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Systematic review

Original

Metformin vs. insulin in gestational diabetes mellitus: A systematic review and meta-analysis of randomized studies

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Abstract

Context: Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy, with most cases resolving after delivery. Adequate glycemic control is essential to reduce the risk of maternal and fetal complications. Historically, insulin has been the standard therapy, but recently, metformin has emerged as an alternative treatment.

Objectives: This meta-analysis aims to evaluate maternal outcomes in gestational diabetes mellitus patients treated with insulin versus metformin.

Methods: A systematic search was performed in PubMed, Embase, and Cochrane databases. Randomized controlled trials (RCTs) were included.

Results: Nineteen randomized controlled trials comprising 4,320 patients were analyzed, evaluating six maternal outcomes. Metformin was associated with a reduced risk of gestational hypertension (RR: 0.65; 95% CI: 0.49–0.87; P=0.77; I^2=0%) and preeclampsia (RR: 0.57; 95% CI: 0.46–0.72; P=0.08; I^2=39%). The risk of lower cesarean section rates (LCLS) was also reduced with metformin (RR: 0.92; 95% CI: 0.85–0.99; P=0.0002; I^2=63%). Induced labor was less frequent with metformin (RR: 0.85; 95% CI: 0.76–0.95; P=0.01; I^2=57%). The incidence of spontaneous vaginal delivery was higher in the metformin group (56.1%) (RR: 1.09; 95% CI: 1.03–1.17; P=0.002; I^2=61%). No statistically significant difference was found in preterm birth rates between groups (RR: 0.91; 95% CI: 0.74–1.13; P=0.002; I^2=60%).

Highlights

- The article is original, presenting a new meta-analysis that expands on a 2019 review. In addition to the 1,457 patients included in the previous analysis, new randomized clinical trials were added. This updated study includes a total of 4,320 patients from nineteen randomized clinical trials.
- The main objective of this study was to investigate and compare treatments for gestational diabetes mellitus, including insulin and metformin.
- The results cover six crucial outcomes: induced hypertension, preeclampsia, cesarean section rates, induced labor, normal vaginal delivery, and preterm delivery.

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Conclusion: This meta-analysis provides evidence supporting the use of metformin in the management of gestational diabetes mellitus, showing significant benefits in reducing rates of preeclampsia, gestational hypertension, and cesarean delivery, while also increasing spontaneous vaginal deliveries. Insulin may still be required in selected cases but appears to be associated with less favorable maternal outcomes.

Keywords: Metformin, Insulin, Glucose intolerance, Pregnancy, Preeclampsia, Risk, Incidence.

Metformina frente a insulina en la diabetes mellitus gestacional: una revisión sistemática y metaanálisis de estudios aleatorizados

Resumen

Contexto: la diabetes mellitus gestacional (DMG) se define como cualquier grado de intolerancia a la glucosa con inicio o primer reconocimiento durante el embarazo, la mayoría de los casos se resuelven al finalizar la gestación. El control adecuado de la glucosa es esencial para reducir el riesgo de complicaciones. Tradicionalmente, se ha utilizado la insulina como tratamiento estándar, sin embargo, recientemente la metformina ha emergido como una alternativa terapéutica.

Objetivos: este estudio busca evaluar los resultados maternos en pacientes con diabetes mellitus gestacional tratados con insulina o metformina.

Metodología: se realizó una búsqueda sistemática en PubMed, Embase y Cochrane, incluyendo ensayos clínicos aleatorizados (ECAs).

Resultados: la presente revisión incluyó 19 ensayos clínicos aleatorizados con un total de 4320 pacientes y analizó seis desenlaces maternos. La hipertensión inducida por el embarazo fue menor en el grupo tratado con metformina (RR: 0,65; IC 95 %: 0,49–0,87; p = 0,77; I^2 = 0 %), al igual que la preeclampsia (RR: 0,57; IC 95 %: 0,46–0,72; p = 0,08; I^2 = 39 %) y la incidencia de cesárea (LCLS) (RR: 0,92; IC 95 %: 0,85–0,99; p = 0,0002; I^2 = 63 %). El parto inducido también fue menor con metformina (RR: 0,85; IC 95 %: 0,76–0,95; p = 0,01; I^2 = 57 %). La incidencia de parto vaginal normal fue mayor en el grupo de metformina (56,1 %) (RR: 1,09; IC 95 %: 1,03–1,17; p = 0,002; I^2 = 61 %). No se encontraron diferencias estadísticas significativas entre grupos en el parto prematuro (RR: 0,91; IC 95 %: 0,74–1,13; p = 0,002; I^2 = 60 %).

Conclusiones: Este metaanálisis presenta evidencia del uso de metformina en el tratamiento de la diabetes mellitus gestacional, mostrando diferencias significativas en la reducción de las tasas de preeclampsia, hipertensión gestacional y partos por cesárea, al tiempo que aumenta los partos vaginales espontáneos. La insulina puede utilizarse de manera complementaria si es necesario, aunque parece estar asociada con resultados maternos menos favorables.

Palabras clave: metformina, insulina, intolerancia a la glucosa, embarazo, preeclampsia, riesgo, incidencia.

Highlights

- El artículo es original y presenta un nuevo metanálisis que amplía una revisión de 2019. Además de los 1457 pacientes incluidos en el análisis anterior, se incorporaron nuevos ensayos clínicos aleatorizados. Este estudio actualizado incluye un total de 4320 pacientes provenientes de diecinueve ensayos clínicos aleatorizados.
- El objetivo principal de este estudio fue investigar y comparar los tratamientos para la diabetes mellitus gestacional con insulina y metformina.
- Los resultados abarcan seis hallazgos cruciales: hipertensión inducida, preeclampsia, incidencia de cesárea, parto inducido, parto vaginal normal y parto prematuro.

Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1], which, in most cases, resolves at the end of gestation [2]. Gestational diabetes affects different racial groups [3], with a higher prevalence reported in South Asian countries [4]. Women with GDM must achieve strict glycemic control to avoid the complications associated with hyperglycemia [5].

In past years, insulin was the primary method used to control glycemia during pregnancy, reduce the risks associated with hyperglycemia, and maintain normal glucose levels. However, an alternative medication was deemed necessary—one that would be safe and effective for both mother and infant, as well as acceptable and more affordable for women. Metformin, a biguanide, emerged as such an option, as it reduces insulin resistance and lowers glucose levels. Metformin acts to reduce insulin resistance and improves insulin sensitivity through activation of AMP kinase and decreasing ATP concentrations in hepatocytes [6]. Insulin sensitivity and hyperglycemia are improved by reducing hepatic gluconeogenesis and increasing peripheral glucose uptake and utilization. Metformin also decreases markers of endothelial activation, which are closely associated with insulin resistance [7,8]. This biguanide crosses the placenta and acts as an insulin sensitizer and, therefore, does not cause neonatal hypoglycemia [9]. Moreover, metformin has shown no evidence of teratogenicity in animal models or in human studies, including pregnancies complicated by polycystic ovary syndrome [10–16].

Concerns regarding maternal outcomes associated with insulin or metformin use in gestational diabetes mellitus have been addressed in clinical trials and meta-analyses. However, in recent years, a considerable number of new clinical trials have been published. Therefore, this meta-analysis seeks to evaluate recent publications and to compare insulin and metformin in the treatment of gestational diabetes mellitus, with a focus on maternal outcomes, to determine which of these medications provides better results.

Methods

Study selection

The systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Collaboration recommendations [17]. A bibliographic search was performed in PubMed, Cochrane, and Embase. The search strategy applied was: ("metformin" OR "biguanides" OR "hypoglycemic") AND ("insulin" OR "insulin therapy" OR "insulin analogues") AND ("gestational diabetes" OR "GDM") AND ("RANDOM" OR "RCT"). The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), with registration number CRD42023480992.

Eligibility criteria

The inclusion criteria were based on the PICO framework: P (pregnant women over 18 years old diagnosed with GDM); I (metformin); C (insulin); O (gestational hypertension, preeclampsia, LCLS, induced labor, normal vaginal delivery, preterm delivery).

The eligibility criteria included: (a) randomized trials; (b) comparison of metformin with insulin; (c) patients with GDM older than 18 years; (d) reporting at least one maternal outcome of interest (as described above), related to pregnancy and childbirth.

Exclusion criteria were: (a) studies not reporting outcomes of interest; (b) studies reporting only offspring or neonatal outcomes; (c) studies including adolescent populations; and (d) observational studies.

Study triage and data extraction

Two researchers (MFQT and AO) independently screened articles retrieved from PubMed, Embase, and Cochrane (as described in Figure 1). Selection was performed according to the predefined search strategy.

Data extraction followed the inclusion criteria, based on information from full texts and supplementary materials of eligible studies. Each investigator independently verified the accuracy of the other's data extraction. Discrepancies were resolved through consensus. The authors collected baseline study characteristics and outcomes of interest.

Statistical analysis

Risk ratios (RR) with 95% confidence intervals (CI) were calculated for each binary endpoint. Statistical significance was defined as P<0.05. Only dichotomous outcomes were analyzed. Heterogeneity was assessed using the Cochran Q test and I^2 statistic; P<0.01 and I^2 > 25% were considered indicative of significant heterogeneity. A fixed-effects model was applied to outcomes with substantial heterogeneity. Statistical analyses were performed using Review Manager 5.4 (Cochrane Center, The Cochrane Collaboration). Forest plots were generated by the authors (MFQT).

Quality assessment - Risk of bias

The Cochrane Collaboration's RoB-2 tool was applied to assess the risk of bias in randomized trials. Risk of bias was evaluated across five domains: bias from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each trial was classified as "low risk," "some concerns," or "high risk." Risk of bias was independently assessed by four investigators (MFQT, NCJ, FSLC, and AO). A summary figure (Figure 1) was prepared by the authors to illustrate the assessment.

Results

The search strategy identified 647 records. After removal of duplicates and studies unrelated to the topic of interest based on title and abstract screening, 37 studies were fully reviewed for eligibility. Of these, 12 studies were included in the latest meta-analysis, which originally comprised 13 studies related to maternal outcomes, although one lacked available data. Ultimately, 19 randomized controlled trials (RCTs) were incorporated into the present review (Figure 1).

A total of 2,207 women were assigned to metformin treatment (with or without insulin supplementation), while 2,113 women received insulin (Table 1). The included RCTs reported different dosing regimens for both metformin and insulin (Table 2, developed by the authors MFQT and AO).

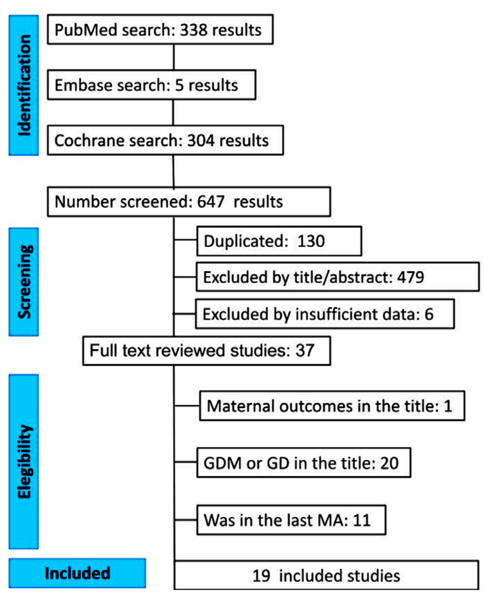


Figure 1. PRISMA flow diagram of study screening and selection

Source: Own elaboration.

Table 1. Studies included in this meta-analysis and corresponding patients assigned to each treatment

Author, year	Country	Participants	Metformin	Insulin
Ainuddin, 2015 (16)	Pakistan	Women aged 20-46 years; 20-36 weeks	75	75
Wasim, 2019 (18)	Pakistan	22-34 weeks - singleton pregnancy	137	141
Khan, 2017 (19)	Pakistan	Women aged 24, 92 – 30, 54 years; 27,32- 32,19 weeks	385	385
Huhtala, 2020 (20)	Finland	Women aged 31,8 – 37,2 years	98	97
Saleh, 2016 (21)	Egypt	24-34 weeks – singleton pregnancy	67	70
Hassan, 2012 (22)	Pakistan	Women aged 18-45 years; 20-36 weeks – singleton pregnancy	75	75
Ashoush, 2016 (23)	Egypt	Singleton pregnancy	48	47
Eid, 2018 (24)	Egypt	Women aged 18-42 years; 22-30 weeks – singleton pregnancy	113	116
Niromanesh, 2012 (25)	Iran	Women aged 18-45 years; 20-34 weeks – singleton pregnancy	80	80
Ijas, 2011 (26)	Finland	Women aged 18-45 years; 12-34 weeks, singleton pregnancy	47	50
Rowan, 2008 (27)	New Zeland and Australia	Woman aged 18-45 years; 20-33 weeks – singleton pregancy	373	378
Muhsen, 2022 (28)	Iraq	Woman, 12-34 weeks - singleton pregancy	50	50
Galal, 2019 (29)	Egypt	Woman, 28-34 weeks - singleton pregancy	56	50
Tertti, 2013 (30)	Finland	Woman, 22-34 weeks - singleton pregancy	110	107
Rodrigues, 2020 (31)	Portugal	Woman, 27-34 weeks	94	41
Picón-César, 2021 (32)	Spain	Woman aged 18-45 years; 14-35 weeks - singleton pregnancy	100	100
Spaulonci, 2013 (33)	Brazil	Woman, 24-34 weeks, singleton pregnancy	47	47
Ghomian, 2018 (34)	Iran	Woman aged 18-40 years; 24-28 weeks - singleton pregnancy	143	143
Rönnemaa, 2014 (35)	Finland	Woman, 24-32 weeks	110	107

Source: Own elaboration.

Table 2. Doses used in each RCT in metformin and insulin

Author, year	Metformin (mg)	Insulin(units)
Ainuddin, 2015 (16)	500-2500	Not Reported
Wasin, 2019 (18)	500-2500	0,7-0,8 U Kg
Khan, 2017 (19)	500- 1000	0,7 U Kg
Huhtala, 2020 (20)	500-2000	Not Reported
Saleh, 2016 (21)	500-3000	Not Reported
Hassan, 2012 (22)	500-3000	Not Reported
Ashoush, 2016 (23)	1000-2500	Not Reported
Eid, 2018 (24)	500-2500	Not Reported
Niromanesh, 2012 (25)	1000-2500	Not Reported
Ijas, 2011 (26)	750-2250	30
Rowan, 2008 (27)	500-2500	42
Muhsen, 2022 (28)	850	Not Reported
Galal, 2019 (29)	500-2000	0,8 U Kg
Tertti, 2013 (30)	500-1000	Not Reported
Rodrigues, 2020 (31)	Not Reported	Not Reported
Picón-César, 2021 (32)	425-2550	0,2 U Kg (determir) 0,1 U kg (aspart)
Spaulonci, 2013 (33)	1700-2550	0,4 U Kg
Ghomian, 2018 (34)	500-1500	0,1 U Kg
Rönnemaa, 2014 (35)	500-2000	Not Reported

Source: Own elaboration.

This review analyzed six maternal outcomes in relation to gestational diabetes mellitus: gestational hypertension, caesarean (LCLS), preeclampsia, preterm delivery, induced labor, and normal vaginal delivery.

The forest plot for gestational hypertension favored metformin (RR: 0.65; 95% CI: 0.49–0.87; P=0.77; I^2=0%), with a higher incidence observed among insulin-treated patients. Heterogeneity analysis showed I^2=0%, P>0.01, and a low Chi² value (5.64). The overall effect was Z=2.93, P=0.003 (P<0.05, as defined in the methods section), indicating a small effect size for this subgroup. Hypertension occurred in 73 of 1,594 patients (4.57%) receiving metformin (Figure 2), compared with 111 of 1,539 patients (7.21%) treated with insulin alone.

The forest plot for preeclampsia also favored metformin (RR: 0.57; 95% CI: 0.46–0.72; P=0.08; I^2=39%). Heterogeneity was moderate, with I^2=39%, P<0.01, and Chi^2=18.15. The overall effect was Z=4.75, P<0.00001, suggesting a strong effect despite moderate heterogeneity. Preeclampsia was reported in 104 of 1,790 patients (5.8%) treated with metformin, compared with 182 of 1,747 patients (10.4%) receiving insulin (Figure 3).

The forest plot for caesarean favored metformin (RR: 0.92; 95% CI: 0.85–0.99; P=0.0002; I^2=63%), with more cases occurring in the insulin group. Heterogeneity was moderate (I^2=63%, P<0.01, Chi^2=45.75). The overall effect was Z=2.14, P=0.03, indicating a small effect size. LCLS occurred in 678 of 1,834 patients (36.96%) treated with metformin, compared with 722 of 1,784 patients (40.47%) treated with insulin (Figure 4).

The forest plot for induced labor favored metformin (RR: 0.85; 95% CI: 0.76–0.95; P=0.01; I^2=57%). Heterogeneity was moderate (I^2=57%, P=0.01, Chi^2=20.77). The overall effect was Z=2.79, P=0.005, indicating a strong effect with moderate heterogeneity. Induced labor occurred in 340 out of 866 patients (39.2%) in the metformin group, compared with 370 out of 820 patients (45.1%) treated with insulin (Figure 5).

The forest plot for normal vaginal delivery (NVD) favored metformin (RR: 1.09; 95% CI: 1.03–1.17; P=0.002; I^2=61%), with a higher incidence among patients receiving metformin. Heterogeneity was moderate (I^2=61%, P<0.01, Chi^2=30.52). The overall effect was Z=2.72, P=0.007, suggesting a strong effect despite heterogeneity. NVD occurred in 842 of 1,500 patients (56.1%) treated with metformin, compared with 740 of 1,452 patients (51.0%) treated with insulin (Figure 6).

The forest plot for preterm delivery showed no significant difference between groups (RR: 0.91; 95% CI: 0.74–1.13; P=0.002; I^2=60%). Heterogeneity was moderate (I^2=60%, P<0.01, Chi^2=32.73). The overall effect was Z=0.86, P=0.39, indicating no meaningful effect. Preterm delivery occurred in 151 of 1,799 patients (8.39%) receiving metformin and in 162 of 1,758 patients (9.21%) treated with insulin (Figure 7).

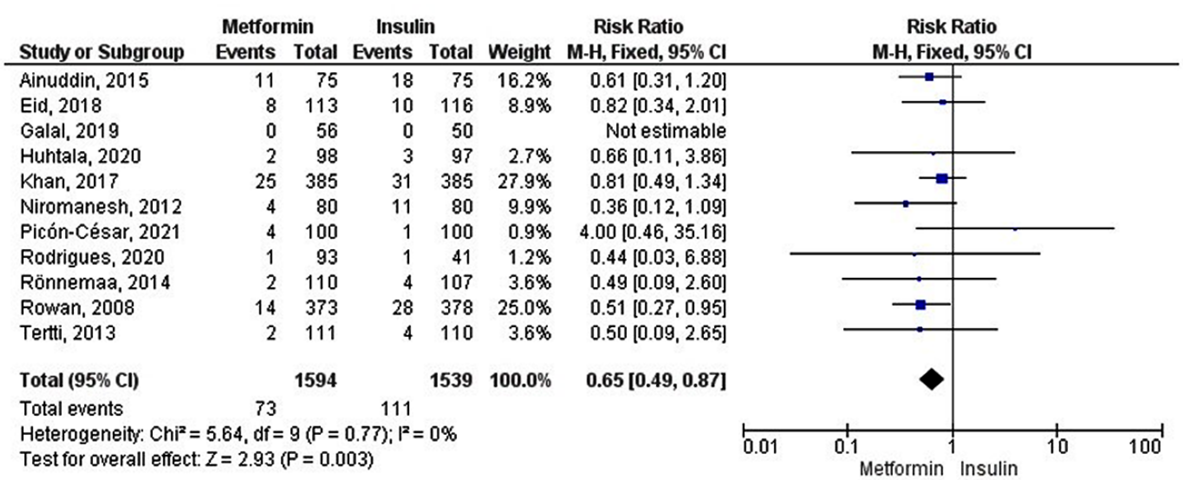


Figure 2. Induced hypertension

Source: Own elaboration.

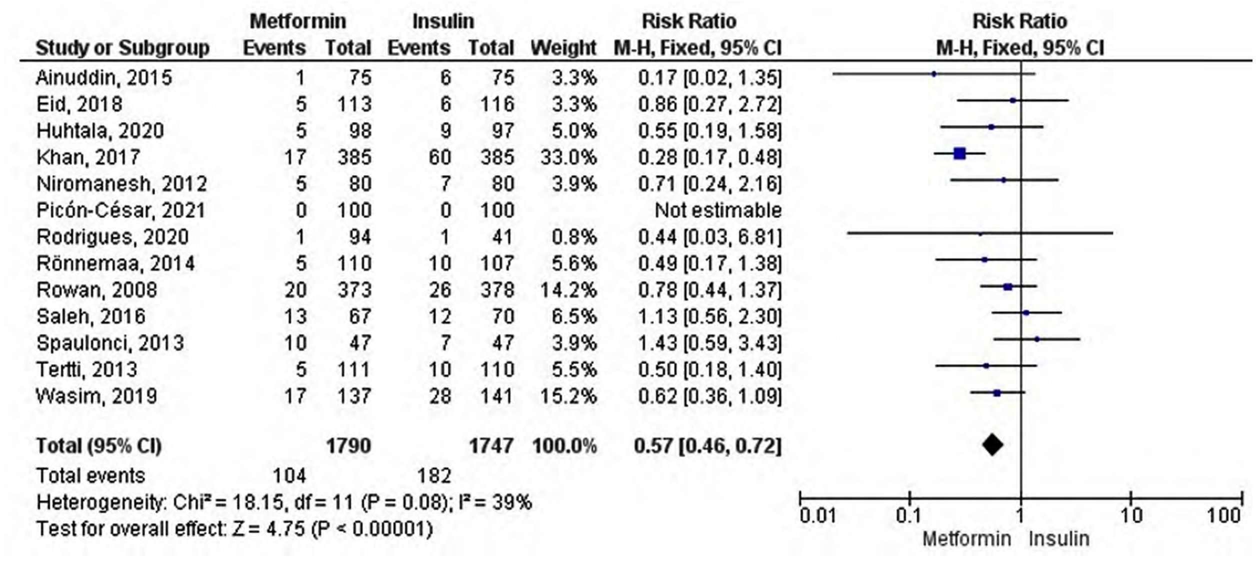


Figure 3. Preeclampsia

Source: Own elaboration.

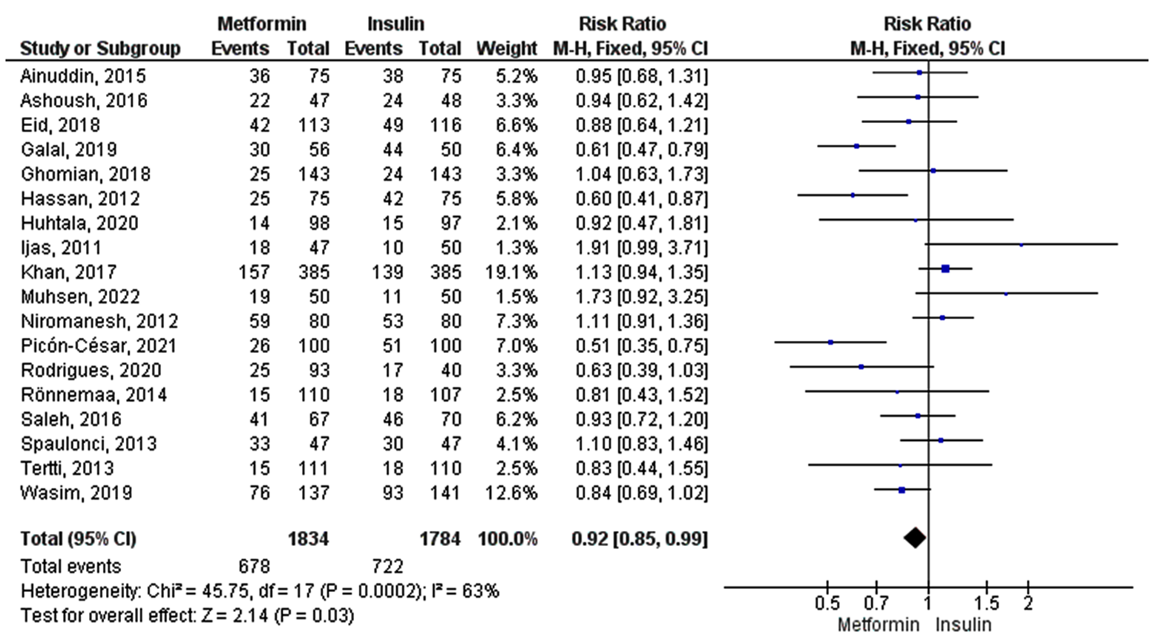
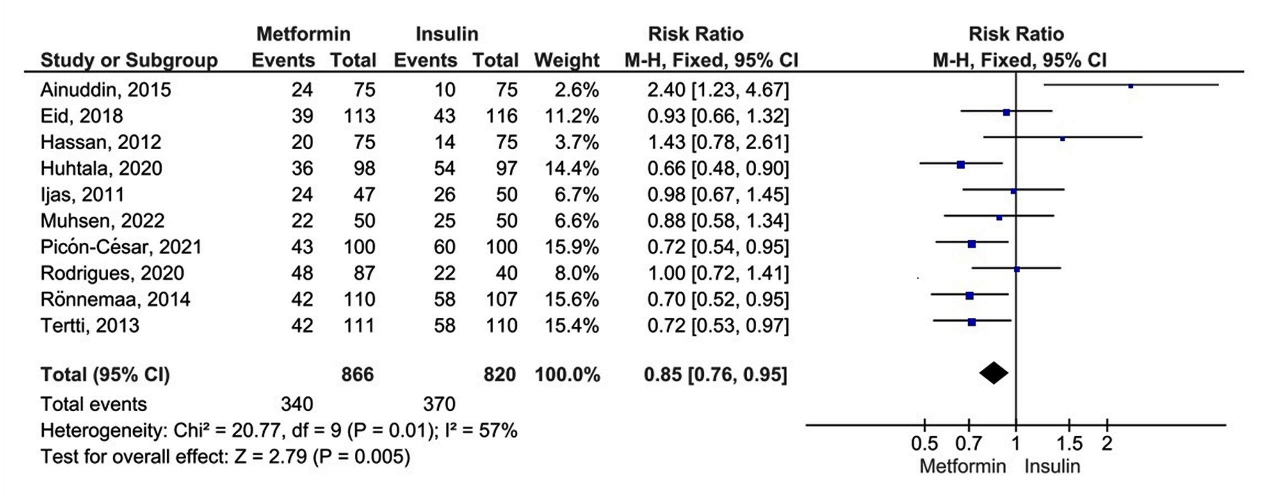


Figure 4. LCLS

Source: Own elaboration.

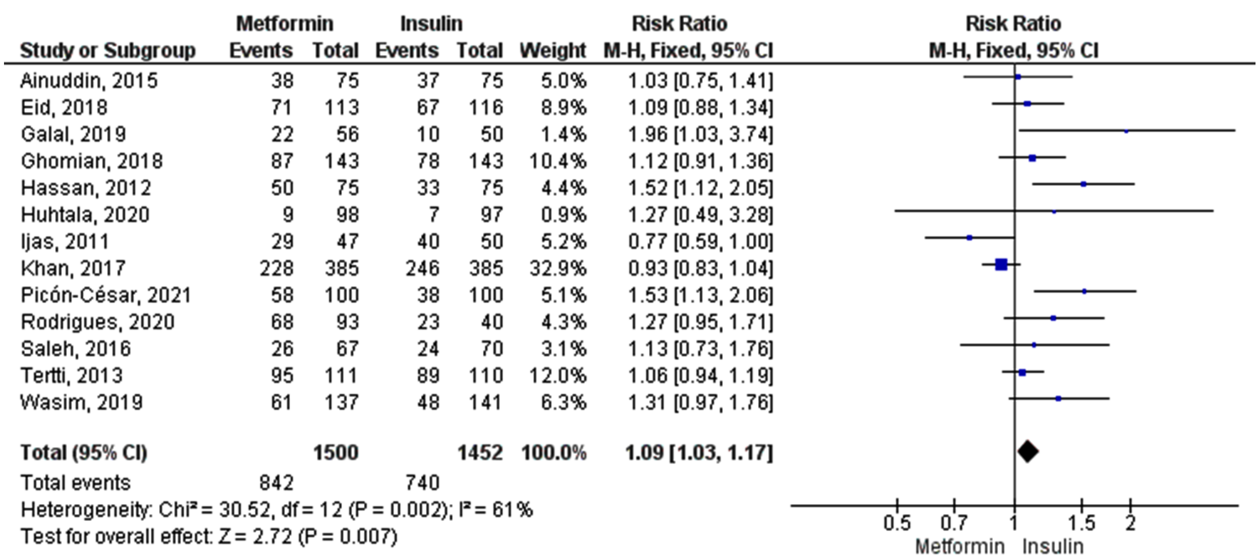


Study or Subgroup	Metformin Events	Metformin Total	Insulin Events	Insulin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ainuddin, 2015	24	75	10	75	2.6%	2.40 [1.23, 4.67]
Eid, 2018	39	113	43	116	11.2%	0.93 [0.66, 1.32]
Hassan, 2012	20	75	14	75	3.7%	1.43 [0.78, 2.61]
Huhtala, 2020	36	98	54	97	14.4%	0.66 [0.48, 0.90]
Ijas, 2011	24	47	26	50	6.7%	0.98 [0.67, 1.45]
Muhsen, 2022	22	50	25	50	6.6%	0.88 [0.58, 1.34]
Picón-César, 2021	43	100	60	100	15.9%	0.72 [0.54, 0.95]
Rodrigues, 2020	48	87	22	40	8.0%	1.00 [0.72, 1.41]
Rönnemaa, 2014	42	110	58	107	15.6%	0.70 [0.52, 0.95]
Tertti, 2013	42	111	58	110	15.4%	0.72 [0.53, 0.97]
Total (95% CI)		**866**		**820**	**100.0%**	**0.85 [0.76, 0.95]**
Total events	340		370			

Heterogeneity: Chi² = 20.77, df = 9 (P = 0.01); I² = 57%
Test for overall effect: Z = 2.79 (P = 0.005)

Figure 5. Induced labor

Source: Own elaboration.



Study or Subgroup	Metformin Events	Metformin Total	Insulin Events	Insulin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ainuddin, 2015	38	75	37	75	5.0%	1.03 [0.75, 1.41]
Eid, 2018	71	113	67	116	8.9%	1.09 [0.88, 1.34]
Galal, 2019	22	56	10	50	1.4%	1.96 [1.03, 3.74]
Ghomian, 2018	87	143	78	143	10.4%	1.12 [0.91, 1.36]
Hassan, 2012	50	75	33	75	4.4%	1.52 [1.12, 2.05]
Huhtala, 2020	9	98	7	97	0.9%	1.27 [0.49, 3.28]
Ijas, 2011	29	47	40	50	5.2%	0.77 [0.59, 1.00]
Khan, 2017	228	385	246	385	32.9%	0.93 [0.83, 1.04]
Picón-César, 2021	58	100	38	100	5.1%	1.53 [1.13, 2.06]
Rodrigues, 2020	68	93	23	40	4.3%	1.27 [0.95, 1.71]
Saleh, 2016	26	67	24	70	3.1%	1.13 [0.73, 1.76]
Tertti, 2013	95	111	89	110	12.0%	1.06 [0.94, 1.19]
Wasim, 2019	61	137	48	141	6.3%	1.31 [0.97, 1.76]
Total (95% CI)		**1500**		**1452**	**100.0%**	**1.09 [1.03, 1.17]**
Total events	842		740			

Heterogeneity: Chi² = 30.52, df = 12 (P = 0.002); I² = 61%
Test for overall effect: Z = 2.72 (P = 0.007)

Figure 6. Normal vaginal delivery

Source: Own elaboration.

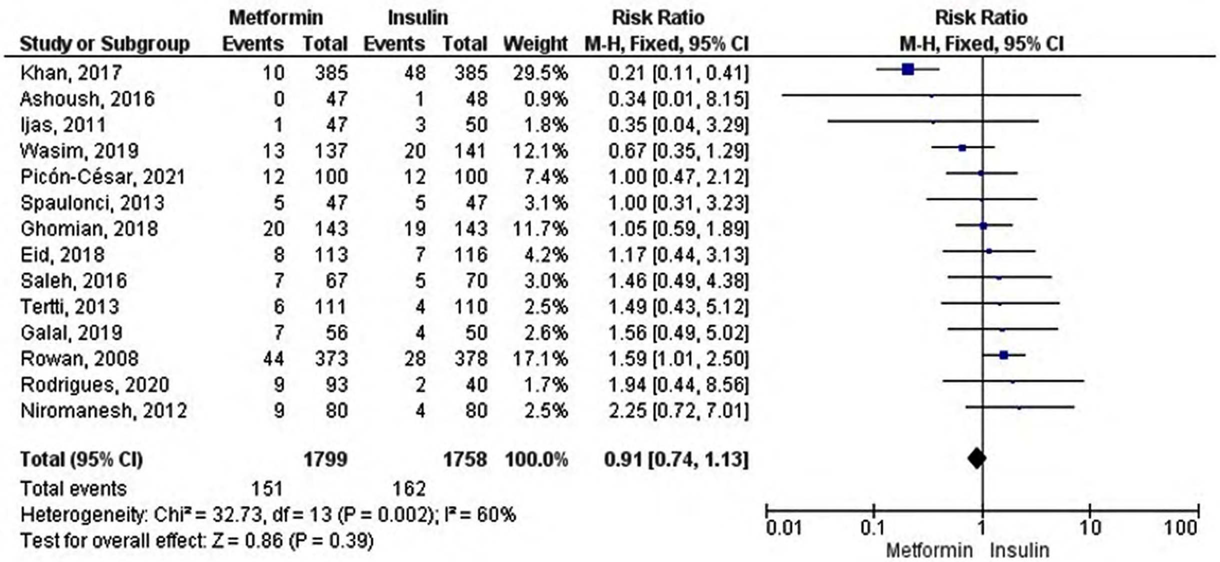


Figure 7. Preterm delivery

Source: Own elaboration.

Risk of bias

In this review, no study was classified as having "low risk" of bias. The majority of the studies (n=17) were categorized as "high risk," namely: Wasim, 2019 (18); Khan, 2017 (19); Saleh, 2016 (21); Hassan, 2012 (22); Ashoush, 2016 (23); Eid, 2018 (24); Niromanesh, 2012 (25); Ijas, 2010 (26); Rowan, 2008 (27); Muhsen, 2022 (28); Galal, 2019 (29); Picón-César, 2021 (32); Rodrigues, 2020 (31); Spaulonci, 2013 (33); Rõnnemaa, 2014 (35), and Tertti, 2013 (30).

Most of the studiesresulted in "high risk", namely: Wasim, 2019 (18); Khan, 2017 (19); Saleh, 2016 (21); Hassan, 2012 (22); Ashoush, 2016 (23); Eid, 2018 (24); Niromanesh, 2012 (25); Ijas, 2010 (26); Rowan,2008 (27); Muhsen, 2022 (28); Galal, 2019 (29); Picón-César, 2021 (32); Rodrigues, 2020 (31); Spaulonci, 2013 (33); Rõnnemaa, 2014 (35), and Tertti, 2013 (30).

Finally, three studies were classified as presenting "some concerns": Ainuddin, 2015 (16); Huhtala, 2021 (20), and Ghomian, 2018 (34) (Table 3).

Table 3. Risk of bias

Study	Bias from randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcomes	Bias in selection of reported result	Overall risk of bias
Ainuddin, 2015 (16)	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns
Wasin, 2019 (18)	Low	Some Concerns	Low	Some Concerns	High	High

Khan, 2017 (19)	Low	Low	Low	Some Concerns	High	HIgh
Huhtala, 2021 (20)	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Saleh, 2016 (21)	Low	Low	Low	Some Concerns	High	High
Hassan, 2012 (22)	Low	Low	Low	Some Concerns	High	High
Ashoush, 2016 (23)	Low	Low	Low	Some Concerns	High	High
Eid, 2018 (24)	Low	Low	Low	Some Concerns	High	High
Niromanesh, 2012 (25)	Low	Low	Low	Some Concerns	High	High
Ijas, 2010 (26)	Low	Some Concerns	Low	High	High	High
Rowan, 2008 (27)	Low	Low	Low	High	High	High
Muhsen, 2022 (28)	Low	High	Low	High	High	High
Galal, 2019 (29)	Low	Some Concerns	Low	High	High	High
Picón-César, 2021 (32)	High	Low	Some concerns	High	High	High
Rodrigues, 2020 (31)	High	Low	Low	High	High	High
Ghomian, 2018 (34)	Some concerns	Low	Low	Low	Some concerns	Some concerns
Spaulonci, 2013 (33)	Low	Low	Low	Some Concerns	High	High
Rönnemaa, 2014 (35)	Low	High	Low	High	Some concerns	High
Tertti, 2013 (30)	Low	Some Concerns	Low	High	High	High

Source: Own elaboration.

Discussion

In this meta-analysis, a total of 4,320 patients were included across 19 randomized controlled trials. Six outcomes were statistically compared: (1) induced hypertension occurred more frequently in patients receiving insulin; (2) preeclampsia was more prevalent in the insulin group, with 10.4% versus 5.8% in the metformin group; (3) large-for-gestational-age infants (LGA) were more common in the insulin group; (4) induced labor occurred significantly more in the insulin group; (5) normal vaginal delivery was more frequent in patients treated with metformin; and (6) preterm delivery was more common in the insulin group.

A previous meta-analysis by Bao et al. [36] evaluated 1,457 patients, focusing on induced hypertension, LCLS, gestational age at delivery, maternal weight gain, and premature delivery. In comparison, this meta-analysis included a larger cohort (4,367 patients) and focused specifically on maternal outcomes and modes of labor. Both meta-analyses consistently demonstrated that metformin was associated with lower rates of induced hypertension [3].

Regarding preeclampsia, the previous meta-analysis did not identify a statistically significant difference; however, the present study observed a trend favoring metformin, reinforcing its potential protective effect against hypertensive disorders in pregnancy [36, 24, 26, 27]. LCLS also demonstrated a statistically significant reduction in the metformin group (P=0.0002) [20, 22, 24, 27, 32].

Importantly, the safety profile of metformin during pregnancy is well established. Several studies indicate that metformin crosses the placenta but does not induce teratogenic effects in humans or animal models [6–12]. Long-term follow-up studies have evidenced no adverse outcomes in offspring, including growth, metabolic parameters, or neurodevelopment, up to early childhood [20, 22, 27]. These findings support the use of metformin as a safe alternative to insulin, particularly in patients with gestational diabetes mellitus requiring glycemic control.

Neonatal implications of metformin use have been thoroughly evaluated. Evidence suggests that metformin does not increase the risk of neonatal hypoglycemia, respiratory distress, or admission to neonatal intensive care units and may reduce the incidence of macrosomia [20, 22, 27]. Furthermore, metformin exposure has not been associated with adverse long-term metabolic outcomes, and children exposed in utero exhibit growth trajectories and body composition comparable to those of insulin-exposed or unexposed infants [20, 22, 27].

In three RCTs included in this review, metformin combined with insulin did not differ significantly from metformin alone, reinforcing its versatility in clinical practice [17, 19, 23]. Therefore, metformin can be recommended as a first-line pharmacological therapy for GDM, with the addition of insulin reserved for cases where glycemic targets are not achieved [17–37].

Overall, this meta-analysis strengthens current evidence that metformin is not only effective in controlling maternal glycemia but also safe for both the mother and neonate in the short and long term, supporting its broader implementation in the management of GDM [6–12,17–37].

Conclusion

This systematic review and meta-analysis of nineteen randomized controlled trials evaluated maternal outcomes and modes of labor in gestational diabetes mellitus treated with metformin and insulin. The analysis demonstrates that insulin therapy is significantly associated with higher rates of large-for-gestational-age infants, induced labor, and preeclampsia, whereas metformin treatment is linked to a higher incidence of normal vaginal deliveries. These findings support the use of metformin as an effective and safe alternative to insulin for glycemic management in GDM, offering favorable maternal outcomes. Nonetheless, combination therapy with insulin should remain an option for patients who do not achieve adequate glycemic control with metformin alone, allowing for individualized treatment and the optimization of both maternal and neonatal outcomes.

Authors' contributions

Maria Fernanda Quandt Treml: Conceptualization, formal analysis, research, writing (original draft); Nicole Caroline Junglos:

Formal analysis, research, methodology, writing (original draft); Agelicia Ott: Formal analysis, writing (original draft); Heloisa Bernardi Hummel: Formal analysis, writing (original draft); Ana Carolina Moreira de Moraes Lima: Formal analysis, writing (original draft); Felipe Silva Luciano Carvalho: Formal analysis, writing (original draft); Matheus José Barbosa Moreira: Writing (referee and editing corrections).

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Conflicts of interest

None of the authors have any conflict of interest to disclose.

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Availability of data and materials

No data are available in a public repository. For inquiries regarding any information related to this article, please contact the corresponding author.

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