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Evidence on: Diagnosing Gestational Diabetes

Gestational diabetes mellitus (GDM) is high blood glucose (high blood sugar) that develops during pregnancy (ADA, 2018). With routine prenatal care provided in the United States (U.S.), most people drink "Glucola" as part of a screening test for gestational diabetes. In other parts of the world, care providers may give mothers a screening test and/or a diagnostic test for GDM using other types of glucose drinks.

Diagnosing GDM is a complex topic with lots of controversy. Even though we have a lot of research on GDM, professionals around the world still disagree on the best way to screen for and diagnose this condition. This article will describe GDM, explain the reasons for the disagreement over how to best diagnose GDM, and discuss the potential risks linked to the condition, as well as the potential benefits from treatment.

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Table 1: Commonly Used Acronyms

Acronyms	Meaning	Acronyms	Meaning
ACOG	American College of Obstetricians and Gynecologists	"HAPO" study	"Hyperglycemia and Adverse Pregnancy Outcomes" study
ADA	American Diabetes Association	IADPSG	International Association of Diabetes and Pregnancy Study
BMI	Body Mass Index	OGTT	Oral Glucose Tolerance Test
FPG	Fasting Plasma Glucose	USPSTF	United States Preventive Services Task Force
GDM	Gestational Diabetes Mellitus		

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What is gestational diabetes?

To understand gestational diabetes, it's helpful to first learn how the body metabolizes sugar. After you eat or drink carbohydrates (often called "carbs"), your gastrointestinal system helps the carbohydrates enter your bloodstream as glucose (often called "sugar"), which your body must turn into energy. *Insulin* is a hormone produced by the pancreas that helps deliver glucose from the blood into your body's cells, where the glucose can be turned into energy that fuels your body's functions. Insulin also helps convert extra glucose into fat for storage.

All pregnant people experience some metabolic changes during pregnancy. In normal pregnancy, hormones from the placenta make it harder for your body to use insulin—you may require up to three times as much insulin to overcome the increased insulin resistance (ADA, 2016). *Insulin resistance* means that your cells are resistant to insulin—it's kind of like if a neighbor (i.e. insulin) keeps knocking on your door (i.e. cell) with gifts of food, and over time, has to knock louder and louder to get you to open the door! In a pregnancy that is not complicated by gestational diabetes, it's harder for insulin to 'open the door,' but the body's *insulin response*, or ability to produce more insulin, is enough to overcome the resistance.

However, with gestational diabetes, there is too much insulin resistance, too little insulin response (called *low beta cell function*), or a combination of both (Powe et al., 2016). Some women with GDM have more of a problem with insulin resistance, while others with GDM have more of a problem with low beta cell function (Personal correspondence, Dr. Barbour, 2018).

Going back to our analogy, low beta cell function is like if the neighbor who is knocking gets tired over time and knocks more softly. So, with GDM, the door doesn't open because of your high reluctance to answer it (insulin resistance), the neighbor's low intensity in knocking (low beta cell function), or a combination of both factors. You can imagine that with either scenario, the neighbor gives up and takes the food somewhere else. In a similar way, when this happens with GDM, glucose builds up in the blood until it reaches abnormally high levels, called *hyperglycemia*.

The routine tests that are done in pregnancy to identify GDM do not directly measure insulin resistance or beta cell function. Instead, the tests measure blood sugar levels, because it is high blood sugar that can cause problems for mother and baby. If you have GDM, treatment with diet, exercise, and sometimes medicine, is necessary to maintain healthy blood sugar levels.

Researchers think insulin resistance exists to help move more nutrients to the baby (instead of the mother) to promote healthy fetal growth and development (Farrar et al., 2017a). The mother's body is making sure that the baby gets enough nutrition from sugar in the blood, even if food becomes scarce for the mother. This adaptation helped us in the past, but most people today have too much food available—including too many processed foods with simple, easily digested sugars. This situation has led to more people putting on extra body weight, which tends to increase insulin resistance and decrease beta cell function, which further increases the risk of high blood sugar.

How many people have gestational diabetes?

Data from 2009 on over four million hospital births in the United States (U.S.) showed that about 7% of pregnant people had any type of diabetes (including GDM) and 6% had gestational diabetes (Correa et al., 2015). In 1993, just over 3% of pregnancies were affected by GDM, but between 1993 and 2009, the rate of GDM increased in every age group.

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Today, gestational diabetes is one of the most common problems of pregnancy (ACOG, 2018). There are substantial medical costs from the high number of people with GDM. It's estimated that GDM creates an annual burden of at least $636 million in the U.S. alone (Chen et al., 2009).

There is a lot of debate over the best way to diagnose GDM, and the rate of people with GDM can change depending on the specific test that is used. Some tests use a lower cutoff level for diagnosis, in which case more people would be diagnosed with GDM. For example, the proposed International Association of Diabetes and Pregnancy Study Groups (IADPSG) cutoff levels would diagnose about 18% of pregnant people in the U.S. as having GDM (ACOG, 2018).

What are the risk factors for gestational diabetes?

(U.S. Preventive Services Task Force, 2014)

Certain factors put people at increased risk for GDM **(Table 2, page 3)**. The main preventable risk factor is being plus size, since the risk of GDM increases with increasing mass. In this article, we define *plus size* as having a pre-pregnancy body mass index (BMI) of 25 kg/m2 or above. BMI (https://bit.ly/1D0ZqDv) is an estimate of body fat based on height and weight. It is commonly used in research to study the link between body fat and health outcomes.

It's estimated that 4.8% of people with a BMI of 25 to 29.9 kg/m2 have GDM, 5.5% of people with a BMI of 30 to 34.9 kg/m2 have GDM, and 11.5% of people with a BMI above 35 kg/m2 have GDM (Kim et al. 2010). Researchers think that if all plus size women had a GDM risk equal to that of women with a BMI < 25 kg/m2, nearly half of GDM cases could be prevented. However, someone who is not plus size can still get GDM; about a quarter of people with GDM have a pre-pregnancy BMI < 25 kg/m2.

Age is another factor strongly linked to GDM; the number of pregnant people with GDM increases from 1.3% of people younger than age 21 to 8.7% of those older than age 35 (Chen et al., 2009).

Table 2: Factors Influencing the Risk of Gestational Diabetes (GDM)

(Moyer and USPSTF, 2014)

Higher Risk for GDM	Lower Risk for GDM
• Being plus-size • Increasing maternal age • History of GDM • History of having a large for gestational age baby • Diabetes in a close relative • Belonging to an ethnic group at increased risk for GDM	• Age younger than 25 years • Caucasian/white race • Weight "normal" before pregnancy (BMI ≤25 kg/m2) • No close relatives with diabetes • No history of glucose intolerance • No history of poor birth outcomes

What problems can result from gestational diabetes?

The "Hyperglycemia and Adverse Pregnancy Outcomes" (HAPO) study is the most important research that has ever been done on the link between maternal blood sugar and risk of poor birth outcomes (HAPO, 2008). In this study, researchers found that increasing blood sugar is linked to an increase in poor outcomes even at levels not considered to be gestational diabetes.

The data from this study were used as the basis for the new cutoffs for GDM diagnosis that were proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG, 2010). The IADPSG recommendations have been very influential, because they represented the group opinion of experts in diabetes and obstetrics from 40 different countries. However, although these guidelines are now in use in many places around the world, they were not adopted in the U.S.

In the HAPO study, researchers followed more than 25,000 people at 15 hospitals in nine countries throughout their pregnancies. The women in this study did not already have a diagnosis of diabetes during the current pregnancy, and they did not have a diagnosis of diabetes requiring medication before the pregnancy. The study included both experienced and first-time mothers, as well as people with a previous Cesarean.

Everyone was screened with a 75-gram oral glucose tolerance test (OGTT) at 24 to 32 weeks of pregnancy. We will talk about this test in more detail later on, but it works by measuring fasting blood sugar, then measuring blood sugar again one and two hours after drinking 75 grams of glucose. The researchers also gave everyone a random blood sugar test between 34 and 37 weeks of pregnancy as a safety measure to identify people with high blood sugar levels.

People in this study were blinded to their test results except (for ethical and safety reasons) when their blood sugar levels were very high (fasting blood sugar levels >105 mg/dL, 2-hour blood sugar levels >200 mg/dL, or random blood sugar levels >160 mg/dL). People were also informed if any measurement was abnormally low, or less than 45 mg/dL. Note that these levels were not the study's criteria to diagnose GDM; they were what the researchers considered high (or low) enough to ethically require that they notify the participants and offer them treatment. Everyone else (23,316 people) remained blinded to their test results, and these people who were blinded were included in the final analysis.

The researchers defined seven categories for blood sugar levels at three different times: after fasting, at 1 hour, and at 2 hours after the test. Then, they compared how frequently bad outcomes occurred within these different categories **(Table 3, page 5)**. Based on the 2-hour test result categories, they found that the absolute risk of giving birth to a large baby (defined as weighing more than 90% of other babies in the study) was 7% for people in the lowest category and 22% for people in the highest category. Similarly, 14% of people in the lowest category had a first-time Cesarean versus 27% in the highest category.

Another outcome they looked at was a marker in cord blood (called serum C-peptide levels) that showed whether the baby's pancreas was producing high levels of insulin during pregnancy. They found high levels in 5.4% of the lowest category group versus 21% of the highest category group. When a pregnant person has high blood sugar levels, more sugar crosses the placenta, which gives the baby high blood sugar levels and causes the fetal pancreas to produce more insulin. This is a concern because fetal insulin acts as a growth factor, leading the baby to store more sugar as fat and grow more rapidly (Arshad et al., 2014).

Rapid fetal growth can lead to fetal *macrosomia* (https://mayocl.in/2PWD7zp), or a birth weight commonly defined as more than 8 pounds, 13 ounces (4,000 grams). Having a large baby can increase the risk of injury to the mother or baby during childbirth and increase the risk of Cesarean. Sometimes, large babies can get their shoulders stuck during birth, called shoulder dystocia, and this can lead to birth injury. People with high blood sugar levels during pregnancy are at increased risk of experiencing shoulder dystocia during birth regardless of the baby's weight—it has more to do with how the weight is distributed on the baby. Problems can occur when the baby's head size is relatively small compared to the size of its shoulders and abdomen (Kamana et al., 2015). Learn more here evidencebasedbirth.com/bigbaby in our Evidence Based Birth® Signature Article all about Big Babies.

The HAPO study found a link between higher blood sugar levels in the mother and higher risk of shoulder dystocia or birth injury. They also found a link between high blood sugar levels in the mother and higher rates of premature birth, newborn intensive care, newborn jaundice, newborn low blood sugar, and pre-eclampsia (pregnancy-induced high blood pressure and protein in the urine).

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Even with more than 23,000 people in the final analysis, stillbirth (when a fetus dies in utero) and newborn death are such rare outcomes that this study did not have a big enough sample size to look at deaths (HAPO, 2008).

The key finding from the HAPO study was that the relationship between a mother's blood sugar levels and the risk of poor birth outcomes is *continuous*. This means that there is no specific cutoff for risk—the risk of poor outcomes increases step-by-step with every small increase in blood sugar levels, even within blood sugar ranges previously considered normal for pregnancy (ADA, 2018). In other words, there is no clear cutoff where we can say, "This is normal and this is abnormal." This is a major reason why there is so much controversy over how best to diagnose GDM (Farrar et al., 2017a).

To help you visualize this continuous relationship, we have included a graph of data from the HAPO study. As you can see, the number of large babies goes up with every increasing blood sugar category—even in the categories less than five, *which would not even be diagnosed as gestational diabetes*. The categories correspond to the blood sugar levels defined in **Table 3 (page 5).**

Figure 1. Birth Weight > 90th Percentile and Maternal Blood Sugar Category

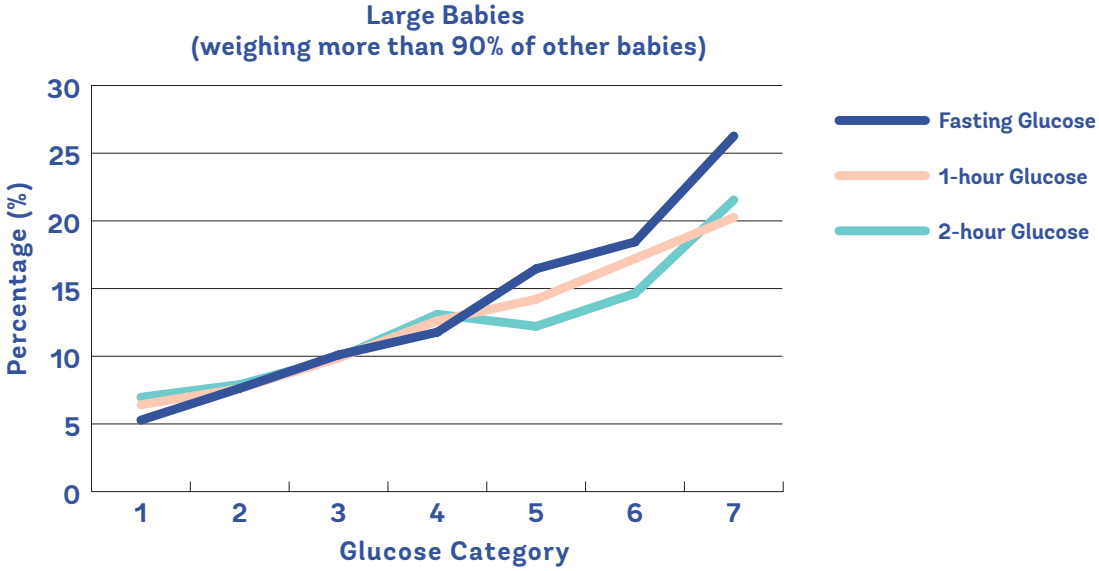

Table 3: Plasma Glucose Categories in HAPO study

Glucose Category	Fasting (mg/dL)	At 1-hour (mg/dL)	At 2-hours (mg/dL)
1	Less than 75	Less than 105	Less than 90
2	75 - 79	106 - 132	91 - 108
3	80 - 84	133 - 155	109 - 125
4	85 - 89	156 - 171	126 - 139
5	90 - 94	172 - 193	140 - 157
6	95 - 99	194 - 211	158 - 177
7	100 or more	212 or more	178 or more

* Category five crosses into gestational diabetes levels

Other researchers have found that women with GDM have a higher risk of developing diabetes, heart disease, and stroke later in life (England et al., 2009; Tobias et al., 2017). However, when researchers

followed nearly 90,000 women for over 20 years, they found that the mothers who followed healthy lifestyles (maintaining a healthy weight, regular physical activity, no smoking, and a heart-healthy diet) after their GDM diagnoses did not have a significantly increased risk of heart disease compared to those who never had GDM (Tobias et al., 2017). Earlier work by the same researchers found that when women with a history of GDM make lifestyle improvements, they also lower their risk of developing high blood pressure and type 2 diabetes. Breastfeeding has also been shown to significantly lower the risk of type 2 diabetes among people with a history of GDM (Gunderson et al., 2015).

A concerning finding is that babies who are exposed to GDM during pregnancy may be more likely to develop excess body weight and type 2 diabetes as an adult (Clausen et al., 2009). A recent review reported a 19 times higher risk of type 2 diabetes in offspring if the mother was both plus size and had GDM (Silva-Zolezzi et al., 2017).

So gestational diabetes has been linked to higher rates of:

- Pre-eclampsia
- Fetal high blood sugar
- First-time Cesarean
- Premature birth
- Higher birth weight/having a large baby
- Shoulder dystocia or birth injury
- Newborn intensive care
- Newborn jaundice
- Newborn low blood sugar
- The mother developing diabetes and/or heart disease later in life
- The baby developing excess body weight and/or diabetes later in life

Let's define some terms

Let's define some terms that are often misused or misunderstood, even among researchers (Personal Communication, Diane Farrar, 2018).

Screening is defined as identifying from a large or general population those individuals more at risk of a condition. An example of a screening test for GDM would be giving all mothers the 50-gram oral glucose challenge, or "Glucola" drink, to determine which of those mothers are at a greater risk for GDM. Another example of a screening test is a risk factor assessment, which involves checking each mother for factors that put her at increased risk for GDM. So, the 50-gram glucose drink and the risk factor assessment are two different ways to screen for GDM.

On the other hand, *diagnosis* is defined as identifying whether or not a condition is actually present. The only diagnostic test used for GDM is the oral glucose tolerance test (OGTT) with 75 or 100 grams of glucose.

If you get a positive result on the glucose screening test, this suggests an increased risk for GDM, but most of the time you will still need to take the diagnostic test before being actually diagnosed with GDM. However, some providers (such as those at the Mayo Clinic (https://mayocl.in/2ltKBJl), for example) will go ahead and diagnose a mother with GDM based on a really high screening test result. The Mayo Clinic diagnoses people with GDM if their one-hour test results are above 190 mg/dL. We did not find practice guidelines on when to diagnose someone with GDM based on a high screening test result, but new research suggests results >200 mg/dL are sufficient to diagnose GDM without an OGTT (Tita et al., 2017).

Screening tests and diagnostic tests can also be universal or selective. An example of a *universal* screening test would be giving everyone the 50-gram Glucola regardless of whether or not they have individual risk factors for GDM. A *selective* screening test would be giving the 50-gram Glucola only to

people with certain risk factors for GDM. Likewise, selective diagnostic testing is giving the OGTT only to people at higher risk for GDM based on a screening test. Universal diagnostic testing is giving everyone the OGTT regardless of risk factors for GDM.

Does everyone need to take a glucose test for gestational diabetes, or only people with risk factors?

People have asked us if they still need to take the routine Glucola screening test if they are healthy and "low risk"for gestational diabetes.

Back in the early 2000s, before universal screening with Glucola was normal in the U.S., the American Diabetes Association (ADA) and the American College of Obstetricians and Gynecologists (ACOG) stated that some women did not need screening for GDM if all of the following criteria were met (Note: ACOG no longer recommends this) (ADA, 2003; ACOG, 2001):

- Age younger than 25 years
- Not a member of an ethnic group with an increased risk for diabetes (examples include people of Hispanic, African, Native American, South or East Asian, or Pacific Islands ancestry)
- Weight "normal" before pregnancy (BMI ≤25 kg/m2)
- No history of abnormal glucose tolerance
- No history of poor obstetric outcome
- No close relatives with diabetes

Only about 10% of pregnant people in the U.S. meet all of the above criteria to qualify as low risk for GDM (Danilenko-Dixon et al., 1999). If you fall in that 10%, then you are at very low risk for GDM. However, you aren't completed protected from GDM, even if you qualify as low risk. Researchers estimate that about 5% of people who have gestational diabetes would have been labeled as "low-risk" by the ADA-identified criteria (Avalos et al., 2013).

In 2014, the U.S. Preventative Services Task Force (USPSTF) made a recommendation for universal screening with a glucose test at 24 weeks or later (Moyer and USPSTF, 2014). Their reason for switching to universal screening with the 50-gram Glucola was that most people had one or more risk factors and thus needed to be screened with the glucose test, anyways. Also, trying to identify the small number of people with no risk factors makes the screening process more complex, which would lead to some mistakes, where people who do have GDM might go undetected and not receive potentially beneficial treatment.

Selective testing based on risk factors for GDM is still used in some countries today. For example, in the United Kingdom (https://bit.ly/2M1aI6C) only those with risk factors for GDM are recommended to receive a diagnostic test (NICE, 2015).

Right now, we don't have enough evidence from randomized controlled trials to know if it leads to better outcomes to screen everyone with a 50-gram oral glucose challenge, or just people with risk factors for GDM. A Cochrane review on this topic found only one trial that compared universal screening to selective screening based on risk factors (Tieu et al., 2017). More women were diagnosed with GDM in the universal screening group; however, the trial didn't report on birth outcomes for the mother or baby. As we'll discuss, we also don't have enough evidence to know if it is better to test everyone with a diagnostic OGTT, or just those with positive screening tests (Farrar et al., 2017a).

What are the different glucose tests for gestational diabetes?

Overall, there is consensus that we should use an oral glucose tolerance test (OGTT) to officially diagnose gestational diabetes (Agarwal, 2018). The disagreement is about the amount of glucose (75 grams or 100 grams), the number of blood samples (three or four), the time to test (over two hours or three hours), and where to set the cutoffs for diagnosis (higher or lower) **(Table 4, page 9)**. In 2013, the U. S. National Institutes of Health (NIH) held a conference to try and resolve these disagreements. Unfortunately, they were not able to reach agreement (NIH, 2013).

The two-part screening and diagnostic method

The most common way of screening and testing for GDM in the U.S. is with the **two-part screening and diagnostic method**. As you might guess, this test has two parts, an initial screening part, and a follow-up diagnosis part.

You might have already heard of the first part of this method. It is sometimes called the "50-gram, 1-hour screening test," the "oral glucose challenge," or the "Glucola screening test." This screening test was first introduced in 1973 and the criteria used were those first established by O' Sullivan and Mahan in 1964, with a few changes (Brown and Wyckoff, 2017). This screening test was originally designed to identify women at risk for developing diabetes later in life—not to identify people who were at risk for poor outcomes in pregnancy (HAPO, 2008).

The two-part screening and diagnostic method is currently supported by ACOG and used by around 95% of obstetricians in the U.S. for universal screening and selective testing (ACOG, 2018). The ADA also supports this approach although they prefer the one-part diagnostic method (discussed below). Pregnant people can eat and drink normally on the day of the screening test.

How this test works, is that the mother drinks 50 gram of a glucose solution (Glucola) all at once, and her blood sugar level is tested one hour later. If her *screening* test shows a high blood sugar level (130-140 mg/dL or higher, depending on the institution), then the mother is asked to follow up with a second OGTT *diagnostic* test on a different day to actually diagnose GDM (ACOG, 2018). Between 14% and 23% of people get a positive screening test and are advised to take the diagnostic test (NIH, 2013).

Method, part 1:

- Drink a 50-gram glucose solution (non-fasting), with blood sugar measured 1 hour later.
- If the blood sugar level result is ≥ 130 mg/dL, 135 mg/dL, or 140 mg/dL (set by the institution), then the screening test shows an increased risk for GDM. Schedule a 100-gram diagnostic OGTT to diagnose GDM.

Those who screen positive go on to take part two of the test, which is a diagnostic test. The diagnostic test is a **100-gram, 3-hour** OGTT and it measures blood sugar after fasting overnight, then again at one, two, and three hours after drinking the glucose solution. GDM is usually diagnosed when someone has two or more abnormally high blood sugar results on the test; however, some providers diagnose GDM based on only one high value (ACOG, 2018). Most hospitals set their own cutoffs for diagnosing GDM, based on either of the two different criteria that have been proposed. So, if the hospital uses a lower cutoff, the test results in more people diagnosed with GDM.

Method, part 2:

- Drink a 100-gram diagnostic OGTT after you've been fasting for 8 or more hours.
- The diagnosis of GDM is made when at least one or two (set by the institution) of the following blood sugar values (measured fasting and 1-hour, 2-hours, and 3-hours after the test) are met or exceeded using either of the criteria listed in **Table 4** (the institution chooses which criteria they follow):

Table 4: Carpenter-Couston (CC) or National Diabetes Data Group (NDDG) Criteria

	CC	NDDG
Fasting	95 mg/dL	105 mg/dL
1-hour	180 mg/dL	190 mg/dL
2-hours	155 mg/dL	165 mg/dL
3-hours	140 mg/dL	145 mg/dL

The one-part diagnostic method

Outside of the U.S., most countries promote some variation of the one-part diagnostic method (universal or selective), although in Canada they have endorsed a different version of the two-part screening and diagnostic method **(Table 5, page 10)**. According to IADPSG criteria, the one-part diagnostic test is a **75-gram, 2-hour** OGTT, which requires fasting before the test. This OGTT measures blood sugar after fasting and again at one and two hours after the test. Gestational diabetes is diagnosed with one or more high blood sugar values.

Method:

- Drink a 75-gram diagnostic OGTT, with blood sugar measured after fasting (≥8 hours) and at 1 and 2-hours after the test.
- The diagnosis of GDM is made when any of the following blood sugar values are met or exceeded:
    - Fasting: 92 mg/dL
    - 1-hour: 180 mg/dL
    - 2-hour: 153 mg/dL

Unlike the two-part screening and diagnostic method, the one-part diagnostic method test cutoffs were developed based specifically on pregnancy and birth outcomes instead of the mother's future risk of diabetes (IADPSG, 2010; ADA, 2018). As we already mentioned, adopting the IADPSG criteria would greatly increase the rate of people diagnosed with GDM (NIH, 2013).

Using the one-part diagnostic method, more people would potentially benefit from treatment for high blood sugar. However, there are also downsides (which is why there is no agreement on which method is best). Using the 75-gram test with IADPSG criteria, everyone has to fast before the test, which may be difficult for some people. Also, an increase in the number of people diagnosed with GDM comes with an increase in personal and health care costs. Mothers diagnosed with GDM face more medical appointments (to meet with a registered dietitian, a diabetes educator, or both) and they are told to carefully watch what they eat and monitor blood sugar levels several times a day (NIH, 2013). Testing supplies, blood sugar medication (if needed), and extra monitoring all come with significant costs, which are not always fully covered by insurance in the U.S.. A diagnosis of GDM can be stressful for some mothers, and care providers may pressure women to schedule an induction simply because they have been diagnosed as having GDM.

Table 5: Different organizations recommend different ways of diagnosing GDM at 24 to 28 weeks of pregnancy

(Chiefari et al., 2017; Brown and Wyckoff, 2017)

One-part diagnostic method (75-gram diagnostic OGTT)	Two-part screening and diagnostic method (50-gram screening test; if positive, then schedule 100-gram diagnostic OGTT)	Two-part screening and diagnostic method (50-gram screening test; if positive, then schedule 75-gram diagnostic OGTT)
• American Diabetes Association (ADA) "Preferred option" • International Association of Diabetes and Pregnancy Study Groups (IADPSG) • World Health Organization (WHO) • The International Federation of Gynecology and Obstetrics (FIGO) • The Canadian Diabetes Association (CDA)/Society of Obstetricians and Gynecologists of Canada (SOGC) "Alternative option" Among people at high risk for GDM: • The National Institute for Health and Care Excellence (NICE) • The Australasian Diabetes in Pregnancy Society (ADIPS)	• American College of Obstetricians and Gynecologists (ACOG) • American Diabetes Association (ADA) "Alternative option" *Using either National Diabetes Data Group criteria or Carpenter & Coustan criteria*	• The Canadian Diabetes Association (CDA)/Society of Obstetricians and Gynecologists of Canada (SOGC) "Preferred option"

Note: Most organizations promote the one-part diagnostic method; however, there are still differences between them in whether they use universal testing or selective testing based on risk factors, the number of times they draw blood after the test, and the cutoffs they use for diagnosis. Also, as you can see, two of the listed organizations have both a preferred and an alternative method.

What are the known side effects of the glucose solutions used in testing for GDM?

In a Cochrane review, Farrar et al. (2017a) included seven randomized controlled trials (1,420 participants) that compared different ways of identifying women with GDM. Three of the studies reported on side effects such as bloating, pain, nausea, headache, dizziness, tiredness and vomiting.

A small trial from Mexico (2003) found that women who received 50 grams of glucose in their food, rather than as a drink, reported far fewer overall side effects (7% versus 80%).

Another trial from the U.S. (1992) compared people who received two different kinds of 50-gram glucose drinks (monomer versus polymer). The Glucola drink widely available in the U.S. is usually a monomer glucose drink. More women developed symptoms after the monomer drink than those who had symptoms after the polymer drink (51% versus 27%).

Another trial from the U.S. (1994) compared people who received a candy bar versus two different kinds of 50-gram glucose drinks, a monomer and a polymer. Women preferred the taste of the candy bar, but about half of the people in the candy bar group still reported one or more side effects—the same frequency of side effects as with the monomer glucose drink. Of the three types of glucose screening

tests, the fewest side effects were reported after the polymer glucose drink (9%). We do not have any evidence from randomized controlled trials on whether the polymer glucose solution results in fewer or more diagnoses of GDM compared to the monomer glucose solution, which is more common and considered the standard.

A large observational study from the United Arab Emirates followed more than 5,000 pregnant women who took the 3-hour, 100-gram OGTT (Agarwal et al., 2004). They found that 503 participants (9.8%) were not able to finish the test due to side effects. Vomiting was the most common reason for not being able to complete the test, with more than 8% of women in the study vomiting due to the test.

What is the evidence on different ways to diagnose GDM?

The Cochrane review on this topic included seven trials (with a total of 1,420 participants), and the researchers found disappointing results (Farrar et al., 2017a). The studies in the review were of poor quality, had small sample sizes, did not study the best time during pregnancy to test for GDM, and often did not report important infant or maternal outcomes, such as higher birth weight. Because the evidence was so limited, the Cochrane reviewers could not recommend one strategy over another. They concluded that large, randomized trials are needed before we can establish the best way to identify people with GDM.

Glucose drinks: the one-part diagnostic method versus the two-part screening and diagnostic method

One trial in the review compared the one-part diagnostic method (75-gram OGTT, ADA criteria) with the two-part screening and diagnostic method (50-gram Glucola screening test followed by 100-gram OGTT, Carpenter and Coustan criteria). They did not measure maternal or infant outcomes, but rates of GDM diagnosis only. They found that the one-part diagnostic method resulted in more diagnoses of GDM compared to the two-part screening and diagnostic method.

Although the evidence was low quality due to problems with the study design, the finding that more people are diagnosed with GDM using the 75-gram OGTT is supported by other research and widely accepted (Sacks et al., 2012; ADA, 2018; ACOG, 2018). In fact, this is the primary reason that ACOG has refused to adopt the one-part, 75-gram OGTT for diagnosis at this time—they state it would lead to a much higher number of people diagnosed with GDM, and an enormous increase in health care costs without clear evidence that it results in improvements to maternal and infant health that match the treatment costs (ACOG, 2018).

The cost issue is especially important in countries that have government-funded healthcare systems, such as the U.K., where researchers must show that the benefits of an intervention outweigh the costs of treatment. A recent economic analysis found evidence that the short and longer-term effects of treating GDM might not be cost-effective (Farrar et al., 2016). But other researchers believe that the increased costs of treatment may justify the potential benefits, such as a lowering of rates of Cesareans, neonatal intensive care admissions, and even future type 2 diabetes (Brown and Wyckoff, 2017). The bottom line is that at this point we do not have enough evidence on the cost-effectiveness of treating GDM to guide decisions about where to define the method or cutoff for diagnosis.

Candy alternatives to the glucose drink

The Cochrane researchers compared eating a candy bar to drinking a 50-gram Glucola (one trial, 60 people). They found that mothers preferred the taste of the candy bar. However, their 1-hour blood sugar levels were lower with the candy bar, which could mean that people with actual GDM were being missed by the candy bar screening test. We'll explain the possible reasons for this later in the article. Another

trial from Mexico with only 30 women compared receiving 50 grams of glucose from food versus drinking a 50-gram Glucola. Again, mothers preferred getting the glucose from food. But the Cochrane review could not recommend the candy bar test or 50-grams of glucose in food as an alternative to the standard Glucola, since the studies were small and didn't report on important outcomes such as Cesareans or large birth weight.

Non-randomized "cross-over" studies have also looked at testing with candy instead of a glucose drink. In 2015, Racusin et al. conducted a small study with 20 women who had already screened positive for GDM with the 50-gram Glucola and were scheduled to undergo a 3-hour, 100-gram OGTT to confirm the GDM diagnosis. Participants ate 10 strawberry-flavored candy twists within five minutes and had a blood draw one hour later to measure their blood sugar levels. Later on, they went ahead with the 3-hour OGTT as scheduled. All 20 women screened positive for GDM with the 50-gram Glucola (before they were recruited to the study) and only 11 of the 20 screened positive with the candy twists. The candy twists test had a sensitivity of 100%, so it correctly identified the two participants who, ultimately, were diagnosed with GDM after the 100-gram diagnostic test. So, the candy twist method did a better job of avoiding false-positive screenings compared to the 50-gram Glucola. Using candy twists would have avoided 3-hour, 100-gram diagnostic OGTTs in 9 subjects (45%) who did not actually have GDM.

In 1999, researchers assigned 136 participants to either eat 28 jelly beans within ten minutes or drink the 50-gram Glucola, and then take a 1-hour blood test (Lamar et al., 1999). Within one week, everyone switched and repeated the 1-hour test with the other sugar source. Then, within the next 7 to 10 days, everyone received the diagnostic OGTT to confirm whether or not each woman had GDM. Mothers had fewer side effects after the jelly beans (20% versus 38%). The jelly bean test had a lower sensitivity than the Glucola drink (40% versus 80%); however, this difference was not statistically significant (the sample size may have been too small to detect a difference). The ideal screening test must have a high sensitivity, which means fewer false negatives and thus fewer missed cases of GDM.

In the jelly bean study, researchers also sent the specific brand of jelly beans to a lab to measure the amount of simple sugars. The total dose to provide 50 grams of simple sugars was 72 grams of carbohydrates total. They found that the amount of simple sugars in every batch of 28 jelly beans varied, which means that it is hard for providers to accurately recommend a number of jelly beans to match the Glucola drink.

Although many people are interested in food-based or candy-based tests, it's important to realize that there are different kinds of sugars and they don't all have the same effect on blood sugar levels (Wong and Jenkins, 2007). The official oral glucose tolerance tests were designed specifically for use with glucose (also called dextrose). So, taking the test with other kinds of sugar, or with glucose in combination with fats and proteins (such as in cake or candy bars), may alter the results. This means that someone who has true GDM might not get a positive result on the test after taking sugar in the form of candy or juice—resulting in a missed diagnosis. Also, candy alternatives have only been examined for the 50-gram glucose screening test—not for a diagnostic oral glucose tolerance test. In other words, the studies served only for screening and not diagnosis; people with positive results with the candy had to follow up with OGTTs to test for the presence of GDM.

People who object to drinking the standard glucose beverage because of the additives (preservatives/stabilizers, flavorings, dyes) may prefer to measure out exactly the equivalent grams of dextrose, and drink dextrose dissolved in 8 ounces of water. Glucose is the name given for sugar in blood, and dextrose is the name given to glucose that comes from corn and other foods. You can buy dextrose many places, including Amazon, vitamin stores, and home brew supply stores, and there are even organic and non-GMO options. We didn't find evidence in the literature to support this option, but some providers

recommend it over candy or juice for people who otherwise would decline to be screened/tested (Personal Communication, Lily Nichols, 2018). However, to our knowledge, this method has not been tested in research settings yet.

The research on alternatives is very limited at this time, so we do not have high-quality evidence that eating candy or taking glucose in food will correctly identify people with GDM as well as the standard screening and diagnostic tests do.

Fasting blood sugar test

Screening with a fasting blood sugar test would be quick, cheap, and help people avoid side effects such as vomiting. However, researchers are uncertain about the fasting plasma glucose (FPG) test's potential for a GDM screening test (Agarwal, 2016). The U.S. Preventative Services Task Force (USPSTF) reviewed the evidence and concluded that screening with a FPG test after 24 weeks of pregnancy may be useful to rule out people who do not have GDM; however, the 50-gram glucose screening test is better at identifying those who have GDM with fewer false positives (Moyer and USPSTF, 2014).

In a recent review (Brown and Wyckoff, 2017), researchers talked about one interesting idea for using FPG screening in the third trimester. The FPG test could be used to "rule out" GDM in people with lower blood sugar levels (<80 mg/dL) and to "rule in," or diagnose GDM in people with higher levels (≥ 92 mg/dL). They point out that in the HAPO study, health and birth outcomes were much better when the FPG was <80 mg/dL. Screening with an FPG test this way –using a two-cutoff approach—could cut the need for a diagnostic OGTT in half, since only people with FPG levels between 80 mg/dL and 92 mg/dL (in the uncertain range) would need the OGTT for a diagnosis. For everyone else, no other testing would be needed. This FPG approach has potential, but it needs research before it can be recommended. It's also possible that relying on this approach could miss people who have normal fasting blood sugar but abnormally high post-meal blood sugar.

Home blood sugar monitoring

Another alternative could be for people to monitor their blood sugar levels at home and discuss the results with their care provider. This is another controversial way to screen for GDM. We didn't find any studies on GDM screening that compared home blood sugar monitoring versus a standard oral glucose drink.

However, we hear of some people using this method. Basically, they are following a similar path that people do when they've been actually diagnosed with GDM. Usually, after a GDM diagnosis, mothers monitor their blood sugar levels four times a day, once after fasting (first thing in the morning) and again after each meal (ACOG, 2018).

The ADA and ACOG recommend that fasting blood sugar levels should be <95 mg/dL, and post-meal blood sugar levels should be <140 mg/dL at 1-hour. Other recommendations for healthy blood sugar level targets during pregnancy are even lower. For example, the California Diabetes and Pregnancy Program (CDAPP) Sweet Success recommends fasting/premeal levels at <90 mg/dL and post-meal levels at <130 (Shields and Tsay, 2015).

Monitoring your blood sugar levels at home might be an option for someone who cannot take a glucose test because of the side effects, or prefers not to drink the glucose solution. However, home blood sugar monitoring is demanding and has some drawbacks. Mothers may have to purchase their own testing kits, and they have to remember to set alarms and carry their testing supplies with them throughout the day. Some people would consider it a major downside that blood sugar monitoring requires constant finger sticks, although others may not mind. Since home blood sugar monitoring is usually done *after*

GDM diagnosis, there is no clear-cut standard for screening/diagnosing GDM based on home blood sugar checks. It's important to discuss any results with a care provider to determine if testing can be stopped, if home monitoring should be continued, or if consistent high values mean that treatment for GDM is needed. Also, with this method, it is important that mothers follow their normal diet while testing, to get a "real-life" picture of their blood sugar results over time.

When is the best time during pregnancy to screen for GDM?

One of the challenges in diagnosing GDM is that many people are not screened for diabetes before pregnancy, so it can be difficult for the provider to tell if GDM is undiagnosed, pre-existing type 2 diabetes or new onset GDM. Currently, ACOG recommendations suggest that providers test people with risk factors for type 2 diabetes at their first prenatal visit (ACOG, 2018). People diagnosed with diabetes in the first trimester are classified as having pregestational (pre-existing) type 2 diabetes, instead of GDM. There is disagreement about the best test for type 2 diabetes in early pregnancy. Some providers use the one-part diagnostic method, others use the two-part screening and diagnostic method, and others measure hemoglobin A1c. We won't be covering the evidence on type 2 diabetes screening in this article, as our focus is on GDM.

Right now, researchers are conducting studies to evaluate early testing for GDM, and it's possible they may discover that GDM can be identified in the first or second trimester. But as we've already mentioned, most guidelines today recommend that GDM be diagnosed between 24 and 28 weeks of pregnancy. In 2014, the U.S. Preventive Services Task Force concluded that there is not enough evidence on the benefits and harms of screening for GDM before 24 weeks of pregnancy (Moyer and USPSTF, 2014).

However, professional organizations disagree on this matter. The IADPSG criteria recommend that everyone, or at least women with risk factors for type 2 diabetes, be tested at their first prenatal visit with a fasting plasma glucose, glycosylated hemoglobin (HbA1c), or random (non-fasting) plasma glucose test. They promote diagnosing GDM even in the first trimester in mothers who do not meet the criteria for pregestational diabetes but have fasting blood sugar levels ≥ 92 mg/dL (IADPSG, 2010). Also, they recommend that mothers who test negative for pregestational diabetes or GDM early in pregnancy should still be tested for GDM at 24 to 28 weeks of gestation with an OGTT, since blood sugar problems can increase over the course of the pregnancy.

What are the benefits of being treated for GDM?

As we have seen, there is a lot of discussion about the best way to diagnose gestational diabetes. But perhaps a more important question is, does treatment actually lead to a benefit for the mother or baby? A recent systematic review and meta-analysis by Farrar et al. (2017b) includes 42 trials, two of which are large and of high-quality (Crowther et al., 2005; Landon et al., 2009). The findings suggest that treatment does improve the health of the mother and baby.

Many of the included studies compared different medications (insulin, metformin, or glibenclamide/glyburide). However, we are going to focus on the 12 trials that compared 'bundles of care' (starting with lifestyle changes then using medication as necessary to lower blood sugar levels) versus routine care. The reason we are focusing on the trials that looked at bundles of care is because that is the recommended approach for treating mothers with GDM—exercise and nutrition counseling as the first line of action, followed by medication if values are routinely greater than or equal to target values (ACOG, 2018). It's estimated that about 40% of people diagnosed with GDM (using IADPSG criteria) require medication, usually insulin, to manage their blood sugar levels (Bogdanet et al., 2017).

The meta-analysis found that bundles of care cut the risk of large birth weight by 50% and shoulder dystocia by 60%. They did not find a significant difference in the risk of pre-eclampsia, Cesarean, newborn intensive care, newborn low blood sugar, preterm birth, low Apgar scores, use of forceps/vacuum, or labor induction. In two of the trials, mothers reported higher quality of life after treatment for GDM.

What if I want to decline the GDM test?

Having a test for GDM is considered evidence-based care because there are substantial risks to mothers and babies if abnormally high blood sugar levels are not identified and treated. However, it is a human right to decline medical treatment unless the individual is formally found to be incapable of making medical decisions. In the U.S., ACOG has affirmed that mothers with GDM have the right to individualized care and the right to refuse care (ACOG, 2018):

This information [about gestational diabetes] should not be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care…Variations in practice may be warranted.

ACOG's Committee on Ethics states that:

Pregnancy does not lessen or limit the requirement to obtain informed consent or to honor a pregnant woman's refusal of recommended treatment.

(You can read the full text of ACOG's statement on "Refusal of Medically Recommended Treatment During Pregnancy" here: ACOG, 2016).

Bottom Line

- We have strong evidence that treating GDM improves birth outcomes for mothers and babies.
- Gestational diabetes begins during pregnancy, but some people enter pregnancy with pre-existing diabetes (type 2 diabetes) that was previously undiagnosed. To detect pre-existing diabetes, care providers may offer screening in early pregnancy to mothers with risk factors for type 2 diabetes.
- There is widespread agreement that screening or testing for GDM should take place between 24 and 28 weeks of pregnancy. However, researchers and organizations disagree about the best way to screen and diagnose GDM:
    - Some countries and professional organizations (such as ACOG in the U.S.) prefer a two-part method that includes a screening test (frequently the "Glucola" drink), and if that is positive, women take a diagnostic test (which involves fasting, drinking a glucose beverage, and having multiple blood tests).
    - However, most other countries and organizations prefer a one-part method where everybody (or at least everybody with risk factors for GDM) receives the one-part diagnostic test.
    - With the two-part screening and diagnostic method used in the U.S., cutoffs for GDM diagnosis vary by hospital. When you get your results, it may be helpful to obtain the actual numbers, rather than a statement that you "passed" or "failed" the glucose test. Compare your test results with the Carpenter-Coustan or National Diabetes Data Group Criteria to get a better feel for where your results fall.

- Although many people contact us about alternatives to drinking the standard glucose solution, the evidence on alternatives is very limited at this time:
    - We don't know if getting a sugar load from candy, juice, or food screens for GDM as well as the standard glucose drink.
    - Researchers have suggested that a fasting plasma glucose test in the third trimester may be useful as a screening test when it is used with upper and lower cutoffs to 'rule-in' or 'rule-out' GDM. However, more research is needed.
    - People who would rather not drink the standard glucose beverage, or who can't due to vomiting or other reasons, could discuss alternative methods with their provider. However, we do not have sufficient evidence on alternatives at this time to state which alternative is best, or how accurate these alternatives may be.

Receiving a diagnosis of GDM can be stressful for many people. However, the benefits of a positive test result are that you can uncover the potential for health problems before they become a real problem, and take action to improve your health and birth outcomes.

Resources

The book Real Food for Pregnancy (https://amzn.to/2Q077uc) by Lily Nichols, RDN, CDE, is a great source of information on eating well throughout the entire pregnancy. She also has a book called Real Food for Gestational Diabetes (https://amzn.to/2DEg4Ui) for people who have been diagnosed with GDM and want to try and manage their blood sugar levels with diet. Ms. Nichols is a specialist in gestational diabetes and prenatal nutrition. Both books are evidence-based resources with citations to the research articles she used to formulate her recommendations.

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