International Journal of Medical Toxicology & Legal Medicine Volume 27, No. 4, 2024
e-ISSN: 0974-4614
p-ISSN: 0972-0448

Comparison of Metformin and Insulin in the Treatment of Gestational Diabetes

Faris Mohammedamin Qari[1], Maaz Ahmed Raei[2], Nahd Hasan M Alesawy[3], Abdullah Mohammed Al Yamani[4], Sultan Obaid Abed Almalki[5], Marwan Faisal Ismail[6], Azizah Ibrahim Al Wagdany[7], Kawther Hassan Aleisawi[8], Fahad Hassan Aleisawi[9], Atallah Mater Alamri[10], Mofareh Bakheet Alzahrani[11], Ali Yahya Alzahrani[12], Alharthi Yaseer Awad H[13]

[1]General Psychiatric Doctor, Eradh Complex for Mental Health – Jeddah.
[2]General Psychiatric Doctor,Eradh Complex for Mental Health – Jeddah.
[3]King Abdullah Medical Complex-Jeddah,Health Surveillance Centers - King Abdulaziz International Airport
[4]X-Ray Technician,Health Surveillance Centers - King Abdulaziz International Airport
[5]RadiologistHealth Surveillance Centers - King Abdulaziz International Airport
[6]NurseHealth Surveillance Centers - King Abdulaziz International Airport
[7]NurseHealth Surveillance Centers - King Abdulaziz International Airport, Alaziziah Children Hospital
[9]Health Surveillance Centers - King Abdulaziz International Airport
[10]Health Surveillance Centers - King Abdulaziz International Airport
[11]Nurse, Health Surveillance Centers, King Abdulaziz International Airport
[12]Epidemiology Technician, Health Surveillance Centers, King Abdulaziz International Airport
[13] Nurse, Health Surveillance Centers, King Abdulaziz International Airport

Received: 12.10.2024 Revised: 25.11.2024 Accepted: 09.12.2024

ABSTRACT
Background: Gestational diabetes mellitus (GDM) is a prevalent complication of gestation, impacting up to sixteen percent of all pregnancies, contingent upon the criteria for diagnosis.
Aim: To evaluate the efficacy of metformin versus insulin in managing GDM.
Patients and methods: A comprehensive literature review has been performed in the following databases: PubMed, EMBASE, Cochrane Library, and Google Scholar. The search technique encompassed the terms: "gestational diabetes," "metformin," "insulin," "treatment," "randomized controlled trial," and "outcome." The search has been confined to papers published between January 2008 and December 2023.
Results: Nine studies reported (NICU admissions) and all can be used. A significant heterogeneity has been identified. Therefore, a random-effect model has been utilized for analysis (I^2 = 49%, P-value equal 0.05). The combined mean difference and ninety five percent confidence intervals were 0.72 (0.56 to 0.93). The combined result exhibits a highly statistically significant distinction among groups regarding (NICU admissions) (Z = 2.53, P-value equal 0.01). Seven studies reported (Neonatal hyperbilirubinemia) and all can be used. Insignificant heterogeneity has been detected. Therefore, a random-effect model was used for analysis (I^2 = 0%, P=0.53). The combined mean difference and ninety five percent confidence intervals were 0.96 (0.65 to 1.42). The combined result demonstrates no statistically significant variance among groups regarding (Neonatal hyperbilirubinemia) (Z-value equal 0.19, P-value equal 0.85).
Conclusion: Metformin offers short-term benefits in treating gestational diabetes mellitus (GD), but long-term studies are needed to evaluate its safety and effectiveness.

Keywords: Metformin, Insulin, GDM.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a prevalent complication of gestation, impacting up to sixteen percent of all pregnancies, contingent upon diagnostic criteria (1).
Gestational diabetes mellitus typically arises from an inability to adapt to heightened insulin resistance during late pregnancy, particularly in females with pre-existing risk factors. The risk factors encompass elevated pre-pregnancy weight, high weight gain during gestation, a familial diabetes history, advanced age, and polycystic ovarian syndrome (2).

The implementation of the International Association of Diabetes in Pregnancy Study Groups (IADPSG) criteria for diagnosing hyperglycemia in pregnancy resulted in a significant rise in the occurrence of gestational diabetes mellitus. The IDF currently predicts that the occurrence of a history of G will stabilize over the next twenty-five years; nevertheless, these projections are constrained by different diagnostic criteria for gestational diabetes mellitus (3).

Females with gestational diabetes mellitus have an elevated risk of negative outcomes, involving pre-eclampsia, macrosomia, cesarean delivery, & stillbirth, due to inadequately managed blood glucose levels throughout pregnancy. Progeny of mothers with gestational diabetes mellitus exhibit an elevated risk of being large for gestational age (LGA), having birth traumas, and developing cardiometabolic diseases in later life (4).

Moreover, new studies indicate that large for gestational age offspring exhibit early indicators of diminished insulin sensitivity & impaired insulin secretion in comparison to those with appropriate birth weight for gestational age (5).

Consequently, attaining and sustaining normoglycemia throughout pregnancy is essential for both the mother and the fetus (6).

Clinical trials & observational data indicate that the majority of females with gestational diabetes mellitus acquire normoglycemia by dietary and lifestyle modifications (7), (8).

Consequently, the majority of professional guidelines concur that dietary and lifestyle modifications are the primary therapies (9), (10).

When lifestyle adjustments alone fail to reach glycemic objectives, the initiation of pharmacotherapy is contemplated (11).

Although the escalating insulin resistance observed during gestation in cases with gestational diabetes mellitus, insulin is a commonly approved and secure treatment option as it doesn't cross the placental barrier, thus protecting fetal well-being. Nonetheless, barriers to insulin therapy throughout gestation may include expense, accessibility, fear of injections and hypoglycemia, as well as personal preferences. In these cases, metformin may function as an alternative solution (12).

Metformin is a medication that inhibits hepatic gluconeogenesis and enhances peripheral insulin sensitivity. A pivotal randomized controlled trial (RCT) conducted in 2008 (13) established that metformin didn't result in an increased incidence of perinatal problems. Significantly, about fifty percent of cases with gestational diabetes mellitus necessitated supplementary insulin therapy to achieve pregnancy objectives. Consequently, its application continues to be a topic of contention (14). The Society for Maternal-Fetal Medicine (SMFM) endorses the use of metformin for regulating blood glucose levels in gestational diabetes mellitus (GDM) (15); nonetheless, specific research has highlighted the need for caution and further investigation (16).

This systematic review and meta-analysis examined the efficacy of metformin and insulin in managing gestational diabetes.

Patients and methods

A comprehensive literature review has been performed in the following databases: PubMed, EMBASE, Cochrane Library, and Google Scholar. The search technique encompassed the terms: "gestational diabetes," "metformin," "insulin," "treatment," "randomized controlled trial," and "outcome." The search has been confined to papers published between January 2008 and December 2023.

Participants and Study Population

The pooled analysis involved 2,855 pregnant women diagnosed with GDM. These participants have been separated into two groups based on the treatment modality: Metformin Group: Women treated with metformin, an oral hypoglycemic agent.Insulin Group: Women receiving insulin therapy as the standard care for GDM.

Inclusion Criteria: Pregnant females diagnosed with gestational diabetes mellitus based on standardized criteria, such as the IADPSG ,participants within a broad gestational age range, ensuring comprehensive analysis across different pregnancy stages and studies with complete data on maternal and neonatal outcomes.

Exclusion Criteria: Women with pre-gestational DM (type 1 or type 2) ,participants with contraindications to metformin or insulin, such as renal dysfunction or hypersensitivity and Studies with incomplete datasets or poor methodological quality.

Treatment Modalities and Interventions

Metformin Group: Metformin was administered orally, starting with a low dose and titrated as needed to achieve optimal glycemic control. Its primary mechanism includes increasing sensitivity of peripheral insulin and reducing production of glucose by liver.

Insulin Group: Participants received subcutaneous insulin injections. Doses were tailored based on individual glycemic profiles, with close monitoring to avoid adverse effects such as hypoglycemia. Insulin’s primary advantage lies in its inability to cross the placental barrier, ensuring fetal safety.

Combination Therapy: In cases where metformin alone was insufficient, additional insulin therapy was introduced. This dual approach was noted in approximately 50% of the metformin group in some studies.
Outcome Measures: Maternal Outcomes: Glycemic Control: Achieving target fasting and postprandial blood glucose levels ,weight Gain: Maternal weight gain throughout gestation, a critical indicator of metabolic control, cesarean-Section (CS) Rates: Indications and frequencies of CS and adverse Effects: Hypoglycemia, gastrointestinal discomfort, and adherence challenges.
Neonatal Outcomes: Gestational Age at Delivery: Evaluating the timing of delivery, birth Weight: Monitoring for large-for-gestational-age (LGA) babies or macrosomia, APGAR Scores: Assessing neonatal well-being at 1- and 5-minutes post-birth, NICU Admissions: Neonatal complications requiring intensive care & hypoglycemia and Hyperbilirubinemia: Metabolic disturbances in newborns.

Data Extraction
Two independent reviewers (AA & MM) utilized a standardized data extraction form to extract data. Discrepancies have been resolved via discussion or consultation with a 3rd reviewer (SS). The extracted data involved research features, demographics of cases, treatment details, and consequences.

Quality Evaluation
The quality of the involved research has been evaluated utilizing the Cochrane Risk of Bias Tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational research. Research has been categorized as having low, moderate, or high risk of bias.

Statistical analysis
All data analysis was conducted utilizing Review Manager version 5.4.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. We computed the odds ratio with a ninety-five percent confidence interval (CI for binary outcomes. We computed the mean variance with a ninety-five percent confidence interval for continuous outcomes. To determine the overall effect and estimate with a ninety five percent confidence interval, we utilized a fixed-effect model utilizing the Mantel-Haenszel method in the absence of heterogeneity among researches. A random-effects model utilizing the DerSimonian and Laird approach has been selected. The heterogeneity among research has been assessed utilizing the Q statistic & I^2 test, which quantify the variability percentage in the effect estimates. A P value of less than 0.05 has been deemed significant.

RESULTS
A total of 14 studies have been selected for the current analysis, including a total of 2855patient. The publication year ranged from 2008 to 2023. 3 studies were conducted in Egypt, 3 studies were conducted in Finland, 2 studies were conducted in Pakistan, 2 studies were conducted in Australia and 1 study was conducted in each of the following: India, Iraq, Iran and Brazil. Demographic data of involved studies are exhibited in Table 1.

Table 1

Author, year	**year**	**country**	**Study period**		**Study design**	**Sample Size**		
			from	to		Metformin group	Insulin group	Total
Dr.Shashi L. Kabra,(17)	2023	India	2021	2022	comparative prospective observational study	40	40	80
Kristiina Tertti1, Ulla Ekblad1, (18)	2008	Finland	2003	2006	retrospective study	45	45	90
Esam Awad Abd El-Aziz, (17)	2023	Egypt	2019	2021	randomized controlled study	94	100	194
Hisham Adel Abo Elez, (18)	2019	Egypt	2016	2018		58	58	116
TAYYIBA WASIM, (19)	2019	Pakistan	2016	2017	randomized control study	137	141	278
Sally R. Eid,(20)	2018	Egypt	2016	2017	prospective randomized study	113	116	229
AHLAM NASIR	2020	Iraq	2017	2020	randomized	60	60	120

ABOUD AL HAYANI, M.D, (21)					controlled trial			
Mikael S. Huhtala1, Kristiina Tertti, (22)	2020	Finland			randomized trial	110	107	217
Shirin Niromanesh, (23)	2012	Iran			randomized controlled trial	80	80	160
Jahan Ara Hassan, (24)	2012	Pakistan	2008	2010	randomized clinical trial	75	75	150
HELEN L. BARRETT, BSC, MBBS, FRACP,(25)	2013	Australia			prospective, randomized, and multicenter trial	236	242	478
HELEN L. BARRETT, BSC, MBBS, FRACP, (26)	2013	Australia				219	213	432
Cristiane Pava˜oSpaulonci, MD,(27)	2013	Brazil			Randomized trial	47	47	94
K. Tertti1, U. Ekblad, (8)	2012	Finland			randomized study	110	107	217

Table 2. Patient's characteristics

The mean participants' age in studied groups was 29.23ranging from 21to 37 years, and Gestational age (weeks) was reported in 11 studies with mean of 27.1 as shown in Table 2.

Author, year	**Age (year)**						**Gestational age (weeks)**					
	Metformin group			**Insulin group**			**Metformin group**			**Insulin group**		
	mean	**SD**	**total**	**mean**	**SD**	**total**	**mean**	**SD**	**total**	**mean**	**SD**	**total**
Dr.Shashi L. Kabra, (17)	26.98	4.2	40	28.9	4.8	40						
Kristiina Tertti1, Ulla Ekblad1,(18)	32.8	5	45	32.7	4.7	45	24.8	5.5	45	24.3	5.7	45
Esam Awad Abd El-Aziz, (17)	30.34	4.23	94	29.54	3.92	100	23.66	1.91	94	24.16	1.98	100
Hisham Adel Abo Elez,(18)	30.4	12.8	58	30.6	12.5	58	28.9	1.1	58	29	1.1	58
TAYYIBA WASIM, (19)	29.5	4.8	137	29.7	4.8	141	28.9	2.9	137	28.6	3.1	141
Sally R. Eid,(20)	31.6	3.6	113	30.4	3.5	116	27.4	3.9	113	28.1	3.1	116
AHLAM NASIR ABOUD AL HAYANI, M.D, (21)	30.09	4.1	60	29.97	4.13	60	30.6	2.02	60	30.4	1.32	60
Mikael S. Huhtala1, Kristiina Tertti,(22)	31.9	5.01	110	32	5.47	107						
Shirin Niromanesh,(23)	30.7	5.5	80	31.8	5.1	80	28.7	3.7	80	28.6	3.6	80
Jahan Ara Hassan, (24)	30.29	3.06	75	30.88	3.6	75	29.53	1.33	75	29.2	1.48	75
Cristiane Pava˜oSpaulonci, MD, (27)	31.93	6.02	47	32.76	4.66	47	30.4	3.71	47	30.63	3.35	47
K. Tertti1, U. Ekblad, (8)	31.9	5	110	32.1	5.4	107	30.3	2	110	30.4	1.8	107

GA at delivery

10 studies reported (GA at delivery) and all can be used. An insignificant heterogeneity has been identified. Therefore, a random-effect model has been utilized for analysis (I^2 = 5%, P-value equal 0.40). The combined mean difference & ninety five percent confidence interval was -0.08 (-0.20 - 0.03). The combined result demonstrates no statistically significant difference between groups regarding (GA at delivery) (Z-value equal 1.48, P-value equal 0.14).

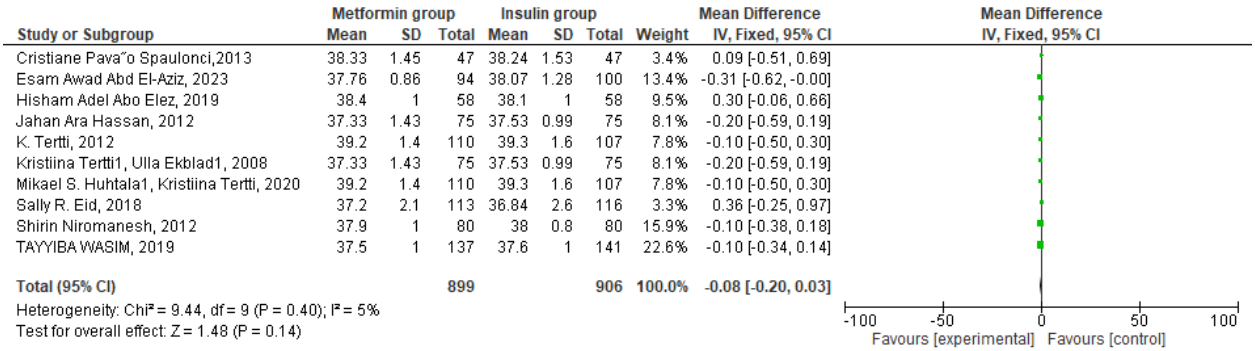

Figure 1. Forest plot of GA at deliveryshows statistically insignificant distinction among Metformin & Insulin groups.

Indication for CS

11 studies reported (indication for CS) and all can be used. A no significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 4%, P=0.41). Thecombined mean distinction and 95% CI was 0.76 (0.62 to 0.94). The combined resultdemonstrates statistically significant difference between groups regarding (indication for CS) (Z = 2.56, P =0.01).

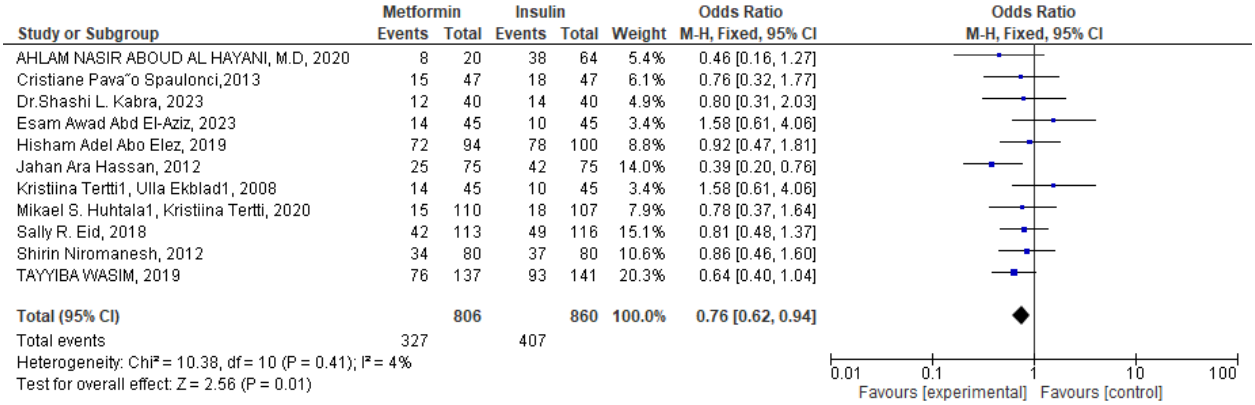

Figure 2. Forest plot of indication for CS exhibits statistically significant distinction among Metformin & Insulin groups.

Weight gain (kg)

7 studies reported (weight gain) and all can be used. A significant heterogeneity has been identified. Therefore, a random-effect model has been utilized for analysis (I^2 = 77%, P-value equal 0.0002). The combined mean difference & 95% CI was -2.19 (-2.46 to 1.93). The combined result demonstrates highly statistically significant difference between groups regarding (weight gain) (Z = 15.98, P-value ≤0.001).

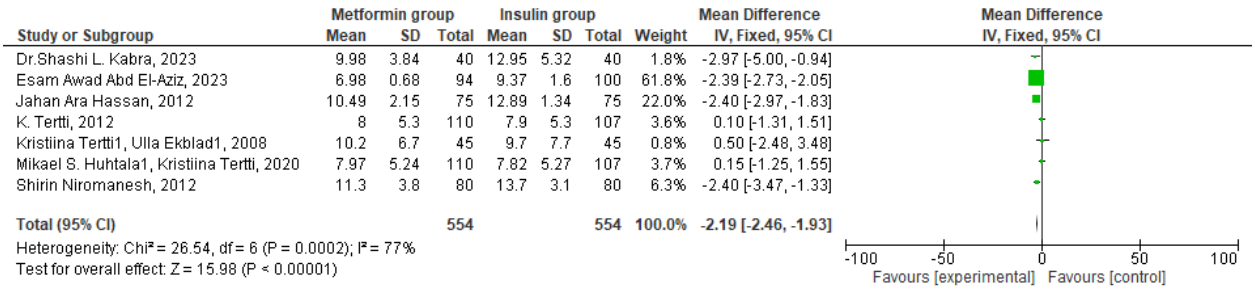

Figure 3. Forest plot of weight gain exhibits highly statistically significant distinction among Metformin & Insulin groups.

APGAR Score 5 min

Nine studies reported (APGAR Score 5 min) and all can be used. A significant heterogeneity was detected. Therefore, a random-effect model was used for analysis (I^2 = 91%, P≤0.001). The combined mean difference and 95% CI was -0.07 (-0.14 to 0.00). The combined result demonstrates no statistically significant difference between groups regarding (APGAR Score 5 min) (Z = 1.89, P =0.06).

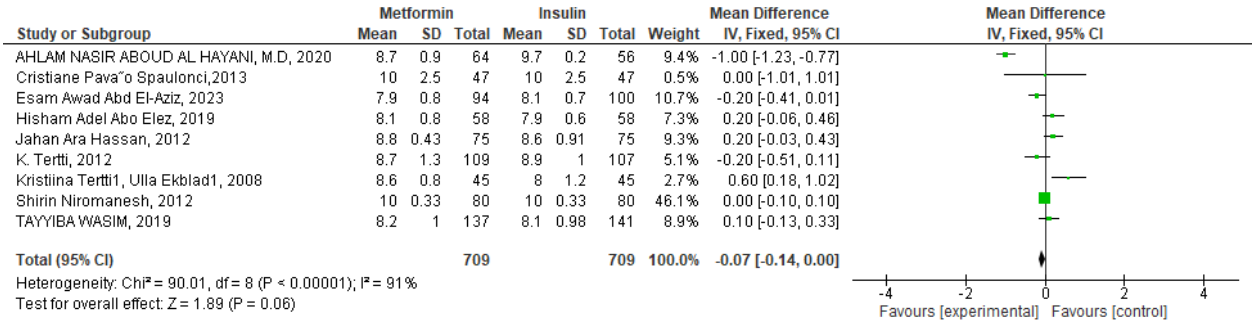

Figure 4. Forest plot of APGAR Score 5 min demonstrates statistically insignificant distinction among Metformin & Insulin groups.

NICU admissions

Nine studies reported (NICU admissions) and all can be used. A significant heterogeneity has been identified. Therefore, a random-effect model was used for analysis (I^2 = 49%, P-value equal 0.05). The combined mean difference & 95% CI was 0.72 (0.56 - 0.93). The combined result demonstrates highly statistically significant difference between groups regarding (NICU admissions) (Z = 2.53, P =0.01).

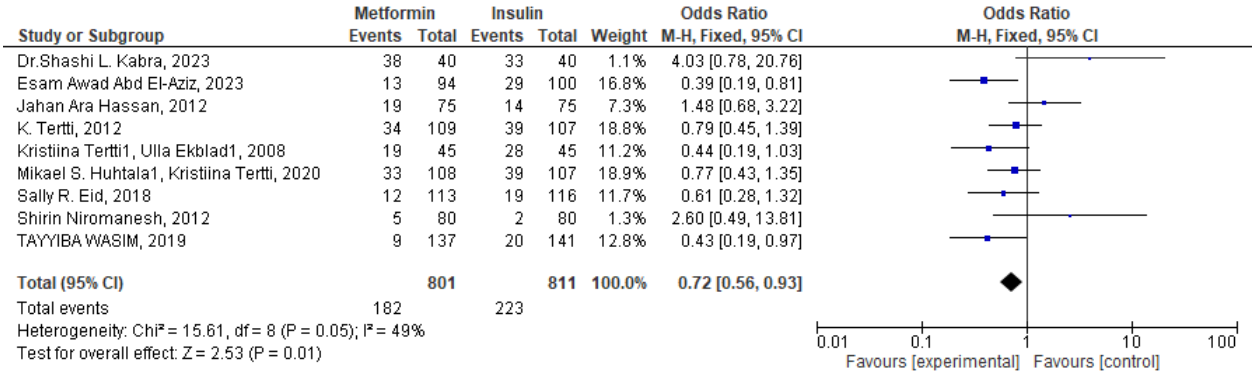

Figure 5. Forest plot of NICU admissions exhibits statistically significant difference among Metformin & Insulin groups.

Hypoglycemia

Nine studies reported (hypoglycemia) and all can be used. A significant heterogeneity has been identified. Therefore, a random-effect model was used for analysis (I^2 = 59%, P-value equal 0.01). The combined mean difference & 95% CI was 0.43 (0.32 to 0.59). The combined result demonstrates highly statistically significant difference between groups regarding (hypoglycemia) (Z = 5.35, P-value ≤0.001).

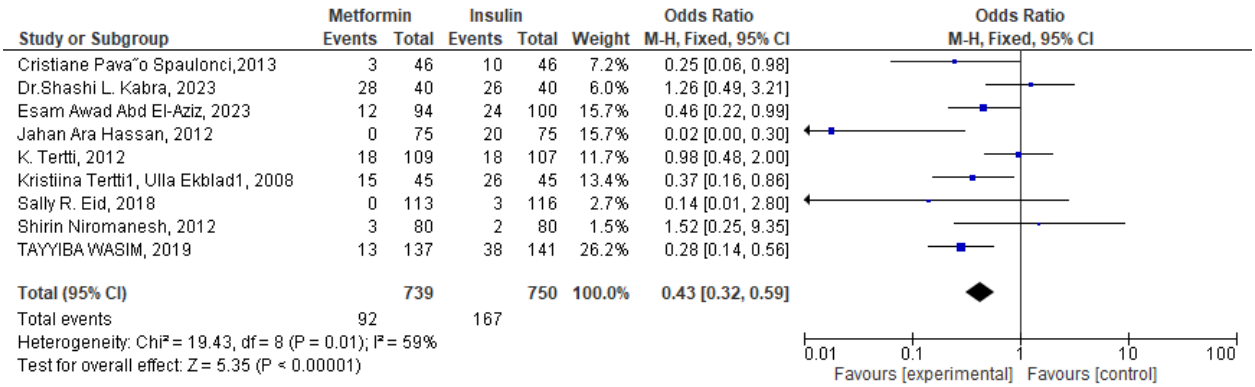

Figure 6. Forest plot of hypoglycemia exhibits highly statistically significant distinction among Metformin & Insulin groups.

Birth weight

8 studies reported (Birth weight) and all can be used. A significant heterogeneity has been identified. Therefore, a random-effect model has been utilized for analysis (I^2 = 100%, P-value ≤0.001). The combined mean

difference & 95% CI was 294.08 (248.67 to 339.49). The combined result demonstrates highly statistically significant difference between groups regarding (Birth weight) (Z-value equal 12.69, P-value ≤0.001).

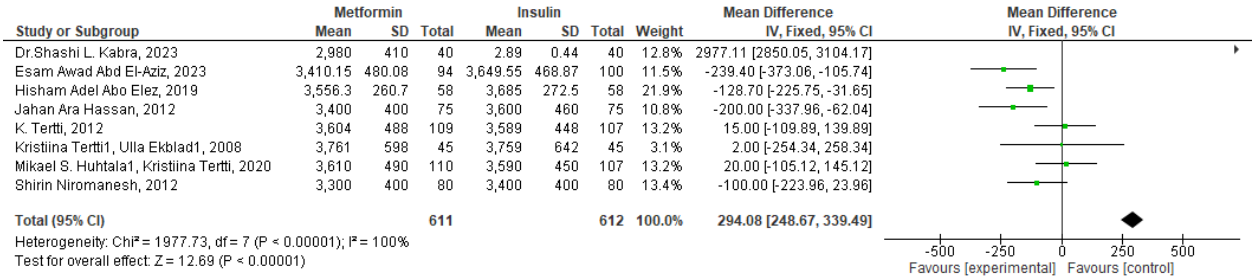

Figure 7. Forest plot of Birth weight exhibits highly statistically significant variation among Metformin & Insulin groups.

Neonatal hyperbilirubinemia

7 studies reported (Neonatal hyperbilirubinemia) and all can be used. An insignificant heterogeneity has been detected. Therefore, a random-effect model has been utilized for analysis (I^2 = 0%, P=0.53). The combined mean difference and ninety five percent confidence interval was 0.96 (0.65 to 1.42). The combined result exhibits statistically insignificant distinction among groups regarding (Neonatal hyperbilirubinemia) (Z-value equal 0.19, P-value equal 0.85).

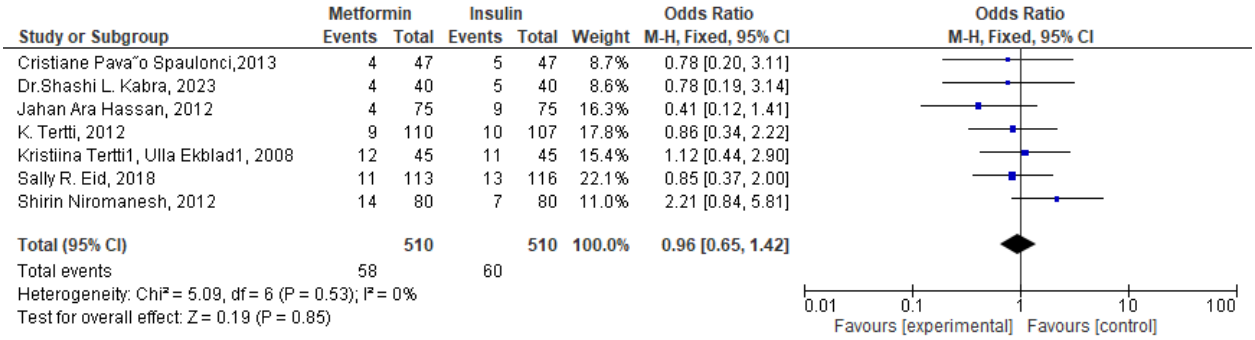

Figure 8. Forest plot of Neonatal hyperbilirubinemia exhibits statistically insignificant distinction among Metformin & Insulin groups.

Macrosomia baby

6 studies reported (Macrosomia baby) and all can be used. A slight significant heterogeneity has been discovered. Therefore, a random-impact model has been utilized for analysis (I^2 = 56%, P-value equal 0.05). The combined mean difference & 95% CI were 0.60 (0.36 - 0.99). The combined result demonstrates slight statistically significant difference between groups regarding (Macrosomia baby) (Z-value equal 1.98, P-value equal 0.05).

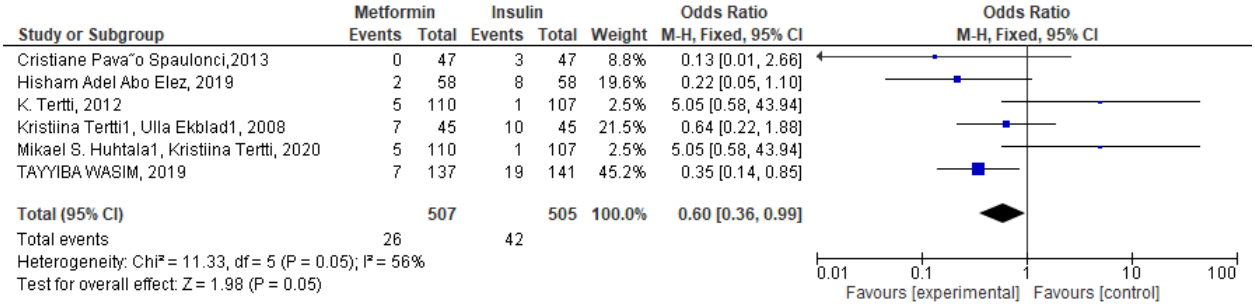

Figure 9. Forest plot of Macrosomia baby exhibits slight statistically significant distinction among Metformin & Insulin groups.

DISCUSSION

This meta-analysis indicated that cases with gestational diabetes mellitus managed with insulin exhibited a greater incidence of cesarean deliveries, neonatal intensive care unit admissions, weight gain, hypoglycemia,

and macrosomia in comparison to those treated with metformin. A statistically insignificant variance has been seen among groups concerning the APGAR Score at five minutes and newborn hyperbilirubinemia. Our findings indicated that metformin has been related to improved maternal glycemic management and significantly fewer newborn problems than insulin in gestational diabetes mellitus cases.

Eid et al. (20) evaluated the hazards and advantages of metformin and insulin concerning short-term results in females with gestational diabetes needing pharmacological intervention in Egypt. Their findings indicated that females using metformin may achieve superior outcomes in several aspects compared to those receiving insulin, with no significant adverse effects noted in their neonates. Metformin may significantly lower neonatal hypoglycemia, birth weight, and duration of hospitalization.

In 2019, Wasim et al. (19) conducted a comparative analysis of maternal and fetal outcomes associated with metformin and insulin in pregnant females diagnosed with GDM. It was disclosed that Metformin administration during pregnancy correlated with improved maternal glycemic regulation. The medication is well tolerated by cases exhibiting high compliance. Metformin treatment in cases with gestational diabetes mellitus resulted in fewer newborn problems, including macrosomia, hypoglycemia, and neonatal intensive care unit admissions, compared to insulin.

Nanda et al. (28) showed that neonates born to women in the insulin group exhibited a significantly greater frequency of hypoglycemia than those in the metformin group (fifteen percent versus. zero percent). Neonates born to moms in the insulin group exhibited a significantly greater frequency of hyperbilirubinemia than those in the metformin group fifteen percent vs. 2.5 percent). It has been noted that ten percent of neonates born to moms in the insulin group required neonatal intensive care unit care for twenty-four hours to one week, while 7.5 percent necessitated admission for more than one week. This was markedly greater compared to neonates born to moms in the metformin group, since ninety-five percent of these infants were in the neonatal intensive care unit for a total of twenty-four hours; one case had been admitted for twenty-four hours to one week, and another for over one week.

Kitwitee and colleagues (29) reported that metformin positively influences newborn hypoglycemia and neonatal intensive care unit admissions, with effects consistent with our results. Nevertheless, they discovered that metformin didn't diminish the incidence of preeclampsia, cesarean birth, or macrosomia, which contrasts significantly with our results. A significant finding from their research is that fourteen to sixty-four of cases on metformin still necessitated insulin supplementation, highlighting that although metformin gives benefits, doctors must be vigilant in monitoring the concentration of glucose and providing insulin as needed.

The 2019 review by Guo et al. (30) produced results that were partially consistent with our results. Similarly, metformin significantly diminished the possibility of pre-eclampsia, neonatal intensive care unit admission, and newborn hypoglycemia. Nevertheless, outcomes like cesarean birth and large for gestational age contradict our findings. They emphasized that although metformin demonstrates effectiveness, there remains a critical need to assess the long-term effects on the offspring of GDM cases administered this medication, signifying a want for additional research. A subsequent investigation by Sheng et al. (31) confirmed the beneficial effects of metformin, concentrating primarily on short-term neonatal results. Metformin decreased the probability of neonatal intensive care unit admission, macrosomia, and newborn hypoglycemia. Nonetheless, the LGA results diverged from our findings.

Conversely, Hamid et al. (32) indicated that insignificant variations have been observed among the examined groups regarding neonatal outcomes, including neonatal hypoglycemia, macrosomia, a 5-minute APGAR score below seven, admission to the neonatal intensive care unit, respiratory distress syndrome, or the necessity for phototherapy. Picon-Cesar et al. (33) similarly found no distinctions among groups for perinatal outcomes, including neonatal intensive care unit stay, neonatalhypoglycemia, respiratory distress syndrome, and jaundice necessitating phototherapy. In summary, although metformin demonstrates potential for the short-term management of gestational diabetes mellitus, subsequent research should focus on examining its long-term effects.

CONCLUSION

This meta-analysis indicated that metformin could have advantageous effects relative to treatment with insulin, decreasing the risk of specific maternal and newborn outcomes in cases with gestational diabetes mellitus. Metformin is both safe and effective, and it is evidently attractive than insulin for the short-term treatment of females with gestational diabetes. However, long-term research with bigger sample sizes are necessary to assess the safety of metformin prior to its widespread usage.

REFERENCES

1. Moon JH, Jang HC. Gestational diabetes mellitus: diagnostic approaches and maternal-offspring complications. Diabetes Metab J. 2022;46(1):3–14.
2. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The pathophysiology of gestational diabetes mellitus. Int J Mol Sci. 2018;19(11):3342.

3. Yuen L, Saeedi P, Riaz M, Karuranga S, Divakar H, Levitt N, et al. Projections of the prevalence of hyperglycaemia in pregnancy in 2019 and beyond: Results from the International Diabetes Federation Diabetes Atlas. Diabetes Res Clin Pract. 2019;157:107841.
4. Tobias DK, Stuart JJ, Li S, Chavarro J, Rimm EB, Rich-Edwards J, et al. Association of history of gestational diabetes with long-term cardiovascular disease risk in a large prospective cohort of US women. JAMA Intern Med. 2017;177(12):1735–42.
5. Dong Y, Luo ZC, Nuyt AM, Audibert F, Wei SQ, Abenhaim HA, et al. Large-for-gestational-age may be associated with lower fetal insulin sensitivity and β-cell function linked to leptin. J Clin Endocrinol Metab. 2018;103(10):3837–44.
6. Doi SAR, Furuya-Kanamori L, Toft E, Musa OAH, Islam N, Clark J, et al. Metformin in pregnancy to avert gestational diabetes in women at high risk: meta-analysis of randomized controlled trials. Obes Rev. 2020;21(1):e12964.
7. Bashir M, E. Abdel-Rahman M, Aboulfotouh M, Eltaher F, Omar K, Babarinsa I, et al. Prevalence of newly detected diabetes in pregnancy in Qatar, using universal screening. PLoS One. 2018;13(8):e0201247.
8. Crowther CA. Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005;352:2477–86.
9. Association AD. 14. Management of diabetes in pregnancy: standards of medical care in diabetes—2020. Diabetes Care. 2020;43(Supplement_1):S183–92.
10. Bulletins-Obstetrics C. ACOG practice bulletin no. 190: gestational diabetes mellitus. Obs Gynecol. 2018;131(2):e49–64.
11. Alfadhli EM. Gestational diabetes mellitus. Saudi Med J. 2015;36(4):399.
12. Nakshine VS, Jogdand SD. A Comprehensive Review of Gestational Diabetes Mellitus: Impacts on Maternal Health, Fetal Development, Childhood Outcomes, and Long-Term Treatment Strategies. Cureus. 2023;15(10).
13. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;358(19):2003–15.
14. Ouyang H, Al-Mureish A, Wu N. Research progress of metformin in gestational diabetes mellitus: A narrative review. Ann Palliat Med. 2021;10(3):3423437.
15. Committee S of MFMP. SMFM statement: pharmacological treatment of gestational diabetes. Am J Obs Gynecol. 2018;218(5):B2–4.
16. Barbour LA, Scifres C, Valent AM, Friedman JE, Buchanan TA, Coustan D, et al. A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes. Am J Obstet Gynecol. 2018;219(4):367-e1.
17. Awad E, Khalil Ahmed A, Khamis Galal S. METFORMIN VERSUS INSULIN IN GESTATIONAL DIABETES. Al-Azhar Medical Journal. 2023 Apr 1;52(2):541-54.
18. Tertti K, Ekblad U, Vahlberg T, Rönnemaa T. Comparison of metformin and insulin in the treatment of gestational diabetes: a retrospective, case-control study. The review of diabetic studies: RDS. 2008;5(2):95.
19. Wasim T, Shaukat S, Javaid L, Mukhtar S, Amer W. Comparison of metformin and insulin for management of gestational diabetes mellitus: a randomized control trial. Pakistan Journal of Medical & Health Sciences. 2019;13:823-7.
20. Eid SR, Moustafa RS, Salah MM, Hanafy SK, Aly RH, Mostafa WF, Ghanem AI. Is metformin a viable alternative to insulin in the treatment of gestational diabetes mellitus (GDM)? Comparison of maternal and neonatal outcomes. Egyptian Pediatric Association Gazette. 2018 Mar 1;66(1):15-21.
21. Aboud Al Hayani Md, Nasir A. Metformin versus Insulin in Treatment of Gestational Diabetes. The Medical Journal of Cairo University. 2020 Sep 1;88(September):1967-74.
22. Huhtala MS, Tertti K, Juhila J, Sorsa T, Rönnemaa T. Metformin and insulin treatment of. BioMed Central. 2020 Jul 11;2020:07-11.
23. Niromanesh S, Alavi A, Sharbaf FR, Amjadi N, Moosavi S, Akbari S. Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial. Diabetes research and clinical practice. 2012 Dec 1;98(3):422-9.
24. Hasan JA, Karim N, Sheikh Z. Metformin prevents macrosomia and neonatal morbidity in gestational diabetes.
25. Barrett-Lee P, Casbard A, Abraham J, Hood K, Coleman R, Simmonds P, Timmins H, Wheatley D, Grieve R, Griffiths G, Murray N. Oral ibandronic acid versus intravenous zoledronic acid in treatment of bone metastases from breast cancer: a randomised, open label, non-inferiority phase 3 trial. The Lancet Oncology. 2014 Jan 1;15(1):114-22.
26. Barrett HL. Maternal lipids and placental lipases in complicated pregnancy.

27. Spaulonci CP, Bernardes LS, Trindade TC, Zugaib M, Francisco RP. Randomized trial of metformin vs insulin in the management of gestational diabetes. American journal of obstetrics and gynecology. 2013 Jul 1;209(1):34-e1.
28. Nanda P, Kabra SL, Madaan R, Priya. Comparison study of metformin versus insulin in the treatment of gestational diabetes during pregnancy. Int J Reprod Contraception, Obstet Gynecol. 2023;12(4):1112–5.
29. Kitwitee P, Limwattananon S, Limwattananon C, Waleekachonlert O, Ratanachotpanich T, Phimphilai M, et al. Metformin for the treatment of gestational diabetes: an updated meta-analysis. Diabetes Res Clin Pract. 2015;109(3):521–32.
30. Guo L, Ma J, Tang J, Hu D, Zhang W, Zhao X. Comparative efficacy and safety of metformin, glyburide, and insulin in treating gestational diabetes mellitus: a meta-analysis. J Diabetes Res. 2019;2019(1):9804708.
31. Sheng B, Ni J, Lv B, Jiang G, Lin X, Li H. Short-term neonatal outcomes in women with gestational diabetes treated using metformin versus insulin: a systematic review and meta-analysis of randomized controlled trials. Acta Diabetol. 2023;60(5):595–608.
32. Hamid AA, Abd El-Gayed A, Saif-Elnasr I, Soliman M. Comparison the efficacy and safety between Insulin and Metformin in gestational diabetes mellitus management. Menoufia Med J. 2019;32(4):1376.
33. Picón-César MJ, Molina-Vega M, Suárez-Arana M, González-Mesa E, Sola-Moyano AP, Roldan-López R, et al. Metformin for gestational diabetes study: metformin vs insulin in gestational diabetes: glycemic control and obstetrical and perinatal outcomes: randomized prospective trial. Am J Obstet Gynecol. 2021;225(5):517-e1.