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Metformin versus insulin in the management of gestational diabetes mellitus: A meta-analysis

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Abstract:

OBJECTIVE: To determine the efficacy of metformin and insulin in the management of gestational diabetes mellitus (GDM).

METHODOLOGY: Randomized controlled trials (RCT) were retrieved from the databases. All references cited in the articles were also searched by hand to identify additional publications. Studies included were limited to trials on metformin and insulin in the management of GDM in singleton pregnancies. Four RCTs were analyzed in the study. The risk of bias was assessed using Preferred Reporting Items for Systematic reviews and Meta-Analyses Cochrane Collaboration's tool (Rob 2). Random effects meta-analysis was carried out to pool the data. All analyses were conducted in Review Manager 5.3.5 (2014).

RESULTS: Meta-analysis of four RCT involving 807 participants (405 were treated with metformin and 402 were treated with insulin) shows that there was no significant difference between metformin and insulin in achieving glycemic control as to fasting blood sugar (FBS), postprandial blood glucose (PPBG), and glycosylated hemoglobin, mean difference (MD) −0.43 (95% confidence interval [CI] −2.77–1.91; *P* = 0.72), MD −2.13 (95% CI −5.16–0.90, *P* = 0.17), MD −0.09 (95% CI −0.20–0.02, *P* = 0.10), respectively. For maternal outcomes, there was a statistically significant 69% decreased risk of hypoglycemia in the metformin group (risk ratio [RR] 0.31, 95% CI 0.20–0.49; *P* < 0.001). There was no difference in terms of risk of preterm birth (RR 1.11, 95% CI 0.75–1.64, *P* = 0.60); hypertensive disorders (RR 1.06, 95% CI 0.71–1.60, *P* = 0.77); polyhydramnios (RR 1.04, 95% CI 0.51–2.14, *P* = 0.91); and risk of cesarean delivery (RR 0.90, 95% CI 0.75–1.08, *P* = 0.27). For neonatal outcomes, there was statistically significant 34% reduction on the risk of neonatal hypoglycemia (RR 0.66, 95% CI 0.46–0.94; *P* = 0.02) in the metformin group. There was no statistical difference in terms of mean birthweight (MD – 81.34, 95% CI −181.69–19.02, *P* = 0.11). Metformin has decreased the risk of newborns weighing more than 4000 g, babies with birthweight >90th percentile by 27% (RR 0.73, 95% CI 0.28–1.90, *P* = 0.52), and 20% (RR 0.80, 95% CI 0.54–1.18, *P* = 0.26), respectively, but these were not statistically significant. There was no significant difference in terms of risk of birthweight <10th percentile (RR 1.17, 95% CI 0.60–2.31, *P* = 0.65); APGAR <7 (RR 1.17, 95% CI 0.65–2.08, *P* = 0.60), birth trauma (RR 0.77, 95% CI 0.23–2.58, *P* = 0.67), and jaundice requiring phototherapy RR 1.04, 95% CI 0.66–1.65, *P* = 0.85). Neonatal intensive care unit admission (RR 0.89, 95% CI 0.64–1.23, *P* = 0.48), respiratory distress syndrome (RR 0.73, 95% CI 0.36–1.50, *P* = 0.39), transient tachypnea (RR 0.78, 95% CI 0.27–2.19, *P* = 0.63), and any congenital anomaly (RR 0.58, 95% CI 0.20–1.67, *P* = 0.31) were decreased in the metformin group but was not statistically significant.

CONCLUSION: There was no significant difference between metformin and insulin in achieving glycemic control as to FBS and PPBG among patients with GDM. There was a statistically significant reduction in the risk of maternal and neonatal hypoglycemia in the use of metformin.

Keywords:

Gestational diabetes mellitus, glycemic control, insulin, metformin

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Introduction

The rising incidence of gestational diabetes mellitus (GDM) has been a global health concern in the recent years. It is a common medical complication of pregnancy defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[1] The reported prevalence worldwide varies between 1% and 45% of pregnancies. It varies depending on the population studied and the diagnostic criteria used.[1-3] GDM has become an economic burden for the health-care system and individuals. The disease has been a potential cause of maternal and perinatal morbidity and mortality if glycemic control is not achieved.

GDM has been linked both to short- and long-term maternal and neonatal complications. Women with GDM have a higher risk of developing preeclampsia, higher rates of cesarean delivery, and developing type 2 diabetes later in life.[4,5] The offsprings born to a diabetic mother usually exhibit macrosomia, large for gestational age, small for gestational age (due to insufficient weight gain), and neonatal hypoglycemia.[4,6] Furthermore, those born to the mothers with badly treated GDM are at increased risk of higher body mass index, obesity or type 2 diabetes mellitus early in life.[7,8]

Glycemic control is integral in the management of GDM. Women should achieve a glycemic control to prevent adverse outcomes resulting from hyperglycemia. Most women can control their blood glucose levels with medical nutrition therapy or proper exercise. However, in cases when glycemic targets are not achieved, pharmacological treatment should be initiated. Patients with excessive weight gain during pregnancy are likely to have uncontrolled blood sugar.[4]

For years, insulin has been the drug of choice for the management of hyperglycemia in pregnancy.[9] However, insulin has several disadvantages such as maternal weight gain, the need for multiple injections, higher cost and inconvenient modes of administration, and monitoring.[10] A logical alternative would be safe and economic oral agents that are effective in achieving glycemic targets. The use of oral hypoglycemic agents, particularly metformin has been increasing worldwide. Metformin (N, N-dimethylbiguanide), a biguanide oral glucose-lowering drug, can improve hepatic and peripheral sensitivity to insulin and is approved for use in the treatment of GDM. However, metformin crosses the placenta and accumulate in fetal and placental tissues that could affect fetal physiology, hence, several randomized clinical trials of metformin for GDM treatment have been carried out including its long-term impact of intrauterine exposure.[11]

As an increasing worldwide health concern, it is important to continuously evaluate these two pharmacological treatments in achieving glycemic control hence preventing adverse maternal and perinatal outcomes.

Objectives

A. General:

- To determine the efficacy of metformin and insulin in the management of GDM

B. Specific:

1. To compare the efficacy of metformin and insulin in achieving glycemic control in patients with GDM as to:
   a. Mean fasting blood sugar (FBS) throughout treatment
   b. Mean postprandial blood glucose (1 h-PPBG or 2 h-PBBG) throughout treatment
   c. Mean glycosylated hemoglobin (HbA1c, %) throughout treatment
2. To compare the effect metformin and insulin on maternal outcomes:
   a. Any maternal hypoglycemic event
   b. Preterm birth
   c. Hypertensive disorders (pregnancy induced hypertension [PIH], preeclampsia)
   d. Polyhydramnios
   e. Cesarean delivery
3. To compare the effect of metformin and insulin on neonatal outcomes:
   a. Mean birthweight
   b. Birthweight > 4000 g
   c. Birthweight > 90th percentile
   d. Birthweight < 10th percentile
   e. APGAR5 < 7
   f. Birth trauma
   g. Neonatal hypoglycemia
   h. Neonatal intensive care unit (NICU) admission
   i. Respiratory distress syndrome (RDS)
   j. Transient tachypnea
   k. Jaundice requiring phototherapy
   l. Any congenital anomaly

Methodology

The study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines for the meta-analysis of randomized controlled trials (RCTs).

A systematic electronic search of published clinical trials was done in databases of Cochrane Library, Clinicaltrials.gov, PubMed, Embase (last search was updated on December 12, 2021) using the following MeSH Terms (glycemic control and gestational diabetes mellitus) and key words (gestational diabetes mellitus, metformin, insulin, and gycemic control). Searches were restricted to RCTs.

Only studies published in English from 2010 to present were included. All references cited in the articles were also searched manually to identify additional publications.

Study selection

Study selection, data extraction, and quality assessment were done by the three authors. Any discrepancies were reviewed and discussed accordingly. The study included RCTs on metformin and insulin in the management of GDM in singleton pregnancies. A total of 69 titles were identified both from the databases using the provided keywords and citation searches. After removal of duplicates and nonrandomized controlled studies, 17 records were screened. Among these studies, four records were excluded due to irrelevance (the articles focused the on the prevalence and biochemical cause of GDM instead of the comparative effects of insulin and metformin). Only 11 articles were retrieved in full-text and were assessed for eligibility. Four randomized controlled studies were included for the meta-analysis as the seven articles were excluded for differences in the subjects (i.e., multifetal gestation and overt diabetes mellitus), and multiple medical interventions were employed (metformin in combination with other oral hypoglycemic agent and insulin was used as adjunct to metformin).

Types of participants

Studies that were included met the following criteria:

1. Patients with GDM
2. Interventions: Metformin and insulin
3. Outcomes: Glycemic control, one or more maternal outcomes, one or more neonatal outcomes
4. Study design: RCT.

Studies involving overt diabetes mellitus, retrospective studies, observational studies, and case series will be excluded.

Table 1 summarizes the characteristics included in the study. Three investigators independently reviewed all articles for eligibility. Disagreements were resolved by discussion of all investigators.

Types of intervention

The participants in the study were diagnosed with GDM during the second or third trimester. They were

Table 1: Study characteristics of randomized controlled trials of metformin versus insulin in the management of gestational diabetes mellitus

Author, year (participating country)	Design	MET group	INS group	Participants		Outcomes
				MET	INS	
Saleh *et al*.,[13] 2018 (Egypt)	RCT	500 mg/day PO; 3000 mg/day maximum; start INS if still uncontrolled	Combination of short- and intermediate-acting BID	67	70	Glycemic control (mean throughout): FBS <100 mg/dL; 2hPPBG <120 mg/dL Maternal outcomes: Preeclampsia, preterm birth, polyhydramnios, mode of delivery Neonatal outcomes: Hypoglycemia, transient tachypnea, respiratory distress, jaundice requiring phototherapy, NICU admission, birth trauma, Apgar 5<7, BW >90th percentile and <10th percentile, congenital anomalies
Eid *et al*.,[14] 2018 (Egypt)	RCT	500 mg/day; 2500 mg/day maximum	NPH 2/3 + regular1/3 AM; NPH 1/2 + regular1/2 PM	113	116	Glycemic control (mean throughout): FBS and 2hPPBG Maternal outcomes: Hypoglycemia, PIH/preeclampsia, preterm birth, polyhydramnios, mode of delivery Neonatal outcomes: Apgar 5<7, BW >4000 g, BW >90th percentile and <10th percentile, hypoglycemia, respiratory distress, transient tachypnea, NICU admission, jaundice requiring phototherapy, congenital anomalies, birth trauma
Ghomian *et al*.,[12] 2018 (Iran)	RCT	500 mg/day; 1500 mg/day maximum; some changed to INS	Levemir HS; aspart before meals	143	143	Glycemic control (mean throughout): FBS and 2hPPBG, HbA1c (%) Maternal outcome: Mode of delivery Neonatal outcomes: Mean BW, preterm birth, Apgar 5<7, hypoglycemia, birth trauma, NICU admission
Picon-Cesar *et al*.,[15] 2021 (Spain)	RCT	425–850 mg/day; 2550 mg/day maximum	Detemir HS; aspart premeals	88	88	Glycemic control (mean throughout): FBS and 1hPPBG, HbA1c (%) Maternal outcomes: Hypertensive disorders, preterm birth, hypoglycemia Mode of delivery Neonatal outcomes: Mean BW, birth trauma, NICU admission, respiratory distress syndrome, hypoglycemia, jaundice requiring phototherapy, BW >4000 g, BW >90th percentile and <10th percentile, congenital anomalies

RCT: Randomized controlled trial, MET: Metformin, INS: Insulin, FBS: Fasting blood sugar, PPBG: Postprandial blood glucose, NICU: Neonatal intensive care unit, BW: Birth weight, PIH: Pregnancy-induced hypertension, HbA1c: Glycosylated hemoglobin, NPH: Neutral protamine hagedorn insulin

randomized to receive insulin or metformin for glycemic control.

Types of outcome measures

Glycemic control was the primary interest of the study. Maternal and neonatal outcomes were discussed as the secondary outcomes. Maternal outcomes include risks for: (1) any maternal hypoglycemic event, (2) preterm birth, (3) hypertensive disorders (PIH, preeclampsia), (4) polyhydramnios, and (5) cesarean delivery. Neonatal outcomes include: (1) Mean birthweight, (2) birthweight >4000 g, (3) birthweight >90th percentile, (4) birthweight <10th percentile, (5) APGAR at 5 min <7, (6) birth trauma, (7) neonatal hypoglycemia, (8) NICU admission, (9) RDS, (10) transient tachypnea, (11) jaundice requiring phototherapy, and (12) any congenital anomaly.

Glycemic control will be determined as to FBS. 1-h or 2-h postprandial capillary blood glucose and mean glycosylated hemoglobin throughout the treatment.

Results

Description of studies

Results of the search

This study identified references with 69 studies included. Sixty-two were retrieved from databases and seven were from the manual search based on citation. There were 20 records which were not RCTs. There were 32 duplicate records removed. Ten studies were screened for abstract and title where four articles were excluded due to irrelevance. Eleven out of thirteen trials were retrieved in full text and assessed for eligibility. Those that were excluded included twin gestation, used insulin as adjunct in the metformin group and no blood sugar determination throughout the study. Finally, four studies, published in English were included in the study [Figure 1].

Included studies

There were four RCTs in this meta-analysis involving 852 participants. The number of participants ranged from 67 (Saleh *et al*., 2016) to 143 (Ghomian *et al*., 2018). The trials were varied in the geographical location. All studies were conducted in multicenter teaching or academic hospitals in Iran, Egypt, and Spain.[12-15]

Participants

Included participants were singleton pregnancies diagnosed with GDM during their second or third trimester (22–34 weeks) using the following criteria:

1. WHO criteria: Fasting plasma glucose (FPG) more than or equal to 7.0 mmol/L or 2-h value more than 7.8 mmol/L following a 2-h 75-g oral glucose tolerance test (OGTT)[12,13]
2. The American Diabetes Association criteria: Two or more abnormal values in the 75-g OGTT. Fasting value >95 mg/dL (5.3 mmol/L), 1-h value >180 mg/dL (10.0 mmol/L), 2-h value >155 mg/dL (8.6 mmol/L), and 3-h serum glucose >140 mg/dL (7.8 mmol/L)[1,14]
3. National Diabetes Data Group criteria: Using a 50-g 1-h oral glucose screening (O'Sullivan test) followed by a 100-g 3-h OGTT. The criteria stipulate using fasting, 1-h, 2-h, and 3-h plasma glucose levels of

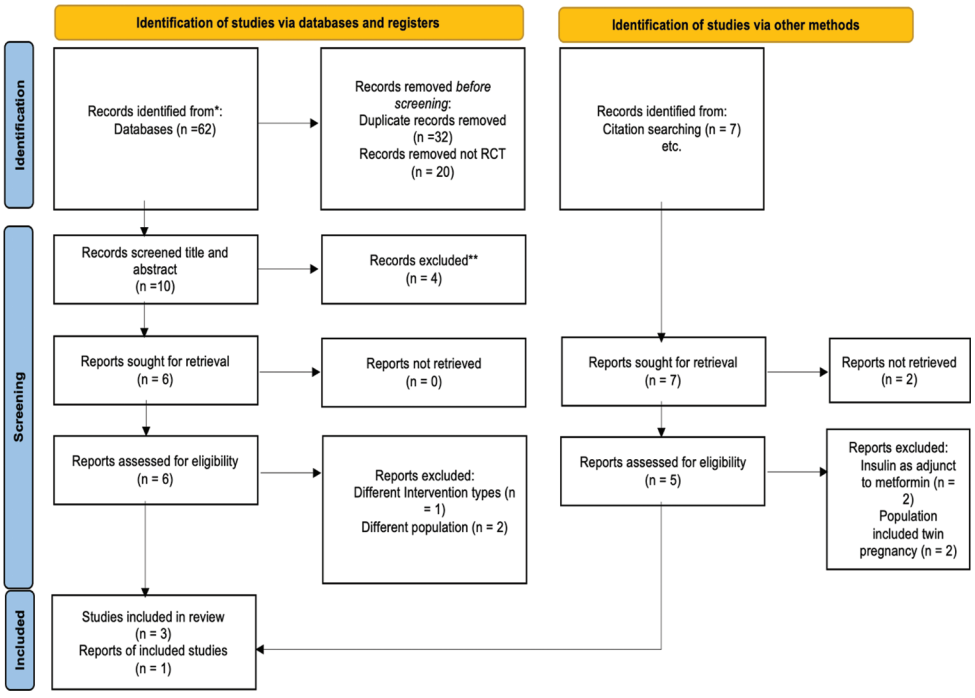

Figure 1: Identification of study. RCT: Randomized controlled trial

105 mg/dL, 190 mg/dL, 165 mg/dL, and 145 mg/dL, respectively. Isolated fasting glycemia at 100 mg/dL (5.6 mmol/L) was also considered GDM.[15]

Interventions

The four included trials employed different criteria for initiation of medical therapy using metformin and insulin. Saleh *et al*. included those participants who did not respond to diet modifications or nutritional instructions alone in 3 weeks.[13] Patients who failed to achieve a FPG and 2-h PG of 95 and 120 mg/dL, respectively, were entered into the study of Ghomian *et al*.[12] In the study of Picon-Cesar *et al*.,[15] initiation of medical therapy was considered when two or more fasting glucose measurements were >95 mg/dL (5.3 mmol/L) per week and/or when two or more 1-h postprandial measurements were >140 mg/dL (7.8 mmol/L) per week.

Outcomes

Assessment of risk of bias

The risk of bias was assessed using the criteria provided in the PRISMA Cochrane Collaboration's tool (RoB 2).[16] The following criteria will be assessed in each included trial: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. The authors provided categories such as "low risk" of bias, "high risk" of bias or "some concerns" of bias. The risk of bias in each trial included was assessed individually by three reviewers. Any differences of opinion regarding assessment of risk of bias were resolved by discussion.

The risk of bias is generally high across all studies except for random sequence generation which has two studies assessed as low risk for selection bias and the other two with unclear risk [Figures 2 and 3].

Effects of intervention

All analyses were performed using Review Manager 5.3.5, a downloadable computer program from The Cochrane Collaboration (Copenhagen). The overall effect estimate was calculated as the mean difference (MD with 95% confidence interval [CI]) between the metformin and insulin group for continuous outcomes as blood sugar level and birthweight. The overall effect estimate was calculated as the risk ratio (RR with 95% CI) between the metformin and insulin group for the rest of the outcomes of interest. Random effects meta-analysis was carried out to pool the data. Pooled summary estimates were derived using the inverse-variance method for continuous outcomes and Mantel–Haenszel method for categorical outcomes.

Comparison of metformin and insulin

Primary outcome: Glycemic control

Mean FBS levels were reported in four studies (n = 828). Three studies show that in metformin group mean FBS levels were slightly lower mean as compared to insulin group, but this was not statistically significant (MD – 0.43, 95% CI – 2.77–1.91; P = 0.72) [Figure 4].

There was also no significant difference in PPBG throughout treatment between the two groups (MD – 2.13, 95% CI – 5.16–0.90, P = 0.17) [Figure 5]. Two relevant studies (n = 441) included HbA1c as to parameters for glycemic control assessment. The results show that there was no difference in HbA1c throughout treatment between the metformin group and insulin group (MD – 0.09, 95% CI – 0.20–0.02, P = 0.10) [Figure 6].

According to the results, there was no statistically significant difference in the efficacy of metformin

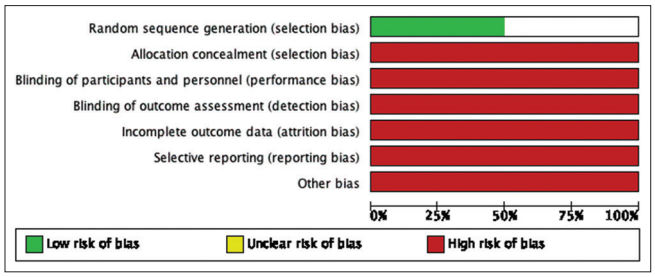

Figure 2: Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies

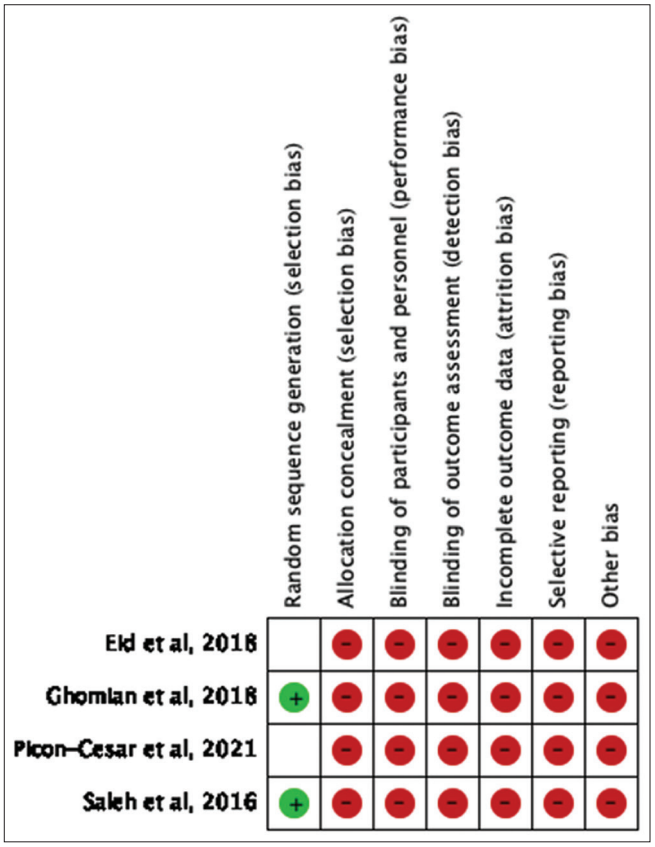

Figure 3: Risk of bias summary: Review authors' judgements about each risk of bias item for each included study

and insulin in achieving glycemic control in patients with GDM as to mean FBS, mean PPBG, and mean glycosylated hemoglobin throughout the treatment.

Secondary outcomes

Maternal outcomes

Any hypoglycemic event

Two trials (n = 418) provided data comparing the risk of any hypoglycemic event between metformin and insulin group. The risk of any hypoglycemic event was 0.31 times less likely (RR 0.31, 95% CI 0.20–0.49; $P < 0.001$) in the metformin group compared to the insulin group. The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 7].

Preterm birth

The risk for preterm birth was included in all four trials (n = 843). The result shows no difference in the risk of preterm birth between the two groups (RR 1.11, 95% CI 0.75–1.64, P = 0.60) with minimal level of variability due to heterogeneity (I^2 = 0%) [Figure 8].

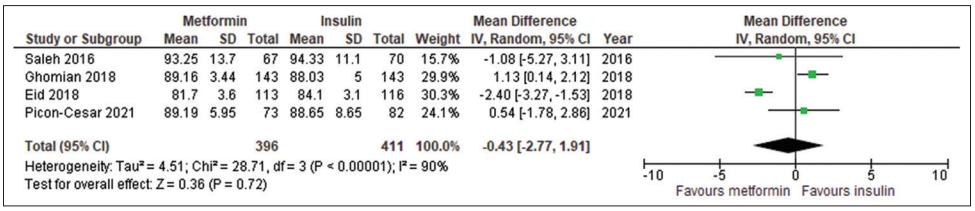

Figure 4: Forest plot of comparison of glycemic control as to mean fasting blood sugar throughout the treatment. SD: Standard deviation, CI: Confidence interval

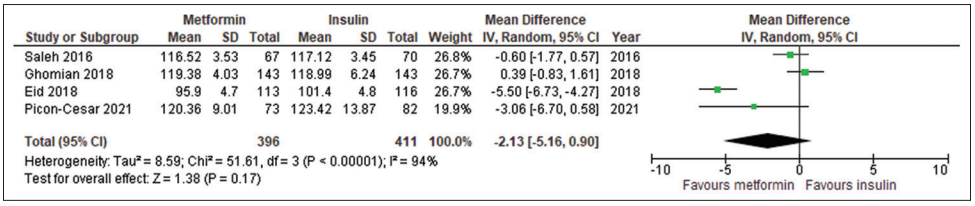

Figure 5: Forest plot of comparison of glycemic control as to mean postprandial blood glucose (PPBG) (1h-PPBG or 2h-PBBG) throughout the treatment. SD: Standard deviation, CI: Confidence interval

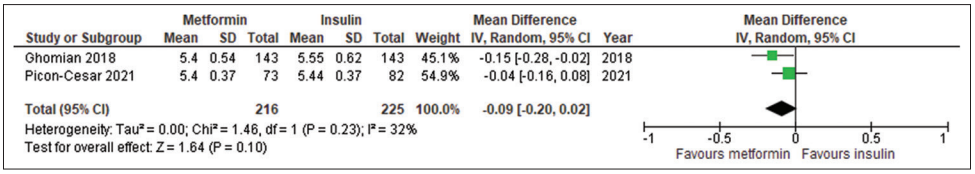

Figure 6: Forest plot of comparison of glycemic control as to mean (glycosylated hemoglobin, %) throughout the treatment. SD: Standard deviation, CI: Confidence interval

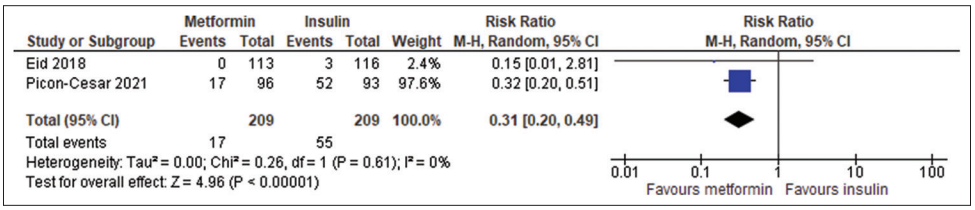

Figure 7: Forest plot of comparison of the outcome: Any hypoglycemic event. CI: Confidence interval

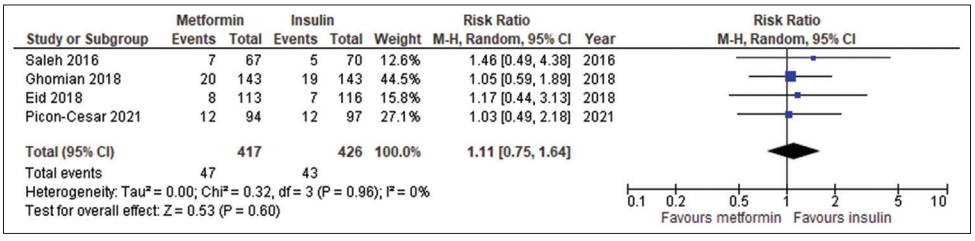

Figure 8: Forest plot of comparison of the outcome: Preterm birth. CI: Confidence interval

Hypertensive disorders

According to the three studies (n = 557) included, there was no difference in the risk of hypertensive disorders between the two groups (RR 1.06, 95% CI 0.71–1.60, P = 0.77). The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 9].

Polyhydramnios

Two studies (n = 366) provided data regarding the risk of polyhydramnios. There was no difference in the risk of polyhydramnios between the two groups (RR 1.04, 95% CI 0.51–2.14, P = 0.91). The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 10].

Cesarean delivery

There was no difference in the risk of cesarean delivery between the two groups (RR 0.90, 95% CI 0.75–1.08, P = 0.27) based on the three included studies (n = 557). The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 11].

Neonatal outcomes

Mean birthweight

Two trials (n = 477) provided data. There was no difference in mean birthweight between the metformin group and insulin group (MD −81.34, 95% CI −181.69–19.02, P = 0.11). The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 12].

Birthweight >4000 g

According to the provided data of two trials (n = 420), there was no difference in the risk of birthweight >4000 g between the two groups (RR 0.73, 95% CI 0.28–1.90, P = 0.52). The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 13].

Birthweight >90th percentile

There was no difference in the risk of birthweight >90th percentile between the two groups (RR 0.80, 95% CI 0.54–1.18, P = 0.26) based on three included trials (n = 557). The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 14].

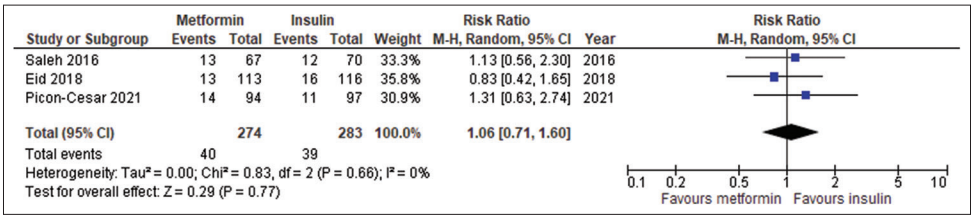

Figure 9: Forest plot of comparison of the outcome: Hypertensive disorders. CI: Confidence interval

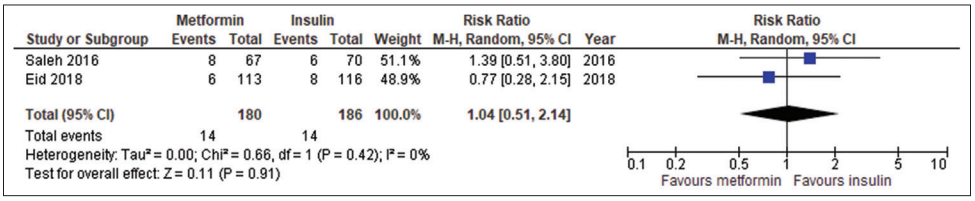

Figure 10: Forest plot of comparison of the outcome: Polyhydramnios. CI: Confidence interval

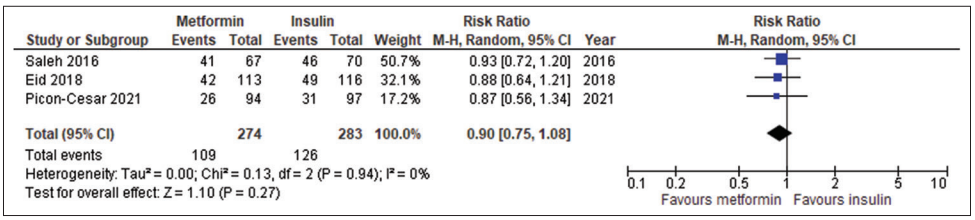

Figure 11: Forest plot of comparison of the outcome: Cesarean delivery. CI: Confidence interval

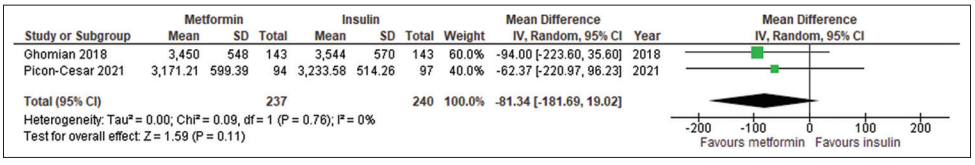

Figure 12: Forest plot of comparison of the outcome: Mean birthweight. SD: Standard deviation, CI: Confidence interval

Birthweight <10th percentile

There was also no difference between metformin and insulin groups as to risk of birthweight <10th percentile (RR 1.17, 95% CI 0.60–2.31, $P = 0.65$) based on three included studies ($n = 557$). The level of variability due to heterogeneity was minimal ($I^2 = 0\%$) [Figure 15].

APGAR at 5 min <7

There was no difference in the risk of APGAR at 5 min <7 between the two groups (RR 1.17, 95% CI 0.65–2.08, $P = 0.60$). The level of variability due to heterogeneity was minimal ($I^2 = 0\%$) [Figure 16].

Birth trauma

There was no difference in the risk of birth trauma between the two groups (RR 0.77, 95% CI 0.23–2.58, $P = 0.67$) according to two studies ($n = 477$) which provided data. The level of variability due to heterogeneity was minimal ($I^2 = 34\%$) [Figure 17].

Neonatal hypoglycemia

Four studies ($n = 843$) provided data. There was statistically significant 34% reduction on the risk of neonatal hypoglycemia (RR 0.66, 95% CI 0.46–0.94; $P = 0.02$) in the metformin group compared to the insulin

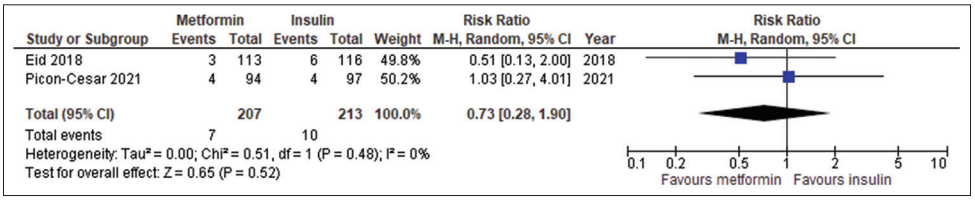

Figure 13: Forest plot of comparison of the outcome: Birthweight >4000 g. CI: Confidence interval

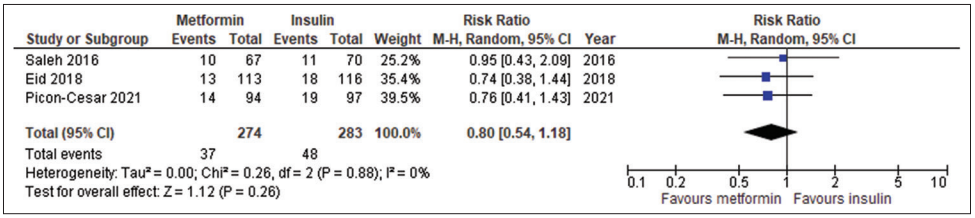

Figure 14: Forest plot of comparison of the outcome: Birthweight >90th percentile. CI: Confidence interval

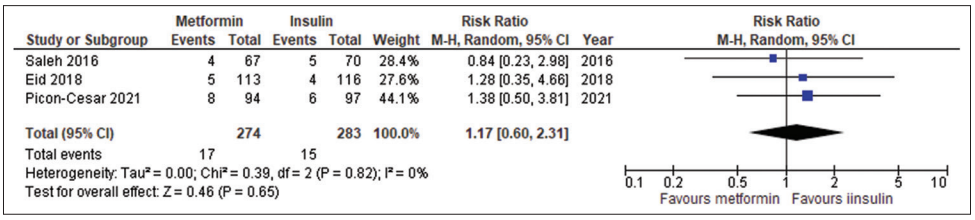

Figure 15: Forest plot of comparison of the outcome: Birthweight <10th percentile. CI: Confidence interval

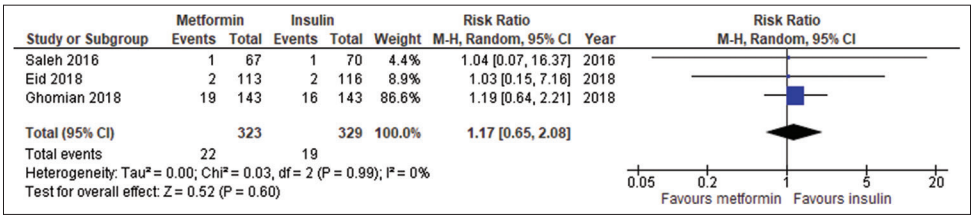

Figure 16: Forest plot of comparison of the outcome: APGAR at 5 min <7. CI: Confidence interval

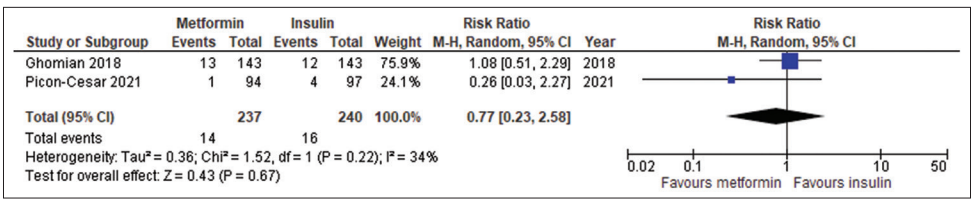

Figure 17: Forest plot of comparison of the outcome: Birth trauma. CI: Confidence interval

group. The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 18].

Neonatal intensive care unit admission

There was no difference in the risk of NICU admission between the two groups (RR 0.89, 95% CI 0.64–1.23, P = 0.48) based on four included studies (n = 443). The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 19].

Respiratory distress syndrome

Three relevant studies (n = 557) provided data. The risk of RDS was 0.73 less likely (RR 0.73, 95% CI 0.36–1.50, P = 0.39) in the metformin group compared to insulin group, but it was statistically not significant. The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 20].

Transient tachypnea

Two trials (n = 366) provided data. There was no difference in the risk of transient tachypnea between the two groups (RR 0.78, 95% CI 0.27–2.19, P = 0.63). The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 21].

Jaundice requiring phototherapy

There was no difference in the risk of jaundice requiring phototherapy between the two groups (RR 1.04, 95% CI 0.66–1.65, P = 0.85) based on two three trials (n = 557) which provided data. The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 22].

Any congenital anomaly

Two trials (n = 328) provided data. There was no difference in the risk of any congenital anomaly between the two groups (RR 0.58, 95% CI 0.20–1.67, P = 0.31). The level of variability due to heterogeneity was minimal (I^2 = 0%) [Figure 23].

Discussion

GDM poses both short- and long-term maternal and neonatal complications if mismanaged and left unaddressed. These complications arise depending on the glycemic control of the mother all throughout her pregnancy. Hence, the primary goal of therapy is to achieve glycemic targets and thus decrease adverse perinatal outcomes. Medical therapy was initiated when medical nutrition therapy or proper exercise failed to achieve target glycemic values. The use of metformin in GDM patients has been increasing worldwide, with some countries using this as initial glucose-lowering treatment.[17] With the current trend in pharmacological management of GDM, the safety and efficacy of metformin should be investigated.

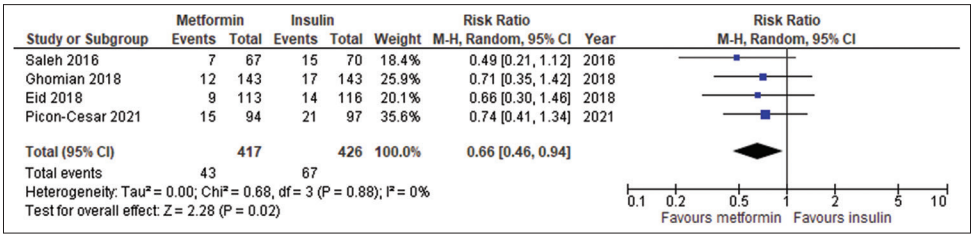

Figure 18: Forest plot of comparison of the outcome: Neonatal hypoglycemia. CI: Confidence interval

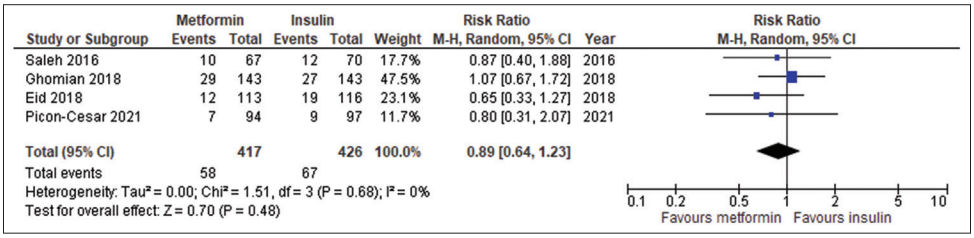

Figure 19: Forest plot of comparison of the outcome: Neonatal intensive care unit Admission. CI: Confidence interval

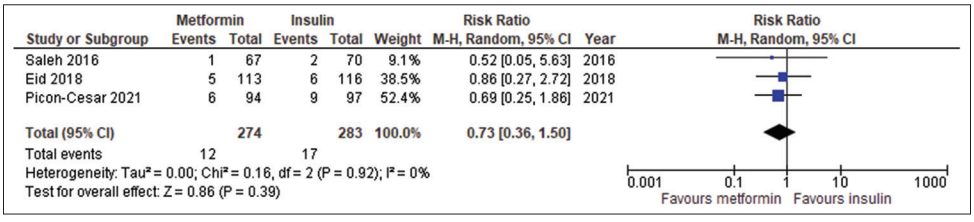

Figure 20: Forest plot of comparison of the outcome: Respiratory distress syndrome. CI: Confidence interval

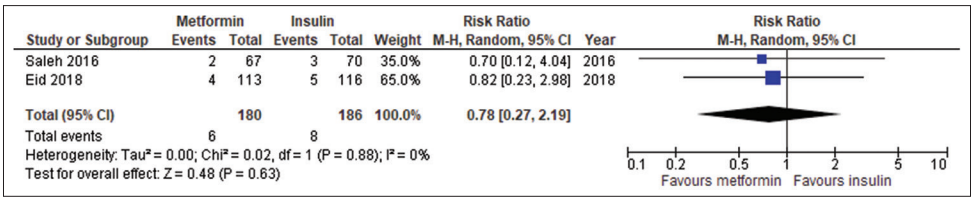

Figure 21: Forest plot of comparison of the outcome: Transient tachypnea. CI: Confidence interval

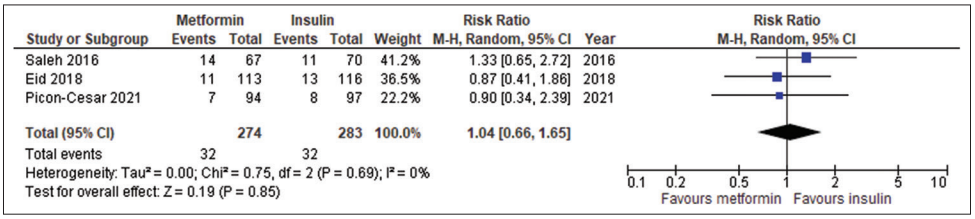

Figure 22: Forest plot of comparison of the outcome: Jaundice requiring phototherapy. CI: Confidence interval

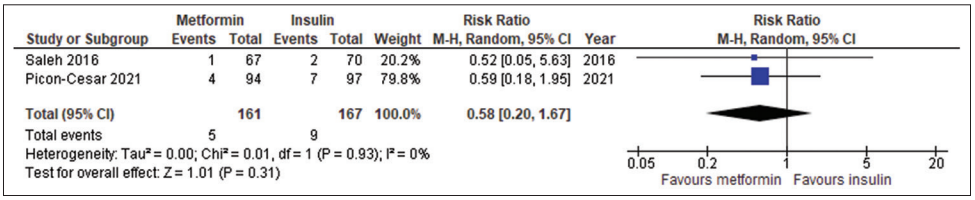

Figure 23: Forest plot of comparison of the outcome: Any congenital anomaly. CI: Confidence interval

This meta-analysis of four RCTs compared the efficacy of metformin and insulin in the management of GDM. The study provides evidence that metformin and insulin have no significant difference in achieving glycemic control may it be on FBS, postprandial and glycosylated hemoglobin. These findings are consistent with other reviews stating that metformin is comparable with insulin in terms of glycemic control.[18-20] In a meta-analysis, glycemic control seemed to reach sooner in the metformin group, although a proportion of women in the metformin group, specifically those with high body mass index and high baseline blood glucose, required additional insulin to achieve adequate glycemic control.[19] Metformin improves peripheral insulin resistance, decreases hepatic gluconeogenesis and enhancing peripheral glucose uptake. These effects responds to the insulin resistance as the main pathogenesis of GDM.[11]

Among the maternal outcomes assessed in this study, the incidence of maternal hypoglycemia was statistically significantly lower among the women who received metformin. This finding was consistent with the study of He *et al*.[20] Similarly, other studies found no significant difference between the two groups in the incidence of preterm birth and cesarean deliveries.[19-22]

Several studies show that the risk for pregnancy-induced hypertension is reduced in women randomized under metformin.[19,21,22] This is in contrast with the result of this study, wherein metformin did not show significant difference as compared to insulin in terms of incidence of hypertensive disorders (PIH) (gestational hypertension and preeclampsia). One study by Butalia, *et al*. (2017) correlated that the finding of decreased pregnancy-induced hypertension with metformin use may be related to decrease inflammation and perhaps the lower pregnancy weight gain in women who used metformin.[22]

In terms of neonatal outcome, the incidence of nenonatal hypoglcyemia is also lower in the metformin group as compared to the insulin group. This finding is consistent with several publications.[19,20,22] Other neonatal outcomes being investigated: mean birthweight, incidence of birthweight >4000 g, birthweight >90th percentile, birthweight <10th percentile, APGAR score at 5 min <7, Birth trauma, NICU admission, RDS, transient tachypnea, jaundice requiring phototherapy, and any congenital anomaly have shown no significant difference between the two groups. Similarly, other studies showed no difference in terms of incidence of SGA, APGAR score at 5 min <7, RDS, jaundice requiring phototherapy and congenital anomaly.[21,22]

Previous publications also investigated on these outcomes and obtained contrasting results. Outcomes concerning fetal birthweight: mean birthweight, incidence of birthweight more than 4000 g or macrosomia, and birthweight more than 90th percentile were all

significantly lower in the metformin group. According to these reviews, NICU admissions was also found to be lower in the women who used metformin probably equating to the decreased incidence of neonatal hypoglycemia but this was also not reflected in the result of this study.[19-22]

Strength of this study would be the number of neonatal outcomes included albeit the limited participants. Weaknesses include the high risk of bias and the limited number of included randomized controlled studies. Inclusion of high-quality studies and follow-up or reviews on long-term effects of metformin can strengthen its benefits for the management of hyperglycemia in pregnancy.

Conclusion

There was no significant difference between metformin and insulin in achieving glycemic control as to FBS and PPBG among patients with GDM. There was a statistically significant reduction in the risk of maternal and neonatal hypoglycemia in the use of metformin. Metformin has its potential to benefit pregnant women with GDM to prevent adverse perinatal outcomes.

Authorship contributions

Laurice Gizelle C. Ramos - Involved in Conceptualization, methodology, Resources, Data curation, Writing of the original draft, Visualization, Review and editing.

Maribel Emma Co-Hidalgo - Conceptualization, Methodology, Review and editing.

Brenda Bernadette B. Zamora - Conceptualization, Methodology, Data Curation, Review and Editing.

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Conflicts of interest

There are no conflicts of interest.

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