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THERAPIES AND NEW TECHNOLOGIES IN THE TREATMENT OF DIABETES (M PIETROPAOLO, SECTION EDITOR)

The Use of Non-insulin Agents in Gestational Diabetes: Clinical Considerations in Tailoring Therapy

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Abstract

Purpose of Review To assess evidence to date for use of non-insulin agents in treatment of gestational diabetes mellitus.

Recent Findings There has been increasing interest in the use of non-insulin agents, primarily metformin and glyburide (which both cross the placenta). Metformin has been associated with less maternal weight gain; however, recent studies have shown a trend toward increased weight in offspring exposed to metformin in utero. Glyburide has been associated with increased neonatal hypoglycemia.

Summary Glycemic control during pregnancy is essential to optimize both maternal and fetal outcomes. There are a myriad of factors to consider when designing treatment programs including patient preference, phenotype, and glucose patterns. While insulin is typically recommended as first-line, some women refuse or cannot afford insulin and in those cases, non-insulin agents may be used. Further studies are needed to assess treatment in pregnancy, perinatal outcomes, and particularly long-term metabolic profiles in mothers and offspring.

Keywords Gestational diabetes · Pregnancy · Impaired glucose tolerance · Hyperglycemia · Diabetes mellitus · Perinatal outcomes

Introduction

Recent estimates suggest over 16.9% of women develop hyperglycemia in pregnancy [1] and there is ongoing interest in determining the safest and most effective means of treatment of gestational diabetes (GDM) [2]. It is well established that treatment of hyperglycemia in pregnancy is associated with improvement in maternal and fetal outcomes [3•, 4•, 5, 6]. Insulin has long been considered the first-line pharmacotherapy since it is effective and does not cross the placenta [3•, 4•]. However, in recent years, the use of non-insulin medications has become increasingly popular [7–9]. The two major non-insulin agents used for treatment of GDM include metformin and glyburide (a sulfonylurea medication also known as glibenclamide). There has been debate among experts as to whether the use of some oral agents, particularly metformin, should be considered as a reasonable alternative to insulin [3•, 4•, 10, 11].

There is a major research gap in the pharmacologic management of gestational diabetes (GDM) with little data on placental transfer of oral glucose-lowering medications, effects on perinatal outcomes, and effects on the long-term metabolic profile of both mothers and offspring [2]. There are some patients for whom oral agents may be appropriate for glycemic control, particularly if insulin is not affordable, the patient refuses insulin treatment, or the patient cannot safely use insulin due to physical or cognitive limitations.

Lifestyle Modification

For about 70 to 80% of women diagnosed with GDM, lifestyle measures such as changing dietary intake and engaging

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in physical activity are sufficient to achieve glycemic control [4•]. Lifestyle measures are an important foundation on which pharmacologic therapy can be added if necessary [12, 13]. All women with GDM should ideally be referred to a registered dietician [12]. As well, the healthcare team caring for a woman with GDM should be aware of Institute of Medicine (IOM)'s recommendations for appropriate weight gain during pregnancy (Table 1) [14].

Nutrition

While nutrition is a key part of GDM treatment, it has not been definitively proven that a certain type of dietary intervention is superior. In general, guidelines recommend moderate carbohydrate intake (175 g per day over 3 meals and 2 snacks, one of which should be at bedtime) [15]. However, there is increasing evidence that diets emphasizing low glycemic index (GI) foods seem to have benefit [15]. The glycemic index is used to estimate the blood glucose response to the intake of a food item (food items with higher GI values cause a greater increase in blood glucose) [16]. In a meta-analysis that included 4 low GI trials, there were decreases in fasting and postprandial glucose compared with control [13]. A systematic review found lower rates of large for gestational age (LGA) infants [17] and another meta-analysis showed decreased risk of macrosomia [18].

In practice, we recommend a lower GI diet by avoiding "white foods" (e.g., white bread, pasta, white rice). We also recommend that snacks and meals include both carbohydrate as well as protein and/or fat rather than carbohydrates alone. We find that encouraging a high-protein, high-fat bedtime snack, such as almonds or cheese, seems to provide benefit for women with elevated fasting blood glucose values.

Physical Activity

Engaging in physical activity is an important aspect of managing GDM. Numerous studies have shown that physical activity interventions have been associated with reduction in insulin use and/or improvement in glycemic control [19]. Evidence supports encouraging physical activity unless patients have an obstetrical contraindication. The American College of Obstetricians and Gynecologists recommends that women engage in moderate intensity aerobic exercise for 30 minutes per day, 5 times per week (or 150 minutes weekly) during pregnancy [3•].

Walking is an excellent activity since it is low-impact and safe during pregnancy, does not require a substantial level of fitness, and can be done indoors or outdoors. One study published in 2017 particularly illustrated the benefits of walking after eating [19]. In our clinic, we often counsel women to try to walk for even 10 to 20 minutes after meals. This approach

Table 1 Lifestyle modifications in gestational diabetes mellitus

	Physical Activity	Dietary Approach	Gestational Weight Gain in Second and Third Trimesters
Guidelines (ACOG and/or IOM)	Moderate intensity aerobic exercise for 30 minutes/day, 5 times/week (or 150 minutes weekly) unless obstetrical contraindication [3]	175 grams of carbohydrates per day over 3 meals and 2 snacks [3]	IOM recommendations based on pre-pregnancy weight*: • Normal weight: 25-35 lbs total, ~1 lb/week • Overweight: 15-25 lbs total, ~0.6 lbs/week • Obese: 10-20 lbs total, ~0.5 lbs/week [14]
Key research findings	Walking after meals lowers postprandial glucose levels [19]	Low glycemic index associated with lower fasting and postprandial glucose levels, lower risk of LGA infants, less macrosomia [13, 17,18]	Obesity associated with increased risk of maternal and fetal complications (including congenital anomalies, pre-eclampsia, stillbirths) [27]
Our clinical approach	Recommend walking (even if only for 10-20 minutes) after meals	• Recommend a combination of carbohydrate and protein and/or fat in snacks and meals (not carbohydrates alone) • High protein, high fat bedtime snack can be helpful for women with elevated fasting blood glucoses	• Refer women with overweight and obesity to registered dietician • Inform women of weight gain recommendations

* Normal weight is defined as a body mass index (BMI) of 19–24.4 kg/m^2. Overweight is defined as a BMI of 25–29.9 kg/m^2. Obesity is defined as a BMI of ≥ 30 kg/m^2

Abbreviations: *lb*, pound; *ACOG*, American College of Obstetricians and Gynecologists; *IOM*, Institute of Medicine; *LGA*, large for gestational age

can help lower postprandial glucose and keep levels in target range.

Gestational Weight Gain

The IOM recommendations for weight gain during pregnancy depend on the pre-pregnancy weight category [14] (Table 1). Informing patients of these recommendations and monitoring weight gain throughout pregnancy can be quite useful, in addition to referral to a registered dietician for overweight or obese women.

Metformin

The role of metformin for treatment of GDM is controversial. Several guidelines including those of Society of Maternal-Fetal Medicine (SMFM), the National Institute for Health and Care Excellence (NICE) of the United Kingdom, and Diabetes Canada recommend metformin as a first-line option along with insulin [11, 15, 20]. However, other guidelines including the American Diabetes Association (ADA) and American College of Obstetricians and Gynecologists (ACOG) exclusively recommend insulin as a first-line pharmacotherapy [3•, 4•].

Mechanism of Action

Metformin is a biguanide and decreases glucose production from the liver (gluconeogenesis) and promotes glucose uptake by peripheral tissues [21]. It has multiple other mechanisms that are not fully understood, including suppression of mitochondrial respiration [21]. Metformin crosses the placenta during pregnancy. Barbour and colleagues note in their 2019 commentary that the embryo has few mitochondria during early gestation, and low levels of organic cation transporters that transport metformin into cells, making metformin likely safe in early pregnancy [10].

Possible Benefits

Metformin is a generic, affordable medication. Since it is an oral medication, it is relatively simple to take properly and well accepted by patients [22]. It is very unlikely to cause hypoglycemia.

Meta-analyses have found decreased risk of neonatal hypoglycemia, LGA babies, pregnancy-induced hypertension, and maternal weight gain when comparing metformin with insulin [23–26]. As there are multiple adverse outcomes for both women and fetuses secondary to maternal obesity [27], decreased maternal weight gain is of interest, although the data have not demonstrated large absolute differences in weight. For instance, in a study in which 94 women were randomized to insulin or metformin, women on metformin gained an average of 0.53 ± 2.52 kg compared with women on insulin who gained an average of 2.3 ± 2.77 kg ($p = 0.002$) [28].

There have been several studies examining the effect of metformin on pregnancy complications in women with polycystic ovarian syndrome (PCOS) which show possible benefits. In 2019, the PregMet 2 trial results were published, demonstrating a trend toward fewer late miscarriages and preterm births in women with PCOS who were treated with metformin compared with those treated with placebo during pregnancy (odds ratio (OR) 0.50, 95% CI 0.22–1.08, $p = 0.08$) [28]. Interestingly, there was no difference in the secondary outcome of incidence of GDM. In a post-hoc analysis of 3 trials including PregMet 2, metformin significantly decreased the risk of late miscarriage or preterm delivery (OR 0.43, 95% CI 0.23–0.79, $p = 0.004$).

Possible Risks

Several studies and meta-analyses have found an increased risk of preterm delivery in women taking metformin compared with insulin, including the Metformin in Gestational diabetes (MiG) trial of 751 women [22, 26]. However, not all studies and meta-analyses demonstrate an increased risk (including a meta-analysis that also included women with type 2 diabetes) [24, 25].

Since metformin does cross the placenta, it could have long-term effects on offspring exposed to metformin in utero. Two recent studies have addressed this issue by analyzing the offspring of women who took metformin during pregnancy after several years of follow-up. The Metformin in Gestational diabetes: the offspring follow-up (MiG TOFU) study compared the offspring of 2 cohorts of women with GDM who were randomized to metformin (and supplemental insulin if needed) or insulin for treatment [30••]. In this study, offspring of women included in the trial were assessed at either 7 or 9 years of age. Two-hundred and eight children were assessed (28% of the original cohort). In the 7 year cohort, there were no differences in offspring measures including body size measurements, imaging findings on dual-energy X-ray absorptiometry or abdominal magnetic resonance imaging, or fasting blood tests. In the 9 year cohort, metformin offspring had significantly larger arm and waist circumferences, waist to height ratios, and triceps skinfold. Other measures were not statistically significantly different.

Another study examined offspring of women with PCOS who were randomized to metformin or placebo during the pilot and full PregMet study [31••]. Of the participants, 22.8% of women in the metformin group and 32.2% of women in the placebo group had GDM based on a 75-gram oral glucose tolerance test (OGTT). There were 182 children (of 292) who were analyzed at 4 years of age, and those who were exposed to metformin had a higher body mass index (BMI;

difference in z score = 0.45, 95% CI 0.11–0.78, $p = 0.010$) compared with those exposed to placebo.

There is an ongoing study (Metformin in Women with Type 2 Diabetes, MiTy) in which women on insulin are randomized to concurrent treatment with metformin or placebo, and investigators plan to follow offspring in MiTy Kids as well [32].

Another risk is treatment failure of metformin monotherapy. Trials in which women were randomized to insulin or metformin (and insulin if needed) have shown that 20 to 46% of women treated with metformin eventually required insulin to meet glycemic targets [22, 25, 28].

Possible Indications for Use

For women who cannot afford insulin, who decline insulin, or who cannot administer insulin safely, metformin is a reasonable alternative therapy (Table 2).

Metformin tends to be most effective in women with fasting hyperglycemia given the suppression of hepatic gluconeogenesis (as opposed to women with predominantly postprandial hyperglycemia). Given that metformin can decrease maternal weight gain, it might also be considered in women who are overweight or obese or who have excessive gestational weight gain. However, several studies have examined factors that predict the need for supplemental insulin (in addition to metformin) to achieve adequate glucose control in GDM. Those factors include higher fasting glucose at diagnosis, early detection of GDM, higher baseline hemoglobin A1c (HbA1c), and higher BMI [22, 25, 33]. Thus, since women who are overweight or obese are more likely to require supplemental insulin, clinicians should engage in shared decision-making with their patients, explaining that they may still require insulin but could have less weight gain.

Many women with PCOS and concurrent insulin resistance are already on metformin at conception, and metformin is often continued through the first trimester. Analysis of recent trials suggests that metformin may decrease risk of preterm birth or late miscarriage in women with PCOS [29]. Given some of the possible long-term risks for offspring, it may be stopped during the second and third trimesters. The decision of whether to use or continue metformin again requires shared decision-making.

Dosing

Metformin can be prescribed in various forms including immediate release or extended release, and as either 500 mg or 1000 mg tablets. In pregnant patients, metformin is often titrated much more quickly than in non-pregnant patients. The typical starting dose is 500 mg twice daily. If glucoses are not at goal after several days, the dose can be increased by 500 mg increments.

Metformin has been reported to cause gastrointestinal side effects including nausea and loose stools in 4 to 46% of women with GDM [23]. While metformin can cause loose stools, in our experience, this side effect is typically less bothersome during pregnancy, likely because many pregnant women experience constipation.

The extended release form is not very well studied in pregnancy, with only one study in women with gestational diabetes [22]. Metformin should not be started in women with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2 or with liver disease, as metformin has a rare risk of lactic acidosis which is greater in these two conditions.

Glyburide

Mechanism of Action

Glyburide (also known as glibenclamide) is a sulfonylurea and these agents have been widely used in patients with type 2 diabetes [34]. The sulfonylurea receptor is part of the adenosine triphosphate-sensitive potassium channel in the pancreatic beta cells; this class of medications acts to increase insulin secretion from the pancreatic beta cell and improve peripheral insulin sensitivity. Despite the rise in use of glyburide in pregnancy, it is not recommended as a first-line therapy in guidelines [3•, 4•, 8].

Early in vitro studies suggested that glyburide had minimal to no placental transfer [35] and glyburide was undetectable in cord blood when measured by high-performance liquid chromatography in a study conducted in 2000 [36]. However, a more recent study demonstrated cord blood levels of glyburide to be approximately 70% of maternal levels of glyburide [37], illustrating that glyburide does cross the placenta.

Possible Benefits

Glyburide is effective in lowering blood glucose, particularly in patients with elevated postprandial blood glucose levels. Similar to metformin, it is an oral medication so it is relatively simple to take and well accepted by patients (with 78.7% of women reporting they would use it in a subsequent pregnancy compared with only 19.1% of women on insulin in a randomized trial) [38•]. It is also inexpensive and tends to be well tolerated with few side effects if taken correctly.

Possible Risks

There have been adverse effects of glyburide reported when compared with other pharmacologic agents for the treatment of gestational diabetes. All sulfonylureas can cause weight

Table 2 Pharmacologic agents used in the treatment of gestational diabetes mellitus

Medication	Metformin	Glyburide	Insulin
Mechanism of Action	Biguanide: suppression of glucose production by liver, increased glucose uptake by peripheral tissues, and many others (not all understood)	Sulfonylurea: increase of insulin secretion from pancreatic beta cell, increased insulin sensitivity by peripheral tissues	Allows glucose to enter cells
Placental Transfer	Yes	Yes	No
ADA/ACOG recommendations [3,4]	Second-line	Second-line	First-line
Pregnancy Class (FDA)^	B	C	B (insulin detemir, NPH, insulin aspart, insulin lispro, insulin regular) or C (insulin glargine)
Patient Factors That May Favor Use	• Fasting hyperglycemia • Obesity (though more likely to need supplemental insulin) • PCOS	Postprandial hyperglycemia	
Benefits	• Decreased maternal weight gain • Less neonatal hypoglycemia* • Less pregnancy-induced hypertension*		• Highly effective in achieving glucose control • Ability to tailor regimen to fasting and/or post-prandial hyperglycemia
Risks/Adverse Outcomes	• Possible increased obesity in offspring exposed *in utero* • Possible increased risk of preterm birth*	• Increased risk of neonatal hypoglycemia • Possible increased risk of macrosomia, higher birth weight*	• Could contribute to maternal weight gain • Since doesn't cross placenta, no known adverse effects on offspring
Cost	Inexpensive	Inexpensive	Varies depending on type of insulin and health insurance coverage
Dosing	Typical starting dose 500 mg BID PO with food. Can uptitrate to 1000 mg BID. (Extended released also available, less well-studied)	Typical starting dose 2.5 mg PO at least 15 minutes prior to breakfast. Can uptitrate to 10 mg BID	Variable depending on type of insulin, patients' weight and pattern of dysglycemia
Risk of Maternal Hypoglycemia	Low	Moderate (particularly if not taken pre-meal)	Moderate
Possible Side Effects	GI: nausea, loose stools/diarrhea, flatulence	Rare	Rare
Postpartum Considerations	• Sometimes continued postpartum if persistent glucose metabolism abnormalities • May be continued while breastfeeding	Typically stopped after delivery	Typically stopped after delivery

* Conflicting data

Abbreviations: *PCOS*, polycystic ovarian syndrome; *ADA*, American Diabetes Association; *ACOG*, American College of Obstetricians and Gynecologists; *FDA*, Food and Drug Administration; *BID*, twice daily; *qhs*, at bedtime; *NPH*, neutral protamine Hagedorn; *PO*, by mouth

^ Prior to 2015, the Food and Drug Administration (FDA) used several pregnancy and lactation categories. Pregnancy category class B = Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Pregnancy class C = Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits many warrant use of the drugs in pregnant women despite potential risks. [50]

gain. They can also cause maternal hypoglycemia, particularly if taken without food.

Meta-analyses have demonstrated a higher risk of neonatal hypoglycemia in women taking glyburide [26, 39]. There have been mixed conclusions from meta-analyses regarding the outcomes of birth weight and macrosomia. A 2015 meta-analysis was conducted that included 7 randomized control trials comparing insulin to glyburide and 2 trials comparing

metformin to glyburide [26]. When compared with insulin, glyburide was associated with higher birth weight (mean difference 109 g, 95% CI 35.9–181), more macrosomia (risk ratio 2.62, 95% CI 1.35–5.08) and higher risk of neonatal hypoglycemia (risk ratio 2.04, 95% CI 1.30–3.20). There was no difference in maternal weight gain, third trimester HbA1c, and severe maternal hypoglycemia when comparing glyburide with insulin. When comparing the use of metformin with glyburide in pregnancy, metformin was associated with less maternal weight gain (− 2.06 kg, 95% CI − 3.98 to − 0.14), less macrosomia (risk ratio 0.33, 95% CI 0.13–0.81), and fewer LGA babies (risk ratio 0.44, 95% CI 0.21–0.92). Both metformin and glyburide had similar treatment failure rates. There was no difference in severe maternal hypoglycemia or third trimester HbA1c levels between women taking metformin and women taking glyburide. In another retrospective study evaluating over 10,000 women on medical therapy for gestational diabetes, glyburide was associated with LGA infants and higher rates of neonatal intensive care unit stay when compared with insulin [40]. In contrast, a 2017 meta-analysis comparing glyburide with insulin did not find higher rates of macrosomia or higher birth weights in infants of mothers taking glyburide [39]. A 2017 Cochrane review found insufficient high-quality evidence to recommend one oral agent over another [7]. They identified one study of 159 infants in which metformin was associated with a decrease in death or serious morbidity composite compared with glyburide, which they classified as low-quality evidence.

A randomized controlled trial comparing glyburide with insulin in 914 women with GDM was published in 2018 [38•]. The primary outcome was a composite criterion including macrosomia, neonatal hypoglycemia, and hyperbilirubinemia. The frequency of the primary outcome was 27.6% in the glyburide group compared with 23.4% in the insulin group (difference between groups 4.2%, one-sided 97.5% CI up to 10.5%, $p = 0.19$), primarily driven by higher rates of neonatal hypoglycemia in the glyburide group. The authors had pre-specified that the non-inferiority margin was 7% and because the upper limit of the confidence interval of the difference was more than 7%, they could not conclude that glyburide is non-inferior to insulin. In other words, the authors still recommended insulin as first-line therapy based on this study.

Unfortunately to date, there are no studies examining the offspring of women exposed to glyburide in utero, which makes it difficult to compare to metformin. Glyburide does cross the placenta so there could be risks to offspring in long-term follow-up.

Regarding treatment failure, 4–16% of women initially treated with glyburide required addition of insulin to achieve glycemic control [3].

Possible Indications for Use

Glyburide can be used for women who decline insulin and/or are unable to tolerate metformin due to gastrointestinal side effects. It is likely to be most effective for those with pronounced postprandial hyperglycemia (Table 2).

Dosing

Glyburide is typically started at a dose of 2.5 mg to be taken 15 to 30 minutes prior to breakfast. It can be uptitrated to a maximum dose of 20 mg daily, which is typically split into two doses (e.g., 10 mg prior to breakfast and dinner). Importantly, it should not be taken at bedtime to treat fasting hyperglycemia. That dosing puts women at risk of hypoglycemia overnight and will not effectively treat fasting hyperglycemia.

Interestingly, when the pharmacokinetics of glyburide in pregnancy were studied, concentrations of the drug began to increase within 30 to 60 minutes after ingestion [37]. Thus, the investigators recommended that women take glyburide 30 to 60 minutes prior to eating so that the rise in glyburide concentration occurs prior to the elevation in blood sugar [37, 41], though this timing could be difficult to adhere to on a daily basis.

Other Glucose-Lowering Agents

There is scarce data on other glucose-lowering agents during pregnancy. Acarbose is an alpha-glucosidase inhibitor that reduces intestinal carbohydrate absorption, but typically causes gastrointestinal side effects. In a randomized trial of seventy patients, women were randomized to insulin, acarbose, or glyburide [42]. Eight of 19 women on acarbose (41.5%) did not achieve adequate glucose control and required insulin, but average newborn weight did not differ from insulin. There is also a case report in which six pregnant women were treated with acarbose and it successfully lowered blood glucose [43]. However, all women had gastrointestinal side effects, though none needed to stop treatment because of them. Acarbose is not typically included in guidelines for treatment of GDM.

Other agents that can be used to treat diabetes outside of pregnancy include glucagon-like peptide 1 agonists (GLP1a), dipeptidyl peptidase-4 inhibitors (DPP4i), and sodium-glucose cotransporter 2 inhibitors (SGLT2i). These agents have not been adequately studied during pregnancy and thus should not be used to treat GDM at this time [44].

Clinical Approach

For all women diagnosed with GDM, we counsel about lifestyle changes and refer to a registered dietician. If women are unable to reach target glucose levels with lifestyle interventions, then pharmacologic intervention is warranted (Fig. 1).

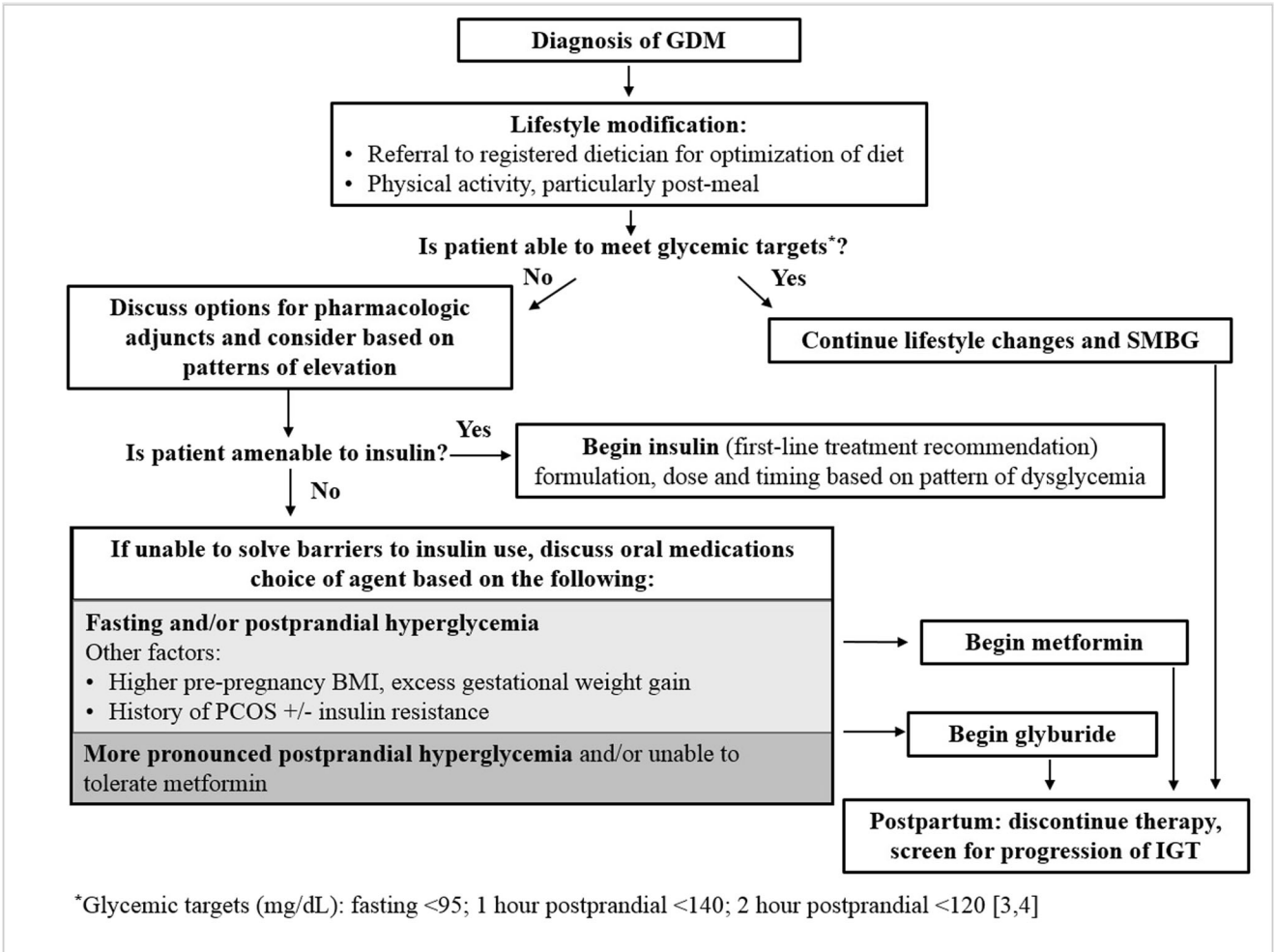

Fig. 1 Clinical approach to treatment of gestational diabetes mellitus. GDM, gestational diabetes mellitus; BMI, body mass index; SMBG, self-monitoring of blood glucose; PCOS, polycystic ovarian syndrome; IGT, impaired glucose tolerance

Medications should be tailored to the GDM phenotype, which can be divided into three categories. Woman can have an insulin resistance phenotype, which manifests as fasting hyperglycemia, an insulin secretion phenotype, which manifests as postprandial hyperglycemia, or a mixed phenotype with both abnormalities [45]. The first-line pharmacologic intervention is typically insulin. Insulin NPH (neutral protamine Hagedorn) or other intermediate or long-acting insulins are often started to assist in control of fasting hyperglycemia. Rapid-acting insulin can be added for postprandial hyperglycemia. However, if the patient cannot afford insulin, refuses insulin, or cannot safely use insulin, metformin or glyburide can be considered (Fig. 1).

If the primary issue is fasting hyperglycemia (an insulin-resistance phenotype), then metformin can be started. If the primary issue is postprandial hyperglycemia (an insulin secretion phenotype), then glyburide may be an effective option (Table 2).

Transitions of Care

Postpartum Screening

After delivery, pharmacologic adjuncts are often discontinued. While GDM frequently resolves after delivery, up to one-third of women will have glucose abnormalities in postpartum screening. After delivery, it is recommended that all women undergo a 75-gram, 2-hour OGTT between 4 to 12 weeks postpartum [3]. Abnormalities on OGTT include impaired fasting glucose (fasting plasma glucose 100–125 mg/dL) and impaired glucose tolerance (140–199 mg/dL). HbA1c should also be monitored at least every three years in women who are overweight and obese and have a history of GDM [46]. Prediabetes is diagnosed with an HbA1c of 5.7 to 6.4% [46].

If the patient is found to have abnormalities in glucose metabolism, the first-line recommendation involves lifestyle counseling, focusing on achieving a normal

weight, physical activity, and eating a healthy diet. Women can be referred to National Diabetes Prevention Programs (DPP) sites in their area, which offer intensive, behavioral interventions proven to decrease progression from prediabetes to diabetes. There are now certified DPP-based programs offered virtually as well (www.cdc.gov/diabetes/prevention/lifestyle-program) [47].

Metformin for Diabetes Prevention and Treatment

The ADA recommends considering metformin for women with prediabetes and a prior history of GDM because it has been found to be particularly effective for prevention of type 2 diabetes in this population [47]. In contrast, other drugs including sulfonylureas have not been studied for diabetes prevention in women with prediabetes and are not recommended.

Metformin is safe to continue in women who are breastfeeding. Metformin is excreted into breast milk but in very small amounts that are not clinically significant. In two pharmacokinetic studies of women on metformin breastfeeding their infants, daily infant intake of metformin was 0.5–0.65% of the mother's weight-adjusted dose [48, 49]. The equivalent daily intake was 0.13 to 0.28 mg of metformin [49].

Metformin is also a first-line pharmacotherapy for all patients diagnosed with diabetes given its efficacy, safety, and affordability.

Conclusion

Given the heterogeneity of GDM, it is important to consider patient preference and phenotype to guide the choice of therapeutic options. Lifestyle modification continues to be the foundation of treatment for GDM. If glycemic targets are not met and patients are not amenable to insulin injections or unable to use insulin due to cost or other reasons, other pharmacologic adjuncts should be considered.

Specifically, metformin and glyburide can be used in the management of gestational diabetes as alternatives to insulin, yet their effects on offspring are still being investigated. While oral agents have benefits, namely low cost and ease of use, they are not as efficacious and some women will fail oral agent monotherapy and will require insulin to achieve glycemic targets in pregnancy. Some guidelines consider metformin as first-line therapy along with insulin. Metformin is associated with less maternal weight gain, decreased risk of pregnancy-induced hypertension, and less neonatal hypoglycemia. Additionally, for women with higher pre-pregnancy BMI and/or excess gestational weight gain, metformin may be of benefit as it has been associated with less weight gain during pregnancy. However, metformin crosses the placenta and could lead to higher risk of obesity in offspring exposed in utero. It is most appropriate for women with insulin resistance and fasting hyperglycemia. The use of glyburide in pregnancy has been associated with increased neonatal hypoglycemia, increased birthweight, and macrosomia. It has traditionally been considered when patients are not amenable to insulin, are unable to tolerate metformin, and have more pronounced postprandial hyperglycemia.

Experience with acarbose has been limited to one randomized controlled trial and when compared with insulin did not show a difference in maternal or fetal outcomes; however, clinical use may be limited due to adverse gastrointestinal effects. There is no evidence to date on the use of DPP4i, GLP1a, or SGLT2i agents; therefore, most experts do not recommend use in pregnancy at this time. Given the paucity of evidence and gaps in literature, further studies and long-term follow-up data are needed.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Guariguata L, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. Diabetes Res Clin Pract. 2014 Feb;103(2):176–85.
2. Wexler DJ, Powe CE, Barbour LA, Buchanan T, Coustan DR, Corcoy R, et al. Research gaps in gestational diabetes mellitus: executive summary of a National Institute of Diabetes and Digestive and Kidney Diseases workshop. Obstet Gynecol. 2018;132(2):496–505. https://doi.org/10.1097/AOG.0000000000002726.
3. • Committee on Practice Bulletins—Obstetrics: ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol 2018;131(2):e49–e64. Doi: https://doi.org/10.1097/AOG.0000000000002501. **A detailed overview of recommendations for diagnosis and management of gestational diabetes in the USA.**
4. • American Diabetes Association. Management of diabetes in pregnancy: standards of medical care in diabetes—2019. Diabetes care. 2019;42(Supplement 1):S165–72. **The most recent guidelines from the American Diabetes Association briefly summarizing diagnosis and treatment of gestational diabetes.**
5. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, et al. Hyperglycemia and

adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991–2002. https://doi.org/10.1056/NEJMoa0707943.
6. Landon MB, Carpenter MW, Wapner RJ, Thorp JM, Harper M, Sorokin Y, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med. 2009;10.
7. Brown J, Martis R, Hughes B, Rowan J, Crowther CA. Oral antidiabetic pharmacological therapies for the treatment of women with gestational diabetes. Cochrane Database Syst Rev. 2017;1:CD011967. https://doi.org/10.1002/14651858.CD011967.pub2.
8. Camelo Castillo W, Boggess K, Stürmer T, Brookhart MA, Benjamin DKJ, Jonsson Funk M. Trends in glyburide compared with insulin use for gestational diabetes treatment in the United States, 2000–2011. Obstet Gynecol. 2014 Jun;123(6):1177–84.
9. Goh JEL, Sadler L, Rowan J. Metformin for gestational diabetes in routine clinical practice. Diabetic Med. 2011;28:1082–7. https://doi.org/10.1111/j.1464-5491.2011.03361.x.
10. Barbour LA, Scifres C, Valent AM, Friedman JE, Buchanan TA, Coustan D, et al. A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes. Am J Obstet Gynecol. 2018;219(4):367.e1–7.
11. Society for Maternal-Fetal Publications Committee. SMFM statement: pharmacological treatment of gestational diabetes. Am J Obstet Gynecol. 2018;218(5):B2–4.
12. Song C, Li J, Leng J, Ma RC, Yang X. Lifestyle intervention can reduce the risk of gestational diabetes: a meta-analysis of randomized controlled trials: lifestyle intervention and GDM. Obes Rev. 2016;17(10):960–9.
13. Yamamoto JM, Kellett JE, Balsells M, García-Patterson A, Hadar E, Solà I, et al. Gestational diabetes mellitus and diet: a systematic review and meta-analysis of randomized controlled trials examining the impact of modified dietary interventions on maternal glucose control and neonatal birth weight. Diabetes Care. 2018;41(7):1346–61.
14. Institute of Medicine and National Research Council Committee to reexamine IOM pregnancy weight guidelines. Weight gain during pregnancy: reexamining the guidelines. Washington, DC: National Academies Press; 2009. Available from: http://www.ncbi.nlm.nih.gov/books/NBK32813/. Accessed 15 June 2019.
15.• Feig DS, Berger H, Donovan L, Godbout A, Kader T, Keely E, et al. Diabetes and pregnancy. Can J Diabetes. 2018;42:S255–S282. **A detailed guideline from Canada about treatment of gestational diabetes, with a helpful summary of evidence about dietary approaches.**
16. Jenkins DJ, Wolever TM, Taylor RH, Barker H, Fielden H, Baldwin JM, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr. 1981;34:362–6.
17. Yamamoto JM, Kellett JE, Balsells M, García-Patterson A, Hadar E, Solà I, et al. Dietary intervention in patients with gestational diabetes mellitus: a systematic review and meta-analysis of randomized clinical trials on maternal and newborn outcomes. Diabetes Care. 2018;41:1346–61. https://doi.org/10.2337/dc18-0102.
18. Wei J, Heng W, Gao J. Effects of low glycemic index diets on gestational diabetes mellitus: a meta-analysis of randomized controlled clinical trials. Medicine (Baltimore). 2016;95(22):e3792.
19. Coe DP, Conger SA, Kendrick JM, Howard BC, Thompson DL, Bassett DR, et al. Postprandial walking reduces glucose levels in women with gestational diabetes mellitus. Appl Physiol Nutr Metab. 2017;43(5):531–4.
20. National Institute for Health and Care Excellence. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. 2015. www.nice.org.uk/guidance/ng3. Accessed 15 June 2019.
21. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017 Sep;60(9):1577–85.
22. Rowan JA, Battin MR. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;13.
23. Farrar D, Simmonds M, Bryant M, Sheldon TA, Tuffnell D, Golder S, et al. Treatments for gestational diabetes: a systematic review and meta-analysis. BMJ Open. 2017 Jun 1;7(6):e015557.
24. Butalia S, Gutierrez L, Lodha A, Aitken E, Zakariasen A, Donovan L. Short- and long-term outcomes of metformin compared with insulin alone in pregnancy: a systematic review and meta-analysis. Diabet Med J Br Diabet Assoc. 2017;34(1):27–36.
25.• Priya G, Kalra S. Metformin in the management of diabetes during pregnancy and lactation. Drugs Context 2018;7:212523. doi: https://doi.org/10.7573/dic.212523. **A comprehensive summary of primary studies and meta-analyses of metformin in gestational diabetes mellitus.**
26. Balsells M, García-Patterson A, Solà I, Roqué M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. 2015;21(350):h102.
27. Committee on Practice Bulletins—Obstetrics: ACOG Practice Bulletin No. 156: Obesity in pregnancy. Obstet Gynecol 2015;126(6): e112–e126. doi: https://doi.org/10.1097/AOG.0000000000001211
28. Spaulonci CP, Bernardes LS, Trindade TC, Zugaib M, Francisco RPV. Randomized trial of metformin vs insulin in the management of gestational diabetes. Am J Obstet Gynecol. 2013 Jul;209(1):34.e1–7.
29. Løvvik TS, Carlsen SM, Salvesen Ø, Steffensen B, Bixo M, Gómez-Real F, et al. Use of metformin to treat pregnant women with polycystic ovary syndrome (PregMet2): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2019 Apr 1;7(4):256–66.
30.•• Rowan JA, Rush EC, Plank LD, Lu J, Obolonkin V, Coat S, et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7–9 years of age. BMJ Open Diabetes Res Care. 2018;6(1):e000456. **This study demonstrated that offspring of women with GDM exposed to metformin in utero had several body measurements that were larger than offspring exposed to insulin when assessed at 7 to 9 years of age.**
31.•• Hanem LGE, Stridsklev S, Júlíusson PB, Salvesen Ø, Roelants M, Carlsen SM, et al. Metformin use in PCOS pregnancies increases the risk of offspring overweight at 4 years of age: follow-up of two RCTs. J Clin Endocrinol Metab 2018 Apr 1;103(4):1612–21. **This study showed that offspring of women with PCOS randomized to metformin (compared to placebo) had a higher BMI at 4 years of age.**
32. Feig DS, Murphy K, Asztalos E, Tomlinson G, Sanchez J, Zinman B, et al. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multi-center randomized controlled trial. BMC Pregnancy Childbirth. 2016 Jul 19;16(1):173.
33. Corbould A, Swinton F, Radford A, Campbell J, McBeath S, Dennis A. Fasting blood glucose predicts response to extended-release metformin in gestational diabetes mellitus. Aust N Z J Obstet Gynaecol. 2013;53(2):125–9.
34. Bressler R, Johnson DG. Pharmacological regulation of blood glucose levels in non-insulin-dependent diabetes mellitus. Arch Intern Med. 1997 Apr 28;157(8):836–48.
35. Elliot BD, Langer O, Schenker S, Johnson RF. Insignificant transfer of glyburide occurs across the human placenta. Am J Obstet Gynecol. 1991;165(4):807–12.
36. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med. 2000 Oct 19;343(16):1134–8.
37. Hebert M, Ma X, Naraharisetti S, Krudys K, Umans J, Hankins G, et al. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. Clin Pharmacol Ther. 2009 Jun;85(6):607–14.

38.• Sénat M-V, Affres H, Letourneau A, Coustols-Valat M, Cazaubiel M, Legardeur H, et al. Effect of glyburide vs subcutaneous insulin on perinatal complications among women with gestational diabetes: a randomized clinical trial. JAMA. 2018;319(17):1773. **This trial showed that glyburide could not be concluded to be non-inferior to insulin on a composite outcome of neonatal hypoglycemia, macrosomia, and hyperbilirubinemia.**
39. Song R, Chen L, Chen Y, Si X, Liu Y, Liu Y, et al. Comparison of glyburide and insulin in the management of gestational diabetes: a meta-analysis. PLoS One. 2017 Aug 3;12(8):e0182488.
40. Cheng YW, Chung JH, Block-Kurisch I, Inturrisi M, Caughey AB. Treatment of gestational diabetes mellitus: glyburide compared to subcutaneous insulin therapy and associated perinatal outcomes. J Matern Fetal Neonatol. 2012;25:379–84.
41. Caritis SN, Hebert MF. A pharmacologic approach to the use of glyburide in pregnancy [internet]. Obstet Gynecol. 2013;121:1309–12. https://doi.org/10.1097/AOG.0b013e31829007f0.
42. Bertini AM, Silva JC, Taborda W, Becker F, Lemos Bebber FR, Zucco Viesi JM, et al. Perinatal outcomes and the use of oral hypoglycemic agents. J Perinat Med. 2005;33(6):519–23.
43. Zárate A, Ochoa R, Hernández M, Basurto L. Effectiveness of acarbose in the control of glucose tolerance worsening in pregnancy. Ginecol Obstet Mex. 2000 Jan;68:42–5.
44. Alexopoulos AS, Blair R, Peters AL. Management of preexisting diabetes in pregnancy: a review. JAMA. 2019;321(18):1811–9. https://doi.org/10.1001/jama.2019.4981.
45. Powe CE, Allard C, Battista M-C, Doyon M, Bouchard L, Ecker JL, et al. Heterogeneous contribution of insulin sensitivity and secretion defects to gestational diabetes mellitus. Diabetes Care. 2016;39(6):1052–5. https://doi.org/10.2337/dc15-2672.
46. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical Care in Diabetes—2019. Diabetes Care. 2019 Jan;42(Suppl 1):S165–72.
47. American Diabetes Association. Prevention or delay of type 2 diabetes: standards of medical Care in Diabetes—2019. Diabetes Care. 2019 Jan;42(Suppl 1):S13–28.
48. Briggs GG, Ambrose PJ, Nageotte MP, Padilla G, Wan S. Excretion of metformin into breast milk and the effect on nursing infants. Obstet Gynecol. 2005;105:1437–41.
49. Eyal S, Easterling TR, Carr D, Umans JG, Miodovnik M, Hankins GDV, et al. Pharmacokinetics of metformin during pregnancy. Drug Metab Dispos. 2010;38:833–40.
50. Pregnancy and Lactation Labeling (Drugs) Final Rule. Food and Drug Administration https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule. Accessed 15 June 2019.