Metformin or insulin for gestational diabetes: beyond glucose control

Written by The Life Science Feed Editorial Team · Edited by Mara Voss

> Gestational diabetes mellitus (GDM) complicates a significant proportion of pregnancies, posing risks for both mother and child. Untreated or poorly managed GDM increases the likelihood of adverse outcomes, including macrosomia, neonatal hypoglycemia, and pre-eclampsia. The primary goal of GDM management is to achieve normoglycemia, thereby mitigating these risks.

KEY TAKEAWAYS

- The Pivot: While both metformin and insulin control glucose, their effects on maternal weight gain and neonatal complications vary.
- The Data: Metformin is associated with less maternal weight gain and a lower incidence of neonatal hypoglycemia compared to insulin.
- The Action: Consider metformin as a first-line oral agent for GDM, particularly in patients without contraindications, while closely monitoring for potential neonatal implications.

Gestational diabetes mellitus, defined as glucose intolerance first recognized during pregnancy, affects approximately 1 in 7 live births globally. This condition is not merely a transient elevation of blood sugar; it represents a complex metabolic challenge with profound implications for maternal and fetal health. The underlying pathophysiology involves insulin resistance, often exacerbated by placental hormones, leading to hyperglycemia. If left unmanaged, GDM can lead to a cascade of complications, including fetal macrosomia, shoulder dystocia, birth trauma, neonatal hypoglycemia, hyperbilirubinemia, and respiratory distress syndrome. For the mother, risks include pre-eclampsia, operative delivery, and an increased long-term risk of developing type 2 diabetes. The established standard of care for GDM begins with medical nutrition therapy and regular physical activity. When lifestyle interventions alone are insufficient to achieve target glucose levels, pharmacologic therapy becomes necessary. Historically, insulin has been the mainstay of treatment, given its established safety profile in pregnancy and its inability to cross the placenta in significant amounts. But insulin therapy carries its own challenges, including the need for injections, potential for hypoglycemia, and often, significant maternal weight gain.

Metformin, an oral biguanide, has emerged as an alternative pharmacologic option for GDM. Its mechanism of action involves reducing hepatic glucose production and improving insulin sensitivity in peripheral tissues. Unlike insulin, metformin crosses the placenta, reaching the fetal circulation. This transplacental passage has been a point of contention and careful consideration in its use during pregnancy. The debate around metformin versus insulin extends beyond mere glycemic control, encompassing a broader spectrum of maternal and neonatal outcomes. Clinicians must weigh the benefits of an oral agent, such as improved adherence and reduced maternal weight gain, against potential concerns

regarding fetal exposure and long-term effects. The choice of pharmacotherapy in GDM is not a simple one, requiring a thorough understanding of each agent's profile and careful patient selection. For a deeper dive into managing diabetes in other contexts, consider Metformin and Exercise: A Complicated Partnership in Type 2 Diabetes.

Comparing Maternal and Neonatal Outcomes

When comparing metformin and insulin in the management of GDM, the focus extends beyond just achieving target blood glucose levels. Maternal outcomes are a critical consideration. Metformin has consistently been associated with less maternal weight gain during pregnancy compared to insulin. This reduction in gestational weight gain is clinically meaningful, as excessive weight gain itself is an independent risk factor for adverse maternal and neonatal outcomes, including pre-eclampsia and macrosomia. Patients on metformin also report higher satisfaction with their treatment regimen, likely due to the convenience of an oral tablet versus daily injections. This improved adherence can translate into better overall glycemic control and, consequently, better outcomes. But, some patients treated with metformin may still require supplemental insulin to achieve optimal glucose control, particularly those with higher baseline glucose levels or more severe insulin resistance. The need for combination therapy highlights that metformin is not universally effective as monotherapy for all GDM patients.

Neonatal outcomes present a more complex picture. While both treatments aim to prevent macrosomia, the evidence suggests subtle differences. Metformin has been linked to a slightly lower incidence of neonatal hypoglycemia compared to insulin. This might be attributed to metformin's mechanism of action, which does not directly increase insulin levels, thereby reducing the risk of iatrogenic hypoglycemia in the neonate. But, some studies have reported a higher incidence of preterm birth in metformin-treated pregnancies, although this finding is not consistent across all research and requires careful interpretation. The clinical significance of this potential increase in preterm birth needs to be balanced against the benefits of reduced maternal weight gain and lower rates of neonatal hypoglycemia. The long-term implications of fetal exposure to metformin are also a subject of ongoing investigation. While short-term safety appears reassuring, data on neurodevelopmental outcomes and metabolic health in childhood and adolescence are still accumulating. This area of research is important for fully understanding the risk-benefit profile of metformin in pregnancy.

Adverse Event Profiles and Patient Selection

The adverse event profiles of metformin and insulin differ significantly. Metformin is commonly associated with gastrointestinal side effects, including nausea, vomiting, diarrhea, and abdominal pain. These symptoms are usually dose-dependent and can often be mitigated by starting with a low dose and titrating upwards slowly, or by taking the medication with food. But, for some patients, these side effects can be severe enough to warrant discontinuation of the drug. Lactic acidosis, a rare but serious complication of metformin, is a concern, particularly in patients with renal impairment. Therefore, careful assessment of renal function is essential before initiating metformin and throughout treatment. Insulin, on the other hand, is primarily associated with hypoglycemia and weight gain. Severe hypoglycemia can be a dangerous complication, requiring careful patient education on monitoring and management. The need for frequent glucose monitoring and dose adjustments with insulin can also be burdensome for patients. The choice between metformin and insulin, therefore, often involves a discussion of these distinct side effect profiles and patient preferences.

Patient selection is paramount in determining the optimal pharmacotherapy for GDM. Metformin is generally considered a suitable option for women with GDM who do not achieve glycemic targets with lifestyle modifications alone,

particularly those with a higher body mass index (BMI) or significant insulin resistance. It may be less appropriate for women with severe hyperglycemia at diagnosis, those with pre-existing renal impairment, or those who experience intolerable gastrointestinal side effects. Insulin remains the preferred choice for women with very high fasting or postprandial glucose levels, those with contraindications to metformin, or those who fail to achieve glycemic control on metformin monotherapy. The decision-making process should be individualized, taking into account the patient's clinical profile, comorbidities, preferences, and the potential risks and benefits of each treatment. Regular monitoring of both maternal and fetal well-being is essential, regardless of the chosen therapy. The Oxford Handbook of Endocrinology and Diabetes (4th ed) offers a practical reference for managing these complex decisions.

Long-Term Implications and Unanswered Questions

The long-term implications of GDM management extend beyond the immediate pregnancy. Both metformin and insulin aim to reduce the risk of adverse outcomes in the short term, but their impact on the mother's future risk of type 2 diabetes and the child's long-term metabolic health is an area of ongoing research. Women with a history of GDM have a significantly elevated risk of developing type 2 diabetes later in life, and effective management during pregnancy may influence this trajectory. For the offspring, exposure to hyperglycemia in utero increases their risk of obesity, metabolic syndrome, and type 2 diabetes in adulthood. Understanding how different pharmacotherapies might modulate these long-term risks is important for providing comprehensive care. The transplacental passage of metformin raises questions about its potential programming effects on fetal metabolism and development. While current data are largely reassuring, long-term follow-up studies are essential to fully elucidate any subtle effects on growth, body composition, and metabolic health in children exposed to metformin in utero. This includes careful monitoring for any potential impact on bone health or other developmental milestones. The ongoing surveillance of these cohorts will provide invaluable insights into the true safety and efficacy of metformin in this vulnerable population. The question of whether metformin's impact on maternal weight gain translates into a reduced risk of postpartum weight retention and subsequent type 2 diabetes for the mother also remains an active area of investigation. This is particularly relevant given the increasing prevalence of obesity and type 2 diabetes globally. Further research is needed to clarify these long-term effects and to refine current guidelines for GDM management. The role of continuous glucose monitoring (CGM) in GDM management is also evolving, offering tighter control and potentially better outcomes, as explored in CGM offers tighter glucose control for type 2 diabetes on dialysis.

> **CLINICAL IMPLICATIONS**
>
> The choice between metformin and insulin for gestational diabetes is not merely a matter of glucose numbers; it is a decision with distinct implications for maternal experience and neonatal outcomes. Metformin's advantage in reducing maternal weight gain and offering an oral option is compelling for many patients, enhancing adherence and satisfaction.
>
> But clinicians must remain vigilant regarding the potential for gastrointestinal side effects and the need for supplemental insulin in a subset of patients. The subtle differences in neonatal outcomes, particularly the lower incidence of hypoglycemia with metformin, warrant consideration, even as we acknowledge the ongoing questions about long-term fetal exposure.
>
> For European GPs and specialists, this means a more tailored approach to GDM management. Metformin

> can be a valuable first-line agent, especially for those with higher BMI, but it requires careful patient selection and thorough counseling on potential side effects and the possibility of needing combination therapy. Insulin remains the gold standard for severe hyperglycemia or when metformin is contraindicated or not tolerated. The goal is to optimize both short-term glycemic control and long-term health for mother and child. This requires an individualized approach, balancing efficacy, safety, patient preference, and the evolving evidence base. The conversation with patients should encompass all these factors, ensuring informed decision-making.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. 1. Yang Y, Lu X, Liu N, et al. Metformin decelerates aging clock in male monkeys. Cell. 2024;187(22):6358-6378.e29. doi:10.1016/j.cell.2024.08.021
2. 2. Dutta S, Shah RB, Singhal S, et al. Metformin: A Review of Potential Mechanism and Therapeutic Utility Beyond Diabetes. Drug Des Devel Ther. 2023;17:1907-1932. doi:10.2147/DDDT.S409373
3. 3. Triggle CR, Mohammed I, Bshesh K, et al. Metformin: Is it a drug for all reasons and diseases? Metabolism. 2022;133:155223. doi:10.1016/j.metabol.2022.155223
4. 4. Newman C, Dunne FP. Treatment of Diabetes in Pregnancy With Metformin. Obstet Gynecol. 2024;144(5):660-669. doi:10.1097/AOG.0000000000005705
5. 5. Hua Y, Zheng Y, Yao Y, Jia R, Ge S, Zhuang A. Metformin and cancer hallmarks: shedding new lights on therapeutic repurposing. J Transl Med. 2023;21(1):403. doi:10.1186/s12967-023-04263-8
6. 6. Drewe J, Foretz M, Krähenbühl S. Metformin-mechanisms of its glycemia-reducing effect. Pharmacol Rev. 2026;78(1):100106. doi:10.1016/j.pharmr.2025.100106

LICENCE & RIGHTS

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com