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DIABETIC Medicine

SYSTEMATIC REVIEW

Impact of gestational diabetes mellitus treatment on medium/long-term outcomes after pregnancy: A systematic review and meta-analysis

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Abstract

Aim: We aimed to evaluate the effect of gestational diabetes mellitus (GDM) treatment on medium/long-term outcomes both the mother and offspring.

Methods: We performed a systematic review on randomized clinical trials addressing specific treatment of women with GDM versus usual care and its impact on maternal and offspring outcomes at medium/long-term. MEDLINE, EMBASE and CENTRAL were searched from inception to 8 October 2021. Outcome variables: maternal (diabetes, metabolic syndrome, 12 secondary); offspring (diabetes, impaired fasting glucose, impaired glucose tolerance, high body mass index, 15 secondary). Risk of bias was assessed with Cochrane tool and aggregation performed with Revman 5.4.

Results: We included five studies (1140 women, 767 offspring) with follow-up ranging 4–16 years after delivery. GDM treatment likely does not reduce risk of maternal diabetes (RR 1.00; [95% CI 0.82–1.23]) and may not reduce that of metabolic syndrome (RR 0.93; [95% CI 0.71–1.22]). We obtained very uncertain evidence that treatment may increase maternal HDL-cholesterol. Findings showed that GDM treatment may not have an impact on infants' outcomes (RRs 0.79; [95% CI 0.39–1.69] for impaired fasting glucose; RR 0.91; [95% CI 0.74–1.12] for body mass index >85th centile and 0.89; [95% CI 0.65–1.22] for body mass index >95th centile respectively).

Conclusions: With current evidence is uncertain if specific treatment of women with GDM has an impact on medium/long-term metabolic outcomes either in the mother or in the offspring. These results add evidence to the recommendation of systematically reevaluating mother and offspring after delivery.

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KEYWORDS

gestational diabetes mellitus, long-term, mother, offspring, treatment

1 | INTRODUCTION

Gestational diabetes mellitus (GDM) entails an increased risk of unfavourable pregnancy outcomes for both the mother and the fetus,[1–3] the risk being higher with increasing hyperglycemia.[4] Specific treatment of women with GDM improves maternal and fetal pregnancy outcomes as evidenced in different randomized controlled trials (RCT) and corresponding meta-analysis.[5,6]

As to long term outcomes, GDM identifies women with a higher risk of later diabetes,[7] metabolic syndrome[8] and cardiovascular events.[9] As to offspring, they also display higher levels of blood glucose and body mass index (BMI) Z-scores, the last no longer significant when adjusted for maternal BMI.[10] Among the few RCTs addressing specific treatment of GDM in front of usual care,[11–19] only some of them have studied the impact of treatment during pregnancy on medium and long-term outcomes[20–24] and a clear effect was not seen. This has also been the conclusion of a recent meta-analysis.[25] To know if GDM treatment influences long-term health outcomes would be of interest for women, offspring and healthcare providers.

With the hypothesis that specific treatment of GDM during pregnancy is beneficial for maternal and offspring metabolic outcomes at medium/long-term, we aimed to review the evidence coming from RCTs addressing GDM treatment, and summarize the information if appropriate.

Novelty Statement

- It is uncertain if gestational diabetes treatment improves long-term outcomes.
- This systematic review and meta-analysis showed that gestational diabetes treatment likely does not reduce maternal diabetes and may not reduce that of metabolic syndrome. Similarly, findings showed that gestational diabetes treatment may not have an impact on infants' outcomes.
- These results imply that additional interventions may be required after delivery to improve long-term outcomes for the mother and the offspring

2 | METHODS

The study protocol is described in Open Science Framework, a cloud-based management for open access science that facilitates centralized workflows from the development of a research idea to its publication (OSF, DOI 10.17605/OSF.IO/KFN79s, 9th October 2021), no major amendments were made in the process of conducting the review.

The report of this systematic review has been prepared according to standardised methods[26] and reported following the 2020 update of the PRISMA statement (Tables S1–S2).[27]

2.1 | Eligibility criteria

We aimed to include studies reporting metabolic outcomes in mothers and offspring at medium/long-term follow-up after a pregnancy where the mother was diagnosed with hyperglycemia (after any diagnostic criteria available at the time of the study) and had been enrolled in RCTs addressing specific treatment compared to usual obstetric care.

Pregestational diabetes was used as an exclusion criterion.

2.2 | Outcomes of interest

We pre-defined two primary outcomes at follow-up for the mother (diabetes mellitus and metabolic syndrome) and five for the offspring (DM, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and high BMI (≥P85% and ≥P95%)).

Additionally, we defined 12 secondary outcomes for the mother (decompensated diabetes, fasting plasma glucose (FPG), 2 h plasma glucose (PG) after 75 g oral glucose tolerance test (OGTT), IFG, homeostatic model assessment of insulin resistance (HOMA-IR), abdominal circumference, high abdominal circumference, hypertension, triglycerides, high triglycerides, HDL-cholesterol and low HDL-cholesterol) and 15 for the offspring (FPG, 2 h PG after 75 gr OGTT, HOMA-IR, abdominal circumference, abdominal circumference > P90, height, BMI Z-score, hypertension, systolic blood pressure, diastolic blood pressure, triglycerides, high triglycerides, HDL-cholesterol, low HDL-cholesterol and metabolic syndrome).

2.3 | Search strategy

We searched MEDLINE, CENTRAL and EMBASE of RCT from their inception until 8th October 2021 as described in Table S3. Main search terms were "Diabetes, Gestational" [Mesh], treatment*, "Follow-up studies" [Mesh] and randomized controlled trials. We used validated search filters to identify clinical trials in MEDLINE and EMBASE.[28] Reviews on the subject were checked for additional references and citations of primary RCT publications were searched in Web of Science in order to identify follow-up studies.

Studies were limited to those performed in human and published in English, roman languages or Chinese.

2.4 | Study selection and data extraction

Abstract screening, full text review, decision on eligibility, and data collection using a previously designed form was performed by two independent investigators (Apolonia García-Patterson, Montserrat Balsells) and discrepancies were solved after reviewing the source and by consensus with a third investigator (Rosa Corcoy)

We collected information on initial study characteristics (country, year of publication, definition of hyperglycemia, intervention, number of patients, maternal age, ethnicity and baseline BMI) and on follow-up studies (years of follow-up, number of subjects and their characteristics at baseline). We extracted numerical data regarding the outcomes of interest.

We foresaw to contact authors for queries in case of unclear information or missing data that could be potentially available.

2.5 | Risk of bias assessment

Two researchers (Apolonia García-Patterson, Montserrat Balsells) assessed independently the risk of bias of included studies discussing discrepancies with a third investigator (Rosa Corcoy) until reach a consensus. We assessed risk of bias at the study level through explicit judgements on selection bias (randomisation process and quality of allocation concealment), performance and measurement bias (blinding), selective outcome reporting, and attrition bias (sample size calculation, attrition rates, and comparability of subjects' baseline characteristics). The assessment was essentially qualitative, except in the case of attrition rates where a quantitative criterion was predefined: a cut-off of 15% both for overall attrition rate and for differences between treatment groups (unless otherwise foreseen by the authors). No automation tools were used. In a second step, we assessed the risk of bias at the outcome level to make judgements on its impact on the confidence of effect estimates for main outcomes.

2.6 | Effect measures and synthesis methods

We calculated relative risks (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes with their 95% confidence intervals (CI).

We anticipated converting continuous outcomes reported as median and ranges into mean and standard deviations. We combined data from comparable studies for each outcome of interest obtaining summary statistics through the Mantel–Haenszel method and a random effect model because it usually gives more conservative effect estimations than fixed model. We explored heterogeneity for all the analysis interpreting values provided by the I^2 statistic. All the analyses were conducted using RevMan version 5.4.

Information concerning risk of bias was used to consider the need to perform a sensitivity analysis, excluding articles with relevant weaknesses in trial design or execution. Unbalanced baseline characteristics alone were not considered an exclusion criterion for the sensitivity analysis. We planned to perform subgroup analysis according to period of diagnosis and intervention, severity of hyperglycaemia, offspring sex and treatment in the intervention group.

We classified the certainty of the evidence for primary outcomes (and HDL-cholesterol as consequence of a post hoc decision) according to the GRADE approach making explicit judgements on both internal (risk of bias, inconsistency, imprecision, publication bias) and external validity (such as directness of results). We summarized the quality of evidence and estimates of the magnitude of the effect for each outcome in a 'Summary of findings' table.

3 | RESULTS

We identified 2671 references (after de-duplication) from the literature search and tracking citations to primary eligible trials. We reviewed the full text of 53 articles and five of them met inclusion criteria reporting follow-up data of four trials that compared treatment of women with GDM to routine obstetric care. We display the complete eligibility process in a PRISMA flow chart (Figure 1). One of the follow-up articles[29] was not included due to inconsistencies in the number of subjects of each treatment arm at follow-up and no answer of the authors to our queries. Instead, we included a second article of the same group with a lower number of subjects at follow-up.[21]

We describe the included studies in Table 1. They had been performed in USA,[11,16] Canada,[13] and Australia,[14] and used different diagnostic criteria. The number of women enrolled went from 299[13] to 1006.[14] Interventions included diet advice, some form of glucose monitoring and insulin treatment either universal[11] or when certain glycemic cut-offs were reached.[13,14,16] Advice to women in the control group was null or minimal although further assessment for hyperglycemia could be allowed if required

after clinical suspicion.[14,16] Mean maternal age was around 30 years. Two studies reported body mass index (in the overweight range) and ethnicity (most women being White in one study[14] and Hispanic in the other[16]).

These primary trials reported follow-up data on either the mother,[20] the offspring[22] or both.[21,23,24] Follow-up studies collected data between 4[22] and 16 years[20] after the original study and reported data of subjects from about 20%[22] to 100%[20] of the original samples. At follow up, maternal baseline characteristics were similar to those of the initial study. The only remark is that pre-pregnancy BMI in treated and non-treated groups was unbalanced in one study (27.7 vs. 25.3 kg/m^2).[22]

We did not identify major relevant weaknesses in trial design or execution of included studies, although most of them made an unblinded measure of the outcomes of interest (we summarise the risk of bias of included studies at Figure S1).

3.1 | Maternal outcomes

Maternal outcomes are summarised in Table 2, Figure 2 and the Summary of findings table (Table 3). Forest-plots of maternal metabolic syndrome and HDL-cholesterol are depicted in Figures S2 and S3.

Our results showed that, compared to usual care, GDM treatment during pregnancy likely does not reduce the risk of maternal diabetes (1042 women in two trials,[20,24] RR 1.00 [95% CI 0.82–1.23], moderate quality of evidence). Additionally, treatment may not reduce the risk of metabolic syndrome (429 women in one trial,[24] RR 0.93 [95% CI 0.71–1.22], very low quality of evidence). We downgraded confidence in maternal outcomes due to the indirectness and imprecision of effect estimates (Table 3).

Among the 12 secondary outcomes, significance was only reached for HDL-cholesterol, where treatment of GDM during pregnancy compared to usual care may increase HDL at follow-up but the evidence is very uncertain (68 women in one study, mean difference of 0.24 mmoL/L [95% CI 0.06; 0.42], very low quality of evidence).[21] Heterogeneity was substantial on two of these secondary outcomes, no specific investigation for potential causes was performed. Overall, the direction of the summary statistic was neutral in one outcome, favourable in eight and unfavourable in five.

3.2 | Offspring outcomes

Offspring outcomes are summarized in Table 4, Figure 2 and the summary of findings table (Table 3). Forest-plots of offspring diabetes mellitus and BMI ≥95th percentile are depicted in Figures S4 and S5.

Two studies[21,23] assessed diabetes but did not register any event during its follow-up and, in consequence, it was not possible to calculate any effect estimate for this outcome. On the other hand, the evidence suggests that compared to usual care, GDM treatment during pregnancy likely does not reduce the risk of IFG in the children (458 children in two trials,[21,23] RR 0.79 [95% CI 0.39–1.69]), and may have not an impact in their BMI according to the number of children with BMI ≥85th or 95th percentiles (RR 0.91 [95% CI 0.74–1.12] and RR 0.89 [95% CI 0.65–1.22] respectively). The certainty of evidence for offspring outcomes was very low due to the indirectness and imprecision of effect estimates. As to offspring IGT, it was reported in two follow-up articles of the Garner's trial.[13] The first follow-up article[29] was not included due to inconsistencies as indicated above. In the article of Keely,[21] IGT was reported in three offspring but not according to treatment arm. Thus, we are not describing IGT in the offspring.

No differences according to treatment group were observed for any of the 15 secondary outcomes, heterogeneity had little impact on the estimates in eight of these outcomes.

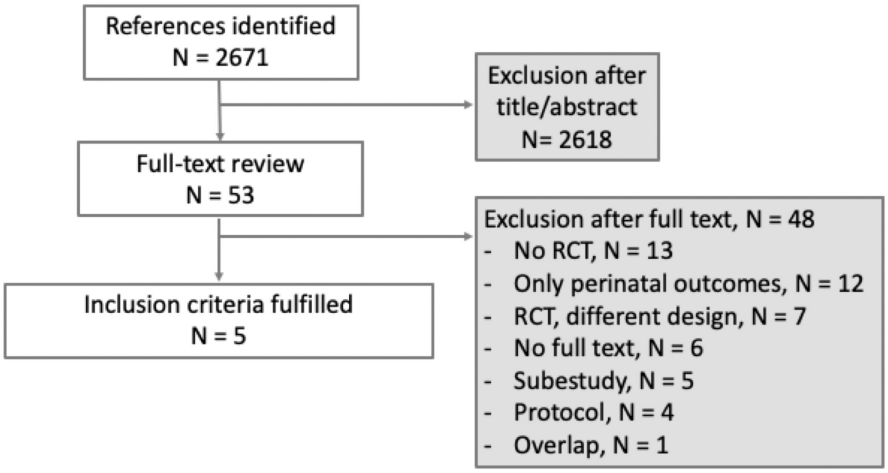

FIGURE 1 Flow chart of article selection process.

TABLE 1 Main characteristics of the follow-up and initial studies

Studies on maternal follow-up	Studies on offspring follow-up	Years of follow-up	N of patients at follow up	Initial study	Country	Definition of hyperglycemia	Intervention	N of patients	Maternal age (years)	Maternal BMI (Kg/m^2)	Ethnicity
O'Sullivan[20] 1980		16	307 (100%)	O' Sullivan[11] 1966	USA	RF or + 50 g GCT and 2 abnormal points at 100 g OGTT	Treatment - diet: 30 kcal/kg ideal weight, 40% CHO and - initially 10 UI NPH - home or clinic glycosuria	307	30.3 ± 4.15	Balanced distribution of weight status	No data
			308 (100%)				Control - printed routine obstetric and dietary instructions by the obstetrician	308	31.2 ± 4.20	Balanced distribution of weight status	No data
Keely[21] 2008	Keely[21] 2008	7–11	43 (28.9%)	Garner[13] 1997	Canada	Sc with 75 g at 24–28 wks, 1 h PG ≥ 8.0 mmoL/L and 75 g OGTT with 2 h PG ≥ 7.5 mmoL/L 2nd T 2 h PG ≥ 9.6 mmoL/L 3rd T	Treatment • biweekly visits • calorie-restricted diet of 35 kcal/kg ideal BW/day • insulin if fasting ≥ 4.4 or postprandial ≥ 7.8 mmoL/L	149	30.7 ± 4.80	Not reported	No data
			25 (16.7%)				Control • unrestricted healthy diet for pregnancy according to the Canada Food Guide	150	30.7 ± 4.60	Not reported	No data
	Gillman[22] 2010	4–5	94 (18.6%)	Crowther[14] 2005	Australia	Women with > = 1 RF or + 50 g GCT and a 75 gr OGTT at 24–34 wks with FPG <7.8 mmoL/L and 2 h PG 7.8–11.0 mmoL/L	Treatment • individualized diet considering pre-pregnancy weight, activity, dietary intake and weight gain • insulin if fasting ≥ 5.5 mmoL/L, 2 h pp ≥ 7.0 mmoL/L if <=35wks, or ≥ 8.0 if >35wks, or one CBG in a 2 wk period > = 9.0 mmoL/L	496 women 506 newborns	30.9 ± 5.40	26.8 ± 5.85	White 73% Asian 19% Other 9%
			105 (20.0%)				Control • standard practice at each center • at the discretion of the attending clinician, if indications suggestive of diabetes arose, further assessment for GDM was permitted	510 women 524 newborns	30.1 ± 5.50	26.0 ± 5.93	White 78% Asian 14% Other 8%
	Landon[23] 2015	5–10	264 (54.4%)	Landon[16] 2009	USA	50 g GCT at 24–30 + 6 wks between 7.5–11.1 mmoL/L and blinded 3 h OGTT with FPG <5.3 mmoL/L and > = 2 values > = CC cut-offs	Treatment • formal diet therapy and insulin if most fasting CBG were ≥ 5.3 mmoL/L or 2 h pp ≥ 6.7 mmoL/L	485	29.2 ± 5.7	30.1 ± 5.0 at enrolment	Hispanic 57.9% White 25.4% Black 11.5% Asian 4.5% Other 0.6%
			236 (49.9%)				Control • usual prenatal care; if during a visit there was a clinical suspicion of hyperglycemia, the blood glucose could be measured	473	28.9 ± 5.6	30.2 ± 5.1 at enrolment	Hispanic 56.9% White 25.2% Black 11.4% Asian 5.9% Other 1.5%
Casey[24] 2020		6–8	243 (50.1%)				Treatment (see above)				
			214 (45.2%)				Control (see above)				

Abbreviations: BW, body weight; CBG, capillary blood glucose; CC, Carpenter & Coustan; CHO, carbohydrates; FPG, fasting plasma glucose; GCT, glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PG, postprandial glucose; RF, risk factors; Sc, screening; T, trimester; Wks, weeks.

TABLE 2 Maternal outcomes at follow-up according to treatment for gestational diabetes mellitus during pregnancy versus usual care

	Outcomes	*N* studies	*N* women	I^2 (%)	Relative risk (CI 95%)	Mean difference (CI 95%)
Primary	Diabetes mellitus (%)	2[11,24]	1042	0	1.00 (0.82–1.23)	
	Metabolic syndrome (%)	1[24]	429	NA	0.93 (0.71–1.22)	
Secondary	Decompensated diabetes mellitus (%)	1[11]	615	NA	0.98 (0.63–1.50)	
	Fasting plasma glucose (mmol/l)	2[21,24]	498	0		0.05 (−0.04 to 0.14)
	2 h plasma glucose after 75 g OGTT (mmol/l)	2[21,24]	498	76		−0.56 (−1.77 to 0.64)
	Impaired fasting glucose (%)	1[24]	427	NA	1.08 (0.79–1.46)	
	HOMA-IR (mUI/l * mmol/l)	2[21,24]	498	40		−0.06 (−1.03 to 0.90)
	Abdominal circumference (cm)	2[21,24]	525	76		−0.87 (−7.45 to 5.71)
	High abdominal circumference (%)	1[24]	457	NA	1.03 (0.88–1.19)	
	Hypertension (%)	1[24]	457	NA	1.02 (0.69–1.50)	
	Triglycerides (mmol/l)	1[21]	68	NA		−0.10 (−0.64 to 0.44)
	High triglycerides (%)	1[24]	427	NA	1.23 (0.91–1.68)	
	HDL-cholesterol (mmol/l)	**1**[21]	**68**	NA		**0.24 (**0.06 to 0.42)
	Low HDL-cholesterol (%)	1[24]	427	NA	0.95 (0.81–1.10)	

Abbreviations: HOMA-IR: Homeostatic model assessment of insulin resistance; I^2, measure of heterogeneity; NA, not applicable; OGTT, oral glucose tolerance test.

Overall, the direction of the summary statistic was non estimable in one outcome, neutral in two, favourable in six and unfavourable in nine.

Sensitivity analyses were considered unnecessary due to the acceptable risk of bias of the initial studies. Due the limited number of subjects and events, no subgroup analysis was performed.

4 | DISCUSSION

We have performed an exhaustive systematic review and meta-analysis of the existing literature addressing the impact of GDM treatment during pregnancy on maternal and offspring metabolic outcomes at long-term follow-up. No significant effect was observed for either the mother or the offspring with the exception of maternal HDL-cholesterol (impact on offspring diabetes not estimable). Overall quality of the evidence being very low to moderate. The direction of the effects was mixed for both the mother and the offspring.

4.1 | Comparison to existing literature

The number of RCTs addressing treatment of GDM versus routine obstetric care is limited[11–19,30–32] and only some of them[11,13,14,16] have performed follow-up studies. A systematic review and meta-analysis on long-term follow-up was disregarded in 2010 due to limited information.[5] Recently, a systematic review and meta-analysis has been included within the Updated Evidence Report to support the US Preventive Services Task Force (USPSTF) on GDM screening.[25]

The study of Pillay to support the USPSTF recommendation[25] only has included three RCTs and has analysed a limited number of outcomes. The RCT that was not included is the report of O'Sullivan[20] that addressed maternal diabetes in the larger study population and longer follow-up that are available. They analysed four outcomes in the mother (DM, metabolic syndrome, IFG and obesity) and five in the offspring (BMI ≥ 85%, BMI ≥ 95%, IFG, IGT and diabetes). All of them with the exception of maternal obesity were included in our study while we also analysed 26 additional outcomes (11 in the mother and 15 in the offspring). The main difference is regarding maternal diabetes at follow-up. While RRs in the two studies were similar, 1.09 (95% CI 0.59; 2.01) in the USPSTF evidence synthesis[33] versus 1.00 (95% CI 0.82; 1.23) in the current study, the certainty of the results increased from low in the study of Pillay[25] to moderate in the present study. These results are relevant both for women and the society in that we are reasonably sure that GDM treatment in itself does not improve the odds of developing diabetes at follow-up and that interventions after delivery are required for this purpose.

Among outcomes analysed by both meta-analyses (maternal metabolic syndrome and child high BMI and abnormal glucose status), the two studies concurred in no difference being observed.

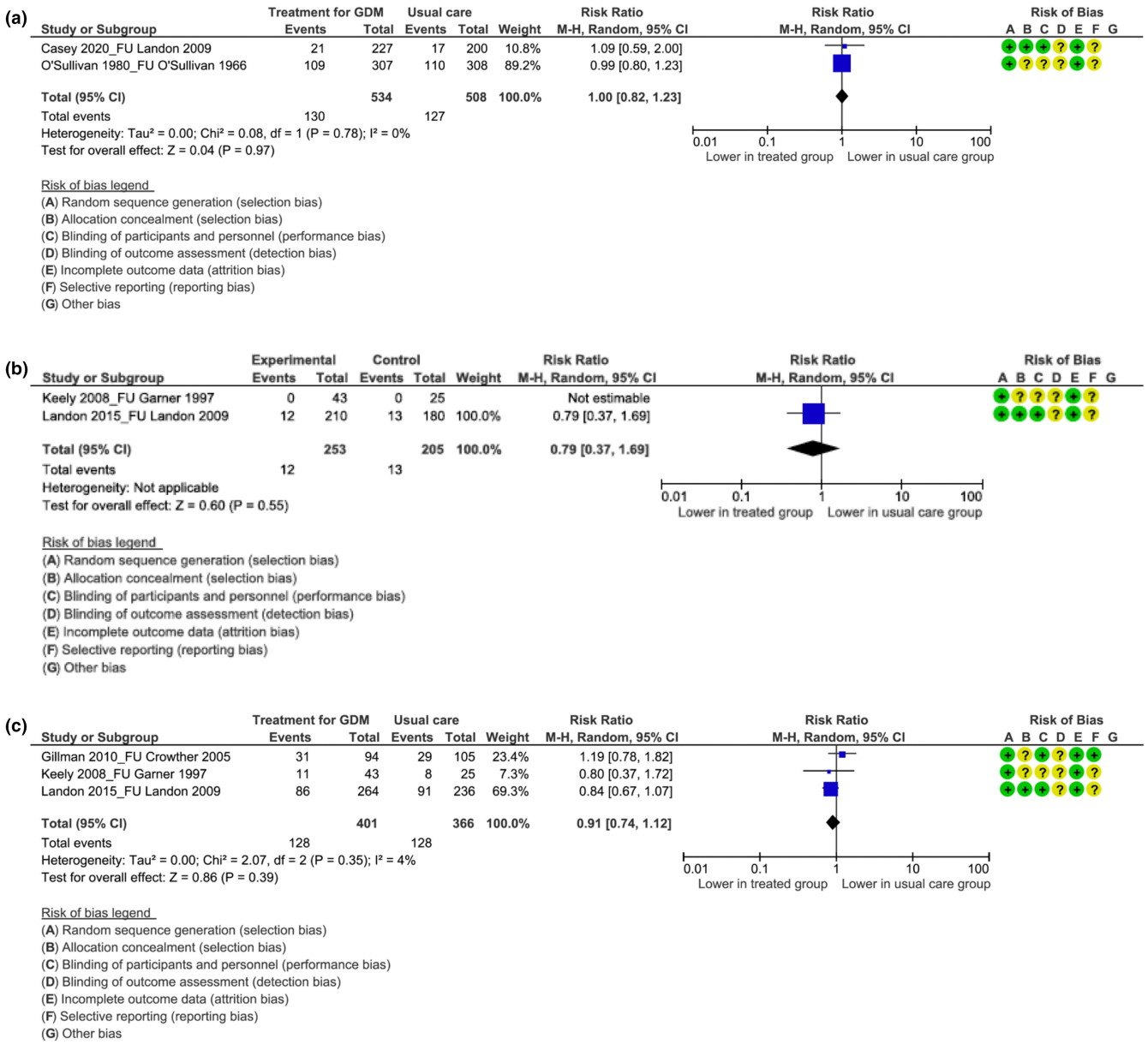

FIGURE 2 Forest plot of maternal and offspring outcomes at follow-up according to treatment of gestational diabetes mellitus versus routine obstetric care in index pregnancy. (a) Maternal diabetes mellitus. (b) Offspring impaired fasting glucose. (c) Offspring body mass index ≥ P85%.

In the additional secondary maternal and offspring outcomes only addressed by the current study, no differences were observed according to treatment arm with the exception of maternal HDL-cholesterol which was higher in treated mothers at follow-up by 0.24 mmoL/L. This result would be potentially relevant but its certainty is very low (Table 3).

While not addressing the impact of maternal treatment during pregnancy, it is important to note that IGT at follow-up is detected in offspring at a time when IFG is not.[21,29] This is in line with the meta-analysis of Kawasaki[34] where 2 h PG is significantly higher in offspring of GDM mothers (vs control ones) earlier at follow-up than FPG. Similarly, in HAPO-FUS, at 10–14 years of follow-up, 2 h PG was higher in offspring of GDM mothers while FPG was not significantly different,[35] overall implying that hyperglycemia screening in offspring of GDM mothers should preferably include an OGTT.

Overall, current results imply that we cannot assume that treatment of women with GDM during pregnancy prevents adverse metabolic outcomes in mother and child at medium/long-term. They add evidence to the recommendation of regularly re-evaluating mother and offspring and take advantage of the fact that, several interventions can be of benefit.[36]

TABLE 3 Treatment of gestational diabetes mellitus during pregnancy and medium/long term follow-up. Summary of findings table

Outcomes	Certainty of the evidence	Relative effect (95% CI)	Absolute effects with usual care[k]	Absolute risk difference with treatment
Maternal outcomes				
Diabetes Mellitus: 1042 participants from 2 trials with a follow up ranging from 6 to 16 years	Moderate[ab]	**RR 1.00** (0.82–1.23)	25 per 100	**0 fewer per 100** (5 fewer to 6 more), $p = 0.85$
Metabolic syndrome: 429 participants from 1 trial with a follow up ranging from 6 to 8 years	Very low[b,c,d,j]	**RR 0.93** (0.71–1.22)	343 per 1.000	**24 fewer per 1.000** (100 fewer to 76 more), $p = 0.61$
HDL-cholesterol: 68 participants from 1 trial with a follow up ranging from 7 to 11 years	Very low[b,c,e,f]	–	The mean HDL-cholesterol was **1.16** mmoL/L	MD **0.24 mmoL/L higher** (0.06–0.42 higher), $p = 0.007$
Offspring outcomes				
Diabetes Mellitus: 458 participants from 2 trials with a follow up ranging from 5 to 11 years	Very low[b,g]	The studies that assessed this outcome did not register any event and, in consequence, effect estimates are not estimable		
Impaired fasting glucose: 458 participants from 2 trials with a follow up ranging from 5 to 11 years	Very low[b,h,j]	**RR 0.79** (0.37–1.69)	63 per 1.000	**13 fewer per 1.000** (39 fewer to 44 more), $p = 0.64$
Number of children with BMI > 85th percentile: 767 participants from 3 trials with a follow up ranging from 4 to 11 years	Very low[b,d,j]	**RR 0.91** (0.74–1.12)	350 per 1.000	**31 fewer per 1.000** (91 fewer to 42 more), $p = 0.47$
Number of children with BMI > 95th percentile: 568 participants from 2 trials with a follow up ranging from 5 to 11 years	Very low[b,i,j]	**RR 0.89** (0.65–1.22)	226 per 1.000	**25 fewer per 1.000** (79 fewer to 50 more), $p = 0.46$

[a]Serious imprecision: optimal information size probably not meet; with a 0.25 control group event rate and an anticipated 25% relative risk reduction (RRR) about 1500 participants would be required (2500 for an anticipated 20% RRR).

[b]Publication bias could not be formally assessed due to the limited number of studies included.

[c]We did not assessed inconsistence issues, as only one study informed the outcome.

[d]Very serious imprecision: optimal information size probably not meet; with a 0.3 control group event rate and an anticipated 25% relative risk reduction (RRR) about 1200 participants would be required (2000 for an anticipated 20% RRR).

[e]Very serious indirectness: surrogate of metabolic syndrome, maternal primary outcome.

[f]Serious imprecision: confidence interval limits exceed the 50% of observed effect.

[g]Very serious imprecision: no events collected; in consequence we are uncertain about the impact of treatment on this outcome.

[h]Very serious imprecision: optimal information size probably not meet; with a 0.06 control group event rate and an anticipated 25% relative risk reduction (RRR) about 4000 participants would be required (5000 for an anticipated 20% RRR).

[i]Very serious imprecision: optimal information size probably not meet; with a 0.2 control group event rate and an anticipated 25% relative risk reduction (RRR) about 2000 participants would be required (4000 for an anticipated 20% RRR).

[j]Downgraded due to serious indirectness: outcomes are informed by follow-up data from trials that were designed to assess the impact of the intervention at shorter time periods and with low participation rates.

[k]Calculated from mean control risk for the studies contributing to each outcome.

4.2 | Strengths and limitations

The main strength of this systematic review and meta-analysis is the thorough analysis of the available evidence. Its main limitation derives from the number of subjects and limited period of follow-up that affects the certainty of the evidence. The fact that pre-pregnancy BMI was 2.4 kg/m^2 higher in the treated group in one of the studies[22] could have reduced to a certain extent the apparent benefits in the offspring of the current analysis but certainly would have not affected those of the mother (not addressed in the aforementioned study). As the number of studies is difficult to modify, a possibility to increase the certainty would be to prolong the period of follow-up so that a higher number of events is available for analysis. We planned an exhaustive search strategy to identify the width and breadth of the evidence to inform our review. Although searches in other sources would contribute to identify further references, there is empirical data showing that searches

TABLE 4 Offspring outcomes at follow-up according to treatment for gestational diabetes mellitus during pregnancy versus usual care

	Outcomes	*N* studies	*N* subjects	I^2 (%)	Relative risk CI 95%	Mean difference CI 95%
Primary	Diabetes mellitus (%)	2[21,23]	458	NA	Not estimable	
	Impaired fasting plasma glucose (%)	2[21,23]	458	NA	0.79 (0.37–1.69)	
	Impaired glucose tolerance (%)[a]	0	0			
	BMI ≥ P85 (%)	3[21,22,23]	767	4	0.91 (0.74–1.12)	
	BMI ≥ P95 (%)	2[21,23]	568	0	0.89 (0.65–1.22)	
Secondary	Fasting plasma glucose (mmol/l)	2[21,23]	458	0		0.01 (−0.07 to 0.09)
	2 h plasma glucose after 75 g OGTT (mmol/l)	1[21]	68	NA		0 (−0.48 to 0.48)
	HOMA-IR (mUI/l × mmol/l)	2[21,23]	458	0		−0.06 (−0.21 to 0.10)
	Abdominal circumference (cm)	2[21,23]	568	0		−0.32 (−1.67 to 1.03)
	Abdominal circumference > P90 (%)	1[23]	500	NA	1.03 (0.63–1.67)	
	Height (cm)	1[22]	199	NA		−0.60 (−2.05 to 0.85)
	BMI Z-score	2[22,23]	699	0		0.01 (−0.20to 0.22)
	Hypertension (%)	1[23]	495	NA	1.17 (0.70–1.95)	
	Systolic blood pressure (mmHg)	1[23]	495	NA		0 (−2.12 to 2.12)
	Diastolic blood pressure (mmHg)	1[23]	495	NA		1.00 (−0.41 to 2.41)
	Triglycerides (mmol/l)	2[21,23]	458	0		0.02 (−0.05 to 0.08)
	High triglycerides (%)	1[23]	390	NA	1.12 (0.72–1.74)	
	HDL-cholesterol (mmol/l)	2[21,23]	458	0		0.02 (−0.09 to 0.13)
	Low HDL-cholesterol (%)	1[23]	390	NA	1.05 (0.62–1.78)	
	Metabolic syndrome (%)	0	0			

Abbreviations: BMI, body mass index; I^2, measure of heterogeneity; OGTT, oral glucose tolerance test; NA, not applicable.

[a]One study provided information on IGT but not according to treatment arm.[21]

beyond the sources in our review have a minimal impact in the findings of evidence syntheses.[37,38]

5 | CONCLUSION

It is uncertain if specific treatment of women with GDM has an impact on medium/long-term metabolic outcomes either in the mother or in the offspring. The certainty of the evidence is low or very low due to a limited number of events with the exception of maternal diabetes at follow-up where certainty is moderate, paving the way for further research on this subject.

AUTHOR CONTRIBUTION

All authors contributed to the study conception and design. Literature search was performed by I. Solà. Data collection was performed by A. García-Patterson and M. Balsells. Analysis was done by A. García-Patterson, M. Balsells and R. Corcoy. Solà and I. Gich advised on statistical analysis. The first draft of the manuscript was written by A. García-Patterson, M. Balsells and R. Corcoy. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as relevant datasets were those of the original articles.

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SUPPORTING INFORMATION

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

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