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REVIEW

A review of current treatment strategies for gestational diabetes mellitus

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Abstract

Approximately 90% of diabetes cases in pregnant women are considered gestational diabetes mellitus (GDM). It is well known that uncontrolled glucose results in poor pregnancy outcomes in both the mother and fetus. Worldwide there are many guidelines with recommendations for appropriate management strategies for GDM once lifestyle modifications have been instituted and failed to achieve control. The efficacy and particularly the safety of other treatment modalities for GDM has been the source of much debate in recent years. Studies that have demonstrated the safety and efficacy of both glyburide and metformin in the management of patients with GDM will be reviewed. There is a lack of evidence with other oral and injectable non-insulin agents to control blood glucose in GDM. The role of insulin will be discussed, with emphasis on insulin analogs. Ideal patient characteristics for each treatment modality will be reviewed. In addition, recommendations for postpartum screening of patients will be described as well as recommendations for use of agents to manage subsequent type 2 diabetes in patients who are breastfeeding.

Keywords: gestational diabetes, fetal macrosomia, glyburide, hypoglycemia, hypoglycemic agents, insulin, long-acting insulin, short-acting insulin, metformin, postnatal care.

Abbreviations: GCT, glucose challenge test; GDM, gestational diabetes mellitus; LGA, large for gestational age; NICU, neonatal intensive care unit; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus.

Citation

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Introduction

Gestational diabetes mellitus (GDM) affects 14% of pregnancies annually, and approximately 90% of diabetes cases in pregnant women are considered GDM [1]. GDM is defined as glucose intolerance with onset or initial diagnosis during pregnancy, which includes previously undetected type 1 or 2 diabetes mellitus or first presentation of diabetes during pregnancy [1,2]. Many risk factors for developing GDM are similar to those for type 2 diabetes mellitus (T2DM), including obesity, family history of diabetes, and high-risk ethnicities. Additional risk factors include increased maternal age, previous macrosomic infant, and personal history of GDM [1–6]. GDM can have negative outcomes for both the mother (e.g., preeclampsia and cesarean section) and the fetus (e.g., hypoglycemia, hyperbilirubinemia, birth trauma, death, and obesity or diabetes later in life), with the most common complications being maternal hypertension and fetal macrosomia (defined by the American College of Obstetricians and Gynecologists (ACOG) as birth weight >4500 g) [1,2,5,6]. Additionally, up to 50% of these patients will develop GDM in future pregnancies and/or T2DM later in life [1,5].

Screening and diagnosis

Because screening and diagnosis of GDM vary among guidelines (Table 1), individual institutions should determine the most appropriate criteria for their patient population. Most guidelines recommend screening all patients for GDM at 24–28 weeks gestation [1,5,6]. Screening may be omitted in select low-risk patients [2,3,6]. Early screening (i.e., before 24 weeks gestation) should be considered in high-risk patients, which may include those with a history of GDM, a family history of diabetes, obesity, a history of macrosomic infant, or those of a high-risk ethnicity (Table 2) [1–6]. These patients should be rescreened at 24–28 weeks if an initial diagnosis of GDM was not made [1,2,4–6]. It is unclear if early intervention improves outcomes [5]. While GDM can be diagnosed using fasting glucose readings, screening is typically performed using a 50 g glucose challenge test (GCT), followed by a diagnostic 75 or 100 g oral glucose tolerance test (OGTT) for those with an elevated GCT results [1–4,6]. There is limited evidence supporting the validity of 75 g OGTT; ACOG and the American Diabetes Association (ADA) recommend 100 g OGTT exclusively for diagnosis [1–3]. Most guidelines indicate the need for a

Table 1. Risk factors for GDM—considerations for early screening.

ACOG [1]	ADA[a] [2,3]	CDA [4]	IDF [5]	NICE[b] [6]
History of GDM	History of GDM	History of GDM	Previous GDM or macrosomic infant	History of GDM
BMI ≥30 kg/m^2	Marked obesity	BMI ≥30 kg/m^2	Family history of diabetes mellitus (1st degree relative)	Previous macrosomic infant (≥4.5 kg)
Impaired glucose metabolism	Close family history of diabetes	Prediabetes	Increasing maternal age and weight	BMI >30kg/m^2
	Glycosuria	Ethnicity with high prevalence[c]	Ethnicity with high prevalence[c]	Family history of diabetes mellitus (1st degree relative)
		Age >35 years		Ethnicity with high prevalence[c]
		PCOS or acanthosis nigricans		
		Corticosteroid use		
		History or macrosomic infant		
		Current fetal macrosomia or polyhydramnios		

[a]No screening of low-risk individuals if all of the following criteria are met: age <25 years, normal weight before pregnancy, ethnicity with low prevalence of GDM, no family history of diabetes in 1st degree relative, no history of abnormal glucose, or poor obstetric outcome [2,3].
[b]Early screening only if personal history of GDM. Screening at 24–28 weeks if any other risk factor. No GDM screening if no risk factors [6].
[c]Example: Hispanic, African American, Native American, Asian, Pacific Islander [1].
ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; BMI, body mass index; CDA, Canadian Diabetes Association; GDM, gestational diabetes mellitus; IDF, International Diabetes Federation; NICE, National Institute for Health and Care Excellence; PCOS, polycystic ovarian syndrome.

diagnostic OGTT if the patient's glucose 1 hour after a 50 g GCT is greater than 130 or 140 mg/dL [1,2,4]. A one-step diagnosis can be employed using OGTT alone and is recommended by the ADA, the International Diabetes Federation (IDF), and the National Institute for Health and Care Excellence (NICE) [2,3,5,6]. Specific screening and diagnostic criteria from the various guidelines are listed in Table 2.

Overview of monitoring and general management

As with screening and diagnostic recommendations, glucose testing and treatment goals differ among guidelines (Table 3). All sources agree that elevated postprandial glucose is more predictive of negative outcomes, especially fetal macrosomia, compared with preprandial levels, with some indicating a stronger correlation with 1-hour compared with 2-hour postprandial levels [1,2,5]. It is generally recommended that patients self-monitor fasting glucose (goal <95 mg/dL) and postprandial glucose 1 hour (goal <140 mg/dL) or 2 hours (goal <120 mg/dL) after eating [1,4,5]. NICE guidelines recommend maintaining glucose levels above 72 mg/dL in patients on insulin or a sulfonylurea [6]. In patients without pre-existing diabetes, A1C should not be monitored for GDM management [5,6].

Once diagnosed, all patients should receive extensive diet and exercise counseling [1–6]. It is estimated that 70–85% of cases can be controlled with lifestyle modifications alone [3].

If treatment targets are not met, typically within 1–2 weeks, pharmacotherapy should be initiated [2–6]. Insulin does not cross the placenta and is generally recommended as first-line therapy [2–5]. Glyburide and metformin are both pregnancy category B and are considered safe and effective, though long-term safety data are not available [3]. ACOG states that insulin and oral agents are equally efficacious and either can be used first line while NICE recommends metformin over insulin therapy (Table 4) [1,6]. This review will discuss the available evidence and recommendations for the management of GDM with a focus on insulin, metformin, and glyburide as these are the most extensively studied of currently available therapies.

Evidence for the management of GDM

Glyburide

The first randomized controlled trial (RCT) (n=404) published comparing insulin with glyburide for the management of GDM was in women at 11–33 weeks gestation with singleton pregnancies. The primary outcome was achievement of desired glucose control and secondary outcomes were assessment of maternal and fetal complications. There were no significant differences in the primary endpoint, which included fasting, pre- and postprandial, and mean blood glucose levels as well as A1C. Additionally, maternal (cesarean section or preeclampsia) and fetal (birth weight, macrosomia, admission to a

Table 2. Diagnosis of GDM.

ACOG [1]	ADA [2,3]	CDA [4]	IDF [5]	NICE [6]
Two step: 1-hour, 50 g GCT If positive screen (>135 or 140 mg/dL[a]), proceed to 3-hour, 100 g OGTT (diagnose if >140 mg/dL) *One step*: 2-hour, 75 g OGTT is not recommended due to lack of evidence	Fasting glucose >126 mg/dL or casual glucose >200 mg/dL if confirmed on subsequent day *One step*: Diagnostic 100 g OGTT (mg/dL): Fasting ≥95 1-hour ≥180 2-hour ≥155 3-hour ≥140 2 or more elevations for diagnosis *Two step*: 1-hour, 50 g GCT If positive screen (>130 or 140 mg/dL[a]), give 100 g OGTT confirmatory test as above No preference given to one- or two-step process.	*Preferred:* 1-hour, non-fasting 50 g GCT If positive screen (140–199 mg/dL), proceed to 75 g OGTT Fasting >95 mg/dL 1-hour ≥190 mg/dL 2-hour ≥162 mg/dL 1 or more elevations for diagnosis If 1-hour GCT is ≥200 mg/dL, do not need confirmation *Alternative*: 75 g OGTT Fasting ≥91.8 mg/dL 1-hour ≥180 mg/dL 2-hour ≥153 mg/dL 1 or more elevations for diagnosis	One step preferred (no specific recommendations)	2-hour, 75 g OGTT ≥140 mg/dL or Fasting glucose ≥100 mg/dL

[a]Insufficient evidence to recommend 130 compared with 135 compared with 140 mg/dL. Individualize at each institution.
ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; GCT, glucose challenge test; GDM, gestational diabetes mellitus; IDF, International Diabetes Federation; NICE, National Institute for Health and Care Excellence; OGTT, oral glucose tolerance test.

Table 3. Treatment targets.

ACOG [1]	ADA [2,3]	CDA [4]	IDF [5]	NICE [6]
Insufficient evidence on optimal frequency of testing Generally recommend testing four times daily (fasting, after each meal) Postprandial glucose goals (mg/dL): 1-hour <140 2-hour <120	Monitor glucose daily Plasma glucose goals (mg/dL): Fasting ≤105 1-hour PP ≤155 2-hour PP ≤130 Whole blood glucose goals (mg/dL): Fasting ≤95 1-hour PP ≤140 2-hour PP ≤120 Limited evidence that postprandial monitoring is superior in patients on insulin	Monitor fasting and postprandial glucose daily Goals (mg/dL): Fasting <95 1-hour PP <140 2-hour PP <120	Monitor fasting and postprandial glucose daily, preferably 1 hour after eating Capillary glucose goals (mg/dL): Fasting 90–99 1-hour PP <140 2-hour PP <120–127 Target as low as possible ensuring patient comfort and safety	Multiple insulin injections daily: monitor fasting, pre-meal, 1-hour postprandial, and bedtime All others: monitor fasting and 1-hour postprandial Capillary glucose goals (mg/dL): Fasting <95 1-hour <140 2-hour <115

ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; GDM, gestational diabetes mellitus; IDF, International Diabetes Federation; NICE, National Institute for Health and Care Excellence; PP, postprandial.

neonatal intensive care unit (NICU), fetal hypoglycemia, lung complications, congenital anomalies, still births, and neonatal deaths) outcomes were not significantly different between the groups [7]. The results from this RCT [7] spurred numerous cohort (prospective and retrospective) and RCTs comparing these two medications [7–21]. The cohort studies are typically smaller and range in size from 75 to 584 participants [8–14,17]. However, there are two large prospective cohorts published (assessing over 10,000 in one and over 9000 in the other) [15,16]. All published RCTs to date comparing glyburide with

Table 4. Pharmacologic management of GDM.

ACOG [1]	ADA [2,3]	CDA [4]	IDF [5]	NICE [6]
No conclusive evidence of glucose threshold to start therapy Insulin and oral agents are equally efficacious, either are appropriate first-line agents	If targets not met with lifestyle modifications, initiate pharmacotherapy Insulin preferred Short term data support glyburide and metformin; no long term data (2015 SOC)	If targets not met within 2 weeks of lifestyle modifications, initiate pharmacotherapy Insulin preferred (multiple daily injections) If nonadherent to or refuse insulin, initiate glyburide or metformin	If targets not met with lifestyle modifications, initiate pharmacotherapy Insulin preferred Metformin and glyburide are safe and effective alternatives	If fasting glucose <126 mg/dL at diagnosis, trial of lifestyle modifications If targets not met within 1–2 weeks of lifestyle modifications, initiate metformin. Insulin is recommended if metformin is contraindicated, fasting glucose at diagnosis >126 mg/dL, or fasting glucose at diagnosis 108–125 mg/dL and complications (e.g., macrosomia or hydramnios). Insulin can also be used as add-on therapy Initiate glibenclamide (glyburide) if targets not met with metformin and patient declines insulin or if patient cannot tolerate metformin

ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; GDM, gestational diabetes mellitus; IDF, International Diabetes Federation; NICE, National Institute for Health and Care Excellence.

insulin were recently assessed in a comprehensive meta-analysis by Balsells and colleagues, who analyzed both maternal and fetal outcomes [7,17–25].

In the smaller cohort studies published to date, no differences in macrosomia or fetal birth weight were reported in those treated with glyburide compared with insulin [8–14]. In one study, patients successfully treated with glyburide had higher rates of NICU admissions for fetal hypoglycemia [11]. The glyburide failure rates (i.e., requiring supplemental insulin or a change to insulin therapy) in these trials ranged from 6 to 20%.

One of the largest cohorts published to date assessed 10,682 women with gestational diabetes requiring drug therapy [15]. Eighty-one percent of the women were prescribed insulin, and nineteen percent were prescribed glyburide. Glyburide use was associated with significant increases in NICU admissions (OR 1.4 [95% CI: 1.07–2.00]) and birth weights >4000 g (OR 1.29 [95% CI: 1.03–1.64]), yet there were not significant differences in birth weights >4500 g or birth weights >90th percentile. Based on the ACOG definition for fetal macrosomia (birth weight >4500 g), these results would indicate no statistical or clinical differences in fetal macrosomia with glyburide compared with insulin, which is similar to the smaller cohort studies [26]. The glyburide failure rate in this study was 37%.

The most recently published large cohort assessed over 110,000 patients diagnosed with GDM in a US insurance claims database over an 11-year period [16]. Nine thousand one hundred seventy-three patients (8.3%) were on glyburide (n=4982) or insulin (n=4191). Patients taking glyburide were associated with significantly more NICU admissions (RR 1.41 [95% CI: 1.23–162]), episodes of respiratory distress (RR 1.63 [95% CI: 1.23–2.15]), and large for gestational age (LGA) births (RR 1.43 [95% CI: 1.16–1.76]). There were no significant differences in neonatal hypoglycemia rates, birth trauma, preterm births, jaundice, or cesarean section rates. The increased rate of NICU admissions is consistent with the results of the other large cohort study discussed previously [15].

The most robust meta-analysis published to date assessed seven RCTs comparing glyburide with insulin in a total of 798 patients [25]. Glyburide was found to have significantly higher mean birth weight (mean difference 109 g [95% CI: 35.9–181]), macrosomia (RR 2.62 [95% CI: 1.35–5.08]), and neonatal hypoglycemia (RR 2.04 [95% CI: 1.30–3.20]) compared with insulin therapy. There were no significant findings for the other primary or secondary outcomes. The failure rate with glyburide in this meta-analysis was 6.37%. The meta-analysis findings are different from the cohort findings in regards to significant incidence of macrosomia (no differences in any cohort studies) and fetal hypoglycemia (only in one small cohort) [11].

Table 5. Patient characteristics to consider regarding oral therapies for gestational diabetes management.

Agent	Ideal candidates	Characteristics that are more likely to require supplemental insulin
Glyburide [14,17,27,28]	Fasting OGTT level ≤110 mg/dL	Fasting level on OGTT ≥110 mg/dL
	Gestational age at time of treatment (≥25 weeks)	Earlier gestational age at time of treatment (<25 weeks)
	Singleton pregnancy	Multiparous pregnancy
	No previous history of GDM	Diagnosis of GDM in previous pregnancy
	Younger maternal age	Older maternal age
	Unique characteristics	*Unique characteristics*
	Lack of maternal hypoglycemia awareness	Lower education level (<9 years of school)
	Maternal concern regarding injecting insulin	English as a secondary language or failure to speak English
Metformin [21,22,27]	Fasting OGTT level ≤100 mg/dL	Fasting level on OGTT ≥110 mg/dL
	Later gestational age at time of treatment	Earlier gestational age at time of treatment
	No previous history of GDM	Diagnosis of GDM in previous pregnancy
	Lower BMI	BMI ≥35
	Unique characteristics	*Unique characteristics*
	Lack of maternal hypoglycemia awareness	Multiparous pregnancy
	Maternal concern regarding injecting insulin	Older maternal age

OGTT, oral glucose tolerance test.

Several studies have assessed patient characteristics to determine which patient might be an ideal candidate for glyburide and which patients are more likely to need supplemental insulin [8,11,13,15] (Table 5). Given that failure rates range from as low as 6% to as high as 37%, patient characteristics should be considered to determine which women could benefit from glyburide for the management of GDM. Ideal candidates for a trial of glyburide include women who refuse to take insulin, have lower fasting OGTT levels at screening, are further along in their pregnancy (≥25 weeks gestation) at time of treatment, and have a singleton pregnancy [8,11,13,15].

Metformin

The first study published evaluating metformin use in pregnancy was a cohort of 118 patients with either type 2 diabetes or GDM [27]. This study assessed women on metformin, glyburide, and insulin. Because of increased perinatal mortality with metformin in the third trimester (11.6 *vs* 1.3% with insulin, $p<0.02$), many clinicians were reluctant to consider metformin as an alternative to insulin until the first RCT (n=751) comparing metformin with insulin was published in 2008 [29]. There were no significant differences in the primary composite outcome (neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute APGAR <7, and premature delivery [<37 weeks]) between metformin and insulin [29]. There were more preterm births with metformin compared with insulin (12.1 *vs* 7.6%, $p=0.04$), yet the mean gestational age was not clinically different (38.3 weeks with metformin *vs* 38.5 weeks with insulin, $p=0.02$). There were no differences in complications which is likely due to no clinical differences in mean gestational age at birth even though there were statistical differences in mean gestational age at birth and preterm birth rates. As expected, metformin was associated with less severe hypoglycemia (3.3 *vs* 8.1% with insulin, $p<0.008$). Forty-six percent required supplemental insulin prior to delivery [29].

Since 2008, numerous cohorts and RCTs have evaluated the use of metformin in gestational diabetes [24,28,30–35]. Most compare metformin with insulin, with a few comparing it with glyburide [22–24,28,31,32,34,35]. The most robust meta-analysis published to date assessed six RCTs comparing metformin to insulin (n=1362 patients) and two comparing metformin to glyburide (n=349 patients) [25]. There was significantly less maternal weight gain (mean –1.14 kg [95% CI: –2.22 to –0.06]), lower gestational age at delivery (–0.16 weeks [95% CI: –0.30 to –0.02 weeks]), and more preterm births (RR 1.50 [95% CI: 1.04–2.16]) with metformin compared with insulin therapy. Several secondary outcomes were also reduced with metformin (lower postprandial blood glucose levels, less pregnancy-associated hypertension and less severe neonatal hypoglycemia). The failure rate with metformin in this meta-analysis was 33.8% as opposed to 10–18% in the cohort studies. In the cohort studies and the meta-analysis, metformin use was associated with less maternal weight gain and less fetal hypoglycemia; however, the cohorts found that there were fewer or no difference in preterm births with metformin use, which is contrary to the meta-analysis findings [28,30].

This meta-analysis also compared metformin with glyburide [25]. Metformin was associated with significantly less maternal weight gain (mean –2.06 [95% CI: –3.98 to –0.14]), lower birth weights (–209 g [95% CI: –314 to –104]), less macrosomia (RR 0.33 [95% CI: 0.13–0.81]), and fewer LGA infants (RR 0.44 [95% CI: 0.21–0.92]) when compared with glyburide. The only significant secondary outcome (fasting blood glucose levels) was higher with metformin compared with glyburide. The failure rate with metformin was 26.8% compared with 23.5% with glyburide.

Given the failure rates range from as low as 10% to as high as 46%, patient characteristics should be considered when trying to determine which women could benefit from metformin for the management of GDM. Ideal candidates for a trial of metformin include women who refuse to take insulin, who are in their first GDM diagnosis, and who have lower body mass index (BMI) and lower fasting OGTT levels at screening as well as those who are further along in their pregnancy at time of treatment and experiencing a first episode of gestational diabetes (Table 5) [28,29,32].

Other oral and injectable agents

Other oral and injectable (non-insulin) agents utilized in the management of type 2 diabetes have limited or no human data available regarding safety to the fetus if utilized in pregnancy (Table 6). Based on this, the potential risks outweigh the benefits and they are not considered viable treatment options for the management of GDM.

Summary of recommendations for oral medications

When deciding which oral antidiabetic agent to select, the only two with clinical evidence to support their use in GDM management as either a first-line agent or an alternative to insulin therapy are glyburide and metformin. The other agents have limited or no human data available (Table 6). The general principles for dosing glyburide and metformin in GDM are similar to the management of type 2 diabetes based on all the studies to date.

Recommendations for the use of oral medications in GDM

While ACOG recommendations give no preference to insulin or either oral agent for GDM management, NICE recommends metformin first line over insulin and glyburide (Table 4) [1,6]. Patient-specific factors and preferences should be considered when selecting which patients may be better candidates for metformin, glyburide, or insulin (Table 5). Considering improved fetal outcomes (the lower incidence of macrosomia and LGA) in head-to-head comparisons between metformin and glyburide as well as increased neonatal hypoglycemia in glyburide studies, metformin may be preferred. However, based on the efficacy and safety evidence with glyburide and metformin, it seems reasonable to utilize either agent on a case-by-case basis, considering patient-specific factors. Both glyburide and metformin are: (1) available as generic products and would be lower cost to the patient than insulin therapy; and (2) dosed once to twice a day, depending on the dose and formulation selected. At times, patient-specific factors may make it reasonable to switch from one oral agent to another, based on adverse effects that are intolerable, before changing to insulin.

Insulin

Despite emerging evidence supporting the use of glyburide or metformin in the management of GDM, many guidelines continue to recommend insulin as the first-line therapy. This is primarily the result of two factors: pregnancy category B for all insulins except glulisine and glargine, and safety data indicating clinically insignificant amounts of human insulin that cross the placenta [3,37,38]. Two RCTs demonstrated that insulin compared with usual prenatal care in the management of GDM resulted in decreased numbers of births associated with shoulder dystocia, macrosomia, and preeclampsia [39].

Regular insulin is the standard against which rapid analogs are compared while neutral protamine hagedorn (NPH) insulin is the standard against which long-acting analogs are compared. Concerns with regular or NPH insulin in the general population—hypoglycemia and variations in blood glucose values—arise when these agents are used in the management of GDM [37,40]. While advantages that insulin analogs provide to the general population should translate to the GDM population, controversy exists due to limited or even lack of efficacy and safety data specifically in patients with GDM.

A meta-analysis investigating the safety of insulin analogs in pregnancy (pregestational and GDM) assessed 24 studies that compared regular insulin or NPH with one of the analogs [40]. The included studies reported maternal and fetal outcomes in both the control and treatment arms. These safety results are incorporated into the review of the respective products below.

Rapid analogs

Aspart

Although there are studies utilizing aspart in the management of patients with pregestational diabetes, the data specifically looking at the use of aspart in GDM is limited [40,41]. The use of aspart in the management of pregestational diabetes has been shown to be effective. There is one RCT (n=15) in which women with GDM who were uncontrolled with diet and exercise were given a standard meal on three subsequent days, and glucose, insulin, and C-peptide levels were measured before the administration of insulin and after regular insulin and

Table 6. Medications utilized in type 2 diabetes with limited or no data in gestational diabetes management.

Agent	Summary of available data	Therapeutic considerations
Alpha-glucosidase inhibitors **[36–38]**		
Acarbose [38]	Limited human data available	Not recommended for use currently
Miglitol [38]	There is no human data available	Not recommended for use currently
Dipeptidyl peptidase IV (DDP IV) **inhibitors [36,37]**		
Alogliptin	There is no human data available	Not recommended for use currently
Linagliptin [38]	There is no human data available	Not recommended for use currently
Saxagliptin [38]	There is no human data available	Not recommended for use currently
Sitagliptin [38]	There is limited human data available. Merck maintains a pregnancy registry for women exposed to sitagliptin	Not recommended for use currently
Glucagon-like peptide-1 (GLP-1) receptor agonists **[36,37]**		
Albiglutide	There is no human data available. Animal studies report fetal adverse events	Not recommended for use currently
Dulaglutide	There is no human data available. Animal studies report fetal adverse events	Not recommended for use currently
Exenatide [38]	There is no human data available. Animal studies report fetal adverse events	Not recommended for use currently
Liraglutide [38]	There is no human data available. Animal studies report fetal adverse events	Not recommended for use currently
Meglitinides		
Nateglinide [38]	There is limited human data available	Not recommended for use currently
Repaglinide [38]	There is limited human data available. Animal studies report fetal adverse events	Not recommended for use currently
Sodium glucose cotransporter 2 (SGLT-2) **inhibitors [36,37]**		
Canagliflozin	There is no human data available. Animal studies report fetal adverse events	Not recommended for use currently
Dapagliflozin	There is no human data available. Animal studies report fetal adverse events	Not recommended for use currently
Empagliflozin	There is no human data available. Animal studies report fetal adverse events	Not recommended for use currently
Thiazolidinediones (TZD)		
Pioglitazone [38]	There is no human data available. Animal studies report fetal adverse events	Not recommended for use currently
Rosiglitazone [38]	There is limited human data available. Animal studies report fetal adverse events	Not recommended for use currently

aspart administration [42]. Although both regular insulin and aspart were both effective in lowering glucose, as expected based on aspart's pharmacokinetic profile, the postprandial glucose readings were significantly lower than regular insulin readings, beginning at 60 minutes after the start of the meal [42]. Because of this trial design, it was not included in the meta-analysis analyzing safety [40]. Safety and efficacy outcomes included in a randomized, open-label, parallel trial of patients with GDM compared aspart (n=14) with regular insulin (n=13) administered three times a day for mealtime coverage in addition to twice-daily administration of NPH [43]. A1C values were consistently controlled (<6%) at 36–38 weeks of pregnancy (A1C=5.2%) and 6 weeks postpartum (A1C=5.4%). Additionally, both aspart and regular insulin were effective in lowering postprandial glucose levels; however, as expected, 30 and 60 minutes after a meal, patients taking aspart had a lower mean glucose concentration [43]. Hypoglycemia occurred in both groups (aspart n=10, regular insulin n=9), but none of the episodes required assistance of another person [43]. Mean weights and lengths of infants were similar between

treatment groups, and there were no cases of macrosomia [43]. Additionally, one prospective, randomized trial evaluated the efficacy of insulin analogs to regular insulin [44]. Ninety-six women with GDM were allocated to receive aspart (n=31), lispro (n=33), or regular insulin (n=32) in conjunction with NPH insulin, if needed to control fasting glucose [44]. There were no differences in glucose control, except for higher 1-hour postprandial glucose levels and higher birth weight readings in the regular insulin group. These data suggest that both agents are reasonable options for use in GDM [44].

As part of the safety meta-analysis, six RCTs, comparing aspart (n=567) to regular insulin (n=516), were included [40]. Of note, these trials were some of the only RCTs evaluating the use of insulin analogs in pregnancy and did include the studies outlined above. The meta-analysis did report safety data from an RCT of aspart compared with regular insulin in patients with type 1 diabetes whose efficacy data were described above [41]. Baseline maternal characteristics were similar in these six RCTs [40]. The only neonatal characteristics mentioned in the results, macrosomia and cesarean delivery, were not significantly different when comparing aspart to regular insulin [40].

Lispro

There has been controversy regarding the safety of lispro for the treatment of GDM. Initial literature included retrospective analyses of women with pregestational diabetes managed with lispro for maternal and/or neonatal outcomes [45–48]. All four trials concluded that lispro was not associated with different rates of congenital malformations, preterm delivery, or birth weight when compared with regular insulin [45–48].

There have been reports, including the safe delivery of an infant when lispro was utilized in case of allergy to regular insulin, and trials involving lispro that have included patients with GDM [49–52]. A retrospective cohort study of 635 pregnancies (538 pregnancies were GDM) compared patients managed with lispro (GDM n=75, pregestational n=21) to regular insulin (GDM n=138, pregestational n=42) [50]. In patients with GDM, the incidence of congenital abnormalities between treatment groups was not significant. Lower A1Cs were noted in lispro patients compared with patients taking regular insulin (5.8 *vs* 6.08%, $p<0.05$); however, the clinical significance of this difference is probably small [50]. A subset (n=19) of the overall study surveyed patients regarding their preference of insulin products and showed that lispro was preferred [50].

An RCT compared the use of lispro (n=25) to regular insulin (n=24) in patients with GDM [51]. Maternal glucose levels were significantly lower at 1 hour after eating (lispro 108.4 mg/dL *vs* regular 121.0 mg/dL, $p<0.01$) as expected. There were no significant differences in the neonatal outcomes between lispro, regular insulin, and the control group (pregnant patients who did not have GDM) other than more patients in the regular insulin group having a cranial-thoracic circumference (CC/CT) ratio in the 10th–25th percentile [51].

Two hundred and one South Indian women with GDM were included in a retrospective observational study in which patients took lispro before each meal and NPH based on fasting plasma glucose readings greater than 95 mg/dL [52]. Patients met target blood glucose goals for GDM, and there were no cases of eclampsia. All neonatal outcomes (gestational age at delivery, birth weight, neonatal hypoglycemia, and congenital anomalies) reported aligned with previous studies [52].

In 2010, a review including 27 publications (studies and case reports) of 1265 pregnancies, in which lispro compared with regular insulin was used for the management of pregestational and gestational diabetes, was published [53]. Lispro was associated with lower postprandial glucose and A1C levels. However, the review showed no significant differences between lispro and regular insulin in safety (spontaneous abortion or congenital anomalies) [53]. Recently, a more comprehensive meta-analysis has been published specifically focusing on the safety of insulin analogs [40]. This meta-analysis included nine observational studies comparing lispro (n=452) to regular insulin (n=1089). Maternal baseline characteristics were similar. Differences in neonatal outcomes (decreased incidence of jaundice [RR 0.63, 95% CI: 0.44–0.90], higher incidence of LGA [RR 1.42, 95% CI: 1.20–1.69], higher birth weight [weighted mean differences (WMD)=116.44, 95% CI: 28.78–204.11]) were noted with lispro use. However, when compared with regular insulin, lispro was not associated with an increased incidence of cesarean sections, congenital malformations, macrosomia, neonatal hypoglycemia, NICU admissions, respiratory dysfunction syndrome (RDS), or stillbirths. With regard to maternal outcomes, lispro was associated with a decreased risk of severe maternal hypoglycemia (RR 0.33, 95% CI: 0.12–0.89) compared with regular insulin. However, there were no significant differences in preeclampsia and pregnancy-induced hypertension [40].

Glulisine

Of all of the rapid-acting insulin analogs, glulisine is the only one without human data regarding its use in pregnancy [38]. Glulisine is the only rapid-acting analog that is pregnancy category C; however, there is no information available indicating that the risk to the fetus would be different with glulisine compared with other rapid insulins [37,54]. There were no data reported for glulisine in the meta-analysis investigating the safety of insulin analogs in pregnancy [40].

Long-acting insulin analogs

Detemir

The published information for detemir use in pregnancy is often combined with information for glargine [55,56].

Additionally, the case reports and case-control studies with detemir are exclusively in patients with type 1 diabetes [55–58]. The largest of these studies was a retrospective study comparing detemir (n=67) to glargine (n=46), which showed no significant difference in maternal outcomes (glucose control [A1C], incidence of severe hypoglycemia, and preeclampsia] [55]. Neonatal outcomes were similar except for a significant difference in birth weight (3490 g detemir, 3219 g glargine, p=0.05) and fewer LGA infants with glargine (33 infants with detemir *vs* 14 infants with glargine, p=0.046) [55].

Only two studies—an RCT and a case-control study—were included in the safety meta-analysis of insulin detemir (n=160) compared with NPH (n=166) [40]. These studies noted no significant increase in LGA or neonatal hypoglycemia with detemir use [40].

Glargine

There are numerous case reports and case-control studies describing the use of glargine in patients with type 1 diabetes [56,59–63]. All reports indicated that they are just preliminary reports and well-designed trials are needed before glargine can be routinely recommended. An initial case series reported the benefits of glargine in patients with GDM both on maternal control of glucose and successful pregnancies [64]. Even one of the larger matched case-controlled studies (type 1 diabetes n=20, GDM n=44) indicated their results (no increase in macrosomia or other neonatal complications with glargine use) were preliminary [65]. Two meta-analyses have examined the use of glargine in pregnancy in both pregestational and GDM patients [66,67]. Although both included the same eight studies (insulin glargine n=331, NPH n=371), one focused more on neonatal outcomes while the other included maternal and neonatal outcomes [66,67]. The findings of these earlier meta-analyses included no significant differences in neonatal outcomes—mean gestational age at birth, birth weight, LGA, or congenital anomalies [66,67]. Additionally, the meta-analysis that also analyzed the studies for maternal outcomes concluded that patients using glargine were not more likely to increase their weight; to experience severe hypoglycemia, pregnancy-induced hypertension, or preeclampsia; or to require a cesarean section [67]. These findings were consistent with the larger safety meta-analysis conducted for all insulin analogs [40].

In the safety meta-analysis, eight studies compared insulin glargine (n=331) to NPH (n=371) in women with similar baseline characteristics [40]. Three of the studies differentiated between patients with pregestational diabetes and GDM. However, there was no difference in the safety outcomes (birth weight and severe maternal hypoglycemia) analyzed between the pregestational diabetes and GDM patients. Additionally, there were no significant differences in birth weight noted in glargine compared with NPH, nor were there significantly higher rates of LGA, malformations, macrosomia, neonatal hypoglycemia, neonatal jaundice, NICU admissions, preterm deliveries, or RDS. With regard to maternal outcomes, there were no significant differences in severe maternal hypoglycemia, preeclampsia, or pregnancy-induced hypertension with glarigine compared with NPH [40].

Summary of insulin recommendations

When deciding how to dose insulin in pregnancy, the recommendations are not specific to GDM. The general principles for dosing insulin in pregnancy apply to pregestational and gestational diabetes. Although insulin sensitivity fluctuates throughout pregnancy, by the time insulin is needed for GDM, patients are often at the end of their second trimester or even in their third trimester [3]. Insulin resistance increases throughout pregnancy so the total daily dosing requirements are usually 0.8–0.9 units of insulin per kg of body weight [68]. One case series reported administering glargine at half of the total daily dose calculated (based on trimester) and adjusting doses throughout pregnancy by 3–5 units as needed when patient's blood glucose values were at the upper end of their target range [64].

Recommendations for the use of insulin in GDM

It is accepted that insulin is effective in the management of GDM and is supported as a first-line option by many guidelines [2–5]. However, as noted in the literature reviewed here, there continues to be controversy over the safety of insulin analogs. One 2013 review of the use of insulin analogs in GDM actually concluded that additional safety data are needed despite being clinically effective and did not recommend the use of rapid-acting insulins in GDM solely based on their pharmacokinetic profile [69]. A second review article, including pregnant patients with pregestational diabetes and GDM, analyzed the efficacy and safety of insulin analogs [70]. The authors of this review argue that because lispro, aspart, glargine, and detemir did not differ in fetal outcomes in patients with type 1 diabetes that are well-controlled on their current regimen, even if it is regular insulin/NPH, there is no reason to switch [70]. However, in patients with increased incidence of hypoglycemia, changing to detemir may offer an advantage of improved fasting blood glucose levels without increasing hypoglycemia. This review in particular notes that the authors believe the evidence to be lacking to utilize long-acting analogs for patients with GDM due to their lack of propensity to experience hypoglycemia [70].

Analyzing all of the available evidence regarding efficacy and safety, it seems reasonable to select any of the insulins (regular, NPH, or one of the analogs) for patients with GDM who need insulin therapy. Cost concerns may direct providers to select regular or NPH while the convenience of mealtime

administration may direct providers to one of the rapid-acting analogs. Additionally, the long-acting insulin analogs can provide consistent control of blood glucose, which could be an advantage in patients in whom hypoglycemia is a concern. Ease of delivery of many of the insulins in pen formulation now may also assist patients with the transition to insulin. However, as evidence regarding the safety of the various insulin products continues to be published, providers and patients will have additional data to consider as they decide which insulin product to utilize.

Postpartum management

For women with gestational diabetes, blood glucose levels can be variable for both mother and infant in the immediate postpartum period. If insulin was utilized to manage gestational diabetes, the maternal and infant blood glucose levels should be monitored very closely. Maternal insulin administration may not be needed or the requirements may decrease significantly in the hours following delivery. The requirements may continue to decline over time, especially if the mother is breastfeeding [6]. If oral therapies were utilized, they also may no longer be needed after delivery. Protocols for checking blood glucose levels postpartum may vary from hospital to hospital, but close monitoring of maternal blood glucose levels is needed to determine the best course of management [6].

Women who have had gestational diabetes are strongly encouraged to breastfeed for benefits to both mother and infant [4,5]. If therapy is needed to control maternal blood glucose levels, metformin, glyburide, glipizide, and insulin are considered preferred therapies in breastfeeding women [4–6,36–38,71]. While these medications may be excreted in the breast milk, the risks to the infant are considered low [4–6,36–38,71]. All other medications utilized to manage type 2 diabetes have very limited or no human data available in lactation and are not recommended in breastfeeding (36–38,71). Some clinicians will recommend periodically assessing infant blood glucose levels while the mother is taking medications to ensure that the infant is not experiencing hypoglycemia.

It is recommended that patients with a history of GDM be screened for type 2 diabetes starting no earlier than 6 weeks postpartum and no later than 6 months postpartum [1–6]. Most recommend initial screening in the 6–12 week postpartum window [1–3,6]. A few organizations recommend routine screenings periodically in patients who have had GDM because these patients are considered at risk for developing type 2 diabetes later in life [2,3,5,6]. The interval for periodic screening varies based on patient risk factors from annually for patients considered high risk to every 2–3 years for patients considered low risk [2,3,5,6]. Numerous screening methods are recommended by various organizations, which may include any of the following: an OGTT, a fasting blood glucose level, and/or an A1C [1–6].

Conclusion

Because worldwide guidelines support screening for GDM between 24 and 28 weeks gestation or earlier in those patients at high risk for GDM, all primary care providers need an understanding of safe and efficacious options to manage GDM. Although the efficacy and safety of treatment modalities for GDM has been the source of much debate in recent years, both glyburide and metformin are oral agents now recommended in many guidelines as an appropriate option for the management of patients with GDM. Both agents have convincing efficacy and safety evidence. However, given the potential improvement in fetal outcomes in direct comparisons between glyburide and metformin, metformin may be considered the preferred first-line option when an oral agent is preferred by the patient or provider. It is important to consider patient-specific characteristics when selecting ideal candidates for metformin compared with glyburide. In patients with GDM who require insulin to help obtain target blood glucose or in whom providers decide to use insulin, there are several options for insulin products, including insulin analogs. Given the available efficacy and safety evidence with the various insulin products, it seems reasonable to utilize any of the insulin products (regular, NPH, or one of the analogs) in the management of GDM. This means that providers can select a product and delivery form (pen or vial and syringe) based on the patient's needs. Because GDM may not just be GDM, it is important for patients to be screened for type 2 diabetes between 6 weeks and 6 months postpartum. If management is needed, the safety of agents in breastfeeding must be considered.

As the incidence of GDM continues to rise, there will continue to be a need for management options of GDM. As additional evidence of appropriate management of GDM continue to emerge, providers will need to continue to assess new therapies for efficacy and safety and guidelines to be able to develop an individualized plan for managing each patient's GDM.

Case #1

LK is a 36-year-old african american female. She is a G1P0 and at 28 weeks gestation. She was diagnosed with gestational diabetes 2 weeks ago after failing her screening test. She has tried diet modification to manage her BG levels but has been unsuccessful. Her physician is seeking a recommendation to manage her BG levels. She tells the nursing staff today that she is absolutely terrified of needles. But it is all she can do to test her blood sugars several times each day.

PMH: unremarkable
Allergies/intolerances: none
Medications: Prenatal vitamin 1 Qday

SH: teacher, married, private insurance

Vitals:
BMI (prepregnancy): 24
Weight (today): 165 lbs
Height: 5'8"
BP: 130/80
HR: 76

What medications should be considered to help LK manage her BG levels?

A. glyburide
B. metformin
C. pioglitazone
D. saxagliptin

Answer/Rationale: B. metformin

According to the various guidelines for managing GDM and based on the available evidence, metformin would be a reasonable option to initiate (and considered first line by NICE for the management of GDM). LK has a lower BMI and later gestational age at time of treatment with no previous history of GDM, which makes her an ideal candidate for metformin. Glyburide is a viable option in the management of GDM but is considered second line to metformin unless a contraindication exists to its use. Pioglitazone, a thiazolidinione, and saxagliptin, a dipeptidyl peptidase IV (DDP IV) inhibitor, are both not currently recommended for use in the management of GDM due to adverse fetal outcomes in animal studies and lack of human studies.

Case #2

RP is a 24-year-old hispanic female. She is a G3P2 and at 24 weeks gestation. She was diagnosed with gestational diabetes today after failing her screening test. She has tried diet modification in the past along with metformin to manage her GDM in her previous pregnancy. She failed dietary therapy. She did not tolerate metformin. Her physician is seeking a recommendation to manage her BG levels.

PMH: GDM with previous pregnancy 18 months ago, HTN
Allergies/intolerances: metformin (gi issues)
Medications: Prenatal vitamin 1 QDay, Labetalol 100 mg BID

SH: unemployed, married, immigrant, English as a second language (ESL)

Vitals:
BMI (prepregnancy): 29
Weight (today): 160 lbs
Height: 5'0"
BP: 150/88
HR: 72

OGTT results (today):
Fasting: 100 mg/dL
1 hour: 185 mg/dL
2 hour: 166 mg/dL
3 hour: 148 mg/dL

What medications should be considered to help RP manage her BG levels?

A. exenatide
B. glyburide
C. metformin
D. pioglitazone

Answer/Rationale: B. glyburide

According to the various guidelines for managing GDM and based on the available evidence, glyburide would be a reasonable option to initiate. RP has a fasting OGTT less than 110 mg/dL and is of younger age, which makes her an ideal candidate for glyburide. Because RP did not tolerate metformin in her previous pregnancy, metformin would not be appropriate to start in this pregnancy. Exenatide, a GLP-1 receptor agonist, and pioglitazone, a thiazolidinione, are both not currently recommended for use in the management of GDM due to adverse fetal outcomes in animal studies and lack of human studies.

Case #2—follow-up #1

RP returns to clinic after 4 weeks on a therapeutic dose of oral therapy you recommended. She is now at 28 weeks gestation. She reports her fasting plasma glucose average as 110 mg/dL and her 2-hour postprandial glucose average as 132 mg/dL.

Due to the concern that her glucose values are increasing, what would you recommend as the next step to help RP manage her blood glucose?

A. exenatide
B. glyburide
C. insulin
D. pioglitazone

Answer/Rationale: C. insulin

At this point, RP is a candidate for insulin. Her fasting glucose averages, earlier gestational age at diagnosis, diagnosis of GDM in previous pregnancy, and English as a second language are all characteristics that make it likely that she might need insulin as part of her management of GDM. Exenatide, a GLP-1 receptor agonist, and pioglitazone, a thiazolidinione, are both not currently recommended for use in the management of GDM due to adverse fetal outcomes in animal studies and lack of human studies, given insulin is a viable option to change the patient to for management.

Case #2—follow-up #2

RP has agreed to start insulin but the provider wants her to continue glyburide to assist with control of postprandial glucose. Which of the following insulins would be most appropriate to add to RP's regimen?

A. aspart
B. glulisine
C. glargine
D. regular

Answer/Rationale: C. glargine

Based on the provider's desire to control RP's overall glucose values, glargine would be the most appropriate of the insulins listed. However, it would be reasonable to use intermediate insulin (e.g., NPH) or one of the long-acting insulins (e.g., detemir

or glargine) with evidence of efficacy and safety in GDM. Based on the available evidence, it is thought that either regular insulin or the rapid-acting insulin analogs would be efficacious for use in patients with GDM. However, due to their pharmacokinetic profile, rapid-acting insulin analogs would specifically target postprandial glucose and would require multiple daily insulin injections. They would also be more likely to cause hypoglycemia, especially, if used in conjunction with glyburide.

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