KAISER PERMANENTE

Gestational Diabetes Screening and Treatment Guideline

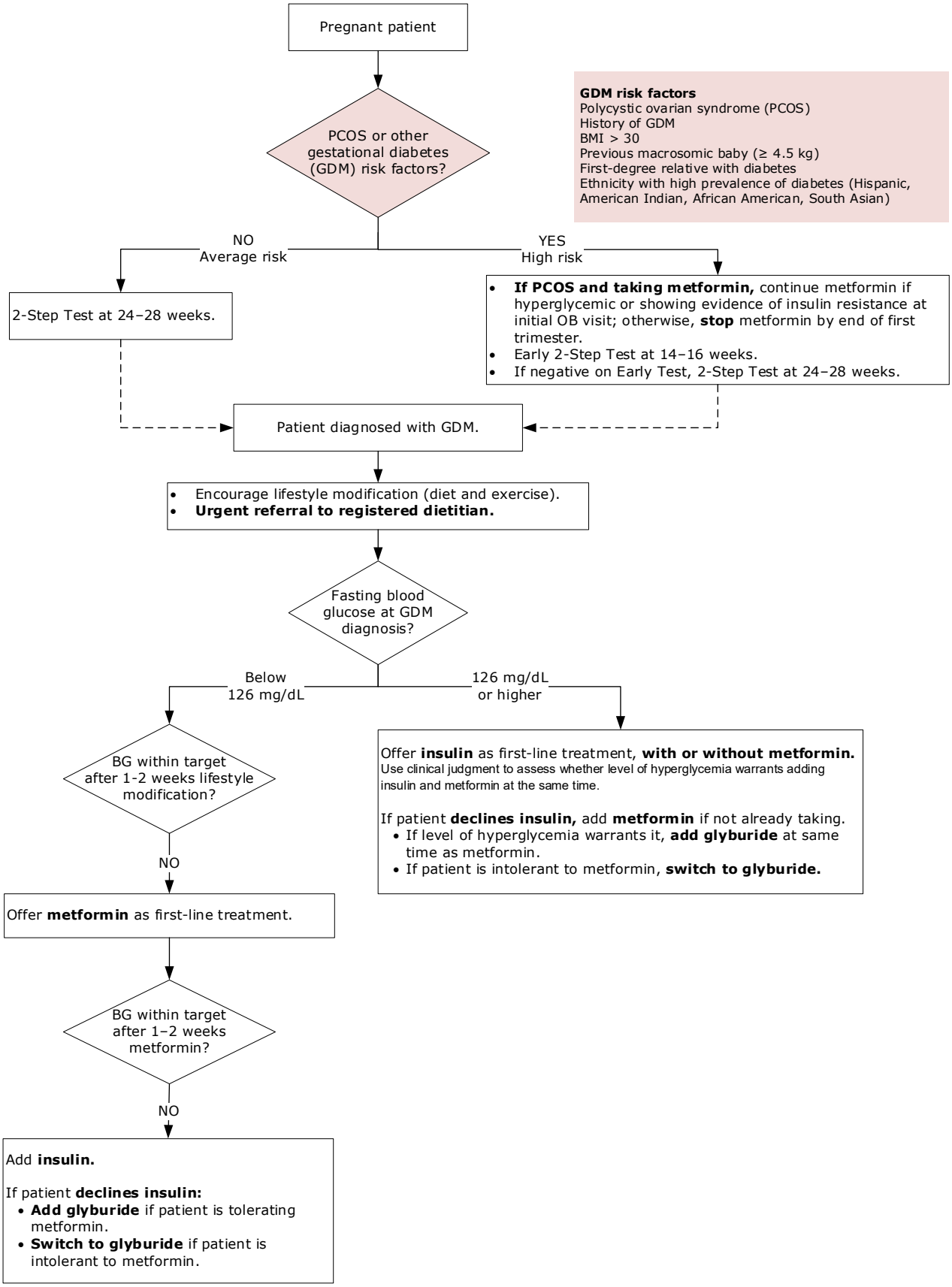
Last guideline approval: September 2021

Guidelines are systematically developed statements to assist patients and providers in choosing appropriate health care for specific clinical conditions. While guidelines are useful aids to assist providers in determining appropriate practices for many patients with specific clinical problems or prevention issues, guidelines are not meant to replace the clinical judgment of the individual provider or establish a standard of care. The recommendations contained in the guidelines may not be appropriate for use in all circumstances. The inclusion of a recommendation in a guideline does not imply coverage. A decision to adopt any particular recommendation must be made by the provider in light of the circumstances presented by the individual patient.

Major Changes as of September 2021

New	Previous
Metformin is first-line treatment for patients whose GDM is not controlled by diet and exercise and have a fasting blood glucose **below 126 mg/dL**. **Insulin,** with or without metformin, along with diet and exercise is the first-line treatment for patients who have a fasting blood glucose of **126 mg/dL or higher**.	Insulin is first-line treatment for patients whose GDM is not controlled by diet and exercise.
Pregnant patients who are taking metformin for **PCOS** are **advised to stop taking metformin** by the end of their first trimester unless they are found to be hyperglycemic or have evidence of insulin resistance at their first OB visit.	There is insufficient evidence on which to base recommendations for continuing metformin during pregnancy for the management of PCOS.
All patients with GDM should be referred to a registered dietitian for nutritional counseling.	Referral to registered dietitian not mentioned in the guideline; KPWA had no RDs in the internal delivery system at that time.
A new **screening and treatment flowchart** has been added. (See following page.)	—

Screening and Treatment Flowchart



Screening Recommendations and Tests

Table 1. Recommendations for screening for previously undiagnosed diabetes and for gestational diabetes [1]

Screen for	Eligible population	Recommended frequency	Recommended tests
Previously undiagnosed diabetes	All pregnant patients [1]	Initial OB visit with nurse	HbA1c (as part of OB lab panel) If HbA1c screen is negative but diabetes is suspected due to symptoms, BMI, or ultrasound findings, a provocative test is recommended (2-step oral glucose tolerance test).
Gestational diabetes	Pregnant patients at high risk for GDM [2]	Consider screening at 14–16 weeks gestation.	2-step oral glucose tolerance test
	Pregnant patients **not** at high risk for GDM [2]	Screen at 24–28 weeks gestation.	

[1] It is reasonable to exclude screening for previously undiagnosed diabetes if the patient is at low risk for diabetes and gestational diabetes. This would include patients who are Caucasian, young (age < 25), thin, and with no personal or family history of diabetes.

[2] Patients at increased risk of diabetes or gestational diabetes include those with a history of gestational diabetes; BMI > 30; previous macrosomic baby (weighing ≥ 4.5 kg); first-degree relative with diabetes; ethnicity with high prevalence of diabetes (Hispanic, American Indian, African American, South Asian); or polycystic ovarian syndrome (PCOS).

Diagnosis

Table 2. Recommendations for confirming diabetes diagnosis

Diagnosis	Recommended tests	Positive result parameters
Previously undiagnosed diabetes	**HbA1c** Confirm the diagnosis with two tests done the same day: HbA1c and either fasting plasma glucose or random plasma glucose. • Abnormal results on both tests are diagnostic of diabetes. • If only one test produces an abnormal result, that test should be repeated. For more information about the diagnostic process, see the Type 2 Diabetes Guideline.	≥ 6.5%
Gestational diabetes at 24–28 weeks	**2-step oral glucose tolerance test** Step 1 is nonfasting 1-hour 50 mg glucose tolerance test. ○ 1-hour result < 135 mg/dL is considered normal. No more testing required. ○ 1-hour result between 135 mg/dL and 200 mg/dL is considered abnormal and the patient needs to move on to step 2. ○ 1-hour result ≥ 200 mg/dL is considered diagnostic of GDM and does not require any further diagnostic tests. Step 2 is fasting 2-hour 75 mg glucose tolerance test. The patient is diagnosed with GDM if any one of these three values is abnormal: ○ Fasting ≥ 95 mg/dL ○ 1-hour ≥ 180 mg/dL ○ 2-hour ≥ 162 mg/dL	

Treatment

Goals

Maintaining glycemic control will lead to improved pregnancy outcomes, including decreases in macrosomia, clinical neonatal hypoglycemia, and cesarean section rates.

Lifestyle modifications/non-pharmacologic options

Most patients who have gestational diabetes can successfully control their blood glucose with diet and exercise. Initiate a trial of lifestyle modifications and provide information about diet and exercise.

Diet and nutrition

- Give simple messages about nutrition: decrease simple sugars, rely more on complex carbohydrates, and increase lean protein and vegetable consumption.
- Diet recommendations for patients with gestational diabetes are different from those for non-pregnant patients with diabetes, in that the diet for GDM includes both more protein and more fat.
- Among patients with gestational diabetes, 75–80% can achieve normoglycemia through dietary changes.

Calorie distribution

Opinions regarding the optimal distribution of calories vary. Most programs suggest three meals and three snacks; however, in patients with overweight or obesity the snacks are often eliminated. Below are recommendations for caloric distribution:

- Breakfast: 10% of total caloric allotment (Carbohydrate intake at breakfast is limited since insulin resistance is greatest in the morning.)
- Lunch: 30% of calories
- Dinner: 30% of calories
- Snacks: 30% of calories

Recommended overall total caloric distribution:

- Carbohydrate: 33–40%
- Protein: about 20%
- Fat: about 40%

Exercise

Moderate exercise is recommended by the American Diabetes Association (ADA):

- All patients, including those who are pregnant, are encouraged to exercise 1 hour daily.
- The current intensity and type of exercise should be modified for obvious safety issues (e.g., activities involving balance, direct contact sports).

Pharmacologic options

Patient home glucose monitoring

Following the diagnosis of gestational diabetes, ask patients to begin home glucose monitoring as outlined in Table 3. Ask them to report the results after 1 week of monitoring and every 2–3 weeks thereafter until delivery. Let patients know that they will be informed if any changes to treatment are needed based on those results.

Table 3. Home glucose monitoring for patients with gestational diabetes

Glucose monitoring time	Goal
Fasting	Average < 95 mg/dL
Before lunch Before evening meal	Average < 95 mg/dL
1 hour after all meals	Average < 140 mg/dL

If the patient is maintaining good glucose control, consider decreasing home monitoring to twice a day: fasting and 1 hour after the biggest meal.

However, the patient should return to the full Table 3 schedule:

- If, at any time, average readings are not below target, and
- Periodically throughout pregnancy as dietary needs change.

Patients taking metformin for PCOS prior to pregnancy

There is insufficient evidence on which to make a strong recommendation about whether to continue metformin during pregnancy for the management of PCOS. Due to limited evidence that suggests that stopping metformin decreases the risks of adverse pregnancy outcomes, including first-trimester loss, we recommend stopping metformin by the end of the first trimester of pregnancy; however, if such a patient is found to have hyperglycemia or evidence of insulin resistance at the initial OB visit, the metformin should be continued.

Initiation of pharmacologic treatment

Pharmacologic treatment is initiated if lifestyle measures are inadequate for reaching target blood glucose.

The glucose level for which pharmacotherapy's benefits clearly outweigh its disadvantages or harms has not been clearly established. The Hyperglycemia and Adverse Pregnancy Outcome trial (HAPO), a large observational trial, demonstrated that a fasting glucose level of > 105 mg/dL is associated with a five-fold increase in the risk of macrosomia compared to a fasting glucose level of < 75 mg/dL (25% versus 5%) (HAPO Study Cooperative Research Group 2008). Lower glucose levels were associated with better primary outcomes, but there were no obvious thresholds at which the risks increased. Since the HAPO trial, more organizations are recommending lower glucose targets.

This guideline recommends initiating pharmacologic treatment if, **during the previous week**, the patient's average readings are:

- Fasting plasma glucose ≥ 95 mg/dL, **or**
- 1-hour postprandial glucose ≥ 140 mg/dL

There is no direct evidence on which to establish treatment thresholds; therefore, if the patient would prefer a higher threshold before initiating pharmacotherapy—after a conversation about the risks of gestational diabetes and the benefits of tight glucose control has occurred—a higher target can be negotiated between patient and clinician.

Note: While **oral anti-hyperglycemic agents** have been used for years to treat gestational diabetes, their use for this purpose has not been approved by the FDA. If oral diabetes agents are used, patients should be clearly informed that these drugs cross the placenta and may have unknown risks to the fetus.

Table 4. Recommended anti-hyperglycemic medications for patients with gestational diabetes		
Population	**Preferred**	**If needed**
Fasting blood glucose 126 mg/dL or higher	Insulin	Add metformin. [1]
Fasting blood glucose under 126 mg/dL and GDM not controlled by diet and exercise	Metformin	Add insulin.
Unwilling to take insulin and GDM not controlled by diet and exercise	Metformin	• Tolerant to metformin: Add glyburide. [2] • Intolerant to metformin: Switch to glyburide.

[1] Use clinical judgment to assess whether level of hyperglycemia warrants adding insulin and metformin at the same time.
[2] Use clinical judgment to assess whether level of hyperglycemia warrants adding metformin and glyburide at the same time.

Table 5. Insulin dosing recommendations
Long-acting insulin analogs (insulin glargine, insulin detemir) are **not** recommended, as they have not been studied extensively in pregnancy.

Step 1: Control fasting hyperglycemia by initiating insulin therapy with NPH.
(Goal: average weekly fasting blood glucose < 95 mg/dL—see Table 3.)

Medication	Frequency	Starting dose	Modified dose
NPH	The entire dose is taken at bedtime.	0.2 units/kg	Every 4 days; if 4-day average is ≥ 95 mg/dL, increase dose by 2 units until 4-day average fasting blood glucose is < 95 mg/dL.

Step 2: After controlling fasting hyperglycemia, control postprandial readings with insulin lispro
(Goal: average weekly postprandial readings < 140 mg/dL—see Table 3.)

Medication	Frequency	Starting dose	Modified dose
Insulin lispro	If for any meal the 1-hour postprandial reading is *persistently* ≥ 140 mg/dL, add insulin lispro to be taken at that meal.	1 unit lispro per 10 g carbohydrate	Increase lispro to 2 units per 15 g carbohydrate until 1-hour postprandial reading is < 140 mg/dL.

Step 3: If control is still not adequate, contact the Diabetes Team for advice on additional adjustments.

Table 6. Oral medication dosing recommendations
See "Prescribing notes" following table.

Medication	Starting dose	Titration
Metformin	500 mg once daily	850 mg t.i.d.
Glyburide	2.5–5.0 mg daily at first meal	2.5 mg once daily to 7.5 mg b.i.d.

Prescribing notes for Table 6

Metformin

Metformin should be titrated as tolerated. A reasonable initial titration schedule is:

a) 500 mg PO once daily x 3 days;
b) 500 mg PO twice daily x 3 days;
c) 500 mg PO three times daily x 3 days;
d) [Three doses per day PO: 1,000 mg - 500 mg - 500 mg] x 3 days;
e) [Three doses per day PO: 1,000 mg - 500 mg - 1,000 mg] daily until delivery

If stomach upset occurs, do not advance to the next higher dose until it has resolved.

Alternatively, consider prescribing the **extended release (XR)** formulation for patients who cannot tolerate ideal dose with regular release formulation.

Glyburide
While the maximum dose is glyburide 10 mg b.i.d., the medication's effectiveness has been found to plateau at 5.0–7.5 mg b.i.d.

Additional Testing/Monitoring

Antenatal monitoring

There is no evidence on which to base the optimal timing for delivery, ultrasound for fetal weight and amniotic fluid index, or for non-stress testing, so the following recommendations are based on community standards and expert opinion.

Table 7. Recommended antenatal monitoring

	GDM diet controlled/GDM A1	GDM med/insulin controlled/GDM A2	GDM poorly controlled
Non-stress test	Not standard practice	Start at 32 weeks/ twice weekly	Start at 32 weeks/ twice weekly
Ultrasound for fetal weight (estimated fetal weight)	Not standard practice	Start at 30–32 weeks Consider repeat in 4–6 weeks	Start at 30–32 weeks/ Consider repeat in 4–6 weeks
Amniotic fluid index/ maximum vertical pocket	Not standard practice	Start at 32 weeks/ once weekly	Start at 32 weeks/ once weekly
Induction of labor	Consider between 40w0d and 40w6d	Consider between 39w0d and 39w6d	Consider between 38w0d and 38w6d

Ketone checking is ***not*** recommended as an antenatal test.

Follow-up after delivery

Gestational diabetes is a risk factor for type 2 diabetes. While only about 5% of patients who have gestational diabetes develop type 2 diabetes within 6 months of delivery, about 60% will develop type 2 diabetes within 10 years (Hartling 2012). Encourage a healthy diet, exercise, and weight control to prevent type 2 diabetes.

Table 8. Recommended follow-up testing

Eligible population	Test	Frequency/timing
All patients with gestational diabetes (place order at 4-week postpartum visit)	HbA1c	3 months postpartum
All patients with a history of gestational diabetes	HbA1c	Annually

Referral

- Family medicine providers or ARNP midwives should consult with an obstetrician if the estimated fetal weight is ≥ 4,500 g, or if the non-stress test or amniotic fluid index is abnormal.
- Obstetricians should consider a consult with Maternal Fetal Medicine if early induction of labor is being considered (at 38 weeks gestation or earlier).
- Patients with gestational diabetes (regardless of whether they are taking insulin) do not need to be managed by an obstetrician unless specific issues arise.
- All patients diagnosed with gestational diabetes should be referred to a registered dietitian for nutritional counseling. (Order as Urgent Referral to avoid delays.)

Evidence Summary

The Gestational Diabetes Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

As part of our improvement process, the Kaiser Permanente Washington guideline team is working towards developing new clinical guidelines and updating the current guidelines regularly. To achieve this goal, we are adapting evidence-based recommendations from high-quality national and international external guidelines, if available and appropriate. The external guidelines should meet several quality standards to be considered for adaptation. They must: be developed by a multidisciplinary team with no or minimal conflicts of interest; be evidence-based; address a population that is reasonably similar to our population; and be transparent about the frequency of updates and the date the current version was completed.

In addition to identifying the recently published guidelines that meet the above standards, a literature search was conducted to identify studies relevant to the key questions that are not addressed by the external guidelines.

External guidelines eligible for adapting

- American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S14-S31. doi:10.2337/dc20-S002
- NICE guideline 2021. Diabetes in pregnancy: management from preconception to the postnatal period. https://www.nice.org.uk/guidance/ng3
- ACOG Practice Bulletin No. 190 Summary: Gestational Diabetes Mellitus. *Obstet Gynecol*. 2018;131(2):406-408. doi:10.1097/AOG.0000000000002498
- Diabetes Canada Clinical Practice Guidelines Expert Committee, Feig DS, Berger H, et al. Diabetes and Pregnancy. *Can J Diabetes*. 2018;42 Suppl 1:S255-S282. doi:10.1016/j.jcjd.2017.10.038
- Duarte-Gardea MO, Gonzales-Pacheco DM, Reader DM, et al. Academy of Nutrition and Dietetics Gestational Diabetes Evidence-Based Nutrition Practice Guideline. *J Acad Nutr Diet*. 2018;118(9):1719-1742. doi:10.1016/j.jand.2018.03.014
- Kaiser Permanente Northwest 2018: Management of Diabetes in Pregnancy Practice Resource, https://cl.kp.org/nw/cpg/cpgs/content/pregnancy-teach-insuldiab.html
- Royal College of Obstetrics & Gynaecology, 2014. Long-term Consequences of Polycystic Ovary Syndrome Green-top Guideline No. 33, November 2014 (NICE accredited). https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_33.pdf
- USPSTF. Gestational Diabetes: Screening. 2021. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/gestational-diabetes-screening

Key questions

1. **In pregnant women with gestational diabetes (GDM), what is the comparative effectiveness and harms of the oral antihyperglycemic drugs metformin and glyburide as compared to insulin therapy?**

The different professional societies and organizations in the US, Canada, and the UK recommend lifestyle behavior change as the first-line treatment for GDM. If glycemic targets are not achieved with nutritional therapy and physical activity, pharmacologic therapy should be initiated.

The ADA (2020), ACOG (2018), and the Canadian Clinical Practice Guidelines for GDM (2018) all recommend insulin as the first-line pharmacologic treatment of GDM when needed to achieve glycemic control. Metformin and, rarely, glyburide are recommended only in certain situations when women cannot tolerate or cannot afford insulin.

The NICE guideline for diabetes in pregnancy (2020) has a different approach on the use of pharmacologic treatment. The guideline recommends the following:

- In women with GDM and a fasting plasma glucose level < 7.0 mmol/liter (< 126 mg/dL) at diagnosis, use metformin if they do not meet blood glucose after 1–2 weeks trial of diet and exercise. If metformin is contraindicated or unacceptable to the woman, offer insulin.
- If blood glucose targets are not met with diet and exercise changes plus metformin, offer insulin as well.
- In women with GDM with a fasting plasma glucose level of ≥ 7.0 mmol/liter (≥ 126 mg/dL) at diagnosis, immediately start treatment with insulin, with or without metformin and diet and exercise changes.
- For women with gestational diabetes who have a fasting plasma glucose level of between 6.0 mmol/liter (108 mg/dL) and 6.9 mmol/liter (124 mg/dL) and complications such as macrosomia or hydramnios, consider immediate treatment with insulin, with or without metformin and diet and exercise changes.
- Consider glibenclamide (glyburide) (off-label use for some brands) for women with gestational diabetes if blood glucose targets are not met with metformin and the woman declines insulin or cannot tolerate metformin.

A literature search for more recently published studies identified several meta-analyses that compared the oral antihyperglycemic drugs and insulin; metformin and insulin; and glyburide and insulin for the treatment of GDM. The search also revealed two more recent RCTs and several observational studies that compared the efficacy of metformin and insulin and/or examined the long-term impact of metformin on the growth of GDM offspring exposed to metformin during the fetal life.

The overall short-term comparative efficacy and safety of pharmacological therapy reported in published studies and meta-analyses (Wang 2021, Guo 2019, Picón-César 2021) show the following:

- There were no significant differences between metformin and insulin in maternal glycemic control.
- Metformin has advantages over insulin for several maternal and neonatal outcomes, including reducing maternal weight gain, pregnancy-induced hypertension, incidence of neonatal hypoglycemia, macrosomia, and NICU admission.
- In the MeDiGes trial (Picón-César 2021), 21.3% of metformin-treated women needed additional insulin.
- Glyburide was found to be associated with a higher risk of neonatal hypoglycemia and higher birth weight versus insulin.
- The limited number of published studies comparing metformin to glyburide suggest that metformin may be associated with a lower incidence of induction of labor and lower gestational weight gain, but glyburide may be superior in controlling fasting blood glucose.
- No significant differences were observed between insulin, metformin, and glyburide in some other outcomes, including fetal or neonatal death, Apgar 5 < 7, congenital anomalies, respiratory distress, shoulder dystocia, maternal glycosylated hemoglobin, and preterm birth.

Weak evidence from limited published follow-up studies suggests that the use of metformin versus insulin for the management of women with GDM may not be associated with clinically significant long-term adverse effects on the offspring in terms of growth and development.

- The 2019 systematic review and meta-analysis by Tarry-Adkins and colleagues showed the following:
    - *At birth:* Neonates born to metformin-treated mothers had lower weight, ponderal indices, macrosomia, and LGA compared to those with insulin-treated mothers. There was no difference between the two groups in neonatal height or incidence of small size for gestational age between groups.
    - *At 18–24 months:* The metformin-exposed infants were significantly heavier compared to those in the insulin-exposed group.
    - *At 5–9 years:* The metformin-exposed children had a significantly higher BMI compared to those in the insulin-exposed group, with no significant difference between the groups in absolute weights.
- The offspring follow-up (MiG TOFU) study (Rowan 2018) found no differences between the offspring of GDM mothers treated with metformin versus those treated with insulin in respect to total and abdominal body fat percent and metabolic measures at 7–9 years. Metformin-exposed children, however, were larger at 9 years.
- The 2018 observational study by Landi and colleagues suggests that there is no long-term (4-year) significant difference between children born to GDM mothers treated with insulin versus those treated with metformin treated in respect to their growth and development.

- A small study (Ijäs 2015) that reported on growth and development at 6, 12 and 18 months in children born to GDM mothers showed that those exposed to metformin were significantly heavier at the age of 12 and 18 months and taller at the age of 18 months. The mean ponderal index (PI) did not differ significantly. There were no differences in motor, social, or linguistic development at 18 months.

More evidence is needed to determine the long-term effect of metformin on children exposed to the drug in their mothers' womb.

2. What is the most appropriate time for screening pregnant women with PCOS for GDM?

The Royal College of Obstetrics & Gynaecology 2014 guideline is the only identified guideline that has a recommendation on screening for GDM in women diagnosed with polycystic ovarian syndrome (PCOS) before pregnancy: "Screening should be performed at 24–28 weeks of gestation, with referral to a specialist obstetric diabetic service if abnormalities are detected. Recommended best practice based on the clinical experience of the guideline development group (evidence level 4 [expert opinion])."

USPSTF 2020: "Screening for GDM may occur earlier than 24 weeks of gestation in high-risk women, but there is little evidence about the benefits and harms of screening before 24 weeks of gestation."

The literature search did not identify any RCT or longitudinal cohort study that examined the effect of screening for GDM on the of maternal or fetal outcomes of pregnancy in women with PCOS, or whether there is an optimal time for screening pregnant women with PCOS.

3. In women with PCOS who get pregnant and were on pre-pregnancy metformin therapy, what is the comparative safety and efficacy of discontinuing metformin, increasing its dose, adding insulin, or replacing it with insulin?

ADA 2020 and ACOG 2018 recommend the discontinuation of metformin in women with PCOS by the end of the first trimester.

The literature search for RCTs and meta-analyses on the use of metformin in women with PCOS who got pregnant identified three RCTs conducted by the same group of investigators—PregMet2 (Løvvik 2019), PregMet (Vanky 2010) and a small pilot (Vanky 2004)—and meta-analysis of RCTs and observational studies (Bidhendi Yarandi 2019).

The PregMet and PregMet2 RCTs were conducted in Norway, Sweden, and Iceland to determine whether metformin had any beneficial effects on preeclampsia, preterm delivery, and gestational diabetes. Both studies were underpowered and showed no difference in pregnancy complications between the metformin and placebo. In order to increase the sample size and statistical power, the investigators performed an unplanned post hoc analysis pooling individual participant data of the two RCTS together with an earlier small pilot study. The results of the post hoc analysis suggest that women with PCOS treated with metformin from the late first trimester until delivery had a significantly lower rate of preterm delivery versus those who received a placebo. There was no significant difference between the two groups in the rate of late miscarriage. However, the authors combined the two outcomes and calculated a number needed to treat with metformin of 18.4 to avoid one late miscarriage or preterm birth. This has to be interpreted cautiously as it is a post hoc analysis. Moreover, the studies were conducted among Nordic women with PCOS who were aware of their diagnosis and might have had a more severe phenotype than those who are undiagnosed.

In conclusion, there is insufficient published evidence from well-designed large RCTs to determine the efficacy and safety of continuing or discontinuing metformin therapy in women with PCOS who get pregnant.

4. **In women with GDM, what is the effectiveness of medical nutrition therapy intervention provided by a registered dietitian nutritionist on fetal/neonatal and maternal outcomes?**
5. **In women with GDM, what is the effect of calorie consumption on fetal/neonatal and maternal outcomes?**

These two questions were informational only and no evidence review was performed. Recommendations from external guidelines were adopted, including ADA 2020, ACOG 2018, and Academy of Nutrition and Dietetics 2018.

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Guideline Development Process and Team

Development process

To develop the Gestational Diabetes Screening and Treatment Guideline, the guideline team adapted recommendations from external developed evidence-based guidelines and/or recommendations organizations that establish community standards. The guideline team reviewed additional evidence in several areas. For details, see Evidence Summary and References.

This edition of the guideline was approved for publication by the Guideline Oversight Group in September 2021.

Team

The Gestational Diabetes Screening and Treatment Guideline development team included representatives from Clinical Improvement & Prevention, endocrinology, family medicine, KPWHRI, nursing, nutritional services, obstetrics/gynecology, pharmacy.

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