), induction of labor (relative risk, 1.36; 95% confidence interval, 1.05—1.77), cesarean delivery (relative risk, 1.31; 95% confidence interval, 1.24—1.38), large-for-gestational-age neonate (relative risk, 1.61; 95% confidence interval, 1.46—1.77), preterm birth (relative risk, 1.36; 95% confidence interval, 1.27—1.46), and admission to the neonatal intensive care unit (relative risk, 1.43; 95% confidence interval, 1.38—1.49). In twin pregnancies with gestational diabetes mellitus, compared with controls, there were increased risks of hypertensive disorders of pregnancy (relative risk, 1.69; 95% confidence interval, 1.51—1.90), cesarean delivery (relative risk, 1.10; 95% confidence interval, 1.06—1.13), large-for-gestational-age neonate (relative risk, 1.29; 95% confidence interval, 1.03—1.60), preterm birth (relative risk, 1.19; 95% confidence interval, 1.07—1.32), and admission to the neonatal intensive care unit (relative risk, 1.20; 95% confidence interval, 1.09—1.32) and reduced risks of small-for-gestational-age neonate (relative risk, 0.89; 95% confidence interval, 0.81—0.97) and neonatal death (relative risk, 0.50; 95% confidence interval, 0.39—0.65). When comparing relative risks in singleton vs twin pregnancies, there was sufficient evidence to suggest that twin pregnancies have a lower relative risk of cesarean delivery (P=.003), have sufficient adjustment for confounders, and have lower relative risks of admission to the neonatal intensive care unit (P=.005), stillbirths (P=.002), and neonatal death (P=.001) than singleton pregnancies.

CONCLUSION: In both singleton and twin pregnancies, gestational diabetes mellitus was associated with an increased risk of adverse maternal and perinatal outcomes. In twin pregnancies, gestational diabetes mellitus may have a milder effect on some adverse perinatal outcomes and may be associated with a lower risk of neonatal death.

Key words: gestational diabetes mellitus, hypertension, maternal outcomes, perinatal outcomes, pregnancy, preterm, singletons, twins

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The protocol and datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AJOG at a Glance

Why was this study conducted?

The effect of gestational diabetes mellitus (GDM) on pregnancy outcomes in twin pregnancies is not well studied. Screening and management of GDM in twin pregnancies have been extrapolated from singleton pregnancies where the beneficial effect of tight control on maternal and neonatal outcomes is better studied. This study aimed to investigate whether twin and singleton pregnancies affected by GDM are at higher risk of adverse maternal and perinatal complications than the respective group without GDM (controls).

Key findings

In both singleton and twin pregnancies, GDM is associated with an increased risk of adverse maternal and perinatal outcomes. Unlike GDM in singleton pregnancies, GDM in twin pregnancies may be associated with fewer adverse outcomes than in twin pregnancies not complicated by GDM, including a lower risk of neonatal death.

What does this add to what is known?

The effect of GDM is milder in twin pregnancies than in singleton pregnancies. Different glycemic targets might be considered in twin pregnancies.

Introduction

Gestational diabetes mellitus (GDM) is defined as impaired glucose tolerance resulting in hyperglycemia of variable severity, diagnosed for the first time during pregnancy.[1] Over the last decades, the incidence of GDM has increased, mainly because of the increasing prevalence of obesity and advanced maternal age.[2,3] Twin pregnancies account for approximately 3% of all births with increasing incidence mostly because of advanced maternal age and widespread use of in vitro fertilization.[4,5]

The increasing prevalence of both GDM and twin pregnancies and the shared risk factors have led to the hypothesis that twinning may further increase the risk of GDM complications.[6,7] However, a meta-analysis by McGrath et al[8] found the risks of adverse neonatal outcomes to be similar in twins born to mothers with GDM compared with controls. In addition, there are some evidences that GDM in twin pregnancies, but not in singleton pregnancies, may be protective of some important perinatal outcomes, such as lower Apgar score and perinatal death.[9] Conversely, a recent meta-analysis by Tu and Fei[10] aggregating data from 8 studies comparing maternal and perinatal outcomes in singleton vs twin pregnancies complicated by GDM found lower risk in singleton pregnancies for several perinatal outcomes.

Screening and management for twin pregnancies complicated by GDM are extrapolated from studies in singleton pregnancies, although good quality evidence that treatment improves adverse outcomes is available only for singleton pregnancies complicated by GDM[11,12] and despite reports showing glucose tolerance to be different in mothers of twins.[13–15] To date, it remains unclear whether GDM has different associations with maternal and perinatal outcomes in twin and singleton pregnancies.

Objectives

This systematic review and meta-analysis aimed to assess the risk of adverse maternal and perinatal complications in twin and singleton pregnancies affected by GDM, compared with the respective group without GDM.

Methods

Eligibility criteria, data sources, and search strategy

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[16] and registered with the International Prospective Register of Systematic Reviews (registration number: CRD42020222733).

A literature search was performed using MEDLINE, Embase, and Cochrane databases. The following search terms were used: "GDM; or gestational diabetes; or diabetes in pregnancy; or glucose intolerance; or hyperglycaemia; AND twins; or multiple; or singleton; AND pregnancy; NOT type 1; or type 2; or t2DM." Filters applied included "humans, female." A manual search of relevant study reference lists was completed to identify additional studies of interest. Search results were exported to EndNote X6 (Clarivate, London, United Kingdom; http: //www.endnote.com) to organize and remove duplicate publications. Searches were performed from January 1980 to May 2023. The start date of the search was set based on the time where GDM screening using thresholds adjusted for plasma became widespread.[17] Of note, 2 authors (M.C. and E.G.) independently screened the titles and/or abstracts of studies to determine eligibility for subsequent full article appraisal. Disagreements were solved by consensus or by a third reviewer (S.I.).

Study selection

Articles were considered eligible for full manuscript review and data extraction if the study was a full article observational study (either retrospective or prospective) comparing maternal and perinatal outcomes in pregnancies complicated by GDM vs pregnancies not complicated by GDM stratified to singleton or twin pregnancies, published between January 1980 and May 2023. No language restriction was imposed.

Studies with insufficient data for interpretation, those without an adequate comparison group, and those with inadequate distinction between preexisting diabetes mellitus (DM) and GDM were excluded. If studies did not report data in sufficient detail, the corresponding author was contacted to request further information.

Data extraction

For data collection, an extraction sheet was developed on Microsoft Excel

(version 2018; Microsoft Corporation, Redmond, WA), including main data categories: study characteristics (study authors, year of publication, and study design), details of GDM screening (method, approach, and diagnostic criteria) and management (lifestyle modifications, diet, and medical treatment with metformin and/or insulin), GDM prevalence (as reported in the study or calculated as the number of GDM cases over total number of cases screened), and maternal demographics (non-GDM and GDM sample sizes, maternal age, main ethnicity, parity, body mass index [BMI], smoking habit, mode of conception, and chronic hypertension). In addition, for studies in twin pregnancies, we extracted data on chorionicity.

Data were extracted from publications by 1 author (M.C.) and cross-checked by another author (E.G.). For studies that separated the groups (ie, 2 control groups or 2 GDM groups based on differences in blood glucose levels), the means and standard deviations were combined using the formula provided by the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0; Cochrane 2011), and the lower glucose threshold used for diagnosis was selected.

Outcomes

Adverse maternal outcomes included any cesarean delivery (CD); induction of labor (IOL); postpartum hemorrhage; hypertensive disorders of pregnancy (HDPs) defined as the sum of all adverse maternal outcomes related to high blood pressure, including pregnancy-induced hypertension, preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelet counts; preterm premature rupture of membranes; and placental abruption.

Adverse perinatal outcomes included small for gestational age (SGA) and large for gestational age (LGA), including definition and reference medical record used; preterm birth, including definition; low Apgar score, including definition; admission to the neonatal intensive care unit (NICU); stillbirth, defined as any death between 24 weeks of gestation and birth; neonatal death (NND), referred to as the death of a live-born infant, regardless of gestational age at birth, within the first 28 completed days of life; and perinatal mortality, defined as the sum of stillbirths and NNDs.

Assessment of risk of bias

To assess the quality of the studies selected and the risk of bias, 2 authors (M.C. and E.G.) classified them independently, according to the Newcastle-Ottawa Scale (NOS) grading and considering scores of $\geq$7 to 9, 4 to 6, and $<$4 low, medium, and high risk of bias, respectively.

Data synthesis

The primary endpoints of this study were to investigate the association of GDM in twin and singleton pregnancies with paired adverse maternal and perinatal outcomes.

Unadjusted pooled estimate risk ratios (RRs) with 95% confidence intervals (CIs) were generated to determine the likelihood of adverse pregnancy outcomes between GDM and non-GDM. Heterogeneity between studies was evaluated in the model and expressed using the I^2 statistic. A P value of $<.05$ was considered statistically significant. The meta-analyses were performed using Review Manager (RevMan Web). Version 5.4. The Cochrane Collaboration, 2020. Meta-regression was used to compare RRs between singleton and twin pregnancies (RStudio, RStudio Team [2020], Boston, MA; version 3.4.1).

Secondary analysis: meta-regression

To address the lack of adjustments of the studies included, multiple covariates were added into a meta-regression model to investigate whether this altered our conclusions regarding the difference in RRs between singleton and twin pregnancies. The covariates included number of fetuses (singleton or twin), diagnostic criteria for GDM (5 most common criteria and an additional "other" category), and 4 demographic maternal characteristics, including ethnicity, age, BMI, and nulliparity. Ethnicity was considered as a categorical variable depending on the most prevalent ethnicity; age and BMI were considered as continuous variables, and the means for each category were used; parity was defined by the percentage of nulliparous mothers out of the total number of mothers with and without GDM.

For this analysis, we have assumed that all women diagnosed with GDM (including those where data on screening methods and management were unavailable) received standard monitoring and treatment as appropriate. Therefore, outcomes presented herein refer to singleton and twin pregnancies diagnosed with GDM and treated as per local policies.

Results

Study selection

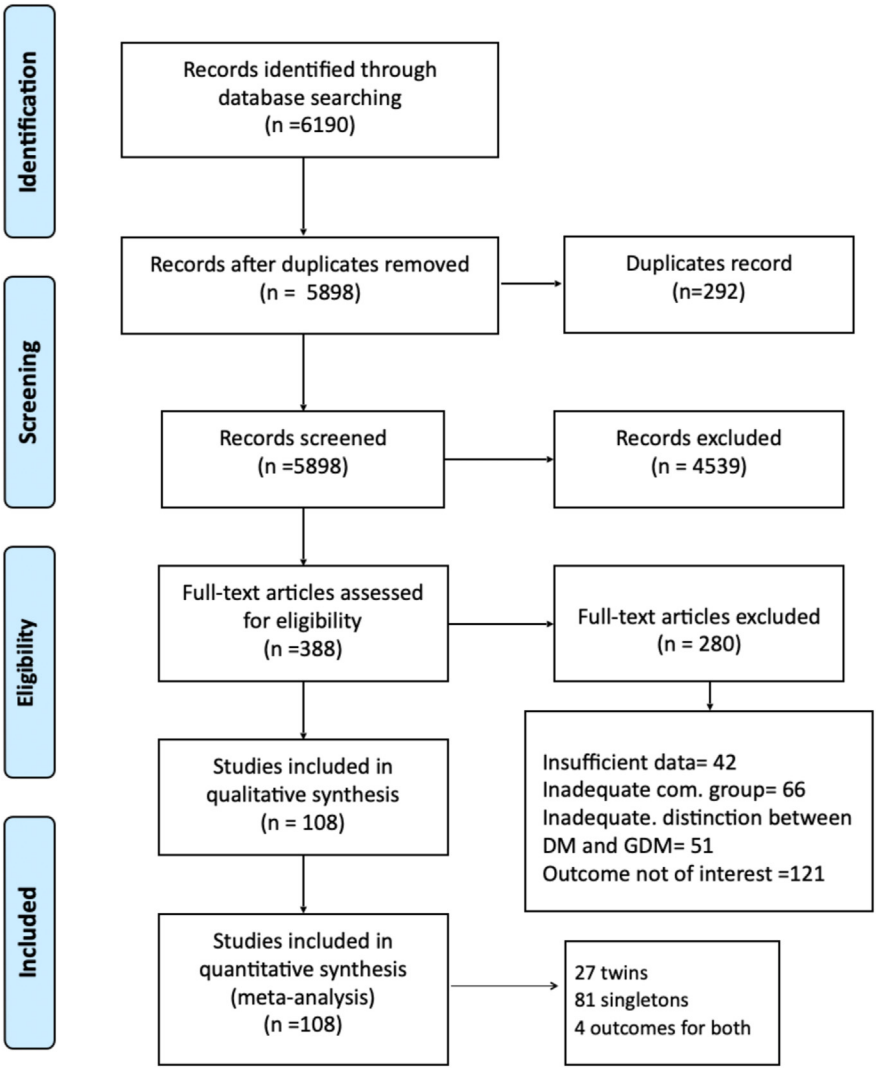
A total of 6190 studies were identified with the search. After the removal of duplicate studies, 5898 studies were screened by title and/or abstract, and 388 studies were deemed suitable for full article appraisal. After the assessment of eligibility, 280 studies were excluded because of the following reasons: insufficient reported study data for interpretation (n=42), inadequate comparison group (n=66), inadequate distinction between preexisting DM and GDM (n=51), and outcomes not of interest (n=121). Screening the study reference lists did not lead to additional studies being incorporated.

A total of 108 studies were included in the final meta-analysis, of which 81 in singleton pregnancies,[18–95] 23 in twin pregnancies,[62,96–117] and 4 studies[6,37,51,118] reporting outcomes for both singleton and twin pregnancies were included in both analyses (Figure 1).

Characteristics of studies in singletons

A total of 14,033,990 pregnancies were examined, including 722,020 singleton pregnancies complicated by GDM and 13,308,855 singleton controls. All studies included were observational in design. Among these studies, 70 were cohort studies, of which 58 were retrospective studies and 12 were prospective studies, and 15 were case-control studies, of which 9 were retrospective studies and 6 were prospective studies. Qualitative assessment using NOS identified a low risk of bias for 56 studies, a medium risk of bias for 21

FIGURE 1
PRISMA study selection flowchart



DM, diabetes mellitus; *GDM*, gestational diabetes mellitus; *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

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studies, and a high risk of bias for the remaining 7 studies (Supplemental Table 1).

Most studies were conducted in Asian women (34%), followed by White (31%), Hispanic (7%), Middle Eastern (6%), Black (3%), and other non-White or unspecified (19%). The average ages were 31.6±4.7 years for patients with GDM and 29.4±4.8 years for controls. The mean BMIs were 26.2±4.6 kg/m^2 for patients with GDM and 24.4±4.3 kg/m^2 for controls. Paired parity data were available for 63% of the studies, which showed a lower percentage of nulliparas among patients with GDM than among controls (47% vs 51%).

Screening strategy was universal in 59 studies, based on risk factors in 12 studies, variable in 2 studies (universal or risk factors), and unspecified in 12 studies. Of the studies reporting a universal screening strategy, the screening approaches were 2-step (glucose challenge test [GCT] in all women, followed by glucose tolerance test [GTT] in those with positive results) in 32 studies, 1-step (GTT in all women) in 25 studies, and variable (1-step or 2-step) in 2 studies. Of the studies adopting a screening strategy based on risk factors, 6 used a 1-step approach, 4 used a 2-step approach, and 2 used a variable or unspecified approach.

The methods of screening and the criteria for diagnosis varied widely across studies with the International Association of Diabetes and Pregnancy Study Group (33% of the studies), the Carpenter and Coustan (CC; 19%), the National Diabetes Data Group (NDDG; 8%), and the American Diabetes Association (5%) being the most used. Half of the studies included details of the management of GDM, with a combination of diet, self-monitoring, oral antihyperglycemic agents, and insulin being the most common measures reported.

Study design, geographic setting, ethnic characteristics of the populations, screening strategy, and GDM prevalence in studies on singleton pregnancies are outlined in Supplemental Table 2.

Characteristics of studies in twins

A total of 167,991 twin pregnancies were examined, including 11,812 pregnancies complicated by GDM and 156,179 controls. All studies included were observational in design, of which 20 were cohort studies (all retrospective but one[115]) and 7 were case-control studies (5 retrospective studies and 2 prospective studies). Qualitative assessment using NOS identified a low risk of bias for 21 studies, a medium risk of bias for 2 studies, and a high risk of bias for 4 studies (Supplemental Table 3).

The most represented ethnicity in studies on twin pregnancies was White (34%), followed by Asians (22%); however, in 44% of cases, ethnicity was unspecified. The average ages were 32.7±5.0 years for patients with GDM and 31.2±5.0 years for controls. The mean BMIs were 25±5.0 kg/m^2 for patients with GDM and 23.6±4.5 kg/m^2 for controls. Paired parity data were available for 15 studies (56%), which showed the percentage of nulliparous women to be higher in the GDM group than in controls (56% vs 55%). Of note, 21 studies (78%) included all type of twin pregnancies, 5 studies (18%) excluded complications in monochorionic diamniotic twin pregnancies

and all monochorionic monoamniotic pregnancies, and 1 study (4%) included dichorionic twin pregnancies only.

The screening strategy was universal in 20 studies, unspecified in 6 studies, and based on risk factors in 1 study. Of the studies adopting universal screening, 12 described a 2-step approach, 7 described a 1-step approach, and 1 described a variable approach (1-step or 2-step). The criteria for diagnosis were the same for singleton pregnancies and varied widely across studies with CC (15%), the NDDG (11%), the CDA (15%), and the Australasian Diabetes in Pregnancy Society (26%) being the most used ones. Details of the management of GDM in twin pregnancies were available in 16 studies, of which self-monitoring, lifestyle measures, and insulin treatment were common in 11 studies and oral antihyperglycemic were used in 5 studies only.

The study design, geographic setting, ethnic characteristics of the populations, screening strategy, and GDM prevalence in studies of twin pregnancies are outlined in Supplemental Table 4.

Gestational diabetes mellitus and maternal outcomes

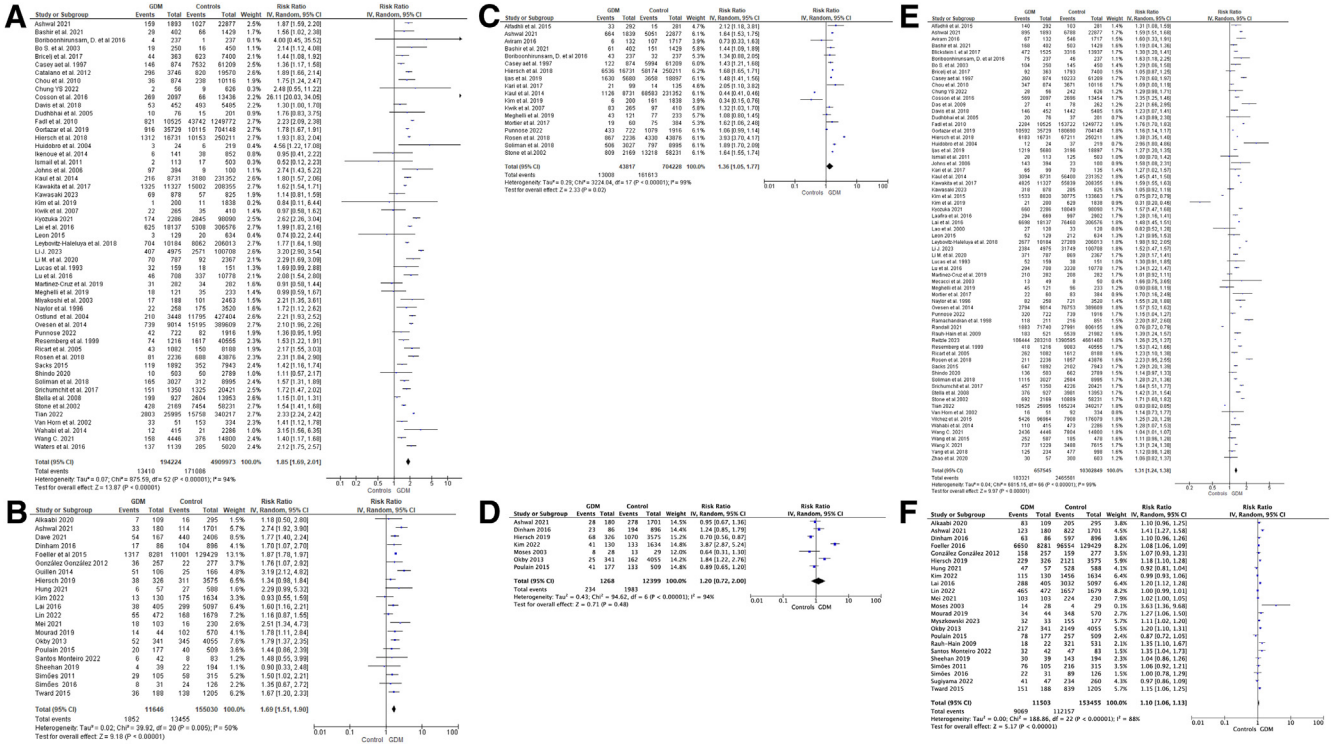
Hypertensive disorders of pregnancy

Of note, 52 studies in singleton pregnancies (including 194,224 mothers with GDM and 4,909,973 controls) and 21 studies in twin pregnancies (including 11,646 mothers with GDM and 155,030 controls) reported outcome data for HDPs, with mean prevalence rates of 9.6% (range, 0.5%−65.0%) and 18.3% (range, 6.4%−48.0%) in mothers of singletons and twins with GDM, respectively. In singleton pregnancies complicated by GDM, compared with those without GDM, the risk of HDPs was increased (RR, 1.85; 95% CI, 1.69−2.01; I^2=94%; P<.00001), and this was also true in twin pregnancies (RR, 1.69; 95% CI, 1.51−1.90; I^2=50%; P<.00001) (Figure 2, A and B). The difference in RRs between singleton and twin pregnancies was not statistically significant (P=.477), and the addition of covariates in meta-regression models did not change this.

Induction of labor

Of note, 18 studies in singleton pregnancies (including 43,817 mothers with GDM and 704,228 controls) and 7 studies in twin pregnancies (including

FIGURE 2
Risk of adverse maternal outcomes in singleton and twin pregnancies with GDM vs controls



Risk of hypertensive disorders of pregnancy in singleton pregnancies complicated by GDM vs controls (**A**) and in twin pregnancies complicated by GDM vs controls (**B**). Risk of induction of labor in singleton pregnancies complicated by GDM vs controls (**C**) and in twin pregnancies complicated by GDM vs controls (**D**). Risk of cesarean delivery in singleton pregnancies complicated by GDM vs controls (**E**) and in twin pregnancies complicated by GDM vs controls (**F**).

CI, confidence interval; *GDM*, gestational diabetes mellitus.

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1268 twins from mothers with GDM vs 12,399 controls) reported data on IOL with prevalence rates of 25.2% (range, 3.0%−60.0%) in singleton pregnancies and 18.5% (range, 5.3%−56.3%) in twin pregnancies. In singleton pregnancies complicated by GDM, compared with those without GDM, the risk of IOL was increased (RR, 1.36; 95% CI, 1.05−1.77; I^2=99%; P=.02); this was not the case in twin pregnancies (RR, 1.20; 95% CI, 0.72−2.00; I^2=94%; P=.48) (Figure 2, C and D). The difference in RRs between singleton and twin pregnancies was not statistically significant (P=.484), and the addition of covariates in meta-regression models did not change this.

Cesarean delivery

Of note, 67 studies in singleton pregnancies (including 657,545 mothers with GDM and 10,302.849 controls) and 23 in twin pregnancies (including 11,503 mothers with GDM and 153,455 controls) reported outcome data for CD, with mean prevalence rates of 36.4% (range, 2.6%−74.0%) and 76.0% (range, 44.0%−100.0%) in mothers of singletons and twins with GDM, respectively. The risk of CD was increased both in singleton pregnancies complicated by GDM (RR, 1.31; 95% CI, 1.24−1.38; I^2=99%; P<.00001) and in twin pregnancies complicated by GDM (RR, 1.10; 95% CI, 1.06−1.13; I^2=88%; P<.00001) compared with their respective controls without GDM (Figure 2, E and F).

The difference in RRs between singleton and twin pregnancies was statistically significant (P=.003), and the addition of covariates in meta-regression models did not change this.

Gestational diabetes mellitus and perinatal outcomes

Small for gestational age

Of note, 31 studies in singleton pregnancies (including 124,873 neonates from mothers with GDM and 2,064,602 controls) and 16 studies in twin pregnancies (including 4986 twins from mothers with GDM and 35,591 twins from controls) provided outcome data for SGA neonates, with mean prevalence rates of 7.3% (range, 1.8%−20.0%) in singleton pregnancies and 20.0% (range, 7.0%−63.2%) in twins born to mothers with GDM. SGA was mostly defined as birthweight below the 10th percentile (70% of the studies in singleton pregnancies and all but 1 study in twin pregnancies[105]) or birthweight of <2500 g.[18,23,46,57,68,70,74,80,105,119] Most studies in singleton pregnancies used reference medical records adjusted for gender and gestational age; 53% of studies in twin pregnancies used medical records for multiples,[51,100,101,103,104,112−115] with the remaining using medical records for singleton pregnancies (41%) or unspecified (6%). In singleton pregnancies complicated by GDM, compared with those without GDM, the risk of SGA was not reduced (RR, 0.99; 95% CI, 0.90−1.08; I^2=92%; P=.78). Conversely, in twin pregnancies complicated by GDM, compared with those without GDM, the risk of SGA was reduced (RR, 0.89; 95% CI, 0.81−0.97; I^2=27%; P=.009) (Figure 3, A and B).

The difference in RRs between singleton and twin pregnancies was not statistically significant (P=.250), and the addition of covariates in meta-regression models did not change this.

Large for gestational age

Of note, 46 studies in singleton pregnancies (including 508,648 neonates from mothers with GDM and 9,834,975 controls) and 14 studies in twin pregnancies (including 4841 twins from mothers with GDM and 34,205 twin controls) looked at LGA, with mean prevalence rates of 16.3% (range, 3.5%−37.7%) in singleton pregnancies and 14.1% (range, 3.8%−34.5%) in twins born to mothers with GDM. LGA was mostly defined as birthweight above the 90th percentile (88% of studies in singleton pregnancies and 100% of studies in twin pregnancies) or birthweight >2 standard deviations (SDs) above the mean[46] or birthweight >4000 g.[64] In singleton pregnancies complicated by GDM, compared with those without GDM, the risk of LGA was increased (RR, 1.61; 95% CI, 1.46−1.77; I^2=99%; P<.00001). Moreover, this was true for twins born to mothers with GDM (RR, 1.29; 95% CI, 1.03−1.60; I^2=58%; P=.02) compared with controls (Figure 3, C and D).

The difference in RRs between singleton and twin pregnancies was not statistically significant (P=.103), and the addition of covariates in meta-regression models did not change this.

Preterm birth

Of note, 53 studies in singleton pregnancies (including 508,766 mothers with GDM and 10,151,968 controls) and 16 in twin pregnancies (including 2804 twins from mothers with GDM and 21,250 controls) reported outcome data for preterm birth (<37 weeks of gestation), with mean prevalence rates of 12.1% (range, 2.5%−100.0%) in singletons and 40.2% (range, 13.6%−73.8%) in twins born to mothers with GDM. Moreover, 9 studies in twin pregnancies reported outcome data for preterm birth at <34 weeks of gestation[37,96,98,100,102,105,113,114,118]; furthermore, several studies both in singleton pregnancies[18,21,33,37,38,42,53,61,83,89,94] and in twin pregnancies[37,62,96,98,100,102,111,113,114,117] reported outcome data for other categories of preterm birth, which were insufficient for meta-analysis because of heterogeneity in outcomes. In singleton pregnancies complicated by GDM, compared with those without GDM, the risk of preterm birth was increased (RR, 1.36; 95% CI, 1.27−1.46; I^2=99%; P<.00001), and this was also true for twin pregnancies (RR, 1.19; 95% CI, 1.07−1.32; I^2=90%; P=.001) (Figure 4, A and B).

The difference in RRs between singleton and twin pregnancies was not statistically significant (P=.161), and the addition of covariates in meta-regression models did not change this.

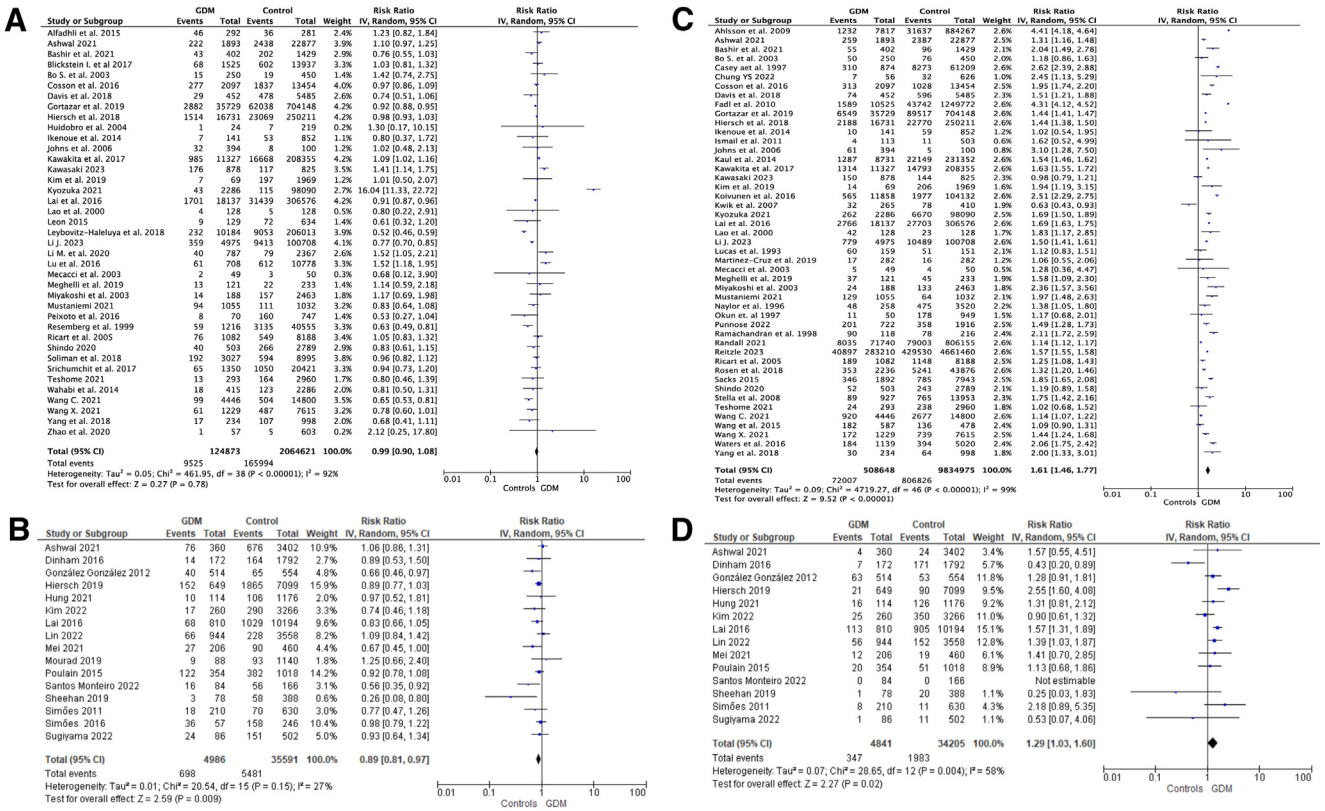
In addition, we considered that preterm birth at <34 weeks of gestation is clinically more relevant than <37 weeks of gestation in twin pregnancies; thus, we produced RRs also for 9 studies in twin pregnancies, including the preterm birth category of <33 or <34 weeks of gestation. However, these showed minimal change in the RR for twin pregnancies (RR, 1.24; 95% CI, 1.04−1.48; I^2=61%; P=.02), and meta-regression analysis did not show a significant difference between singleton and twin pregnancies (P=.440).

Low Apgar score

Of note, 30 studies in singleton pregnancies (including 114,034 neonates from mothers with GDM and 4,243,611

FIGURE 3

Risk of adverse growth outcomes in singleton and twin pregnancies complicated by GDM vs controls



Risk of small for gestational age in singleton pregnancies complicated by GDM vs controls (**A**) and in twin pregnancies complicated by GDM vs controls (**B**). Risk of large for gestational age in singleton pregnancies complicated by GDM vs controls (**C**) and in twin pregnancies complicated by GDM vs controls (**D**).

CI, confidence interval; *GDM*, gestational diabetes mellitus.

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controls) were examined, and 11 studies in twin pregnancies (including 3326 twins from mothers with GDM and 25,277 twins from controls) reported outcome data for low Apgar score, with mean prevalence rates of 2.5% (range, 0.0%−11.7%) in singleton pregnancies and 2.5% (range, 0.0%−10.5%) in twins born to mothers with GDM. Low Apgar score was defined as <7 at 5 minutes of life in all but one study.[113] In singleton pregnancies complicated by GDM, compared with those without GDM, the risk of low Apgar score was not increased (RR, 1.12; 95% CI, 0.97−1.31; I^2=76%; *P*=.13); this was also true for twin pregnancies (RR, 0.90; 95% CI, 0.68−1.19; I^2=16%; *P*=.44) (Figure 4, C and D), but the direction of associations was opposite in the 2 groups. The difference in RRs between singleton and twin pregnancies was not statistically significant (*P*=.129), and the addition of covariates in meta-regression models did not change this.

Admission to the neonatal intensive care unit

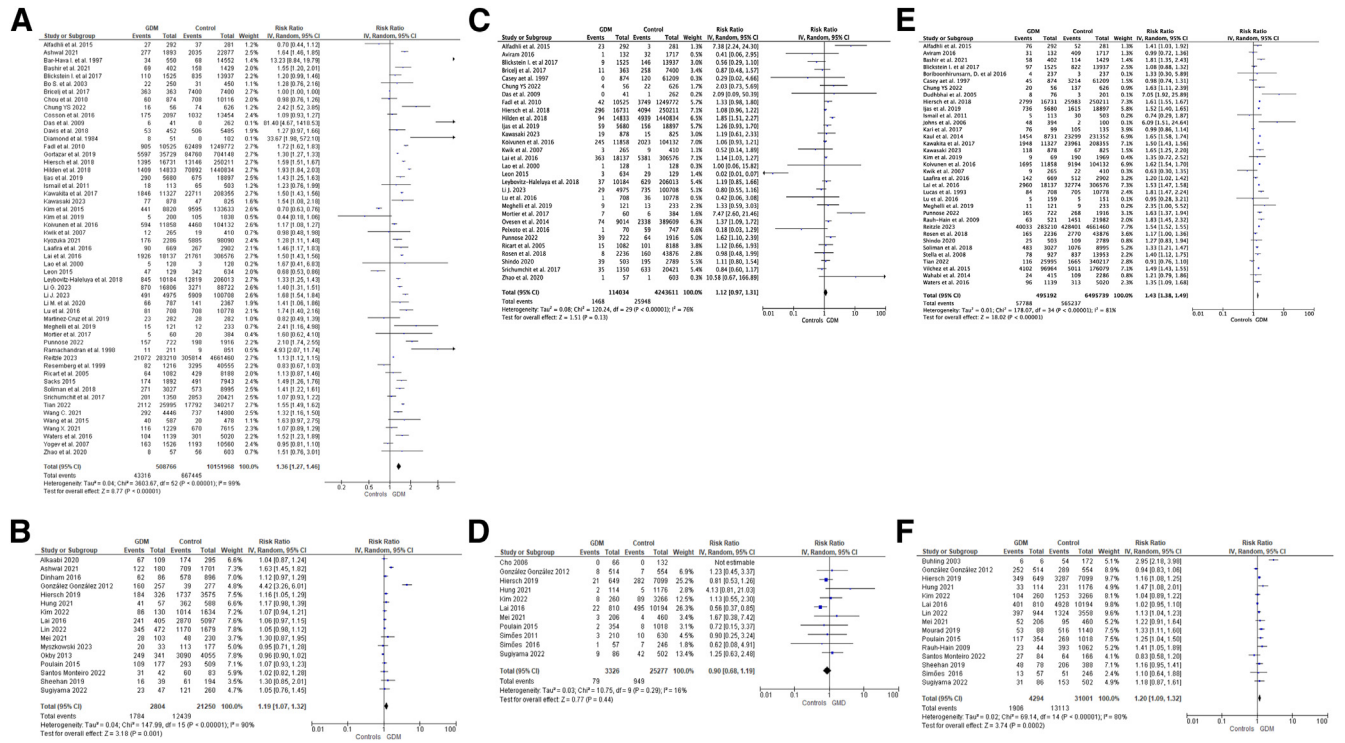
Of note, 35 studies in singleton pregnancies (including 495,192 singletons from mothers with GDM and 6,495,739 controls) and 15 in twins (including 4294 twins born from GDM mothers and 31,001 twins controls) reported outcome data on admission to the NICU, with mean prevalence rates of 14.0% (range, 0.4%−76.0%) in singletons born to mothers with and 45.8% (range, 22.8%−100.0%) in twins born to mothers with GDM. In singletons with GDM, compared with those without GDM, the rate of admission to the NICU was increased (RR, 1:43; 95% CI, 1.38−1.49; I^2=82%; *P*<.0001); this was also true for twin pregnancies (RR, 1.20; 95% CI, 1.09−1.32; I^2=80%; *P*=.0002) (Figure 4, E and F). The difference in RRs between singleton and twin pregnancies was not statistically significant (*P*=.097) when additional covariates were not included. However, when BMI or parity were included in the model, the effect estimates for singletons vs twins became significant (*P*=.033 and *P*=.005, respectively).

Stillbirth

Of note, 22 studies in singleton pregnancies and 8 studies in twin pregnancies reported outcome data for stillbirths, with mean prevalence rates of 1.2% (range, 0.0%−8.3%) in singleton

FIGURE 4

Risk of preterm birth, low Apgar score, and admission to NICU in singleton and twin pregnancies complicated by GDM vs controls



Risk of preterm birth in singleton pregnancies complicated by GDM vs controls (**A**) and in twin pregnancies complicated by GDM vs controls (**B**). Risk of low Apgar score in singleton pregnancies complicated by GDM vs controls (**C**) and in twin pregnancies complicated by GDM vs controls (**D**). Risk of admission to the NICU in singleton pregnancies complicated by GDM vs controls (**E**) and in twin pregnancies complicated by GDM vs controls (**F**).

CI, confidence interval; *GDM*, gestational diabetes mellitus; *NICU*, neonatal intensive care unit.

Greco. Adverse outcomes in twin and singleton pregnancies with gestational diabetes. Am J Obstet Gynecol 2023.

pregnancies and 2.4% (range, 0.0%−8.8%) in twin pregnancies complicated with GDM. A total of 360,647 singletons from mothers with GDM and 8,489,858 singletons from controls were examined vs 1531 twins from mothers with DM and 15,362 twins from controls. In singleton pregnancies complicated by GDM, compared with those without GDM, the risk of stillbirth was not significantly different (RR, 1.00; 95% CI, 0.80−1.25; I^2=73%; *P*=.99). Similarly, in twin pregnancies complicated by GDM, compared with those without GDM, the risk of stillbirth was not significantly different (RR, 1.72; 95% CI, 0.57−5.19; I^2=68%; *P*=.34) (Figure 5, A and B). The difference in RRs between singleton and twin pregnancies was not statistically significant (*P*=.3743). However, when age or diagnostic criteria were added to the meta-regression, the estimate effect of being a singleton vs twin was significant, implying that twins have a greater RR compared to singletons (*P*=.002 and *P*=.042, respectively).

Neonatal death

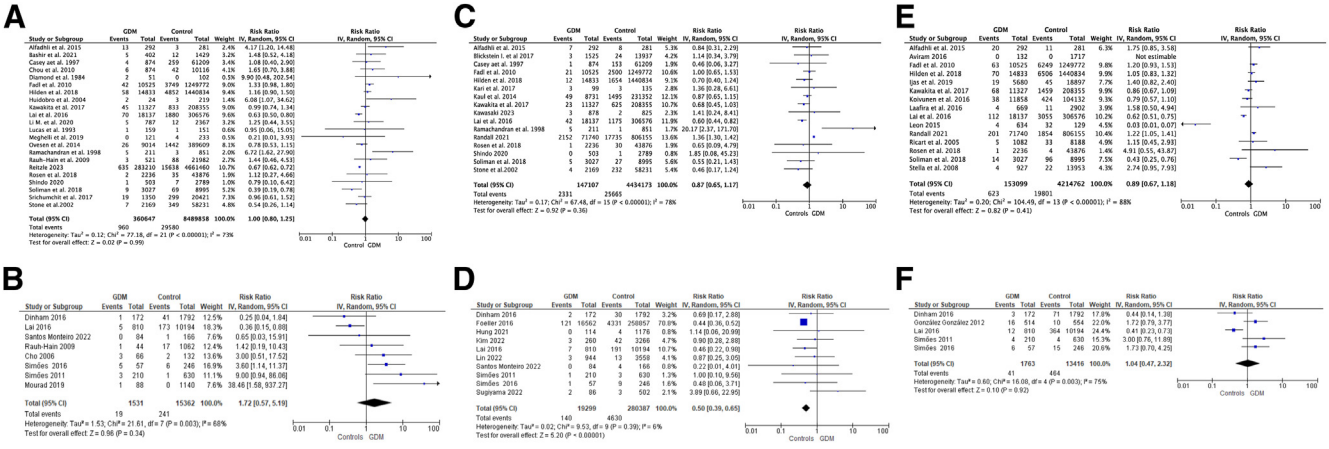
Of note, 16 studies in singleton pregnancies (including 147,107 neonates from mothers with GDM and 4,434,173 controls) and 10 studies in twin pregnancies (including 19,299 twins from mothers with GDM and 280,387 twins from controls) reported data on NNDs, with mean prevalence rates of 0.90% (range, 0.00%−3.00%) in singleton pregnancies and 0.88% (range, 0.00%−2.30%) in twin pregnancies complicated with GDM. In singleton pregnancies complicated by GDM, compared with those without GDM, the risk of NND was not significantly different (RR, 0.87; 95% CI, 0.65−1.17; I^2=78%; *P*=.36). In twin pregnancies complicated by GDM, compared with those without GDM, the risk of NND was markedly reduced (RR, 0.50; 95% CI, 0.39−0.65; I^2=6%; *P*<.00001) (Figure 5, C and D). The RRs for singleton and twin pregnancies did not differ substantially (*P*=.082), which remained unchanged after the inclusion of most covariates in the meta-regression models. However, after including diagnostic criteria for GDM in the meta-regression, the RRs for NND differed between singleton and twin pregnancies, with twin pregnancies having a lower risk of NND than singleton pregnancies (*P*=.0012).

Perinatal mortality

Of note, 15 studies in singleton pregnancies (including 153,099 neonates from mothers with GDM and 4,214,762

FIGURE 5

Risk of stillbirth, NND, and perinatal mortality in singleton and twin pregnancies complicated by GDM vs controls



Risk of stillbirth in singleton pregnancies complicated by GDM vs controls (**A**) and in twin pregnancies complicated by GDM vs controls (**B**). Risk of NND in singleton pregnancies complicated by GDM vs controls (**C**) and in twin pregnancies complicated by GDM vs controls (**D**). Risk of perinatal mortality in singleton pregnancies complicated by GDM vs controls (**E**) and in twin pregnancies complicated by GDM vs controls (**F**).

CI, confidence interval; *GDM*, gestational diabetes mellitus; *NND*, neonatal death.

Greco. Adverse outcomes in twin and singleton pregnancies with gestational diabetes. Am J Obstet Gynecol 2023.

controls) and 5 studies in twin pregnancies (including 1763 twins from mothers with GDM and 13,416 twins from controls) reported outcome data for perinatal mortality, with mean prevalence rates of 1.0% (range, 0.0%−6.8%) in singletons born to mothers with GDM and 3.8% (range, 1.5%−10.5%) in twins born to mothers with GDM. In singleton pregnancies complicated by GDM, compared with those without GDM, the risk of perinatal mortality was not significantly different (RR, 0.89; 95% CI, 0.67−1.18; I^2=88%; P=.41), and this was also true for twin pregnancies (RR, 1.04; 95% CI, 0.47−2.32; I^2=75%; P=.92) (Figure 5, E and F). The difference in RRs between singleton and twin pregnancies was not statistically significant (P=.893), and the addition of covariates in meta-regression models did not change this.

Comment

Principal findings

This systematic review and meta-analysis demonstrated that there was an increased risk of HDPs, IOL, CD, birth of LGA neonate, preterm birth, admission to the NICU in singleton pregnancies complicated by GDM compared with those without GDM; there was no significant difference in the risk of birth of SGA neonate, low-Apgar score, stillbirth, NND, and perinatal mortality.

In twin pregnancies complicated by GDM, compared with those without GDM, there was an increased risk of HDPs, CD, birth of LGA neonate, preterm birth, and admission to the NICU; there were a reduction in the risk of SGA neonate and a 50% reduction in the risk of NND. There was no significant difference in the risk of IOL, low Apgar score, stillbirth, or perinatal mortality.

When comparing RRs in singleton vs twin pregnancies, there was sufficient evidence to suggest that twins have a lower RR of CD than singletons. There was insufficient evidence to suggest a difference in HDPs, IOL, birth of LGA neonate, preterm birth, low Apgar score, stillbirth, and perinatal mortality. With sufficient adjustment for confounders, there was evidence that twins have lower RR than singletons for admission to the NICU, stillbirth, and NND.

Comparison with existing literature

The increased risk of adverse outcomes in singleton pregnancies complicated by GDM is well established[120] and likely to be mediated by the substantial increase in the risk of LGA, which, in turn, leads to an increased risk of IOL and CD and predisposes to other adverse outcomes, such as birth trauma and shoulder dystocia, which have been omitted in this review as were not reported for twins. In addition, GDM in singleton pregnancies is known to be associated with placental dysfunction,[121] chronic hypoxia, and neonatal hypoglycemia, all of which may contribute to increased perinatal risks. Conversely, in twin pregnancies, the effect of hyperglycemia is thought to provide a benefit in terms of fetal growth, by counterbalancing the inherent growth-restricting effect of the inadequate uterine milieu in multiples.[37]

Here, GDM was associated with a 50% reduction in the risk of NND in twin pregnancies but not in singleton pregnancies. Our results were mostly driven by 2 good-quality studies, which showed a positive effect of GDM on the risk of NND[51,110] in twin pregnancies compared with controls without GDM. In the large US birth cohort study by Foeller et al,[110] the trend toward reduced NNDs in twin pregnancies complicated by GDM vs controls (adjusted odds ratio [aOR], 0.84; 95% CI, 0.68−1.02) was

justified by a reduced risk of low Apgar score (aOR, 0.8; 95% CI, 0.68−0.94), reduced prematurity before 32 weeks of gestation (aOR, 0.72; 95% CI, 0.68−0.76), and reduced risk of SGA neonate (aOR, 0.84; 95% CI, 0.81−0.89). In addition, Lai et al[51] observed a reduced risk of NND (odds ratio [OR], 0.45; 95% CI, 0.21−0.97; $P<.05$) and low Apgar score (OR, 0.54; 95% CI, 0.34−0.87; $P<.05$) in twin pregnancies complicated by GDM vs controls but not in singleton pregnancies. Both these studies reported data adjusted for multiple maternal and pregnancy confounders, except prepregnancy BMI, which is known to be an independent predictor of adverse perinatal outcomes.[122] In addition, neither study presented chorionicity data. Interestingly, in our study, the risk of low Apgar score was not significantly reduced; both the risk of admission to the NICU and preterm birth were increased in twin neonates with GDM compared with controls; thus, they could not mediate the risk of NND. It can be hypothesized that the positive effect of GDM on growth in twins is what confers them a real metabolic advantage, whereas low birthweight is one of the most frequent causes of morbidity in twins. Other contributing factors may include closer antenatal surveillance with multidisciplinary input in twin pregnancies complicated by GDM compared with twin pregnancies not complicated by GDM, lower threshold for delivery, higher rates of steroid administration for lung maturation, and increased compliance to follow-up in this group.

Strengths and limitations

The strengths of our analysis include the large sample size and inclusion of studies from a wide number of geographic settings, ethnicities, and cultures without language restriction, which increases the applicability of our findings to different populations. The comprehensive outcome dataset, including paired perinatal and maternal adverse outcomes for singleton and twin pregnancies, helps comparability of findings between these 2 populations.

There are several limitations to this meta-analysis. Estimating risks of adverse outcomes for both twin and singleton pregnancies affected by GDM based on aggregated data is subject to the heterogeneity of the primary studies concerning the study design, demographics of the populations studied, methods of screening, and criteria for diagnosing GDM across the studies. The high between studies heterogeneity reflects great methodological variation, thus suggesting that the findings should be interpreted cautiously. However, adopting a mixed methods approach accounts partially for the within studies heterogeneity. In addition, the inclusion of meta-regression models mitigates the risk of bias because of the lack of adjustment for confounders by assessing whether the variation in confounders accounts for the within-group difference in risk.

Finally, data from birth registry studies incorporated in this analysis included different approaches and/or methods of screening and provided no information on local policies for management of GDM; however, the inclusion of registry data minimizes the risk of selection bias. Data reported in this meta-analysis pertain to women diagnosed and treated with GDM as per local policy; therefore, the effect of treatment on the outcomes could not be measured. However, this was beyond the scope of this review.

Conclusions and implications

This meta-analysis determined the association between GDM and adverse pregnancy outcomes in more than 14 million women with singleton pregnancies and nearly 170,000 women with twin pregnancies. In singleton pregnancies, GDM was associated with an increased risk of adverse maternal and perinatal outcomes, but the effect of GDM on twin pregnancies was milder, with a remarkably reduced risk of NND.

Our findings contribute to a more comprehensive understanding of adverse outcomes of pregnancy related to GDM in singleton and twin pregnancies compared with their counterparts without GDM, which will facilitate evidence-based counseling to the respective group of women. The effect of GDM treatment in mediating adverse outcomes in each group and the optimal thresholds for diagnosing GDM in twin pregnancies warrant further research. ■

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