

REVIEW

Diabetes: how to manage gestational diabetes mellitus

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Abstract

Due to worldwide increases in obesity and average maternal age, the incidence of gestational diabetes mellitus (GDM) is increasing. The primary treatment of GDM is medical nutrition therapy but approximately 15–30% of individuals need pharmacotherapy to reach blood glucose goals to minimize the adverse consequences of hyperglycaemia. In the past, regular and neutral protamine Hagedorn insulin were the mainstays of pharmacological treatment for GDM due to their well-established safety; however, because they are administered as injections and require strict timing of doses and meals to minimize hypoglycaemia, alternatives are often sought. The research around the treatment of

GDM continues to evolve as insulin analogues and oral agents are studied in clinical trials. The short-term and long-term effects of treatment choices on both mothers and progeny are being evaluated, and this narrative review summarizes the current state of information available regarding the treatment of GDM.

Keywords: gestational diabetes, insulin, metformin, nutrition therapy, pregnancy.

Citation

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Introduction

Gestational diabetes mellitus (GDM) is defined by the World Health Organization as hyperglycaemia due to carbohydrate intolerance first identified during pregnancy with the exclusion of patients meeting criteria for type 2 diabetes mellitus (T2DM).¹ As global obesity rates and maternal ages at childbirth are increasing, the worldwide incidence of GDM is rising as well.^{2,3} In 2019, 1 in 6 births was affected by GDM, indicating that it is a significant international public health issue.⁴

Uncontrolled hyperglycaemia during pregnancy has potential deleterious effects on both the mother and child. Well-recognized maternal pregnancy-associated complications in individuals with GDM include a higher risk of preeclampsia and caesarean section.⁵ Higher rates of neonatal macrosomia, hyperbilirubinaemia, hypoglycaemia, shoulder dystocia and birth trauma during labour also occur in the offspring of individuals with uncontrolled blood sugars during pregnancy.⁵ Additionally, stillbirth is more common in pregnancies when maternal blood sugars are elevated.⁵ GDM also has potential long-term effects on both the mother and the child as 50% of those with a history of GDM develop T2DM in the subsequent 5–10 years, and children exposed to high blood sugars in utero have a higher risk of becoming obese as adults.⁴

Given the consequences of hyperglycaemia during pregnancy, optimally treating GDM once it has been diagnosed is imperative. Elevated maternal mean fasting blood glucose has been associated with an increased risk of obesity during the child's lifespan, and elevated postprandial blood sugars have been associated with an increased risk of complications during labour secondary to a large-for-gestational-age (LGA) fetus.⁵ Excessively low blood sugars are also problematic as maternal hypoglycaemia is associated with low fetal birth weight. Insufficient caloric intake and/or insulin levels can potentially lead to high levels of third trimester ketonaemia, which has been associated with impaired fetal brain development, primarily occurring in pregnant women with type 1 diabetes mellitus (T1DM) but also to a lesser degree in patients with GDM.^{6,7} Thus, optimal treatments should consistently control both fasting and postprandial blood glucose, minimize hypoglycaemia, and minimize ketonaemia. Medications that do not cross the placental barrier are advantageous as they are less likely to result in adverse fetal outcomes.

The general consensus based on expert opinion regarding blood glucose goals for patients with GDM is to aim for fasting and preprandial blood glucose less than 5.3 mmol/L (95 mg/dL), 1 hour postprandial blood glucose less than 7.8 mmol/L (140 mg/dL) and 2 hour postprandial blood glucose less than 6.4–6.7

mmol/L (115–120 mg/dL).^{2,5–8} Because excess weight gain can contribute to insulin resistance, several guidelines on GDM refer to guidelines from the National Academy of Medicine regarding desired weight gain during pregnancy.^{6,7,9} The recommendations for weight gain during pregnancy are based on prepregnancy body mass index (BMI) and are as follows: weight gain of 12.5–18 kg if mother is underweight (BMI <18.5 kg/m²), 11.5–16 kg if normal weight (BMI 18.5–24.9 kg/m²), 7–11.5 kg if overweight (BMI 24–29.9 kg/m²) and 5–9 kg if with obesity (BMI ≥30 kg/m²).^{6,9} The weight gain recommendations are based on limited data, especially in women with a BMI of >35 kg/m² and should not be used in a prescriptive manner.⁹

Notably, most people with GDM can control fasting and postprandial hyperglycaemia during pregnancy through changes in diet and lifestyle. About 15–30% of individuals with GDM need medications in addition to lifestyle modifications to reach target blood glucose levels.² For decades, various forms of insulin have been the mainstay of pharmacotherapy for GDM once lifestyle modifications are deemed insufficient to achieve control. However, insulin does have disadvantages, such as its primary modality of administration as an injectable, which requires education and resources to administer, and its ability to cause hypoglycaemia. At present, there are many insulin analogues available as well as oral agents that have been used to treat GDM. The goal of this narrative review is to summarize the available information related to the treatment of GDM.

Methods

An initial literature search of PubMed and Google Scholar through July 30, 2021, was conducted combining the search terms “gestational diabetes” and “guidelines”. The most recent guidelines from organizations specialized in diabetes mellitus and/or obstetrics published within the last 10 years were reviewed. Pertinent articles referenced in the guidelines were identified and reviewed. Secondary searches of PubMed and Google Scholar through August 30, 2021, using the search terms “gestational diabetes” combined with “metformin”, “sulfonylureas”, “acarbose” and “insulin” were used to identify medication-specific research trials. All abstracts of articles identified in the secondary searches were reviewed. All case reports, systematic reviews and clinical trials were assessed; articles that were included were the highest level of evidence for each medication. Review articles were evaluated if published within the past 2 years. Citations of identified articles were reviewed and pertinent references were also included. Information on ongoing clinical trials that were referenced in gathered articles was found using Google Scholar.

Review

Medical nutrition and lifestyle modification therapy

Although medical nutrition therapy, in conjunction with physical activity and/or weight management, is the first line in

treating GDM, there is limited data on the most effective ways to control blood glucose. An individualized approach to diet that is developed by a registered dietitian is recommended by several guidelines.^{5–7} In order to be successfully implemented, cultural eating habits should be considered. In general, carbohydrate intake should be controlled but sufficient to meet weight gain goals and avoid ketosis. Severe caloric restriction of less than 1500 calories per day is not recommended as it has been associated with elevated ketones.⁶ Carbohydrate intake should be about 35–45% of total caloric intake with a minimum of 175 g of carbohydrates per day.^{5–7} Distributing carbohydrates across three meals per day with snacks in between is often recommended to maintain stable blood sugars.^{5,6} If weight gain is occurring at a much greater rate than expected based on National Academy of Medicine guidelines, caloric intake may need to be reduced. Physical activity is safe for most pregnant individuals and moderate-intensity aerobic activity (e.g. walking, swimming or yoga modified for pregnancy) is recommended.¹⁰ Physical activity has been shown to lower blood glucose in small studies evaluating different combinations of aerobic, strength, stretching and balance exercises, but there is insufficient data to broadly recommend it as a treatment for GDM.^{6,11} Blood glucose levels and fetal movement should be monitored before and after exercising. Many pregnant individuals can safely exercise for 15–30 minutes daily; exercising after each meal is a common strategy to reduce postprandial hyperglycaemia.^{5,6} The decision to initiate physical activity should be an individualized decision based on the patient’s physical fitness, comorbid conditions and risk of pregnancy-related complications such as preeclampsia, preterm labour and placenta previa. If blood glucose is not controlled with a trial of medical nutrition therapy and/or other lifestyle modifications within 1–2 weeks, pharmacotherapy should be initiated.⁸

Pharmacological therapy

Insulins and oral therapies have been studied and used clinically in the management of GDM. The decision of which agent to initiate should be patient specific and evidence based. Table 1 summarizes pharmacological therapies that are currently recommended, including dosing recommendations, pregnancy-specific considerations, and recommendations during labour and delivery.

Insulin therapy

General considerations for initiation and monitoring

Similar to the many methods for initiating insulin in the general population, there are many ways to initiate insulin in individuals with GDM.¹² As with patients with newly diagnosed T2DM, levels of insulin resistance and insulin production in patients with newly diagnosed GDM are difficult to estimate. Estimating insulin needs during pregnancy is additionally challenging as insulin resistance progressively increases during each trimester due to pregnancy-related hormonal shifts. In contrast to insulin initiation in patients with T2DM for whom a single daily dose of

Table 1. Agents recommended for use in GDM.

Drug class	Drug	Dosing recommendations in GDM	Considerations during pregnancy	Labour, delivery and postpartum considerations
Insulin – typically considered first-line agents in GDM				
Rapid-acting insulin	Insulin lispro; insulin aspart	Insulin should be titrated to glycaemic goals and dosing individualized. For most, begin with a basal-bolus regimen ^{6,13} ; can consider initiating at 0.7 units/kg/day throughout the first trimester, increasing to 0.8 units/kg/day around weeks 14–18, increasing to 0.9 units/kg/day during weeks 26–27, and increasing to 1 unit/kg/day around weeks 36–37 until delivery ^{6,13} If NPH insulin is chosen as the basal insulin, two-thirds of the TDD can be given prebreakfast (in a 70:30 basal to bolus ratio) and one-third of the TDD can be given pre-evening meal (in a 50:50 basal to bolus ratio) ¹² If using long-acting basal insulin, 50% of the TDD can be given as basal insulin and 50% of the TDD can be split as premeal boluses ¹³ Selected patients with either elevated fasting blood glucose or elevated postprandial blood glucose, but not both, may be candidates for only basal insulin or only prandial insulin, respectively ⁵	Use of lispro and aspart are recommended by several guidelines ^{5–7,13,26} ; lispro has been studied retrospectively in large cohorts where aspart has prospective data available for a smaller group of patients ^{15,16}	Discontinue during labour and delivery ⁴⁵ Is not excreted in breastmilk; may restart postpartum if persistent hyperglycaemia is present ⁴⁵
Short-acting insulin	Regular insulin	Has longstanding safety data ⁸ ; consider risk of hypoglycaemia	During labour and delivery, used in insulin IV infusion protocols to optimize glycaemic control at moment of delivery ⁴⁵ ; discontinue immediately postpartum ⁴⁵ Is not excreted in breastmilk; may restart postpartum if persistent hyperglycaemia is present ⁴⁵	
Intermediate-acting insulin	NPH insulin	Has longstanding safety data ⁸ ; consider risk of hypoglycaemia	Discontinue during labour and delivery ⁴⁵ Is not excreted in breastmilk; may restart postpartum if persistent hyperglycaemia is present ⁴⁵	
Long-acting insulin	Insulin detemir, insulin glargine	Insulin detemir has greater evidence for use in GDM and supported by multiple international guidelines ^{5–7,13,26} ; use of insulin glargine is more controversial due to less evidence but is often used and may be safe ^{5–7,13,26}	Discontinue during labour and delivery ⁴⁵ Is not excreted in breastmilk; may restart postpartum if persistent hyperglycaemia is present ⁴⁵	
Oral agents – typically considered second-line or alternative first-line agents for patients who are not good candidates for insulin therapy				
Biguanide	Metformin	Initiate at 500 mg once or twice a day with food ³² ; increase every 1–2 weeks to meet glycaemic goals, up to a maximum of 2,500 mg ³²	Long-term safety data, particularly effects on offspring after exposure are limited, show some risk or are controversial ^{7,28}	Discontinue during labour and delivery ⁴⁵ Drug is excreted into breastmilk in small amounts ^{27,44,52,53} ; likely safe to use postpartum in lactating mothers ^{27,44,52,53}
Sulfonylurea	Glyburide	Initiate at 2.5 mg once or twice a day with food ⁴⁵ ; increase gradually to meet glycaemic goals, up to a maximum of 10 mg twice daily ⁴⁵	Associated with increased risk of adverse fetal outcomes compared to insulin and metformin ^{6,7,27,45} ; additionally, long-term safety data are lacking ^{7,49}	Discontinue during labour and delivery ⁴⁵ Drug is excreted into breastmilk in small amounts ⁵³ ; likely safe to use postpartum in lactating mothers ^{45,53}

GDM, gestational diabetes mellitus; NPH, neutral protamine Hagedorn; TDD, total daily dose.

basal insulin is usually recommended, guidelines for patients with GDM recommend initiating with basal-bolus insulin regimens that simulate physiological insulin secretion.^{6,12} This is because the risk of immediate harm due to hyperglycaemia during pregnancy is well documented, so achieving blood glucose control quickly is prioritized during the relatively shorter time span of pregnancy. Selected patients with either elevated fasting blood glucose or elevated postprandial blood glucose, but not both, may be candidates for only basal insulin or only prandial insulin, respectively.⁵ Adjustments to insulin can be made every 3 days and frequent blood glucose testing is especially important during the titration period. Frequent premeal, postprandial and prebedtime blood glucose testing may be cumbersome for patients but is important to reach blood glucose goals and minimize hypoglycaemia. Continuous glucose monitoring, if available, should be considered as it has been associated with reduced infant macrosomia and may identify out-of-range blood glucose values more readily with fewer finger sticks.¹³ Hypoglycaemia unawareness is seldom an issue for those with GDM as it more commonly occurs in the first trimester, and GDM is more commonly diagnosed during the second trimester.¹⁴ In most patients with GDM, low blood sugars can be recognized and treated immediately as long as education is provided and patients are prepared.

Notably, regular insulin and neutral protamine Hagedorn (NPH) insulin were the first insulins to be used during pregnancy and have longstanding safety data in humans. They are not without disadvantages in comparison to newer insulin analogues. Due to regular insulin's slower onset of action and longer duration in comparison to rapid-acting insulins, it is less convenient to use because it requires administration 30 minutes before a meal. NPH insulin, an intermediate-acting basal insulin, generally requires two injections for daily coverage, unlike other longer-acting basal insulins that can be administered once daily. Additionally, NPH insulin peaks around 4–8 hours, which can cause hypoglycaemia overnight or if midday meal timing is shifted. Thus, evaluating the risks and benefits of available insulin analogues during pregnancy is warranted.

Rapid-acting insulin analogues

Of the rapid-acting insulins, insulin lispro and insulin aspart are considered safe due to available data comparing them to regular insulin in individuals with pre-existing diabetes and GDM during pregnancy. Use of insulin lispro has been studied retrospectively, whereas insulin aspart has been studied prospectively in 322 pregnant women with T1DM.¹⁵ Insulin aspart was shown to have equal efficacy and less hypoglycaemia in comparison to regular insulin. Despite a lack of prospective data, the combined retrospective trials for insulin lispro evaluated 1265 pregnancies and demonstrated its safety.¹⁶

The safety during pregnancy of insulin glulisine is less clear in comparison to insulin lispro and insulin aspart. Insulin glulisine use during pregnancy was evaluated in a systematic review, which combined data from pharmaceutical company-sponsored studies, case reports in the literature

and postmarketing data. Of the 303 pregnancy exposures, the analysis of the data did not suggest a causal association between insulin glulisine use and congenital malformations.¹⁷ Additionally, a small randomized clinical trial of 16 women with GDM comparing NPH insulin to insulin glulisine was conducted.¹⁸ The mean gestational age of the women was 30.3 weeks and they were followed until delivery. There was no difference between NPH insulin and insulin glulisine regarding the primary endpoint of postprandial blood glucose lowering, but the study was not adequately powered to detect a difference in pregnancy complications.¹⁸

Basal insulin analogues

Of the basal insulins, insulin detemir has the most safety data in pregnancy. In cell line studies, its low affinity to type 1 insulin growth factor (IGF1) receptors indicates that it has a low risk of adversely affecting embryonic transplantation; this finding was replicated in animal studies.^{15,19} Additionally, in a prospective multicentre trial in 310 patients with T1DM during pregnancy, insulin detemir was statistically non-inferior to NPH insulin with respect to glycosylated HbA1c at 36 gestational weeks and hypoglycaemia.¹⁹

There is a lack of consensus on the use of insulin glargine for the treatment of GDM. One consideration when evaluating safety is whether a medication crosses the placenta. Reassuringly, none of the currently available insulins have been shown to be transferred across the placental barrier, and this information has been used by some to support the safety of all available insulins.⁷ Although insulin glargine does not reach the fetus, *in vitro* data indicate that insulin glargine has the potential to adversely affect embryonic implantation.¹⁵ In general, this is more of a theoretical concern for women with pre-existing diabetes mellitus, and less so for individuals with GDM as a diagnosis of GDM is typically made after the first trimester. At present, there are no randomized controlled trials comparing insulin glargine to other basal insulins during pregnancy. However, several retrospective and prospective observational studies have been published comparing insulin glargine to NPH insulin and/or insulin detemir during pregnancy, supporting its safety and efficacy in both fetal and maternal outcomes.²⁰ In an observational prospective study comparing insulin glargine and NPH insulin that included 82 patients with GDM, patients on insulin glargine had lower rates of maternal and fetal complications.²¹ Maternal complications evaluated included hypoglycaemia, new-onset hypertension and albuminuria. Neonatal complications evaluated included jaundice and congenital malformations. Similarly, a meta-analysis of eight observational cohort studies in 702 women with pre-existing DM or GDM found no statistical differences between insulin glargine and NPH insulin when evaluating maternal outcomes, such as new-onset hypertension, pre-eclampsia and caesarean section, and neonatal outcomes such as birth weight and respiratory distress.²²

The safety during pregnancy of insulin degludec is less certain due to limited data in humans. The published data in women

during pregnancy on insulin degludec are limited to case reports in patients with T1DM and T2DM.^{23–25} No maternal or fetal harm was caused by insulin degludec in these case reports.

Summary of recommendations on insulin according to guidelines

To summarize, insulin lispro, insulin aspart and insulin detemir are recommended by multiple guidelines as safe for use during pregnancy for GDM.^{5,6,7,13,26} The United Kingdom's National Initiative for Health and Care Excellence (NICE) recommends insulin lispro and insulin aspart but preferentially recommends NPH insulin as the basal insulin of choice.⁸ Recommendations on insulin glargine use for GDM vary. Based on available data in humans, insulin glargine is recommended for use during GDM by several international guidelines, including the American College of Obstetricians and Gynecologists (ACOG), the American Diabetes Association (ADA) and Diabetes Canada.^{5,7,26} In contrast, the NICE guidelines recommend insulin glargine during pregnancy only in someone with pre-existing diabetes and good glycaemic control as changing insulin could worsen control and hyperglycaemia is known to result in adverse outcomes.⁸ Other guidelines, such as those from the International Federation of Gynecology and Obstetrics (FIGO) and the American Association of Clinical Endocrinologists (AACE), do not provide a recommendation for the use of insulin glargine due to the limited studies published; they acknowledge that it is often used and may be safe.^{6,13}

Once the type of insulin has been chosen, the initial insulin dose needs to be determined. One recommended method of insulin titration for pregnant individuals (with GDM or pre-existing DM) is to use a total daily dose (TDD) of 0.7 units/kg/day throughout the first trimester, increasing to 0.8 units/kg/day around weeks 14–18, to 0.9 units/kg/day during weeks 26–27, and to 1 unit/kg/day around weeks 36–37 until delivery.^{6,13} If using long-acting basal insulin, 50% of the TDD can be given as basal insulin and 50% of the TDD can be split as premeal boluses.¹³ If NPH insulin is chosen as the basal insulin, two-thirds of the TDD can be given prebreakfast and one-third of the TDD can be given pre-evening meal; the ratios of basal to bolus insulin in the morning and evening are recommended as 70:30 and 50:50, respectively.¹² If night-time hypoglycaemia occurs when the NPH insulin is administered pre-evening meal, the evening dose can be administered at bedtime instead.

Oral therapy

Metformin

Metformin is typically considered a second-line alternative for GDM.^{5,7} Metformin is an attractive option especially when compared to insulin as it is considered easier to administer and more affordable.² It also has advantages from a mechanistic perspective, as GDM is typically associated with an increase in insulin resistance particularly seen in the second half of

pregnancy.²⁷ One disadvantage compared to insulin is that metformin crosses the placenta ubiquitously, reaching fetal concentrations that are as high or even higher than maternal concentrations.^{5–7,28} In contrast, insulin does not reach the placenta.^{2,28} Despite its ability to cross the placental barrier, metformin is commonly continued during the first trimester of pregnancy in patients with polycystic ovary syndrome and has been shown to be safe.^{29,30} During the first trimester, the embryo at that age has few organic cation transporters needed to transport metformin into the cells.²⁸ However, during the second and third trimesters, the placenta and fetus do have the necessary metformin transporters. This results in concerns over safety of metformin use in this gestational age.²⁸ Several studies and meta-analyses have been conducted investigating the safety and efficacy of using metformin throughout the duration of pregnancy for GDM.

When treating GDM, an advantage seen with metformin is its improvements in both neonatal and maternal outcomes during pregnancy and labour. In two separate network meta-analyses, metformin was determined as being more effective than insulin and glyburide at reducing the risk of neonatal hypoglycaemia, macrosomia, preeclampsia, pregnancy-induced hypertension, LGA neonates, and admission to the neonatal intensive care unit (NICU).^{27,31} In other studies, when compared to insulin, there is less maternal hypoglycaemia, maternal weight gain, pregnancy-induced hypertension, neonatal hypoglycaemia, low infant birth weight, neonatal LGA, macrosomia, and NICU admission.^{2,7,27,32–38} The most recent evidence is from the 2021 Metformin for Gestational Diabetes Study (MeDiGes) conducted in 200 patients with GDM, which reinforces these findings showing less hypoglycaemia, better postprandial glycaemic values for lunch and dinner, less weight gain, fewer labour inductions, and fewer caesarean sections with metformin compared to insulin.³⁹ The MeDiGes trial found similar rates of mean birth weight, macrosomia, LGA infants and infant complications between both groups.³⁹ Some studies, including a large meta-analysis of over 4000 patients, have found higher rates of smaller-for-gestational-age neonates in patients receiving metformin *versus* insulin.³⁶ When metformin is compared to glyburide, there is a decrease in the composite of neonatal death or serious morbidity.²⁷ Limited evidence suggests that metformin may be helpful in preventing preeclampsia,² though other studies have not found this.³⁶ There is also conflicting evidence regarding whether metformin increases the risk of preterm birth with several studies showing increased risk compared to insulin^{27,28,32,40} but a large meta-analysis showed no difference.⁴⁰

The long-term adverse events of metformin have been assessed in several studies, which found offspring exposed to metformin to generally be heavier; between the ages of 4 and 10 years, these offspring have a higher BMI, waist-to-height ratio, weight-to-height ratio, waist circumference and incidence of obesity.^{7,28} These long-term consequences were first noted in the Auckland subgroup of the Metformin *versus* Insulin

for the Treatment of Gestational Diabetes (MiG) trial; women treated with metformin were found to have offspring that were heavier at 9 years of age, despite having fewer LGA neonates when compared to women treated with insulin.^{28,32} Differences in childhood weight were seen in one study as early as 18 months in children exposed to metformin in utero, who were found to be heavier and taller than those exposed to insulin.⁴¹ A meta-analysis of 778 children found that, at 9 years old, children exposed to metformin in utero had higher body weights but comparable BMI z-scores to controls.⁴² Additionally, a 2019 meta-analysis with 3976 participants demonstrated that, although the infants born to women on metformin have lower average birth weights compared to those born to women on insulin, they seem to then have accelerated growth, resulting in heavier weight and higher BMI in mid-childhood.⁴³ More long-term data are needed to fully understand these risks. Currently, the data on long-term consequences of in utero exposure to metformin are limited to childhood. For mothers continuing metformin postpartum and breastfeeding, metformin is known to cross into breastmilk but the amount is considered clinically insignificant with the infant only receiving 0.5–0.65% of the mother's weight-adjusted dose.^{27,44}

A barrier to metformin use is its limited ability to provide the tight glycaemic control required when managing GDM. Insulin has the advantage of allowing incremental dose adjustments and does not have a dose ceiling, allowing clinicians and patients to optimize glycaemic levels with dose titrations and close monitoring. Metformin is limited by its available doses and maximum daily dose. Patients, especially in mid to late pregnancy, will experience a significant increase in renal clearance of metformin due to the increased renal blood flow in pregnancy.²⁷ This may result in reduced efficacy and the need for higher doses to achieve glycaemic control.²⁷ Some have suggested higher maximum daily doses of 2500–3000 mg in GDM but evidence supporting use over 2500 mg is limited.^{27,45} A common dosing strategy for metformin in GDM follows the MiG trial, starting at 500 mg once or twice a day with food.³² Metformin is then increased every 1–2 weeks to meet glycaemic goals to a maximum of 2500 mg.³² If glycaemic goals are not met at maximum dosages, patients should be switched or supplemented with insulin. In the MiG trial, 46% of patients failed to reach goal glycaemic values on metformin alone and required supplemental insulin.³² Other studies have seen failure rates that range from 21.3% to 85%.^{6,39,46} Due to this high failure rate, it may be prudent to initiate a patient on insulin at the onset rather than delay achieving optimal glycaemic control with a trial of metformin. However, at least one small study has shown benefits for starting the patient on metformin and switching to insulin if needed compared to starting with insulin alone.⁴⁶ These benefits included less maternal weight gain, pregnancy-induced hypertension, hypoglycaemia, and NICU admissions of more than 24 hours.⁴⁶ Newer studies are attempting to identify risk factors for metformin failure, including higher fasting glucose at diagnosis, early detection

of GDM, past history of GDM, older age at diagnosis, higher baseline HbA1c or serum fructosamine concentration, and elevated BMI.^{6,27}

The recent Metformin in Women with Type 2 Diabetes in Pregnancy (MiTy) trial investigated the combination of metformin with insulin compared to insulin alone.⁴⁴ This combination is of benefit to those who may otherwise fail treatment with metformin alone. The theoretical advantage of this combination over insulin alone would be to improve the insulin resistance that is known to occur in GDM, therefore lowering insulin requirements, reducing maternal weight gain and improving outcomes. The MiTy trial found benefit in the combination group compared to insulin alone.⁴⁴ The maternal benefits included improved glycaemic control, less insulin requirements, less maternal weight gain, and less caesarean births in the combination group than insulin alone.⁴⁴ Infants who were exposed to metformin weighed less at birth, were less likely to be LGA, and had reduced adiposity measures.⁴⁴ There is an ongoing follow-up trial, MiTy Kids, to determine the effects of maternal combination therapy during GDM on the 2-year-old children of participants of the MiTy trial, which may shed further light on the long-term effects of metformin on offspring.⁴⁷

It should be noted that there have been at least three trials investigating if metformin is effective at preventing the development of GDM in women starting in early pregnancy (first or early second trimester) and continuing through birth.⁴⁸ All three of the trials had non-statistically significant findings and conclude that metformin is not effective at preventing GDM.⁴⁸

To summarize, the evidence suggests that metformin is as safe and effective as insulin in the short term, and may even have some additional advantages like preventing pre-eclampsia.^{2,33} However, the long-term follow-up is limited or points to some potential risks of metformin use for the offspring such as higher BMI between the ages of 4 and 10 years.^{7,28} International guidelines offer different approaches to the use of metformin in GDM. The ADA, AACE and ACOG agree that metformin should be considered as an alternative for women who refuse insulin, are unable to afford insulin, or cannot safely use insulin (such as those at high risk for hypoglycaemia, difficulty with administration or comprehension, or cultural barriers).^{5,7,13} The FIGO, NICE and Diabetes Canada clinical practice guidelines suggest that metformin can be safely used in patients not meeting glycaemic goals after medical nutrition therapy.^{6,8,26} FIGO specifies that insulin is preferred over metformin in women who are at high risk for failing oral therapy.⁶ Despite evidence, albeit limited, demonstrating that metformin may reduce the risk of pre-eclampsia, the ADA currently does not recommend the use of metformin in pregnant patients with hypertension, pre-eclampsia or at risk for intrauterine growth restriction as it may increase the risk of acidosis or growth restriction.⁷ Until the potential risk of metformin exposure in offspring is better understood, insulin will likely remain the gold standard.

Sulfonylureas

Sulfonylureas (SUs), in particular glyburide or glibenclamide, have been investigated as treatment options for GDM. In general, the use of SUs is largely limited by concerns over the potential of these drugs to cross the placenta, causing neonatal hypoglycaemia and macrosomia.^{7,49} Of the second-generation SUs, glyburide has the least placental transfer with in vitro studies demonstrating a less than 1% transfer rate when using doses of over 100 times the approved doses.¹⁵ There is also a higher rate of maternal hypoglycaemia with SUs compared to insulin.⁵⁰ Studies have shown that glyburide is associated with higher birth weight and significantly increased rates of neonatal hypoglycaemia and macrosomia compared to insulin or metformin.^{6,7,27,45} Additionally, there is no long-term safety data currently available.^{7,49} Glyburide has been shown to have less treatment failures, defined as patients requiring insulin, than metformin.^{49,50} It is important for both clinicians and patients to note that serum concentrations of glyburide typically peak at 2–3 hours post dose.⁴⁵ Self-monitoring of blood glucose should coincide with this peak. If monitoring is performed prematurely, blood glucose values can look elevated 1–2 hours postprandially.⁴⁵ Clinicians may be tempted to increase the dose of glyburide based on these values, placing the patient at an increased risk of hypoglycaemia.⁴⁵ Due to the increased risk of adverse fetal outcomes compared to insulin and metformin, and the lack of long-term data, SUs are not a preferred agent in GDM.

Acarbose

At least one small study was conducted exploring acarbose *versus* insulin for the treatment of GDM.⁵¹ The results indicated that there was no difference in fetal and maternal outcomes compared to insulin but there were more GI adverse events.⁵¹ Similar to the other oral agents, long-term outcomes for oral agents like acarbose have not been established. Due to the limited data overall, acarbose is not typically recommended for the treatment of GDM.

Other non-insulin DM medications

Other commonly used DM medication classes, such as the dipeptidyl peptidyl 4 (DPP4) inhibitors, sodium–glucose co-transporter type 2 (SGLT2) inhibitors and the glucagon-like peptide 1 (GLP1) receptor agonists, currently have no published data on their use during pregnancy.

Labour, delivery and postpartum considerations

Table 1 includes recommendations related to the use of agents during labour and delivery. Patients with GDM treated with pharmacological therapy but in good glycaemic control should consider the induction of delivery around 39 weeks of gestation.^{2,6,45} Recommendations for delivery timing for patients with poor glycaemic control are debated, with a range within 37–39 weeks gestation being recommended.⁴⁵ The

presence of other conditions or complications, like gestational hypertension or fetal macrosomia, can alter delivery timings.^{6,45} During labour, patients should have frequent (every 1–4 hours) monitoring of blood glucose.⁴⁵ Most patients will not require treatment once labour begins and all agents should be discontinued.^{2,13} If blood glucose exceeds 7 mmol/L (126 mg/dL) fasting or 11.1 mmol/L (200 mg/dL) postprandial during labour, an insulin infusion protocol with monitoring every hour can be started during the intrapartum phase.^{2,45} Insulin protocols can vary by institution and guideline but include an infusion of insulin in 5% dextrose or 0.9% normal saline solution aimed to optimize glycaemic control at moment of delivery.⁴⁵ Being euglycaemic at delivery is important for preventing complications, including neonatal hypoglycaemia at birth.⁶ If not already discontinued, all agents (including insulin) should be discontinued postpartum.⁴⁵ If hyperglycaemia persists immediately postpartum, medical nutrition therapy, lifestyle modifications or insulin can be used without concern for neonatal side effects in lactating mothers.⁴⁵ Insulin should be restarted at a lower dose, such as 0.55 units/kg/day.¹³ Additionally, AACE recommends that the night-time basal insulin dose should be decreased by 50% in lactating women to prevent severe hypoglycaemia.¹³ Metformin and glyburide are excreted into breastmilk in small amounts.^{52,53} Although data are limited, most studies conclude that the benefits of these agents outweigh any potential risks to the nursing infant, though monitoring is always prudent.^{45,52,53} Guidelines from AACE and FIGO still advise against the use of metformin and glyburide in lactating mothers.^{2,13} Patients with a history of GDM should be screened for T2DM 6–12 weeks postpartum.^{2,6,15,45}

Discussion

For most patients with GDM, medical nutrition therapy paired with lifestyle modifications to reduce insulin resistance will be sufficient to reach blood glucose goals. For patients who need pharmacotherapy, insulin remains the standard of care for most patients with GDM due to its established safety and efficacy profile. Regular insulin and NPH insulin have the most data supporting their use but have disadvantages compared to newer analogues due to their administration timing and risk of hypoglycaemia. Of the analogues, insulin lispro, aspart and detemir have the most data supporting their use and are recommended by several international guidelines. Although insulin is the safest under ideal circumstances, not all patients are in ideal circumstances. Clinicians need to weigh individual patient characteristics, ability and support to manage a complex insulin regimen. Important considerations when determining if a patient is an appropriate candidate for insulin can include the cost, a patient's level of comprehension and health literacy, ability to administer and understand insulin, ability to understand the role of diet and activity levels, dexterity, access to refrigeration, access to healthcare provider for titration, and risk of hypoglycaemia. Many of these barriers

can be overcome with education accompanied with provider and family support but, for those with substantial challenges, oral agents should be considered. For oral agents, metformin would be the best option due to its demonstrated benefits for maternal and fetal outcomes with good short-term safety data. Patients who may be candidates for metformin use over insulin include patients who refuse to use insulin, whose circumstances make it difficult to use insulin safely, and who cannot afford insulin. If metformin is used, monitoring is critical due to the number of patients that require additional therapy to meet therapeutic goals.

Conclusion

The management of GDM has advanced subsequent to studies evaluating the efficacy of metformin, glyburide and several insulin analogues. Additional research is still needed to determine the long-term adverse events in offspring before metformin is recommended more widely. Future research illuminating the safety and benefits of combination insulin and metformin therapy is intriguing and has the potential to change practice guidelines if the long-term safety of metformin is established.

Key practice points

- Uncontrolled hyperglycaemia in individuals with gestational diabetes mellitus (GDM) has adverse outcomes on both the mother and the fetus.
- Treatment for GDM should consistently control both fasting and post-prandial blood glucose, minimize hypoglycaemia and minimize ketonaemia.
- Blood glucose goals for patients with GDM are to aim for fasting and pre-prandial blood glucose less than 5.3 mmol/L, 1 hour post-prandial blood glucose less than 7.8 mmol/L and 2 hour post-prandial blood glucose less than 6.7 mmol/L.
- Most women with GDM can reach blood glucose goals via lifestyle modifications, primarily by adjusting carbohydrate intake to approximately 40% of total caloric intake.
- Close blood glucose monitoring throughout pregnancy is essential to minimize GDM-associated complications and make timely adjustments in treatment.
- About one-fifth of individuals with GDM will need pharmacotherapy to reach blood glucose goals.
- Basal-bolus insulin remains the standard of care when initiating pharmacotherapy for GDM.
- Insulin lispro, insulin aspart and insulin detemir are the insulin analogues with the most safety data in the treatment of GDM.
- In selected patients, metformin may be an option for treatment of GDM, either as monotherapy or in combination with insulin to minimize maternal weight gain.
- Studies are needed to better clarify the long-term effects of metformin use in GDM on offspring.

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