META-ANALYSIS

Comparative Study of the Impact of Metformin Versus Insulin on Adverse Pregnancy Outcomes in Women Diagnosed with Gestational Diabetes Mellitus: A Meta-Analysis

Li Zhang, MM; Yan Mai, MM; Xia Wang, MM; Dan Liu, MM; Jing Cui, MD; Junping Sun, MM

ABSTRACT

Objective • This systematic comparative analysis aimed to assess the efficacy of metformin (MET) versus insulin (INS) in the treatment of gestational diabetes mellitus (GDM), providing valuable insights for future GDM management strategies.

Methods • We conducted a comprehensive search of clinical studies related to MET and INS interventions in GDM through online literature databases, applying predefined inclusion and exclusion criteria. The quality of the included studies was rigorously evaluated. Data on fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), pregnancy weight gain (PWG), premature delivery rate (PDR), and neonatal outcomes among GDM patients were extracted and analyzed using Review Manager 5.3 software.

Results • We identified eleven high-quality studies comprising 8679 participants following careful screening and assessment. Our meta-analysis revealed a significant reduction in the incidence of excessive PWG and neonatal hypoglycemia in the MET treatment group (research group) compared to the INS treatment group (control group) ($P < .05$).

Conclusions • Our findings support the effectiveness and safety of MET in achieving optimal blood glucose control in GDM. These results suggest the potential for broader clinical adoption of MET in GDM management. (*Altern Ther Health Med.* 2024;30(1):460-465).

Li Zhang, MM; Yan Mai, MM; Xia Wang, MM; Department of Gynaecology and Obstetrics, Sanya Central Hospital (Hainan Third People's Hospital), Sanya, Hainan, China. **Dan Liu, MM; Jing Cui, MD; Junping Sun, MM;** Department of Endocrinology, Sanya Central Hospital (Hainan Third People's Hospital), Sanya, Hainan, China.

Corresponding author: Junping Sun, MD
E-mail: sjp0860@sina.com

INTRODUCTION

Gestational diabetes mellitus (GDM), a common complication during pregnancy, is idiopathic diabetes that occurs after pregnancy due to maternal metabolic abnormalities.[1] GDM usually presents with no specific clinical symptoms and is frequently overlooked by patients.[2] As of 2020, the prevalence of GDM among pregnant women has risen significantly, reaching up to 15%.[3]

GDM can lead to maternal infections, polyhydramnios, hypertension, and fetal complications, including hyperglycemia, excessive insulin (INS) secretion, and macrosomia (MS). These factors increase the risk of neonatal congenital diseases and organ hypoplasia.[4] Additionally, it is noteworthy that approximately 20 to 50 % of GDM patients develop type 2 diabetes mellitus (DM) postpartum, necessitating lifelong intervention.[5] Hence, effective prevention and treatment strategies for GDM are paramount for pregnant women.

Currently, clinical management of GDM primarily relies on drug interventions. Among these interventions, insulin (INS), the first-line choice for treating DM, offers the advantage of not adversely affecting placental tissue, rendering it a viable option for GDM treatment.[6] However, using INS is associated with significant limitations and poor patient compliance. Moreover, dosages must be continuously adjusted based on factors such as body mass index (BMI) and INS levels, making treatment less convenient, especially for pregnant women experiencing substantial weight changes during pregnancy.[7]

In recent years, metformin (MET), an oral hypoglycemic drug, has emerged as a novel option for DM therapy.[8] However, it has been observed that MET can permeate the placental barrier in contrast to INS, resulting in a two-to-three-fold increase in umbilical arterial blood concentration compared to maternal venous levels.[9] The potential impact on delivery outcomes in GDM patients remains an area of investigation. Several recent studies have emerged regarding the comparative effectiveness of MET versus INS. Through systematic review and meta-analysis of these studies, we aimed to provide more robust medication guidance for future clinical management of GDM.

MATERIALS AND METHODS

Study Design

This research adopted a systematic and comprehensive approach to assess the comparative efficacy and safety of MET versus INS in the management of GDM. A systematic literature review and meta-analysis were conducted to identify relevant clinical studies, with a rigorous selection process based on predefined inclusion and exclusion criteria.

Eligibility Criteria

Inclusion criteria: (1) The study included individuals diagnosed with GDM; (2) Study designs encompassed randomized controlled trials or cohort studies; (3) Interventions were centered around MET and INS.

Exclusion criteria: (1) studies on patients with fetal abnormalities as confirmed by ultrasound examination; (2) studies on patients with contraindications to MET treatment; (3) studies on patients with concurrent complications; (4) studies with individuals who switched to INS therapy due to inadequate blood sugar (BS) control following MET treatment; (5) studies on GDM patients lacking a diagnosis through the oral glucose tolerance test (OGTT); (6) Studies that duplicated information on the same subject.

Literature Retrieval

The literature search was conducted and screened within online open-access literature databases, including PubMed, Embase, and the Cochrane Library. The search utilized a carefully selected set of keywords, namely "metformin," "diabetes," "gestational," "gestational diabetes mellitus," and "gestational diabetes." The search was limited to studies published from 2010 to the present, with a language restriction to English.

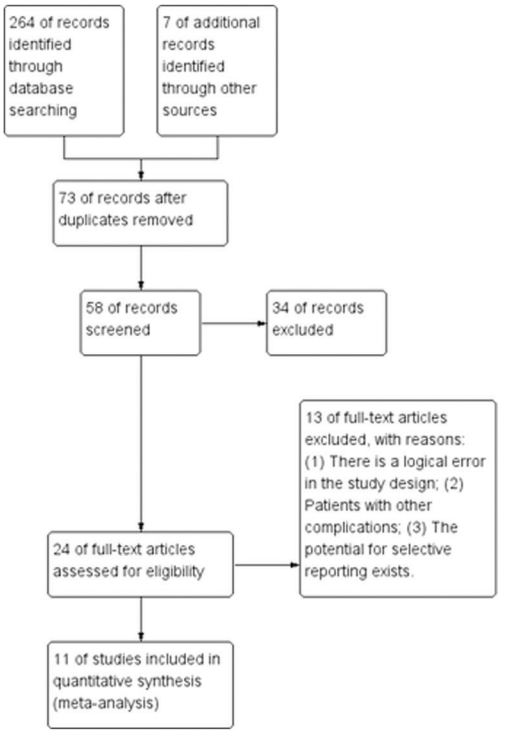
Literature Screening and Data Extraction

A thorough literature screening process was employed to ensure the quality and relevance of the included studies. Two members of the research team independently screened the retrieved studies, carefully examining titles, abstracts, and full-text content. Data extraction was comprised of critical information such as author details, publication years, intervention methods, outcome measures, study design, and grouping strategies. Consistency in screening results between the two team members determined the inclusion of literature for final analysis. In cases of disagreements, a third member's opinion was sought for resolution. Additionally, proactive efforts were made to contact authors when a study lacked essential primary data, ensuring the comprehensiveness and reliability of the dataset for subsequent analysis.

Literature Quality Evaluation

We employed the literature quality evaluation system outlined by the Cochrane Collaboration (www.cochrane.org) to assess the risk of bias in the included documents.[10] This comprehensive evaluation covered several key aspects, including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), completeness of outcome data (attrition bias), selective reporting (reporting bias), and other potential sources of bias.

Figure 1. Flow Chart of Literature Screening



Note: This flow chart illustrates the systematic process of literature screening conducted in the study. It provides an overview of the selection and exclusion criteria applied to identify the relevant studies for inclusion in the analysis.

Statistical Analyses

Statistical analyses were conducted using Review Manager 5.3, a software tool from the Cochrane Collaboration. Enumeration data were expressed as Relative Risk (RR) with corresponding 95% Confidence Intervals (CI), while measurement data were presented as Mean Difference (MD) with 95% CI. To assess heterogeneity among the included studies, the Chi-square test ($\alpha = 0.1$) was applied. Quantitative analysis of heterogeneity was performed using the I^2 statistic. In cases of substantial heterogeneity ($I^2 \geq 50\%$), a random-effects model was employed for analysis, and a funnel plot was generated to assess potential publication bias. Conversely, in the absence of significant heterogeneity ($I^2 < 50\%$), a fixed-effects model was utilized. Statistical significance was defined as a $P < .05$.

RESULTS

Results of Literature Retrieval

After an initial review, a total of 274 papers relating to GDM treatment with MET and INS were identified in the database. Subsequently, after thorough screening by the research team, a final selection of 11 studies[11-21] was made. A visual representation of the literature screening process is provided in Figure 1.

Table 1. Basic Characteristics of the Included Studies

Author And Date of Publication	Research Group (Treatment With ME)	Control Group (Treatment With INS)	Observed Indicators
Ainuddin et al. 2015[11]	72	75	(3)(5)
Ashoush et al. 2016[12]	47	48	(2)(3)(5)
Busarira et al. 2021[13]	70	70	(1)(2)(3)(4)(5)
Ghomian et al. 2019[14]	143	143	(1)(2)(4)(5)
Huhtala et al. 2020[15]	110	107	(2)(3)(4)(5)
Ijäs et al. 2010[16]	50	50	(3)(4)(5)
Jahanshahi et al. 2020[17]	30	30	(1)(2)(3)(4)(5)
Landi et al. 2019[18]	3818	3450	(3)(4)(5)
Picón-César et al. 2021[19]	100	100	(1)(3)(4)(5)
Silva et al. 2010[20]	40	32	(1)(2)(3)(4)(5)
Spaulonci et al. 2013[21]	47	47	(1)(3)(4)(5)

Note: The table presents a summary of the basic characteristics of the literature, including the author, publication date, number of participants in the research and control groups, and the observed indicators. Numerical codes represent the observed indicators: (1) Fasting Plasma Glucose (FPG); (2) Hemoglobin A_{1c} (HbA_{1c}); (3) Pregnancy Weight Gain (PWG); (4) Premature Delivery Rate (PDR); and (5) Neonatal Conditions.

Basic Characteristics and Literature Quality Evaluation

In this meta-analysis, a total of 8,679 subjects were included across the 11 selected studies. Notably, patients undergoing INS therapy were consistently identified as the control group (CG, n = 4152), while those receiving MET therapy were denoted as the research group (RG, n = 4527). Detailed basic characteristics of the literature are presented in Table 1.

Each study reported the utilization of randomization methods, though two studies did not adequately describe allocation concealment. Furthermore, two studies were designed with double-blind protocols, and none of the studies exhibited evidence of selective reporting. The results of the literature quality evaluation are presented in Figure 2. It is worth noting that all included studies were characterized by a low-risk level and demonstrated high reference value.

Comparison of Fasting Plasma Glucose (FPG)

Six studies conducted a comparative analysis of the effects of MET and INS on fasting plasma glucose (FPG) levels in GDM patients. Heterogeneity was observed among these studies, as indicated by an I^2 statistic of 79%. Consequently, a random-effects model was employed for the analysis. The results of this analysis, presented in Figure 3, indicate no significant difference in FPG levels between the RG and the CG ($P > .05$). These findings suggest that MET and INS exhibit similar hypoglycemic effects in the context of GDM.

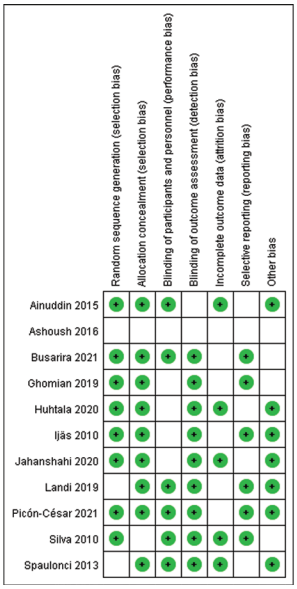
Comparison of Glycosylated Hemoglobin (HbA_{1c})

The impact of MET and INS on glycosylated hemoglobin (HbA_{1c}) levels was investigated across six studies. Due to observed heterogeneity among these studies, as indicated by an I^2 statistic of 93% ($I^2 = 93\%$), a random-effects model was employed for analysis. The results, presented in Figure 4, demonstrate that there was no significant difference in HbA_{1c} levels between the RG and the CG ($P > .05$).

Comparison of Pregnancy Weight Gain (PWG)

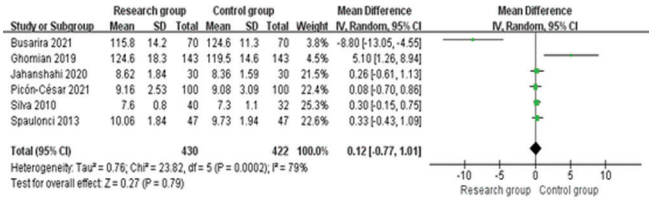
A total of ten studies conducted a comparative assessment of the effects of MET versus INS on pregnancy weight gain (PWG) in GDM patients. It is important to note that studies by Ainuddin et al.,[11] Ashoush et al.,[12] Huhtala et al.,[15] Ijäs et al.,[16] Picón-César et al.,[19] and Silva et al.[20] reported weight gain during pregnancy, while studies by Busarira, IJahanshahi, Landi, and Spaulonci reported changes in BMI.

Figure 2. Results of Literature Quality Evaluation



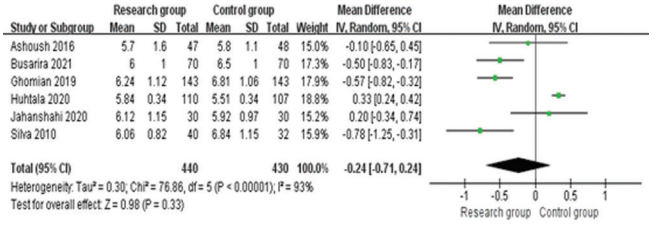
Note: This figure displays the outcomes of the literature quality evaluation conducted according to the Cochrane Collaboration's criteria. The assessment focuses on various aspects of study quality, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias.

Figure 3. Comparison of Fasting Plasma Glucose (FPG)



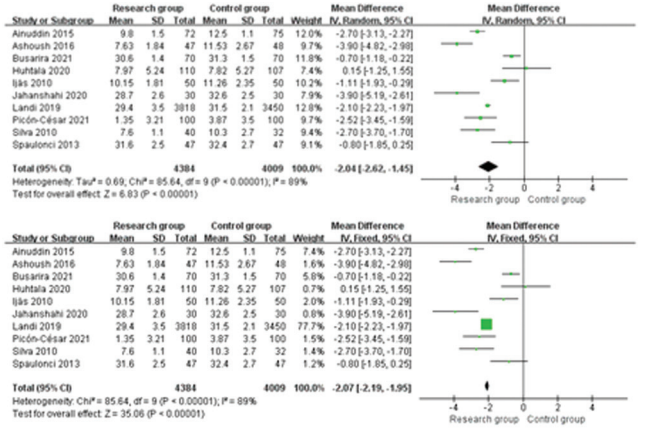
Note: This figure provides a comparative analysis of fasting plasma glucose (FPG) between the research group (MET treatment) and the control group (INS treatment). It presents the results of statistical evaluation, highlighting any significant differences or similarities in FPG levels between the two groups.

Figure 4. Comparison of Glycosylated Hemoglobin (HbA_{1c})



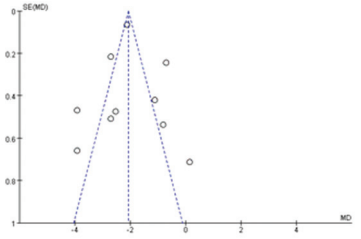
Note: This figure presents a comparative analysis of glycosylated hemoglobin (HbA_{1c}) levels between the research group (MET treatment) and the control group (INS treatment). It represents the outcomes of statistical assessment, emphasizing any significant variations or similarities in HbA_{1c} levels between the two groups.

Figure 5. Comparison of Pregnancy Weight Gain (PWG)



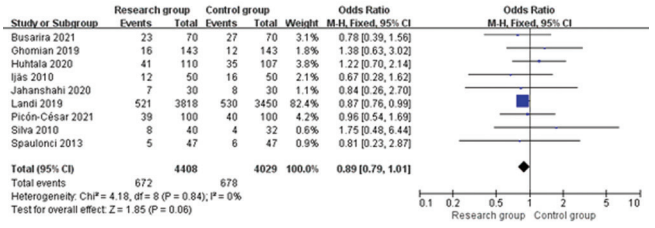
Note: This figure illustrates a comparative analysis of pregnancy weight gain (PWG) between the research group (MET treatment) and the control group (INS treatment). It presents the results of the statistical examination, highlighting any significant differences or similarities in PWG among the study participants.

Figure 6. Funnel Diagram of Pregnancy Weight Gain (PWG)



Note: This diagram, known as a "funnel plot," visually represents the distribution of data points related to pregnancy weight gain (PWG) in the study. It represents the publication bias and the symmetry of data, providing insights into the credibility of the included literature regarding PWG.

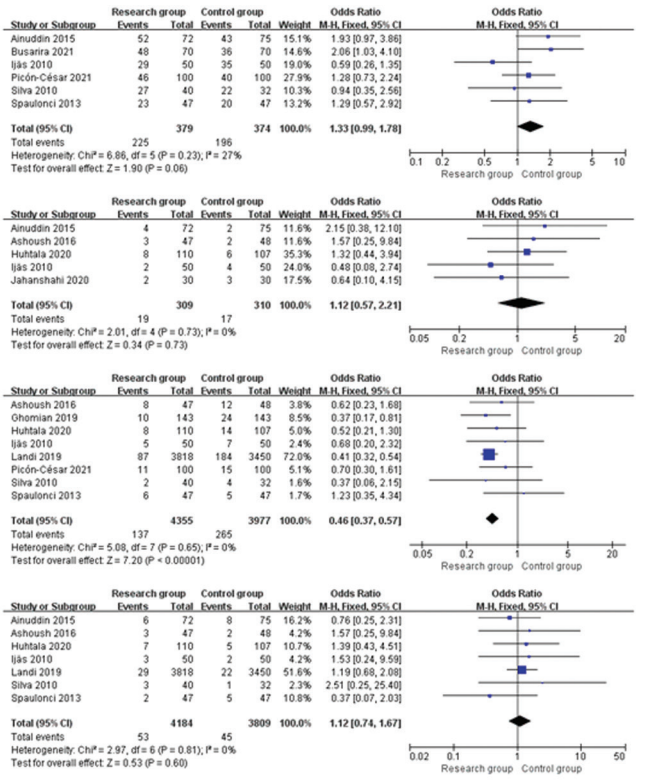
Figure 7. Comparison of Premature Delivery Rate (PDR)



Note: This figure presents a comparative analysis of premature delivery rate (PDR) between the research group (MET treatment) and the control group (INS treatment). It represents the statistical findings, emphasizing any significant differences or similarities in PDR among the study participants.

Given the identified heterogeneity among these studies, with an I^2 statistic of 89%, a random-effects model was applied for analysis. As depicted in Figure 5, RG exhibited significantly lower PWG than CG ($P < .05$), indicating that MET has a less pronounced impact on weight gain in GDM patients during pregnancy. Validation analysis performed with a fixed-effect model also confirmed the lower PWG in RG compared to CG ($P < .05$). Furthermore, the symmetrical distribution of the funnel plot, as illustrated in Figure 6, indicates minimal bias and the high credibility of the included literature.

Figure 8. Comparison of Neonatal Conditions



Note: This figure provides a comprehensive comparison of neonatal conditions, including neonatal jaundice, macrosomia, neonatal hypoglycemia, and neonatal respiratory distress syndrome (NRDS). Each sub-section presents a comparative analysis between the research group (MET treatment) and the control group (INS treatment) for the respective neonatal condition. The results are summarized from top to bottom, providing insights into the impact of different treatments on neonatal outcomes.

Comparison of Premature Delivery Rate (PDR)

Based on the I^2 analysis, which indicated no heterogeneity among the 9 articles comparing the influence of MET and INS on premature delivery in GDM patients ($I^2 = 0\%$), we employed the fixed-effects model for analysis. The results, as displayed in Figure 7, demonstrate no statistically significant difference in PDR between the RG and CG ($P > .05$). This suggests that neither MET nor INS exerts a significant effect on premature delivery.

Comparison of Neonatal Conditions

All included studies reported on neonatal conditions, with six studies providing data on the incidence of neonatal jaundice,[11,13,16,19-21] five studies reporting on the incidence of macrosomia (MS),[11,12,15-17] eight studies detailing the incidence of neonatal hypoglycemia (NH),[12,14-16,18-21] and seven studies documenting neonatal respiratory distress syndrome (NRDS).[11,12,15,16,18,20,21] As illustrated in Figure 8, there were no statistically significant differences between the RG and the CG in the incidence of neonatal jaundice, MS, and NRDS ($P > .05$). However, it is noteworthy that a lower incidence of NH was observed in RG ($P < .05$).

DISCUSSION

Both MET and INS are commonly utilized medications for treating DM, known for their established efficacy and high safety profiles.[22] However, INS is typically favored for cases of GDM that do not respond adequately to dietary or exercise interventions.[23] However, the convenience factor plays a central role, as INS therapy necessitates injections and poses challenges in terms of storage, making it significantly less convenient when compared to MET.[24] As a biguanide, MET exerts its effects by inhibiting gluconeogenesis in the liver, consequently reducing hepatic sugar production. Furthermore, it exerts actions on peripheral tissues, reducing free fatty acids (FFA), facilitating muscle glycogen synthesis, and increasing GLP-1 levels in intestinal cells, thereby inhibiting glucose absorption by intestinal wall cells.[25]

While there are no definitive reports from authoritative sources confirming the adverse effects of MET on neonates, its clinical use has been a subject of controversy owing to its ability to traverse the placental barrier. It is assumed that MET can permeate placental tissue and potentially result in unfavorable fetal and neonatal outcomes, thereby necessitating further investigation to ascertain its long-term impacts on pregnant women and fetuses.[26]

Pregnant women are particularly susceptible to pregnancy-related conditions like pregnancy-induced hypertension, which may have a close connection with GDM and could impact the efficacy of MET.[27] Considering the current use of MET, expeditiously establishing its safety profile can enhance both convenience and security in GDM treatment. In this study, we conducted a meta-analysis to assess the effects of MET and INS in GDM, aiming to offer dependable clinical insights for future research.

Our meta-analysis revealed that MET is more effective in managing the weight of pregnant GDM patients and reducing the incidence of neonatal hypoglycemia. These findings hold substantial clinical significance, providing a more reliable approach to ensuring the safety of pregnancies in future GDM cases.

A total of eight included studies in this analysis exhibited low publication bias risk and high reference value, as confirmed through rigorous evaluation. Through our thorough meta-analysis, we initially observed no statistically significant differences in FPG and HbA_{1c} levels between the two groups of GDM patients. This finding suggests the effectiveness of both drug therapies in controlling blood sugar levels. Additionally, MET intervention therapy demonstrates creditable results without the need for INS administration, thereby not only significantly enhancing the patient's treatment experience but also resulting in economic benefits by reducing medical costs.

However, previous research has indicated that approximately 10-40% of GDM patients may require INS administration when MET alone fails to control glycemic levels adequately.[28] This finding contrasts with our findings. It is conceivable that MET may exhibit a favorable hypoglycemic effect in mild to moderate cases of GDM, but INS remains necessary for those with severe GDM. Consequently, further trials are warranted to delve deeper into the impact of MET on blood sugar control.

Considering these findings, a potential stepwise treatment approach for GDM drug therapy could be proposed. Specifically, INS therapy should be considered as a supplement when MET proves insufficient in blood sugar control. The precise dosage form and quantity of INS should be carefully adjusted based on the patient's blood sugar control status, results of glucose tolerance tests, and local treatment recommendations.

Furthermore, this analysis revealed a lower PWG in the RG, suggesting a more effective weight management effect of MET in GDM patients. It is widely recognized that the majority of GDM patients are overweight. If PWG can be reduced, it holds the potential to benefit blood sugar control in pregnant women significantly and may even contribute to a reduction in the incidence of pregnancy-induced hypertension and preeclampsia.[29] MET achieves this effect by curbing appetite, thus reducing calorie intake, enhancing leptin sensitivity *in vivo*, and promoting GLP-1 secretion. Simultaneously, it ameliorates hyperinsulinemia and decreases both basal and post-load INS levels, ultimately leading to weight reduction.[30]

The meta-analysis also revealed no statistically significant difference in the risk of premature delivery between the RG and CG, thereby providing initial confirmation of the high safety profile of MET, indicating that it does not significantly impact the pregnancies of GDM patients. The risk of premature delivery in GDM patients has long been a topic of debate in previous studies on the clinical use of MET.[31] These findings suggest that regional disparities, patient physique, and hospital conditions may contribute to potential variations in premature delivery rates. Therefore, additional studies should be considered for inclusion in future analyses to investigate further and validate this aspect.

Lastly, in the assessment of neonatal conditions, the RG exhibited comparable instances of neonatal jaundice and macrosomia but notably fewer cases of neonatal hypoglycemia when compared to the CG. This observation underscores the strong safety profile of MET in GDM treatment and its potential to mitigate NH. We suggest that while MET does affect fetal physiological metabolism by crossing the placental barrier, it does not raise the risk of NH since it neither stimulates the release of INS nor elevates the level of INS in the bloodstream. However, it is important to note that the precise mechanism requires further validation through more comprehensive experimental analysis.

Study Limitations

This study has several limitations that warrant consideration. Firstly, the relatively modest sample sizes in the included studies may impact the generalizability of the findings. Secondly, the exclusivity of English-language studies could introduce language bias, potentially excluding relevant research published in other languages. Thirdly, the absence of

long-term follow-up data limits our ability to assess neonatal safety outcomes comprehensively. It is crucial to acknowledge that these factors may exert an influence on the outcomes derived from this meta-analysis.

CONCLUSION

In conclusion, our study highlighted the remarkable efficacy and safety profile of MET in the management of gestational diabetes mellitus. MET emerges as a promising oral alternative to insulin for GDM treatment, showcasing its potential to not only effectively control blood sugar but also curtail pregnancy weight gain and reduce the incidence of neonatal hypoglycemia. These findings collectively present MET as a valuable tool in enhancing the overall well-being and safety of pregnant individuals with GDM, offering a promising avenue for improved maternal and neonatal outcomes.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ACKNOWLEDGEMENTS

None.

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