Metformin and insulin in the treatment of gestational Diabetes Mellitus: Systematic review and meta-analysis

Felipe Augusto de Oliveira Pereira

Maria Fernanda Vianna Marvulo

ABSTRACT

Pregnancy promotes physiological adaptations necessary for fetal development and, consequently, predisposes to the risk of several diseases. Among these changes are changes in metabolic load, highlighting hyperglycemia due to insulin resistance and pancreatic dysfunction in the production of this hormone (PLOWS et al., 2018).

Keywords: Physiological, Development, Highlighting hyperglycemia.

1 INTRODUCTION

Pregnancy promotes physiological adaptations necessary for fetal development and, consequently, predisposes to the risk of several diseases. Among these changes are changes in metabolic load, highlighting hyperglycemia due to insulin resistance and pancreatic dysfunction in the production of this hormone (PLOWS et al., 2018). In this context, Gestational Diabetes Mellitus (GDM) is the most common medical complication in pregnancy, defined as glucose intolerance of varying intensity, initiated or diagnosed during the gestational period (MOON et al., 2022).

Currently, despite the continuous efforts of several institutions and scientific productions, a protocol for the diagnosis of GDM that is adopted worldwide has not yet been established. However, the most commonly used laboratory tests for screening are oral glucose tolerance test (OGTT) and challenge with 50g glucose in 1 hour, fasting glucose, random glucose, and hemoglobin A1c.

Historically, diagnostic thresholds have evolved to reduce perinatal morbidity and mortality and long-term complications, both maternal and offspring. Faced with this reality, the prevalence varies considering the population, screening, and diagnosis (SERT, OZGU-ERDINC, 2020; SWEETING et al., 2022).

The alterations promoted by GDM have maternal and neonatal repercussions, later in childhood and adulthood. Maternal complications that stand out are the increased risk of developing type 2 Diabetes Mellitus, hypertensive disorders - highlighting preeclampsia - cardiovascular diseases and metabolic disorders (MOON et al., 2022). In-hospital parameters such as type of delivery, Apgar score, and admission to the neonatal intensive care unit are also used in the evaluation by studies in the evaluation of outcomes (PICÓN-CÉSAR et al., 2021; GHOMIAN et al., 2019).

Furthermore, the implications of exposure of children of mothers with GDM are diverse and may be present in various interims of the life cycle, from birth to adulthood, the main ones being: prematurity, stillbirth, neonatal death, macrosomia, neonatal hypoglycemia, malformations, shoulder dystocia, injuries and respiratory distress at birth, metabolic disorders, especially related to hyperglycemia and obesity, among other health-disease conditions (MOON et al., 2022; SZMUILOWICZ, JOSEFSON, METZGER, 2019).

Undoubtedly, due to the imbroglios linked to GDM, the treatment lines have great robustness in the literature and continue to be updated based on eminent evidence. Initially, they include the improvement of lifestyle habits to control blood glucose, especially the indication of physical activities and balanced diets. In the initial stage, studies show great resolution, with approximately 80% reaching the therapeutic target of blood glucose (SZMUILOWICZ, JOSEFSON, METZGER, 2019). For patients who maintained high blood glucose levels, the inclusion of pharmacological treatments is indicated, and metformin is considered the safest and most widely discussed oral medication in the literature (OSKOVI-KAPLAN, OZGU-ERDINC, 2020). However, insulin therapy has been indicated as the standard in the management of GDM cases refractory to lifestyle changes (JOHNS et al., 2018).

Previous published meta-analysis studies have investigated the treatment of GDM, but the inclusion criteria do not include more recent publications. In addition, they did not contain analyses comparing habit change, metformin, and insulin (PEREIRA, MARVULO; 2022).

Based on this context, the present study aimed to systematically review and perform a meta-analysis of randomized clinical trials in the treatment of Gestational Diabetes Mellitus that include lifestyle changes, metformin and insulin, in order to investigate their efficacy through perinatal outcomes.

2 GOAL

To systematically review and perform meta-analysis of randomized clinical trials in the treatment of Gestational Diabetes Mellitus (GDM) in order to contribute to the discussion of the best treatments based on GDM outcomes.

3 METHODOLOGY

3.1 SEARCH STRATEGIES OR SEARCH SOURCES

The database used to search for the studies was Pubmed, which includes databases such as Medline, Lilacs, among others. The choice of descriptors was based on the terms MeSH (Medical Subject Headings) and Health Sciences Descriptors (DECS), in which the "PICO" strategy (Appendix 1) will be adopted - population: pregnant women with GDM; Intervention: physical exercise and diet, metformin and insulin; Control: Not applicable; and outcome of interest: maternal and fetal complications.

3.2 SELECTION CRITERIA

The inclusion criteria of the research refer to it being a Randomized Clinical Trial, published in the last ten years. The sample consisted of women with GDM, comparing the non-pharmacological intervention, the use of metformin and/or insulin therapy, and providing information on glycemic control; one or more maternal or offspring outcomes. Articles with methodological flaws related to bias were excluded. After the selection of the studies, the categorization of very low, low, moderate, or high evidence was performed.

Initially, the titles and abstracts were read, excluding those that were not relevant or that did not meet the aforementioned criteria. Subsequently, the full texts were evaluated.

3.3 DATA ANALYTICS

Data were processed and the relative risk (RR) was calculated with a 95% confidence interval. The Review Manager review tool was applied in the non-Cochrane mode to prepare standard tables, meta-analysis, and error-checking mechanisms (REVMAN, 2020).

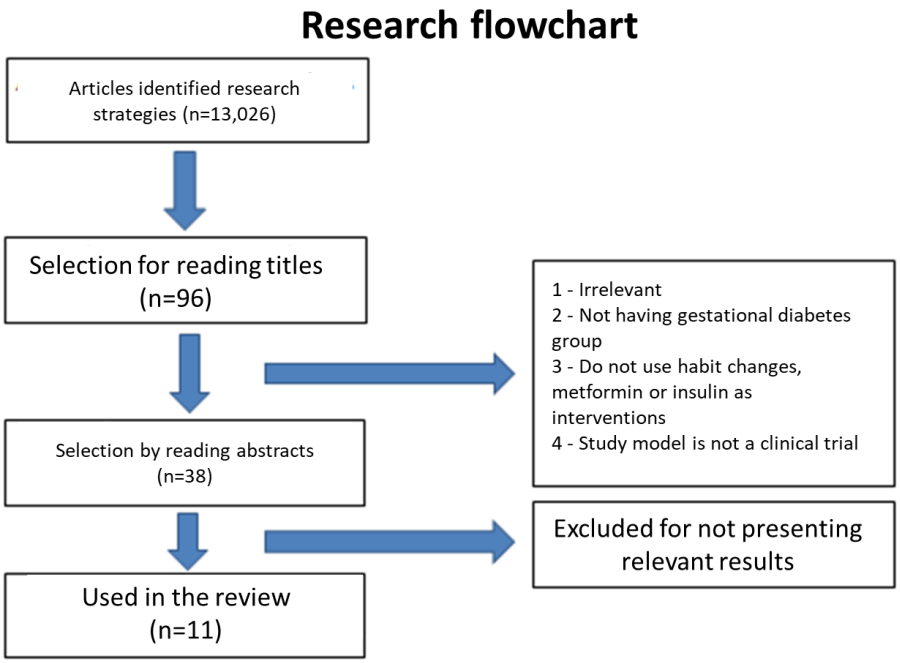
This is a literature review, developed with articles published in the period from 2017 to 2021 in the electronic databases: Capes Portal, Scientific Electronic Library Online - Scielo and Google Scholar, using the descriptors: self-esteem, self-image, aesthetics, oncology, complementary and integrative therapies, and their respective synonyms, in Portuguese and English. Only published articles that dealt with the topic and were available online were included. Articles outside the proposed period, that did not deal with the theme, not available online, and repeated articles found in different databases were excluded.

4 DEVELOPMENT

4.1 SEARCH FOR RESULTS

The initial search showed 13,026 articles through the use of the PICO strategy descriptors, clinical trial filter and published in the last 10 years (2012-2022). After reading the titles, 96 articles were related to the theme and inclusion criteria, of which, upon reading the abstracts, 38 remained included in the review for complete reading of the articles. Finally, 11 studies that met the inclusion criteria were selected, as shown in the figure below:

Figure 1. Quantitative research flowchart of selected articles



It is worth noting the absence of randomized clinical trials that compared the set of non-pharmacological measures with insulin and metformin, presenting only isolated results.

4.2 OUTCOMES OF THE INTERVENTION

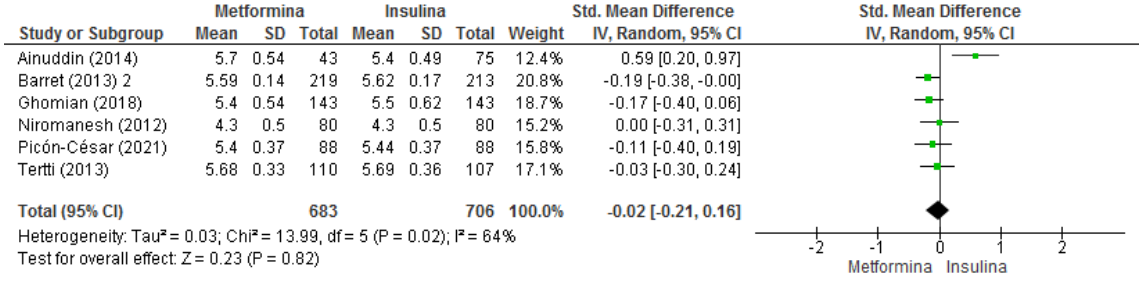
Outcomes compared the effect of insulin and metformin pooled by glycemic control, maternal outcomes, and neonatal outcomes.

4.3 GLYCEMIC CONTROL

For glycemic control, glycated hemoglobin from the end of gestation between 35 and 37 weeks, mean fasting blood glucose and mean postprandial blood glucose after the beginning of treatment were used.

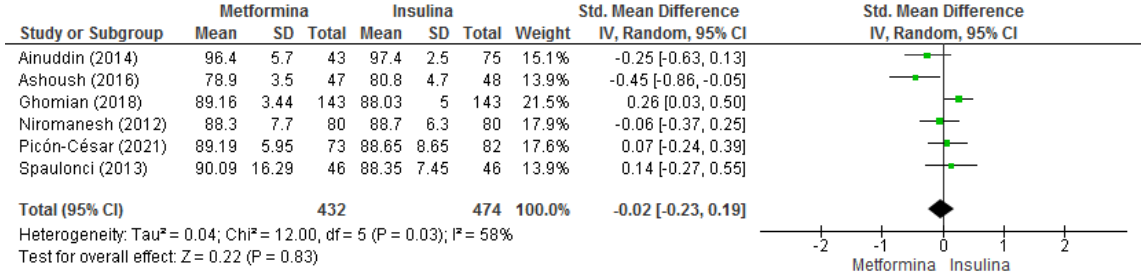
HbA1c% at the end of pregnancy was included in 6 studies, with a total of 1,389 pregnant women with GDM, there was significant heterogeneity (I2 = 64%) and no statistically significant difference -0.02.

Figure 2. Statistical analysis of Metformin and Insulin HbA1c% outcomes in GDM



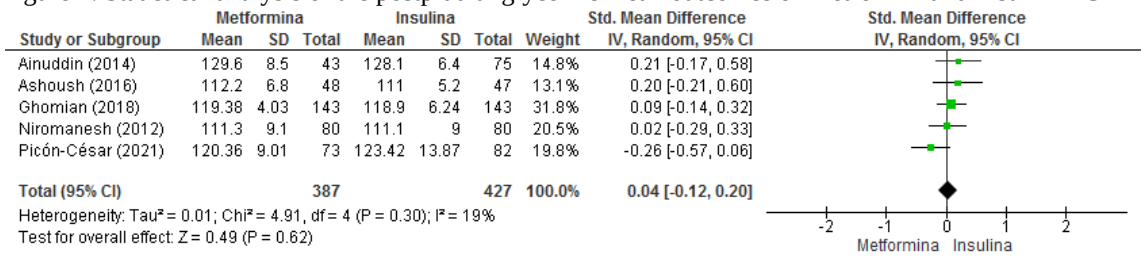
The mean fasting glucose was verified by 6 of the selected articles, a total of 906 patients, with a heterogeneity I2 = 64% with a negligible statistical difference of -0.02.

Figure 3. Statistical analysis of fasting glucose outcomes of Metformin and Insulin in GDM



The postprandial glycemic mean was included in 5 studies, involving 814 women with GDM, with little heterogeneity (I2 = 19%) and a statistical difference of 0.04.

Figure 4. Statistical analysis of the postpradial glycemic mean outcomes of Metformin and Insulin in GDM

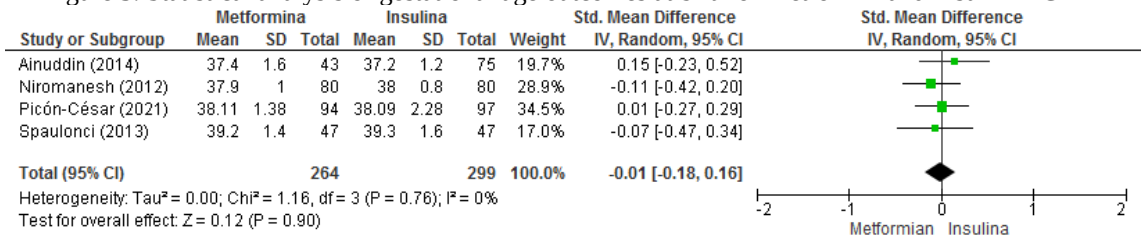


Serum glucose regulation is the tool used for the clinical management of GDM and, consequently, maternal and fetal complications (GHOMIAN et al., 2019). Based on the results of glycemic control of pregnant women with gestational diabetes, it was found that there were no significant differences during the treatment period and the end of pregnancy between patients who used Metformin and Insulin, as shown above. Although the study population presented similar results, it is noteworthy that a contingent of pregnant women with GDM and undergoing treatment with Metformin did not have adequate control and required the addition of insulin (SPAULONCI et al, 2013).

4.4 MATERNAL AND OBSTETRIC OUTCOMES

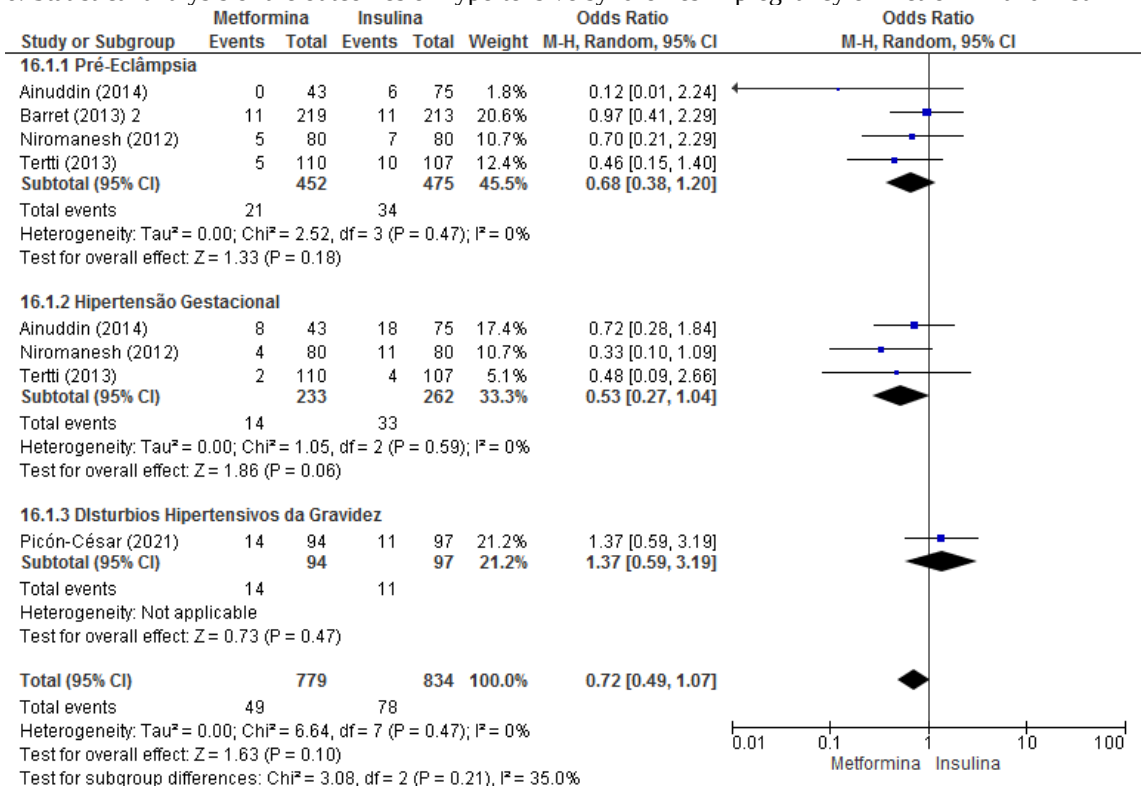
There was no significant difference in the mean gestational age at birth between the Metformin and Insulin groups, a statistical difference of -0.01, and there was no heterogeneity between the 4 studies that analyzed this outcome I2=0, with a sample of 563.

Figure 5. Statistical analysis of gestational age outcomes at birth of Metformin and Insulin in GDM



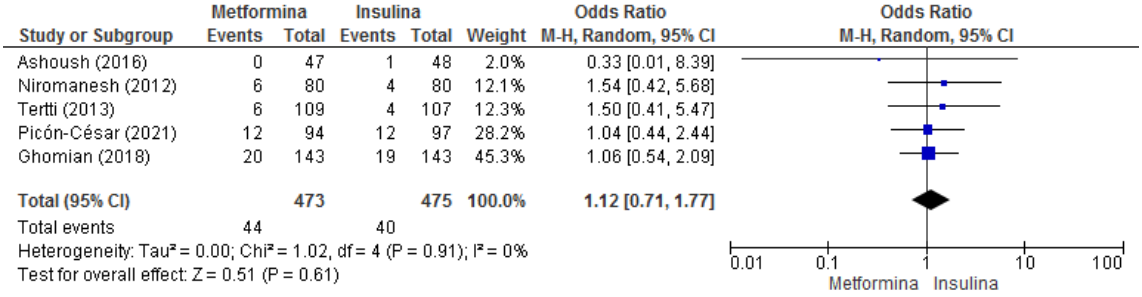
Pregnancy-Specific Hypertensive Syndromes – Preeclampsia, Gestational Hypertension and Hypertensive Disorders in General – were considered as outcomes in 5 articles, comprising 1,613 pregnant women, low heterogeneity, with an OR of 0.72, representing a lower incidence among women who were treated with Metformin.

Figure 6. Statistical analysis of the outcomes of hypertensive syndromes in pregnancy of Metformin and Insulin in GDM



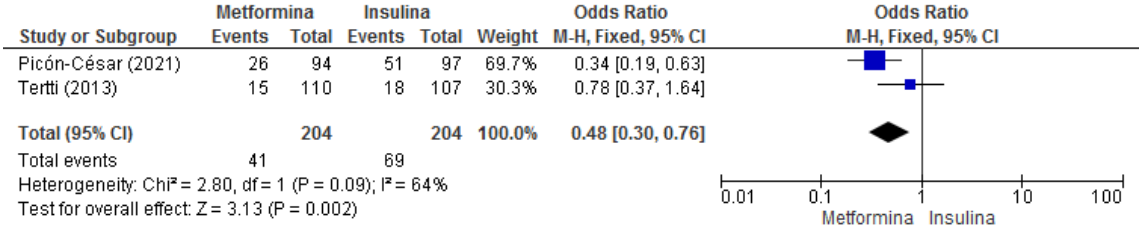
The number of preterm births, contained as an outcome in 5 studies with a total of 948 pregnant women, low heterogeneity (I2=0%), was lower in the group that used insulin therapy with an OR of 1.12.

Figure 7. Statistical analysis of the preterm birth outcomes of Metformin and Insulin in GDM



The mode of delivery was rarely presented with an outcome in studies, only 2 studies, representing 408 women, and the performance of cesarean section was more comprehensive in the group of pregnant women who received insulin as a treatment for GDM, considerable heterogeneity I2=64% and OR of 0.48.

Figure 8. Statistical analysis of the outcomes of the mode of delivery of Metformin and Insulin in GDM



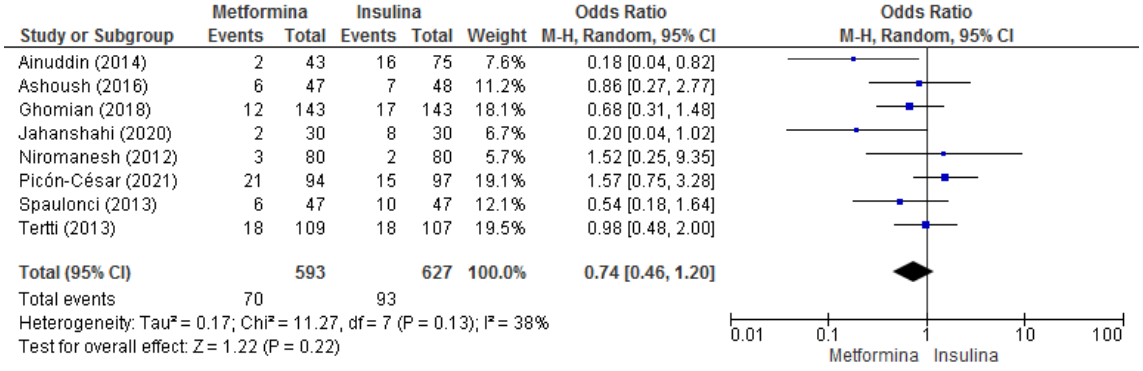
There was no difference in the mean gestational age, which was also represented by the small difference in preterm births. The mode of delivery was poorly represented by the studies, it can be indicated in the face of complications, and cesarean section was considerably higher in the group that treated GDM with insulin. The differences can also be explained by obstetric practices in the countries of origin of the studies (TERTTI et al, 2013), as they did not result in exacerbated differences in other negative outcomes.

Pregnancy-Specific Hypertensive Syndromes were more frequent in the groups of pregnant women who used insulin. Currently, it is hypothesized that Metformin acts by reducing endothelial activation and maternal inflammatory response that occurs through insulin resistance (TERTTI et al, 2013).

4.5 NEONATAL OUTCOMES

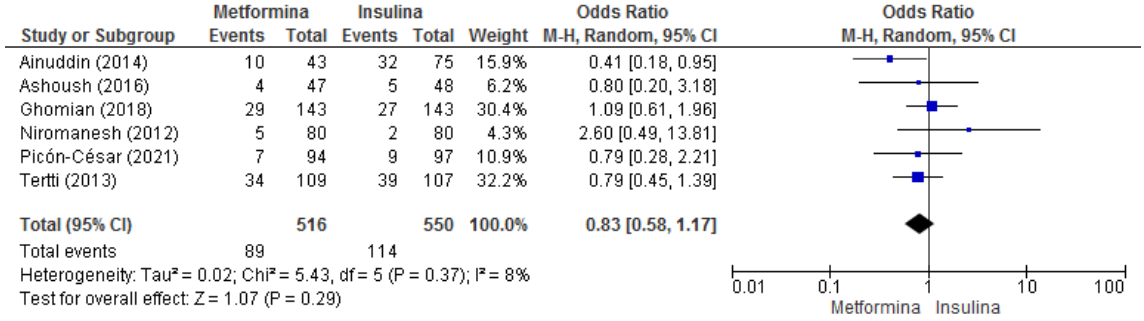
Neonatal hypoglycemia was included in 8 studies, totaling 1,220 neonates, with mean heterogeneity with I2=38% and OR of 0.74, with fewer metformin-related events.

Figure 9. Statistical analysis of neonatal hypoglycemia outcomes of Metformin and Insulin in GDM



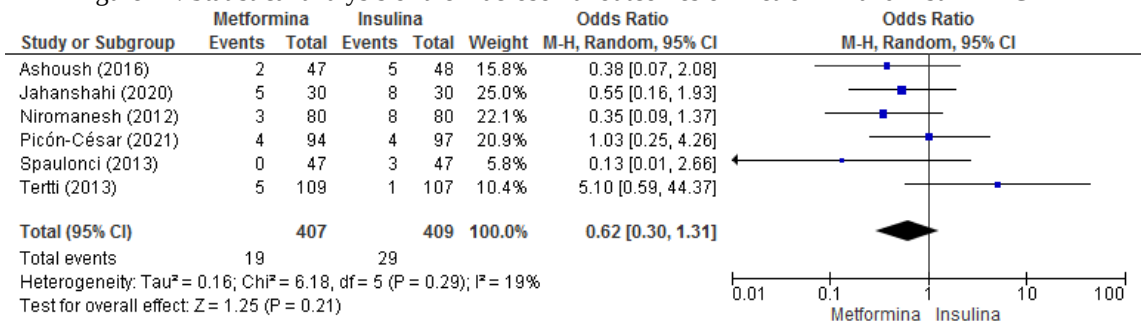
Admission to neonatal intensive care units was present in 6 studies, with a total of 1066 patients, very low heterogeneity with I2=8%, with lower admission in patients in whom GDM was treated with Metformin, with an OR of 0.83.

Figure 10. Statistical analysis of neonatal intensive care unit admission outcomes of Metformin and Insulin in GDM



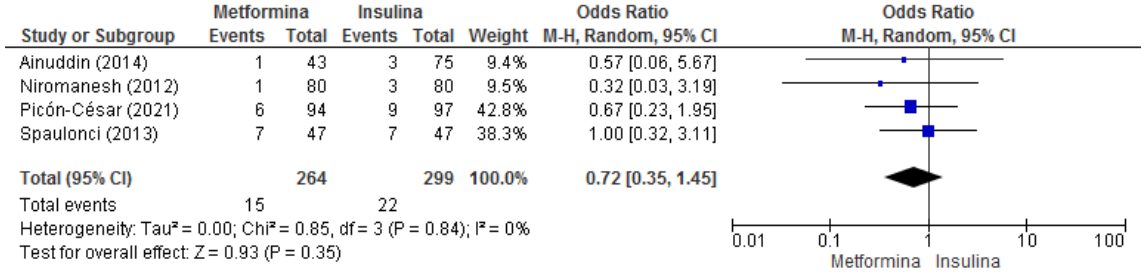
Macrosomia was studied as a neonatal outcome in 5 articles, with more cases in the group treated with insulin with an OR of 0.62, a total of 816 neonates and low heterogeneity with I2=19%.

Figure 11. Statistical analysis of the macrosomal outcomes of Metformin and Insulin in GDM



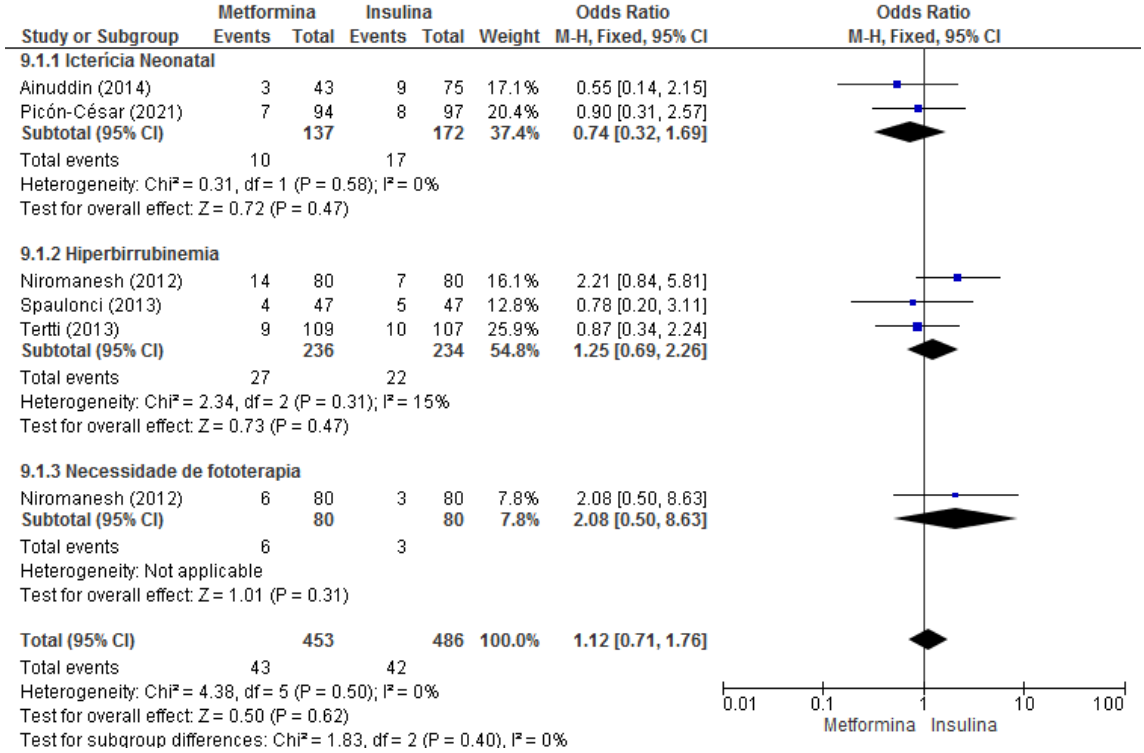
The Respiratory Distress Syndromes were analyzed by only 4 articles, without heterogeneity with I2=0%, containing 563 neonates, with a lower incidence among the offspring of pregnant women treated with Metformin (OR=0.72).

Figure 12. Statistical analysis of the outcomes of Metformin and Insulin Neonatal Respiratory Distress Syndromes in GDM



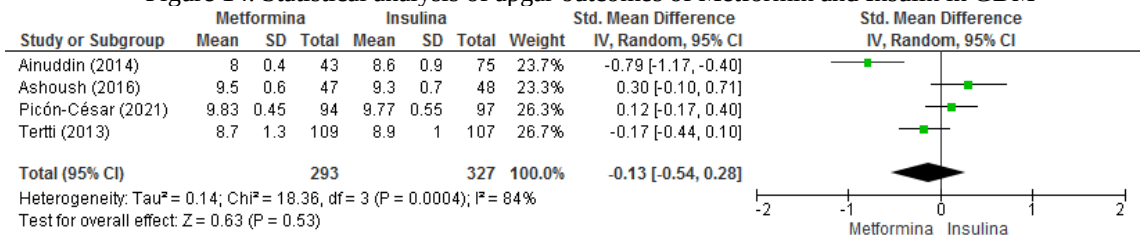
Events related to neonatal jaundice – jaundice, hyperbilirubinemia and need for phototherapy – were analyzed by 5 studies, with no heterogeneity I2=0% and OR of 1.12.

Figure 13. Statistical analysis of neonatal jaundice outcomes of Metformin and Insulin in GDM



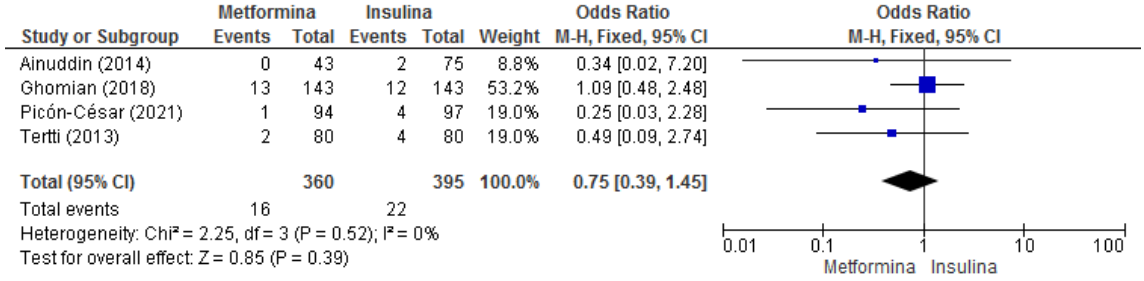
The Apgar score at 5 minutes after delivery was similar in the two groups analyzed, with great heterogeneity between studies I2=84% and a small statistical difference of -0.13, favoring the results of insulin.

Figure 14. Statistical analysis of apgar outcomes of Metformin and Insulin in GDM



The incidence of neonatal trauma during childbirth was higher in the offspring of pregnant women who treated GDM with insulin, with no heterogeneity between articles with I2=0% and OR=0.75.

Figure 15. Statistical analysis of neonatal trauma outcomes of Metformin and Insulin in GDM



In general, metformin had more favorable neonatal outcomes than insulin, especially hypoglycemia, macrosomia, and trauma during childbirth.

5 FINAL THOUGHTS

Based on the results found, it was concluded that metformin presents safety and efficacy in its use compared to insulin therapy, which is the treatment protocol for GDM, while it presents a slight decrease in maternal and fetal outcomes. However, some patients require complementary insulin use after using metformin because they do not reach glycemic goals.

The studies have limitations because they have a small sample size and do not present long-term results. Therefore, for a better understanding of the clinical repercussions and use of metformin in GDM, further studies with a larger sample and longer outcomes are needed.

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