



The efficacy and safety of metformin alone or as an add-on therapy to insulin in pregnancy with GDM or T2DM

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Abstract

Background: Because it is inexpensive, safe, and can be taken orally, metformin has lately attracted a lot of attention and acceptability for treatment in GDM. The FDA presently lists it as a category B medication for usage during pregnancy.

Objectives: to evaluate the safety and effectiveness of metformin either on its own or in combination with insulin for pregnant women with GDM or T2DM.

Materials and methods: We did a thorough search of Cochrane Library, Embase, and PubMed. Text and medical topic headings such as metformin, insulin, gestational diabetes, pregnancy, and gestational diabetes mellitus were utilized in the search. To find other relevant RCTs, we additionally looked through the references in a few chosen publications and reviews as well as ClinicalTrials.gov.

Results, and Conclusion: Unlike insulin, metformin may help expectant mothers and their unborn children without raising the risk of specific results for the mother and the fetus.

Key words: Gestational diabetes mellitus (GDM), Metformin, type 2 diabetes mellitus (T2DM), Insulin.

Introduction

Type 1 or type 2 diabetes that is not clearly identified in the 2nd or 3rd trimester of gestation is known as gestational diabetes mellitus (GDM). [1]. Globally, the prevalence of GDM is increasing due to the obesity and type 2 diabetes epidemics, placing a significant financial strain on both the public health care system and individual patients. Due to varying demographics and diagnostic standards, the precise global incidence of GDM is still unclear; nevertheless, in the USA, the estimated yearly morbidity varies from 1 to 14%. [2,3]. Regrettably, GDM is linked to a number of unfavorable outcomes, such as newborn hypoglycemia, preeclampsia, shoulder dystocia, macrosomia, cesarean birth, and more. [4]. Furthermore, even if glucose homeostasis may be returned to levels not seen during pregnancy, women with GDM are more likely to develop type 2 diabetes (T2DM) in the future. [5]. Children whose moms with GDM are likewise affected by long-term problems. Children whose moms had poorly managed GDM were more likely to develop obesity or type 2 diabetes at a young age. [6–8]. Glycemic control is thus crucial for the treatment of GDM. If appropriate exercise or medical nutrition therapy are unable to help most women regulate their blood glucose levels, insulin is the recommended medication for the therapy of GDM. [1]. But there are a number of drawbacks to insulin treatment, such as the need for more injections, the possibility of hypoglycemia, maternal weight gain, and increased expense.

[9]. The patient's motivation to utilize insulin may be diminished by these drawbacks. On the other hand, metformin is a substitute that may enhance peripheral and hepatic insulin sensitivity. Although metformin

may cross the placenta and may directly impact embryonic physiology, there is no evidence to support the concern that it is teratogenic. Metformin exposure in the first trimester of gestation did not raise the incidence of any nongenetic congenital abnormalities, according to recent case-control research that analyzed data from eleven European congenital abnormality databases. [10].

Materials and Methods

We did a thorough search of Cochrane Library, Embase, and PubMed. Text and medical topic headings such as metformin, insulin, gestation, gestational diabetes, and GDM were utilized in the search. To find other relevant RCTs, we additionally looked through the references in a few chosen publications and reviews as well as ClinicalTrials.gov.

Studies that satisfied the following requirements were accepted: (1) The RCT was the design; (2) The participants were GDM or T2DM pregnant mothers.; (3) The treatments included metformin either by itself or in addition to insulin and insulin alone; and (4) None of the particular results or safety benchmarks were disclosed. Excluded from inclusion were cohort investigations, conference papers, letters, case reports, and comments. Trials that were published in several publications were only included once. The study eligibility was evaluated separately by two investigators who screened entire texts and titles/abstracts. Every issue was settled by talking it over or consulting a more experienced researcher.

Results

Table (1) characteristic of the studied groups.

Authors	Year	Country	Type of study	Age of participants
Ainuddin et al.[11]	2015	Pakistan	Randomized, open label clinical study	31.75 ± 2.82
Ashoush et al.[12]	2016	Egypt	A prospective, open-label, randomized controlled trial (RCT)	31.75 ± 2.82
Ghomian et al.[13]	2018	Iran	Randomized clinical trial.	28.30 ± 5.25
Ijas et al. [14]	2010	Finland	A prospective randomised study	32.3 ± 5.6
Rowan et al. [15]	2008	Australia and New Zealand	Randomized, open-label trial.	33.0 ± 5.1
Feige et al. [16].	2020	Canada and Australia	Randomized, parallel, double-masked, multinational, multicenter, prospective, placebo-controlled study.	34.7 ± 5.0
Spaulonci et al. [17]	2013	Brazil	Randomized controlled trial (RCT)	31.93 ± 6.02

Table (2) showing the main outcomes of the studied groups.

Authors	Study arms and patients	The main findings
Ainuddin et al.[11]	Metformin 16 Insulin + Metformin 90 Insulin 100	Patients with T2DM during gestation may benefit from inexpensive, efficient therapy with metformin alone or in combination with additional insulin.
Ashoush et al.[12]	Metformin 47 Insulin 48	In cases of GDM, metformin is a safe and efficient substitute for insulin. Women on metformin (± supplementary insulin)

		had comparable rates of adverse effects, decreased weight gain, and comparable glycemic control to those on insulin monotherapy. With increased Hr1-GTT and Wk1-mFG, insulin augmentation to metformin treatment was more probable.
Ghomian et al.[13]	Metformin143 Insulin 143	Given that there was no statistically substantial variation in mean FPG or 2-hr PG between the two groups, metformin seems to be a viable option to replace insulin in the management of GDM. Nevertheless, there are still some unfavorable risk factors associated with both therapies that might endanger both the mother and the infant.
Ijas et al. [14]	Metformin 47 Insulin 50	Metformin seems to be helpful in preventing fetal macrosomy, particularly in women who are slim or moderately overweight but develop GDM later in pregnancy. Insulin therapy may be more appropriate for women who are very obese, have high fasting blood glucose, and need pharmaceutical treatment early in their condition.
Rowan et al. [15]	Metformin 363 Insulin 370	Metformin, either by alone or in combination with extra insulin, does not raise the risk of perinatal problems in women with gestational diabetes mellitus as compared to insulin. The metformin was chosen by the ladies over insulin therapy.)
Feige et al.[16].	Metformin+Insulin253 Insulin 249	The metformin group showed many advantages in terms of maternal glycaemic control and neonatal obesity. Fewer big newborns and a larger percentage of small-for-gestational-age infants were the outcome of lower adiposity and baby size assessments, together with decreased maternal weight gain, insulin dose, and better glycaemic management. It will be crucial to comprehend the impact of these effects on unborn children in order to appropriately counsel patients who may be considering using metformin during pregnancy.)
Spaulonci et al. [17]	Metformin46 Insulin 46	With reduced mean levels of glucose throughout the day, less weight growth, and a decreased incidence of newborn hypoglycemia, metformin was shown to offer appropriate glycemic control. When women were first treated with metformin, the mean pretreatment glucose level and gestational age at diagnosis were shown to be predictive of the requirement for further insulin therapy.

Discussion

Between 7% and 18% of pregnancies are found to have gestational diabetes (GDM). A greater incidence of preeclampsia, fetal macrosomia, cesarean sections, and neonatal hypoglycemia are among the potential complications. All of these are significantly reduced when levels of glucose are controlled, primarily through diet and exercise or, if that is not possible, through medication. [18] Insulin therapy is the usual course of treatment for reaching appropriate glucose levels. However, this treatment requires many insulin injections each day, which can decrease patient compliance. Moreover, some patients may not be able to afford therapy due to its high cost. Because they are less expensive and easier to administer than insulin treatment, oral antidiabetic medications have been looked into as a potential substitute. [19, 20] The biguanide hypoglycemic medication metformin lowers hepatic gluconeogenesis while raising peripheral insulin sensitivity. Many research have looked at the usage of metformin to treat GDM in the last few years,

and two randomized trials with comparable neonatal outcomes have concluded that metformin seems to be a useful substitute for treating GDM. [21] Nonetheless, a patient's qualities have a significant impact on how well they respond to therapy in cases of gestational diabetes. The main goal of the current research was to examine glycemic control in women who got metformin or insulin for the management of GDM in our community, as neonatal outcomes depend on the sufficiency of metabolic control. A second goal was to find variables that may indicate whether or not women taking metformin initially will need additional insulin since some patients do not achieve appropriate glucose control and must thus take insulin.[22, 23] In recent years, four comparable meta-analyses [24–26] have been published. The meta-evaluations conducted by **Bao et al. [24]** and **Guo et al. [25]** and **Wang et al. [27]** concentrated on the safety and effectiveness of metformin in pregnant women with GDM; however, we also evaluated metformin in patients with T2DM and at least four more RCTs comparing metformin and insulin in gestation. **Tarry-Adkins et al. [26]** solely evaluated the effects of metformin on the mother; nonetheless, we evaluated the effects of the medication on the mother and the newborn and shown that, during the perinatal stage, the neonatal results are more significant than the maternal outcomes. As a result, we compared metformin and insulin in T2DM or pregnant GDM patients in-depth in our research. These findings imply that metformin treatment throughout pregnancy may have advantages and be safer and more beneficial during the neonatal stage.

Conclusion

Unlike insulin, metformin may assist expectant mothers and their unborn children without raising the risk of certain maternal and fetal outcomes.

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