Gestational Diabetes: Screening Strategies, Glycemic Targets and Pharmacologic Management

Obstetric Consensus Conference

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INTRODUCTION

Gestational diabetes (GDM) occurs in ~7% of pregnancies in the US and increases the incidence of maternal and fetal morbidities such as fetal macrosomia, cesarean delivery, polyhydramnios, hypertension and preeclampsia, and preterm delivery. Women with gestational diabetes have increased risk of developing type 2 diabetes as well as cardiovascular disorders after pregnancy. Given the increased frequency of perinatal complications and potential impact on lifelong health, gestational diabetes screening is currently recommended for all pregnant women, regardless of the presence or absence of known risk factors. However there are multiple recommendations and guidelines regarding suggested screening or diagnostic tests, and threshold values.

The purpose of this consensus statement is to provide suggested guidelines for screening for GDM, as well as guidelines for glycemic control and pharmacologic management in women diagnosed with GDM.

The 1-hour 50gram Glucose Challenge Test
Establishing a diagnostic threshold

The American College of Obstetricians and Gynecologists (ACOG), as well as the National Institute for Child Health and Human Development (NICHD) recommend screening all pregnant women for gestational diabetes with a two-step approach using a 50gm glucose challenge test (GCT) as a screen at 24-28 weeks followed by a diagnostic 100gm 3hr glucose tolerance test (GTT) if GCT results exceed a predetermined institutional threshold (typically 130-140mg/dL). At the University of Washington, we recommend a GCT cutoff of 140mg/dL as criteria for proceeding to the diagnostic 3-hour GTT to diagnose GDM (Figure 1). Carpenter and Coustan criteria have standardly been used at the University of Washington to establish diagnostic cutoffs for the 3-hour GTT values (Fasting <95mg/dL, 1-hour <180 mg/dL, 2-hour <155 mg/dL, and 3-hour <140 mg/dL). However, it has been argued that an upper limit of the 50gm glucose challenge test (GCT) could be diagnostic, thereby eliminating the need to complete the 3 hour glucose tolerance test. Several studies have evaluated what that upper limit should be with mixed results.

Several retrospective studies have evaluated the sensitivity and specificity of the upper limits of the 50 gm GCT for elevated glucose in pregnancy and adverse perinatal outcomes. Using a diagnostic threshold of 180mg/dl, specificities range from 72-90%7-9; using a threshold of 200mg/dl, specificities were 85-99%.7-9 One study by Korucuoglu et al found an increase in both maternal and neonatal morbidities when GCT was greater than 180mg/dl even when a subsequent 3 hour GTT was not diagnostic.8 Although we acknowledge that the quality of the data in support of a diagnostic threshold for GCT are limited (and predictive values will vary based on population prevalence of GDM), the studies did consistently suggest a reasonable correlation between significantly elevated GCT results and GDM diagnosis. Given the costs and effort associated with a 3-hr oral glucose tolerance test, using a diagnostic threshold for the GCT may ultimately be more efficient and cost-effective especially in those with an elevated pre-test probability for GDM.

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<th>SUMMARY OF RECOMMENDATIONS:</th>
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<td>We recommend using a 1-hour GCT level of 180mg/dl as diagnostic of GDM without proceeding to a 3 hour GTT. In select situations based on either clinician’s assessment or patient’s refusal to accept diagnosis based on the GCT, a 3 hour GTT may be considered for GCT results between 180-200mg/dl. A follow up 3 hour GTT is not required for any patient with a GCT ≥200mg/dL, as that value is sufficient for the diagnosis of GDM.</td>
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EARLY SCREENING STRATEGIES
For women at elevated risk of gestational diabetes

It is well established that GDM causes increased fetal and maternal morbidities. This has driven the interest to diagnose GDM at an earlier gestational age to allow for interventions that may ameliorate these morbidities. Studies have examined ideal timing and type of testing that should be used for early screening. ACOG currently recommends early screening in the first trimester among women with noted risk factors for GDM, although they make no recommendation as to the type of test that should be used.

Studies have evaluated abnormal early screening and the risk of later diagnosis of GDM. Abnormal glucose tolerance in the first trimester has been shown to be associated with an incidence of GDM ranging from 10-50% depending on the severity of glucose intolerance and the number of risk factors for GDM. The main focus of these studies was early glucose intolerance as a risk factor for GDM; they performed only a limited analysis of maternal or neonatal outcomes that showed no differences.

We recommend ACOG risk factor based early screening for GDM; providers with a large percentage of high-risk patients may elect to use universal early screening.

Early screening should be done prior to 20 weeks, preferentially in the first trimester. The goal of early screening is to diagnose pre-gestational diabetes. Consider testing in overweight or obese (BMI ≥25 or ≥23 for Asian Americans) who have one or more of the following risk factors:

- Physical inactivity
- First-degree relative with diabetes
- High-risk race or ethnicity (African American, Latino, Native American, Asian Americans, Pacific Islander)
- Prior infant weighing ≥4000g (~9lbs)
- Previous GDM
- Hypertension (140/90 mmHg or on therapy for hypertension)
- High-density lipoprotein cholesterol level <35 mg/dL (0.90 mmol/L),
- Triglyceride level >250 mg/dL (2.82 mmol/L)
- Polycystic ovarian syndrome
- Hemoglobin A1C ≥5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
- Other clinical conditions associated with insulin resistance (ex: prepregnancy BMI ≥40, acanthosis nigricans)
- History of cardiovascular disease

Hemoglobin A1c testing
In the non-pregnant population, screening and diagnosis of diabetes has begun moving away from the use of oral glucose challenge tests due to the difficulties of completion of the test. Since 2010, the American Diabetic Association (ADA), recommends hemoglobin A1c (HgA1c) greater than or equal to 6.5% for diagnosis of type 2 diabetes (with the caveat that in the absence of unequivocal hyperglycemia or clinical signs/symptoms of diabetes, these results should be confirmed by repeat testing). Studies have started evaluating the use of HgA1c in pregnancy as well.
The California Diabetes and Pregnancy Program (CDAPP) implemented guidelines in 2011 known as Sweet Success. These guidelines recommend early screening of all pregnant women before 24 weeks gestation with fasting blood glucose (FBG) and HgA1c. By these guidelines, a FBG between 92-126mg/dL or HgA1c 5.7-6.5% is diagnostic of GDM and treatment is initiated. (A FBG ≥ 126 mg/dL or HgA1c ≥ 6.5% is diagnostic of pre-gestational diabetes). If values are below these cut-offs then routine GDM screening is performed between 24-28 weeks. A retrospective review comparing GDM in California the year prior to instituting this change with the first year after implementation was conducted by Alunni et al. They noted the incidence of GDM nearly doubled from 5.3% to 9.4%. Patients who were diagnosed early, by either FBG and/or HgA1c, were more likely to require medical therapy. This finding was even more significant in obese patients. Despite increased need for pharmacotherapy, there was no apparent difference in maternal or neonatal outcomes when comparing the two cohorts (GDM diagnosed by early screening with FBG or HgA1c vs GDM diagnosed by two-step screening).

Further studies have evaluated the use of HgA1c in pregnancy for screening as well as diagnosis of GDM. One study by Fong et al found that women with early (prior to 20 weeks) HgA1c between 5.7-6.4% had an incidence of GDM of 27.3%; when restricted to women with BMI ≥30, incidence of GDM increased to 50%. Another study showed that HgA1c of ≥ 5.95% had a sensitivity of 28.6% and specificity of 97.2% for diagnosis of GDM. A HgA1c threshold of 5.45% increased sensitivity to 85.7% but decreased specificity to 61.1%.

**SUMMARY OF RECOMMENDATIONS**

Based on the above reported observations and the fact that HgA1c can be done in a non-fasting state without requirement of glucose loading, **we recommend HgA1c as the preferential early risk-based screening modality.** (See Figure 1)

- HgA1c ≥ 6.5% is diagnostic of pre-gestational DM. Diabetes education and therapy should be initiated as soon as possible. We recommend consideration of maternal-fetal medicine consultation for these patients.
- HgA1c 6.0-6.4% should be considered diagnostic of GDM, and these patients should receive diabetic education and treatment,
- HgA1c 5.7-5.9% should be considered concerning for impaired glucose tolerance. We recommend that consideration be given to dietary education and counseling early in pregnancy. We also recommend reevaluation for GDM with a 3 hour GTT at 24-28 weeks (We do not recommend a 1 hour GCT as the initial screen as these women have already been identified as being at elevated risk for GDM; rather we recommend proceeding directly to diagnostic testing)
- HgA1c <5.7% is normal; these women should have routine GDM screening at 24-28 weeks

If the patient and/or provider elect to choose a 1-hour GCT as early screening for gestational diabetes, the standard 2-step approach should then be followed:

- An early 1-hour GCT ≥ 180 mg/dL qualifies is diagnostic for early GDM versus pre-gestational diabetes
- An early 1-hour GCT 140-170 mg/dL qualifies for follow up early 3-hour GTT with Carpenter and Coustan diagnostic cut off values
- In women who have an elevated early 1-hour GCT screening, but negative early 3-hour GTT testing, ACOG recommends that these patients receive follow up GDM screening at the routine screening time of 24-28 weeks gestation. The follow up 24-28 week screening in these women can be the 3-hour GTT, without repeating the 1-hour GCT
TARGETS FOR GLYCEMIC CONTROL IN PREGNANCY

In an effort to define normoglycemia in non-diabetic pregnant women, a pooled analysis of studies of blood sugars in non-diabetic pregnant women calculated a mean fasting glucose of 71 mg/dL, 1 hour post prandial 109 mg/dL, 2 hour prandial of 99 mg/dL and 24 hour average glucose of 88 mg/dL. Studies looking at glucose control during pregnancy in diabetic pregnant women have found that mean blood glucose of 87-104 mg/dL and a 1-hour post prandial goal value of 130 mg/dL had the same incidence of small for gestational and large for gestational age as non-diabetic pregnant women, suggesting this to be the normal glucose range.

No study has found superiority of a 1- versus 2-hour postprandial value, potentially due to the fact that pregnancy postprandial peak glucose is approximately 90 minutes post meal. One study evaluating preprandial versus postprandial measurements found that 1-hour postprandial measurement was associated with better glycemc control, lower incidence of LGA infants, and lower rates of cesarean delivery for cephalopelvic disproportion.

The Australian Carbohydrate Study in Pregnant Women trial (ACHOIS) by Crowther et al in 2005 and the Maternal-Fetal Medicine Units Network (MFMU)/NICHD trial by Landon et al in 2009 were randomized control trials that evaluated whether treatment of GDM improved pregnancy outcomes. The ACHOIS trial of 1000 women showed that treatment of GDM reduced the risk of serious perinatal complications such as death, shoulder dystocia, bone fracture and nerve palsy (1% versus 4%, relative risk [RR] 0.33, 95% confidence interval [95% CI] 0.14 – 0.75, p=0.01), as well as improved maternal postpartum quality of life scores and lowered maternal depression at 3 months postpartum. The MFMU trial in 958 women demonstrated that treatment of GDM was associated with a significant decrease in shoulder dystocia (1.5% versus 4.0%, p=0.02), large for gestational age neonates (7.1% versus 14.5%, p<0.001), birthweight >4000g (5.9% versus 14.3%, p<0.001), preeclampsia and hypertensive disorders (8.6% versus 13.6%, p=0.01) and cesarean delivery (26.9% versus 33.8%, p=0.02). It is important to note that both trials used only insulin for treatment of GDM. The levels used for glycemc control varied between the two trials. The ACHOIS trial used a goal fasting of <99mg/dL and 2-hour postprandial of <126mg/dL at <35 weeks gestation and <144mg/dL at greater than 35 weeks gestation and the MFMU/NICHD trial used a goal fasting of <95mg/dL and 2 hour postprandial of <120mg/dL.

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Trial published in 2008 addressed the risk of adverse pregnancy outcomes with maternal hyperglycemia less severe than that in GDM. The HAPO authors prospectively evaluated 25,505 pregnant women at 15 centers in 9 countries. Patients underwent a 75gm glucose tolerance test between 24-32 weeks, with diagnosis of GDM, treatment of GDM and all prenatal and newborn care determined by standards at the individual centers. The trial results demonstrated a strong continuous association of maternal glucose levels below those diagnostic of diabetes with increased neonatal birth weight and a moderate continuous association with cesarean delivery. The HAPO authors suggested a need to reconsider the criteria for diagnosing GDM and the goals of hyperglycemia treatment during pregnancy.

Despite the ACHOIS, MFM/NICH and HAPO trials, no controlled trials have been performed specifically to further delineate optimal glycemic targets. Both ACOG and the American Diabetes Association (ADA) are concordant in their target glucose values and recommend a fasting of <95mg/dL, and postprandial values of <140mg/dL at 1-hour or <120mg/dL at 2-hours to reduce the risk of macrosomia.
After review of these society recommendations, and the lack of trials specifically addressing optimal glucose targets in GDM, we recommend using the same glucose targets as ACOG and ADA recommendations: fasting or preprandial blood glucose values <95mg/dL, and postprandial blood glucose values <140mg/dL at 1-hour or <120mg/dL at 2-hours. The 1-hour or 2-hour postprandial value should be timed from the START of the meal.

The ACOG and ADA recommended goal values are likely not representative of true normoglycemia comparative to women without GDM. Additionally, the HAPO trial suggests that mildly elevated glucose values below current treatment thresholds is associated with increased neonatal birth weight and cesarean delivery. Thus, some patients, particularly those with additional risk factors for adverse perinatal outcomes, may require more strict control than ACOG recommendations. The decision for tighter glucose control in pregnancy should be decided on a case-by-case basis with the patient’s obstetric provider and/or the assistance of a Maternal Fetal Medicine specialist.

### SUMMARY OF RECOMMENDATIONS
Consistent with the American College of Obstetricians and Gynecologists, as well as the American Diabetes Association, we recommend glucose control targets of fasting blood sugar <95 mg/dL and 1 hour postprandial <140 mg/dL or 2 hour postprandial <120mg/dL. The 1-hour or 2-hour postprandial value should be timed from the START of the meal.

The above recommendations address GDM only, and do not cover glucose targets for more complicated pregestational diabetic patients, or patients with additional comorbidities. Individualized glucose goals may be recommended on a case-by-case basis in coordination with a Maternal Fetal Medicine specialist.

### PHARMACOLOGIC MANAGEMENT OF GESTATIONAL DIABETES

#### Oral hypoglycemics

The initial management of GDM includes dietary education and medical nutrition therapy. If a pharmacologic treatment is needed there are three medications that have been typically used: oral glyburide, oral metformin, and subcutaneous insulin.

Several meta-analyses have been performed to compare these medications. The 2015 analysis by Balsells et al included 15 studies with 2509 subjects, and overall found that when compared to insulin and metformin, glyburide is associated with higher birth weight as well as more frequent macrosomia and neonatal hypoglycemia. Metformin is associated with less maternal weight gain and fewer large for gestational age infants, but higher rates of preterm birth (pooled risk ratio 1.50, 95% CI 1.04-2.16). The authors concluded that glyburide was inferior to both insulin and metformin and that metformin performs slightly better than insulin. The Farrar et al 2017 meta-analysis included 24 randomized trials, evaluating the efficacy of GDM treatment with glyburide, metformin or insulin to prevent adverse maternal and neonatal outcomes. The Farrar meta-analysis concluded that metformin was associated with the lowest risk of neonatal hypoglycemia, macrosomia, LGA infants, preeclampsia, and NICU admission with comparable preterm birth risk. They concluded that there is a general “trend” to favor metformin over insulin or glyburide for the treatment of GDM. Additionally, there have been two Cochrane Reviews in 2017 by Brown et al. The first included 8 studies with 1487 patients, and compared the effect of oral medications (glyburide and metformin) for treatment of GDM. Brown et al overall
concluded there is insufficient high quality evidence to draw any meaningful conclusions as to the benefits of one oral anti-diabetic medication compared to another due to limited reported outcomes data in available studies. The second 2017 Cochrane review included 53 studies with 7381 subjects, evaluating the effects of insulin for treatment of GDM. This second Cochrane review overall reported the quality of evidence was very low to moderate. The authors state that long-term maternal and neonatal outcomes are poorly reported in these studies, but that there are minimal harms associated with the effects of treatment with either insulin or oral anti-diabetic medications. Insulin and oral anti-diabetic medications had similar effects on the multiple maternal and neonatal health outcomes evaluated in this meta-analysis. They finally conclude that the choice to use one medication or the other may be based on physician or maternal preference, availability of medication, or severity of GDM.

There are reassuring, although very limited, studies regarding long term outcomes of neonates exposed to metformin in utero. There are no studies to date evaluating the long-term effects on metabolic or neurodevelopmental outcomes in offspring exposed to glyburide in utero.

In February 2018 ACOG updated its practice bulletin on gestational diabetes. In it ACOG aligns with current ADA recommendations, stating that insulin is the preferred first line treatment when pharmacologic treatment of GDM is indicated. The rationale for insulin as the preferred therapy for pharmacologic treatment of GDM is that the oral anti-diabetic medications are not approved by the US Food and Drug Administration for treatment of GDM, are known to cross the placenta, lack long-term neonatal safety data, and that current studies have poor trial quality and are not designed to assess equivalence or non-inferiority. Additionally, they note that two prospective trials evaluating the use of metformin versus insulin found that 26-46% of women started on metformin eventually required insulin for glycemic control. However, ACOG recognizes that clinical situations may occur that necessitate the use of oral agents. ACOG states that “in women who decline insulin or who the obstetricians or obstetric care providers believe will be unable to safely administer insulin, or for women who cannot afford insulin, metformin (and rarely glyburide) is a reasonable alternative choice in the context of discussing with the patient the limitations of safety data and high rate of treatment failure that requires insulin supplementation.” ACOG later states “the evidence indicates that glyburide treatment should not be recommended as a first-choice pharmacologic treatment because, in most studies, it does not yield equivalent outcomes to insulin or metformin.”

The Society of Maternal Fetal Medicine (SMFM) released a response to this practice bulletin, acknowledging that the updated 2018 ACOG recommendations engendered some controversy and thus provided a separate review of the available scientific literature regarding pharmacologic treatment of GDM. In addition to reviewing similar evidence as presented in the ACOG 2018 Practice Bulletin, SMFM also highlighted the 2008 Rowan et al publication that found a strong patient preference for oral agents, with improved compliance and lower cost as compared to insulin. In its formal published response, SMFM took a slightly different stance than ACOG, stating that “metformin is a reasonable and safe first-line pharmacologic alternative to insulin, recognizing that one-half of women will still require insulin to achieve glycemic control.

In our review of these statements, we conclude that in women with GDM in which hyperglycemia cannot be adequately controlled with nutrition therapy, oral therapy with metformin is a reasonable and safe first-line pharmacologic alternative to insulin. We do not recommend glyburide for the treatment of GDM. Patients starting metformin should be counseled that approximately one half of patients will still require insulin to achieve glycemic control. Patients should also be counseled about side effects of metformin including loose stools, anorexia, and nausea, typically lasting 7-10 days.
We suggest the following metformin dosing algorithm, based on the CDAPP Sweet Success\textsuperscript{14}:

- Begin with 500mg twice daily with meals, depending on the pattern of hyperglycemia
- Increase dose by 500mg every 3-7 days as limited by gastrointestinal side effects until glycemic targets are met or maximum daily dose of 2500mg
- Obtain serum creatinine at start of therapy if renal dysfunction is suspected (metformin is cleared renally)
- Providers can offer metformin self-titration with patients with specific provider instruction

There is no specific glucose threshold outlined by ACOG or SMFM for the initiation and uptitration of medications. \textit{In agreement with the California Sweet Success 2015 Guidelines\textsuperscript{14}, we suggest initiation or adjustment of medication if >20\% of blood sugar values are out of range.} However, providers and patients should develop an individualized care plan that may differ from this using best clinical judgment.

Approximately 50\% of patients with GDM who are started on an oral hypoglycemic will need insulin\textsuperscript{35}. Therefore, if patients remain out of goal range after starting metformin, they should be expeditiously transitioned to insulin to avoid a delay in adequate treatment. In the consideration of first line agents, for patients with very elevated blood sugar values, providers should consider moving directly to insulin as the \textbf{first-line therapy as the failure rate of metformin will be high in this group}. In patients who have started first line therapy with metformin, however require transition to insulin due to failure to achieve appropriate glucose control with metformin alone, providers should consider continuation of metformin in this patient group for dual therapy (using metformin with insulin).

\textbf{SUMMARY OF RECOMMENDATIONS}
We recommend that in women who require pharmacologic therapy for GDM, \textit{oral therapy with metformin is a reasonable and safe first-line pharmacologic alternative to insulin}. \textit{We do not recommend glyburide for treatment of GDM}. Patients starting metformin should be counseled that approximately 50\% will still require insulin and should be counseled about side effects. \textit{We suggest initiation or uptitration of medication if >20\% of blood sugar values are out of range}. If patients remain out of goal range after starting metformin, they should be expeditiously transitioned to insulin to avoid a delay in adequate treatment. In the consideration of first line agents, for patients with very elevated blood sugar values, providers should consider moving directly to insulin as the first-line therapy. In patients who are transitioned to insulin after starting oral therapy with metformin, providers should consider continuation of both agents concurrently.
**SUMMARY OF RECOMMENDATIONS**

50-gram glucose challenge test (GCT) – Threshold Diagnostic for GDM

- 50-gram GCT values ≥ 180 mg/dL can be considered diagnostic for gestational diabetes without the need for a follow-up 3 hour glucose tolerance test (GTT)
- Depending on clinical situation and patient acceptance of diagnosis, values between 180-200 mg/dL may proceed with 3 hour GTT if the clinician feels this additional testing is warranted
- Recommend against a 3-hr GTT following a 1 hour GCT result ≥ 200 mg/dL

**Early Risk-Based Screening for GDM**

- All obese or overweight patients with additional risk factors for GDM should be screened during the first prenatal visit. Clinicians may elect to do universal early screening
- See Table 1 for ACOG risk factors that qualify for early GDM screening
- HgA1c is the preferential early risk-based screening modality

**Early HgA1c GDM Screening**

- HgA1c ≥ 6.5% is diagnostic of pre-gestational DM
- HgA1c of 6-6.4% is diagnostic of GDM, begin dietary education and profiling
- HgA1c of 5.7-5.9% is associated with an increased risk of GDM. Consideration should be given to dietary education/counseling. These women should undergo diagnostic testing for GDM with 3 hour GTT at 24-28 weeks

**Targets for Glycemic Control in Pregnancy**

- Fasting glucose <95mg/dL
- 1-hour post prandial glucose <140mg/dL or a 2-hour postprandial <120mg/dL
- The 1-hour or 2-hour postprandial value should be timed from the START of the meal
- Individualized glucose goals may be recommended on a case-by case basis in coordination with a Maternal Fetal Medicine specialist

**Pharmacologic Treatment of GDM**

- Metformin is a reasonable and safe first-line pharmacologic alternative to insulin
- We suggest initiation or uptitration of medication if >20% of blood sugar values are out of range.
- We do not recommend glyburide for treatment of GDM
- Patients starting metformin should be counseled that approximately 50% will still require insulin
- If patients remain out of goal range after starting and uptitrating metformin, they should be expeditiously transitioned to insulin to avoid a delay in adequate treatment.
- In the consideration of first line agents, for patients with very elevated blood sugar values, providers should consider moving directly to insulin as the first-line therapy.
- In patients who are transitioned to insulin while already on metformin, providers should consider continuation of both agents concurrently (metformin with insulin).
Algorithm for GDM Screening:

**Figure 1.**

Gestational Diabetes Screening

- **Risk Factors**
  - Yes
  - Early HgA1c
    - ≥6.5: Type II DM – Treatment
    - 6.0-6.4: Gestational DM – Dietary education & profiling
    - 5.7-5.9: Consider dietary education, 3 hour GTT at 24-28 weeks
    - <5.7: Routing screening at 24-28 weeks
  - No
    - 1 hour GCT
      - <140: Normal; No further testing
      - 140-179: 3 hour GTT
      - ≥180: GDM

**Disclaimer:** This consensus document is to be used as a guideline for practice management. It is generated by expert review from the Department of Obstetrics and Gynecology.
REFERENCES


