Role of metformin oral hypoglycemic agents (OHAs) in the management of Gestational Diabetes Management. Where does metformin stand?

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Abstract

Background: Gestational diabetes mellitus (GDM) poses risks to both maternal and fetal health. This study conducts a comprehensive analysis of previous research on the use of metformin in managing GDM compared to other therapies. The primary objective is to elucidate the comparative efficacy, safety profiles, and maternal-fetal outcomes associated with metformin use in GDM management.

Methods: A literature review was conducted using different databases of studies from 2013 to 2023 involving GDM-diagnosed populations and comparing oral metformin therapy to other GDM management strategies.

Results: Metformin is a potential alternative for managing GDM due to its ease of administration and cost-effectiveness compared to insulin therapy. Various comparative studies indicate that metformin is associated with favorable outcomes, including improved glycemic control, reduced gestational weight gain, and lower rates of neonatal hypoglycemia compared to insulin. Glyburide, another oral hypoglycemic agent, shows similarities to insulin but with some differences in hypoglycemia risk. However, the advantages of metformin are more pronounced when compared to glyburide. Long-term studies suggest that metformin may reduce the risk of subsequent type 2 diabetes in women with a history of GDM.

Conclusion: Metformin exhibits efficacy and safety in GDM management, with pronounced benefits. While it may not completely replace insulin therapy, metformin offers a viable option in GDM management. Future research should focus on optimizing dosing regimens, long-term safety assessments, and exploring combination therapies to enhance GDM care.

Keywords: Metformin, Gestational Diabetes Mellitus, Maternal outcomes, Fetal outcomes, Insulin, Glyburide

Introduction

Gestational diabetes mellitus (GDM) is characterized by increased blood glucose concentrations during pregnancy. Typically, GDM becomes evident in the late second trimester or early in the third trimester and resolves postpartum. Diagnosing GDM has been complex due to its initial broad definition, encompassing any pregnancy-associated hyperglycemia, regardless of severity or postpartum resolution (1). Recent global increases in diabetes, obesity rates, and delayed childbearing have heightened the variability in hyperglycemia severity. This potentially leads to misclassification of some cases as GDM (2). The International Association of Diabetes in Pregnancy Study Groups (IADPSG) 2010 criteria and the World Health Organization (WHO) 2013 criteria classify women diagnosed during pregnancy but who would have diabetes outside of pregnancy as having "overt diabetes" or "diabetes in pregnancy" (3,4). These individuals exhibit severe hyperglycemia, necessitating immediate treatment, and may have established microvascular diabetes complications.

The occurrence of gestational diabetes mellitus (GDM) exhibits global variation, ranging from 1% to exceeding 30% (5). Discrepancies in screening standards and diagnostic criteria hinder the comparison of regional prevalence. The highest prevalence has been recorded in the Middle East and some North African nations, followed by Southeast Asia, the Western Pacific, South and Central America, sub-Saharan Africa, and North America, and the Caribbean. Europe exhibits the lowest prevalence, marked by substantial variation (6). Most GDM cases may be preventable through lifestyle interventions involving a healthy diet, a BMI below 25 kg/m², regular exercise, and smoking cessation (7). Population-level preventive strategies may necessitate initiation before pregnancy, addressing childhood obesity, adolescent weight gain, and promoting healthy lifestyle patterns in parents. Genetic contributions to GDM remain incompletely elucidated and require larger-scale research across diverse populations. Factors that increase the risk of developing GDM include older maternal age, ethnic background, prior GDM experience, and a family history of diabetes (8). Emerging risk factors encompass environmental pollutants, psychosocial factors, and genetic factors, though associations with the latter remain inconsistent and warrant further investigation (9).

GDM occurs in 15% to 25% of pregnancies, associated with complications for both mother and fetus (10). Maternal risks include increased pre-eclampsia and a higher likelihood of cesarean section (11). Fetal complications involve macrosomia, hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, and congenital defects (12). Traditional GDM management focuses on dietary control and insulin therapy. Metformin is emerging as an alternative, with potential advantages in ease of administration and lower cost, addressing concerns about insulin therapy (13,14). Numerous studies support metformin's efficacy in GDM management. This article conducts an in-depth analysis of scientific studies examining the use of metformin for managing GDM in comparison to other methods like insulin and glibenclamide. Various types of research, including controlled experiments, data analyses, and observational studies were analysed. The main objective was to elucidate the comparative efficacy, safety profiles, and maternal-fetal outcomes associated with the use of metformin in GDM. By systematically summarizing these research findings, this review provides healthcare professionals with evidence-based information to guide their decisions on the best way to manage GDM, ultimately improving prenatal care and maternal health.

Literature Search and Data collection Strategy:
The literature review employed the search term 'diabetes/ gestational diabetes AND pregnancy AND metformin/ insulin.' Two electronic databases, PubMed and ScienceDirect, were utilized for the period from 2013 to 2023. Additionally, manual searches were performed using alternative sources, including Google Scholar and prominent obstetric and endocrinology journals. Studies were incorporated if they met the following criteria:

- The study involved a population diagnosed with gestational diabetes mellitus.
- The study compared oral metformin therapy to other forms of gestational diabetes mellitus management.

Studies were excluded if they did not include human data, were not available in English, or did not distinguish between type 2 diabetes and GDM. Table 1 shows the studies included in this review to analyse the comparative effect of metformin and other treatment methods.

Mechanism of Metformin in glycaemic control

Metformin, a biguanide classified as an oral antidiabetic medication, is primarily utilized for managing type 2 diabetes mellitus (T2DM) (15). Its therapeutic actions involve reducing hepatic glucose production and enhancing peripheral insulin sensitivity by stimulating adenosine monophosphate-activated protein kinase (AMPK) (16). Administered orally, metformin is typically part of a comprehensive diabetes management strategy, often in combination with other antidiabetic medications if glycemic control is insufficient with metformin alone. Gastrointestinal side effects, like diarrhea and nausea, are common but generally diminish over time or with dose adjustments.

Metformin achieves glycaemic control through various mechanisms, including increased insulin sensitivity, promotion of glycogen synthesis, and reduction of hepatic gluconeogenesis (17). It also influences lipid metabolism, reducing hypertriglyceridemia and decreasing Very Low-Density Lipoprotein (VLDL) synthesis (18). Activation of hepatic AMPK is crucial to metformin's efficacy, leading to reduced fatty acid oxidation and suppression of lipogenic enzymes. Metformin delays glucose absorption, increases lactate production, and influences the release of gastrointestinal hormones such as GLP-1 (19).

Molina-Vega et al. (2022) showed that metformin-induced changes in gut microbiota composition and metabolic profiles, with potential implications for postprandial glycemia, weight control, and BMI (20). Moreover, metformin demonstrates a favorable cardiovascular profile, linked to reduced mortality compared to alternative treatments, despite achieving similar glycemic control (18). It inhibits advanced glycation end product (AGE) formation, diminishing diabetic vascular complications (21).

Efficacy and safety of metformin on GDM management

Metformin is widely acknowledged as an effective and well-tolerated option for managing GDM. It helps in controlling blood glucose levels in pregnant women and mitigating maternal complications while improving fetal outcomes. A study implementing the "Metformin First" protocol demonstrated enhanced patient acceptance, as indicated by improved satisfaction scores (22). Additionally, pregnant women treated with metformin exhibited lower rates of adverse outcomes, including preterm delivery and the birth of large-for-gestational-age (LGA) newborns (23). The efficacy of metformin is primarily attributed to its ability to cross the placenta, facilitated by organic cation transporters (OCTs) expressed in the placenta (24). Tertti et al. demonstrated metformin transfer from mother to fetus during late pregnancy, with approximately 73% passage (25). Maternal metformin concentrations correlated with increased levels in maternal serum at 36 weeks, but no significant associations were observed with markers of glycemic control or neonatal outcomes. Importantly, the extent of metformin passage was unaffected by maternal dose or timing of the last drug intake before delivery (25).

GDM management strategies: Comparing Metformin with other options

The management of GDM focuses on controlling elevated blood glucose levels during pregnancy to mitigate potential complications for both the mother and the fetus. Treatment strategies encompass dietary adjustments, emphasizing balanced carbohydrate intake and high-fibre foods, coupled with regular, moderate-intensity physical activity to enhance insulin sensitivity. In severe cases, insulin therapy is advised. Recently, oral hypoglycemic agents like metformin or glyburide have gained much interest due to their convenient use and reduced cost of treatment. Metformin usage has been observed to rise from 2.5% to over 30% in recent years (26). In this regard, the following subsections compare the use of metformin with insulin and glyburide in GDM management.

1. Metformin vs Insulin

In the management of GDM, two primary approaches are employed, metformin and insulin. Insulin, administered via subcutaneous injections, directly lowers blood glucose levels by promoting cellular glucose uptake and inhibiting hepatic glucose production. It is highly effective and safe during pregnancy, but meticulous dose titration is crucial to prevent hypoglycemia. Metformin operates by diminishing hepatic glucose production and enhancing peripheral tissue insulin sensitivity. It is generally considered safe during pregnancy and poses a lower risk of hypoglycemia compared to insulin. The choice between these two options is based on individual factors, with insulin often preferred in severe GDM cases or when rapid glucose control is necessary and metformin may be considered when lifestyle modifications are insufficient.

Comparison of maternal outcomes

Many randomized trials comparing metformin to insulin for managing GDM are reported in literature. Spaulonci et al. investigated the management of glycemic control in women with GDM who did not achieve satisfactory results through diet and exercise alone (27). These women were divided into two groups, with one group receiving metformin and the other receiving insulin. Initial glucose levels before treatment were comparable between the metformin and insulin groups. However, following the initiation of treatment, particularly after dinner, the metformin group exhibited lower mean glucose levels. Additionally, women in the metformin group experienced less weight gain during pregnancy and a reduced incidence of neonatal hypoglycemia (27). Similar comparative studies have found no significant differences, suggesting that metformin is a viable alternative to insulin for managing GDM (28,29). Furthermore, in a retrospective study involving Portuguese women, no significant distinctions in most maternal and neonatal outcomes were observed between the metformin-treated and insulin-treated groups (23). Similar findings were reported by a meta-analysis encompassing eight clinical trials involving 1,712 participants (30). The study showed that there were minor and statistically inconsequential disparities between metformin and insulin in relation to fasting plasma glucose, postprandial plasma glucose, and HbA1c levels at 36-37 weeks of gestation. The study also implicated that metformin therapy was linked to a reduced occurrence of neonatal hypoglycemia and admittance to neonatal intensive care in comparison to the insulin cohort. Many other studies have also suggested the efficacy and safety of metformin in GDM management (31–34). Hypoglycemic episodes are reported to be significantly less frequent in the metformin-treated women compared to the insulin group (55.9%) (35). In contrast to all the above findings, Tew et al. conducted a double-blind trial involving 106 participants and reported that pre-emptive metformin did not significantly reduce HbA1c levels at 36 weeks of pregnancy compared to a placebo (36). However, it led to lower mean birth weights, which raised concerns (36).

Despite its effectiveness in managing GDM, several reports have highlighted the necessity for supplemental insulin during the later stages of pregnancy (27,37,30). In the randomized trial led by Spaulonci and colleagues, approximately 26.08% of women in the metformin group required supplemental insulin to maintain glycemic control. The study identified two factors that predict the need for supplemental insulin in women who initially

received metformin treatment. It was found that women diagnosed with GDM earlier in pregnancy were more likely to require insulin. Additionally, higher glucose levels before starting treatment were associated with a higher likelihood of needing insulin. Ashoush et al. identified additional predictive factors such as initial BMI, HbA1C levels, elevated fasting and postprandial glycemia at the initial oral glucose tolerance test (OGTT), and high glucose levels during the first week of medical treatment (37). They reported cutoff values for each parameter. Women with a Hr1-GTT level exceeding 212 mg/dL and a Wk1-mFG (week 1 mean fasting glucose) level greater than 95 mg/dL had a significantly elevated risk of requiring supplemental insulin during their study (37). However, combining insulin and metformin has been shown to increase CS risk, indicating higher pregnancy risk (26).

A metabolomics-based approach to elucidate the metabolic profiles and pathways in GDM elucidated the intricate relationship between aromatic amino acids (AAA) and branched-chain amino acids (BCAA) concerning insulin resistance in GDM (38). The study conducted a comparative analysis of maternal amino acid and lactate concentrations in GDM-afflicted women undergoing treatment with either metformin or insulin. This analysis revealed that both treatment modalities led to a similar reduction in serum glucose levels. Notably, no significant disparities were observed in the alterations of amino acids such as phenylalanine, tyrosine, or histidine. However, isoleucine and alanine exhibited a more pronounced increase in the metformin-treated group, whereas lactate levels demonstrated a more substantial rise in the metformin cohort compared to the insulin-treated group. At the 36th week of gestation (36 gw), alanine levels were significantly correlated to birth weight, with a particularly pronounced effect observed in the metformin-treated group. Additionally, low glucose levels at this gestational stage were correlated with birth weights falling below the 10th percentile. Elevated glutamine concentrations at 36 gw were found to elevate the cumulative risk of gestational hypertension or preeclampsia. Moreover, a correlation was observed between lower gestational weight gain and histidine levels at 36 weeks of gestation, although this relationship was specific to the metformin-treated group. Subsequently, another study by Huhtala et al. compared the impact of metformin and insulin treatments on various inflammatory markers (39). Metformin administration was found to result in a more substantial increase in IGFBP-1 concentrations compared to insulin therapy, primarily attributed to its favorable impact on improving insulin resistance. Specifically, non-phosphorylated IGFBP-1 (non-pIGFBP-1) levels exhibited an inverse correlation with maternal weight gain during pregnancy, suggesting a potential role in the regulation of maternal weight gain. The study did not detect substantial distinctions between metformin and insulin regarding their influence on inflammatory markers like hsCRP and IL-6. However, both interventions were linked to a reduction in hsCRP levels and an increase in IL-6 levels. Furthermore, serum GlycA levels displayed an elevation in both medication groups, with a slightly more pronounced increase observed in the metformin-treated group. GlycA is a marker associated with cardiovascular risk and insulin resistance. The inflammatory markers and IGFBP-1 levels did not exhibit clear associations with pregnancy outcomes, with the exception of a reduced risk of labor induction observed in patients with elevated IGFBP-1 levels. The study suggested that metformin may offer advantages in terms of IGFBP-1 regulation compared to insulin, although its impact on inflammatory markers remains largely comparable (39).

Comparison of fetal outcomes

While there is evidence suggesting that metformin can decrease gestational weight gain and reduce the occurrences of neonatal hypoglycemia, neonatal intensive care admissions, and gestational hypertension compared to insulin treatment, metformin is associated with a slightly lower gestational age at birth, although it is not linked to preterm labor (26). Eid et al. showed that though patients treated with insulin and metformin achieved similar glycemic control throughout pregnancy, there were significant differences between the two groups in terms of neonatal outcomes (40). The mean birth weight in the insulin group was significantly higher than in the metformin group. The incidence of fetal macrosomia was higher and Large for Gestational Age (LGA) was more common in the insulin group. In addition, the rate of neonatal hypoglycemia was significantly lower in the metformin group. In this study, metformin was shown to be a suitable alternative for GDM (40).

2. Metformin vs Glibenclamide (Glyburide)

Glibenclamide, or glyburide, is a sulfonylurea medication used for GDM. It acts as an insulin secretagogue by binding to pancreatic beta cell receptors, closing ATP-sensitive potassium channels, leading to cell depolarization, calcium influx, and insulin release. It is used when dietary/lifestyle changes are insufficient for GDM control. Recent research shows fetal exposure. Both glyburide and metformin are alternatives to insulin for GDM. Glyburide has a low therapy failure rate, while metformin reduces neonatal hypoglycemia risk compared to insulin. However, a study by George et al. found higher neonatal issues with glibenclamide, favoring metformin for moderate hyperglycemia (41). Metformin improves insulin sensitivity and beta-cell function, while glyburide mainly boosts baseline beta-cell activity. Their combination shows a balanced effect (42). In a clinical trial, Nachum et al. found both drugs failed as first-line therapy in 34% and 29% of cases (43). However, as a second-line therapy, the combination (metformin and glyburide) significantly improved GDM management, reducing the need for insulin (43).

3. Metformin vs Glyburide vs Insulin

In a meta-analysis by Guo et al., metformin exhibited reduced gestational hypertension incidence compared to insulin (44). No significant differences were found in preterm birth or other hypertensive disorders when comparing metformin to insulin and glyburide. Metformin also showed a lower rate of labor induction compared to insulin, along with lower maternal hypoglycemia incidence

and earlier gestational age at delivery. Metformin had lower gestational weight gain compared to insulin. At weeks 36-37, metformin had a lower HbA1c% than insulin, but no significant differences in glycated hemoglobin or fasting blood glucose levels. Metformin also led to a reduced occurrence of Neonatal Intensive Care Unit (NICU) admission, neonatal hypoglycemia, macrosomia, and reduced birth rates . In contrast, glyburide was associated with a higher incidence of neonatal hypoglycemia. The meta-analysis favored metformin in terms of gestational hypertension, maternal hypoglycemia, and certain neonatal outcomes, while glyburide did not show significant advantages over insulin (44). Another meta-analysis by Musa et al. confirmed metformin's favorable outcomes over insulin, particularly in weight gain and hypoglycemia (45). This makes metformin a viable first-line treatment option for GDM women struggling to achieve normal glycemic levels through lifestyle and nutritional interventions. Glibenclamide exhibited overall similarity to insulin, with some differences in hypoglycemia. Consistent with these findings, Wang et al. and other studies also highlighted the advantages of metformin over insulin and glyburide in the context of GDM treatment (46).

5. Long-term health implication

Postpartum metabolic health of the mother: Women with GDM face a significantly increased risk of developing T2DM. A meta-analysis revealed a more than sevenfold higher risk compared to those with normal pregnancy glucose levels, making GDM the primary T2DM risk factor (47). Risk factors for subsequent diabetes in GDM women include higher BMI, early GDM diagnosis, elevated glucose levels at diagnosis, insulin treatment during pregnancy, and postpartum OGTT-detected impaired glucose tolerance (IGT).

Aroda et al. examined diabetes prevention in women with and without a history of GDM (48). Women with prior GDM on placebo had a 48% higher risk of diabetes compared to those without GDM history. With a GDM history, intensive lifestyle intervention (ILS) and metformin reduced diabetes risk by 35% and 40%, respectively. Among those without GDM history, ILS lowered risk by 30%, while metformin had no significant effect (48). Marques et al. found some participants with postpartum OGTTs showed signs of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (23). Pellonperä et al. observed no substantial differences in postpartum body weight, HbA1c levels, or OGTT outcomes between GDM women treated with short-term metformin, insulin, or diet-based approaches (49). Refuerzo et al. reported that both metformin and placebo groups of GDM women experienced a similar approximate 6 kg weight loss at 6 weeks postpartum, with no clear evidence of metformin's effectiveness (50).

Long-term impact on offspring health: A comprehensive study involving a cohort of nearly 100,000 pregnant women observed that offspring born to mothers with GDM exhibited elevated fasting glucose levels, insulin resistance, increased adiposity, and an adverse cardiovascular risk profile. Notably, maternal adiposity emerged as a significant risk factor for offspring obesity, and even after accounting for maternal BMI, GDM remained a substantial risk factor. In the context of offspring cognitive function, the available evidence shows conflicting outcomes regarding the autonomous impact of maternal GDM. There is no conclusive support for the assumption that maternal GDM is a direct cause of impaired cognitive function. Some studies have suggested an elevated risk of autism spectrum disorder in offspring born to women with early GDM diagnosis, whereas the offspring of women necessitating medical treatment for GDM demonstrated an increased risk of attention-deficit hyperactivity disorder (ADHD) (51). Tertti et al. conducted an evaluation of cognitive, language, motor development, and neurological outcomes in children at the age of 2 years who were born to mothers with GDM and received treatment with either metformin or insulin (52). The findings indicated that at the age of 2 years, no noteworthy distinctions were observed in neurodevelopmental outcomes between children born to the two groups of women (52). Paavilainen et al. compared metformin and insulin treatments for GDM in children (53). The metformin group showed higher HDL cholesterol, lower LDL cholesterol, and lower apolipoprotein B. Male children in the metformin group had lower 2-hour glucose levels. In a subsequent study maternal metformin treatment had little impact on the adiposity and body composition of the offspring (54). Metformin-exposed children had higher adiponectin levels, especially in males, and a lower leptin/adiponectin ratio in boys. These findings suggest minimal effects on body composition but potential metabolic differences in offspring based on maternal GDM treatment.

Table 1 shows a summary of the three drugs in the management of GDM.

Future Directions: Potential Improvements in Metformin Therapy

Metformin therapy for GDM can be further improved through systematic scientific inquiry and clinical application. Exploration of optimal dosing regimens, considering maternal variables like body weight and insulin resistance, alongside the careful timing of metformin initiation during pregnancy, are crucial for optimum treatment. Long-term safety assessments are imperative to address concerns surrounding developmental and metabolic effects. Additionally, the potential benefits of combining metformin with other antidiabetic agents and the development of standardized monitoring protocols should be investigated. Pharmacokinetics of metformin during pregnancy can guide dosing adjustments, while studies on lifestyle interventions in conjunction with metformin therapy may improve glucose control. Identification of predictive biomarkers for initiation or cessation of metformin therapy must be studied. Continued research is necessary in advancing the effectiveness and safety of metformin therapy for GDM.

Table 1: Overview of the three drugs used in GDM management

Drug	Metformin	Glyburide	Insulin
Medium of administration	Oral	Oral	Injection
Mechanism of action	Insulin sensitizer	Insulin secretagogue	Hormone replacement
Prevalence of use	Increasing	Limited	Common
Placental crossing	Yes	Yes	Yes
Maternal outcomes	Lower risk of hypoglycemia, often considered when lifestyle modifications are insufficient	No significant advantage in glycemic control, weight gain, and other outcomes. But can lead to higher birth weights and maternal hypoglycaemia.	Highly effective and safe during pregnancy, often preferred in severe GDM cases or when rapid glucose control is necessary
Fetal outcomes	Slightly lower gestational age at birth (not linked to preterm labor), lower risk of neonatal hypoglycemia, neonatal intensive care admissions, and gestational hypertension	Higher incidence of fetal macrosomia, Large for Gestational Age, and neonatal hypoglycemia	Higher birth weights, higher incidence of fetal macrosomia, and Large for Gestational Age
Long term outcomes	Potential reduction in the risk of diabetes development	Increased risk of diabetes development	Insulin may not have a significant effect on reducing the risk of diabetes

Conclusion

Metformin is a viable alternative for the management of GDM. Its efficacy in regulating blood glucose levels, mitigating maternal complications, and improving fetal outcomes has been well-documented. When compared to insulin and glyburide, metformin offers several advantages, including a reduction in maternal weight gain, decreased rates of neonatal hypoglycemia, and, in some cases, enhanced glycemic control. In certain instances, particularly during late pregnancy, supplementary insulin may be required alongside metformin to maintain optimal blood glucose levels. Metabolomics research has shed light on the metabolic alterations induced by metformin, particularly in amino acids and inflammatory markers. These findings contribute significantly to our understanding of the drug's impact on both maternal and fetal health. Metformin has also been shown to have long-term health implications of the potential to reduce the risk of T2DM in mothers who have a history of GDM. Additionally, metformin does not adversely affect offspring development and may even confer metabolic benefits. Future directions in metformin therapy for GDM entail the optimization and customization of dosing regimens and the exploration of combination therapies. It is necessary to conduct assessments of long-term safety, develop robust monitoring protocols, and identify predictive biomarkers to refine the use of metformin in the management of GDM.

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