

# Diabetes in Pregnancy

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## Pregestational diabetes

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# Introduction

- Pregnancy is characterized by insulin resistance and hyperinsulinemia.
- Thus, it may predispose some women to develop diabetes.

# Contd.

The insulin resistance results from

1. Placental secretion of diabetogenic hormones including
  - Growth hormone
  - Corticotropin releasing hormone
  - Placental lactogen, and
  - Progesterone
2. As well as increased maternal adipose deposition, decreased exercise and increased caloric intake

- Hyperinsulinemia is secondary to ?

# A.DM during pregnancy

Diabetes diagnosed during pregnancy is classified as

1. Overt or
2. Gestational.

# Overt diabetes

- A diagnosis of overt diabetes can be made in women who meet any of the following criteria at their initial prenatal visit: IADPSG
    1. Fasting plasma glucose  $\geq 126$  mg/dL [7.0 mmol/L], or
    2. A1C  $\geq 6.5$  percent using a standardized assay, or
    3. Random plasma glucose  $\geq 200$  mg/dL [11.1 mmol/L] that is subsequently confirmed by elevated fasting plasma glucose or A1C, as noted above
- =>These thresholds were chosen because they correlate with development of adverse vascular events, such as retinopathy and coronary artery disease.

# Gestational diabetes

- Diagnosis of gestational diabetes can be made in women who meet either of the following criteria :

1. At any gestational age, Fasting plasma glucose  $\geq 92$  mg/dL , but  $< 126$  mg/dL

2. At 24 to 28 weeks of gestation:

- 75 gram two hour oral glucose tolerance test (GTT) with *at least one abnormal result*:
  - Fasting plasma glucose  $\geq 92$  mg/dL [5.1 mmol/L], but  $< 126$  mg/dL [7.0 mmol/L] or
  - One hour  $\geq 180$  mg/dL (10.0 mmol/L) or
  - Two hour  $\geq 153$  mg/dl (8.5 mmol/L)
- 100 gm oral glucose tolerance test with *two abnormal results*
  - $\geq$  Fasting 95
  - $\geq$  One hour 180
  - $\geq$  Two hours 155
  - $\geq$  Three hours 140



# Significance of diabetes in pregnancy

- Several adverse outcomes have been associated with diabetes during pregnancy
- Importantly, the risk of these outcomes increases continuously as maternal fasting plasma glucose levels increase from the  $\leq 75$  mg/dL [4.2 mmol/L] range, and as the one hour and two hour oral GTT values increase; there is no clear threshold that defines patients at increased risk.

# Adverse outcomes

Adverse outcomes include

- Preeclampsia
- Hydramnios
- Fetal macrosomia
- Fetal organomegaly (hepatomegaly, cardiomegaly)
- Birth trauma
- Operative delivery
- Perinatal mortality
- Neonatal respiratory problems and metabolic complications (hypoglycemia, hyperbilirubinemia, hypocalcemia, erythremia)
- If maternal hyperglycemia is present during organogenesis because of overt (also termed pregestational) diabetes, there is an increased risk of miscarriage and congenital anomalies
- There are also potential long-term consequences to the infant, such as development of **obesity and diabetes during childhood, impaired fine and gross motor functions, and higher rates of inattention and/or hyperactivity**

# Adverse outcomes Contd.

- For the mother with gestational diabetes, there is a 10 percent likelihood of overt diabetes mellitus immediately after the index pregnancy. This risk varies depending upon the diagnostic criteria used and her race/ethnicity.
- The likelihood of developing overt diabetes in the years following the pregnancy has been estimated to be as high as 40 percent within 20 years and varies greatly depending upon characteristics such as geographic location, ethnicity, body mass index, and other risk factors

# Risk factors for diabetes during pregnancy

Pregnant women with any of the following appear to be at increased risk of developing gestational diabetes

- A family history of diabetes, especially in first degree relatives
- Prepregnancy weight  $\geq 110$  percent of ideal body weight or body mass index over  $30 \text{ kg/m}^2$ , significant weight gain in early adulthood and between pregnancies , or excessive gestational weight gain .
- Age greater than 25 years
- Previous delivery of a baby greater than 9 pounds [4.1 kg]
- Personal history of abnormal glucose tolerance
- Member of an ethnic group with higher than the background rate of type 2 diabetes (eg, Hispanic-American, African-American, Native American, South or East Asian, Pacific Islander). In most populations, the background rate had been approximately 2 percent, but is rising rapidly.
- Previous unexplained perinatal loss or birth of a malformed child
- Maternal birth weight greater than 9 pounds [4.1 kg] or less than 6 pounds [2.7 kg]
- Glycosuria at the first prenatal visit
- Polycystic ovary syndrome
- Current use of glucocorticoids
- Essential hypertension or pregnancy-related hypertension

# Prevalence

- The prevalence of diabetes during pregnancy varies worldwide and among racial and ethnic groups.
- Prevalence also varies with the testing method and diagnostic criteria
- It has been increasing over time, possibly related to increases in mean maternal age and weight.

# If IADPSG diagnostic criteria for overt and gestational diabetes are used, about **18 percent** of women would be diagnosed with diabetes during pregnancy

# Screening versus diagnostic testing

The purpose of screening is **to identify asymptomatic individuals** with a high probability of having or developing a specific disease.

- **Screening** is usually performed **as a two-step process** where step one identifies individuals at increased risk for the disease so that step two, diagnostic testing, which is definitive but usually more complicated or costly than the screening test, can be limited to these individuals and avoided in low risk individuals.
- Alternatively, **a diagnostic test** can be administered to all individuals, which is **a one-step process**.

# Screening Contd.

Screening can be

1. One step –IADPSG,ADA
2. Two step-ACOG
3. Serial
4. IV GTT
5. A1C

# Screening Contd.

**Two step approach** - The two step approach is the most widely used approach for identifying pregnant women with diabetes, and is recommended by ACOG.

**One step approach** - The one step approach has been proposed by the IADPSG and endorsed by the ADA, but not by ACOG .

→ It was made practical by simplifying diagnostic testing for diabetes in pregnancy to the performance of a 75 gram two hour oral GTT and requiring only a single elevated value for diagnosis, rather than the previous three hour GTT requiring two elevated values for diagnosis.



# Whom to screen

- Universal screening appears to be the optimum approach because 90 percent of pregnant women have risk factors for glucose impairment during pregnancy

# When to screen?

- Universal screening has traditionally been performed at 24 to 28 weeks of gestation.
- Screening should be performed as early as the first prenatal visit if there is a high degree of suspicion that the pregnant woman has undiagnosed type 2 diabetes (eg, obesity, personal history of gestational diabetes, glycosuria, or strong family history of diabetes).
- In particular, women with a history of gestational diabetes have a **33 to 50 percent risk of recurrence**, and some of these recurrences may represent unrecognized type 2 diabetes.
- Early screening or diagnostic testing is consistent with the IADPSG's new terminology and recommendations for diagnosis of diabetes in pregnancy

# How to screen

- There is no worldwide standard for screening and diagnosis of diabetes during pregnancy. In the United States, the current approach is screening with a glucose challenge test, followed by diagnostic testing in women who screen positive (i.e, two step approach).

# How to screen

## 1. Two step approach

This approach begins with a 50 gram oral glucose challenge test for screening .

- The 50 gram oral glucose load is given without regard to the time elapsed since the last meal and plasma glucose is measured one hour later (sometimes called a "one-hour GTT"); a value  $\geq 130$  or  $\geq 140$  mg/dL (7.2 or 7.8 mmol/L) is considered abnormal.

=>Screening and diagnostic tests that measure glucose concentration should be performed on **venous plasma** using an accurate and precise enzymatic method.

# Screening Contd.

## Steps of Glucose challenge test for screening for gestational diabetes

1. Give 50 g oral glucose load without regard to time of day
2. Measure plasma or serum glucose.
3. Glucose  $\geq 130$  mg/dL (7.2 mmol/L) or  $\geq 140$  mg/dL (7.8 mmol/L) is elevated and requires administration of a full glucose tolerance test

# How Contd.

=>The original threshold for an abnormal test ( $\geq 140$  mg/dL) was arbitrary and validated by the ability to predict a positive three-hour oral GTT in the mother. However, the sensitivity of the 50 gram glucose test is improved if a lower plasma glucose threshold ( $\geq 130$  mg/dL) is used.

- At the 130 mg/dL threshold, the test is positive in **20 to 25** percent of pregnant women and detects 90 percent of women with gestational diabetes; at the 140 mg/dL threshold, 14 to 18 percent of tests will screen positive and 80 percent of gestational diabetics will be detected.
- Based on these findings, ACOG has stated that either threshold may be used. Women with an abnormal value are then given a 100 gram three hour oral GTT for definitive diagnosis

# 100 gram three hour oral glucose tolerance test

- The oral GTT is an imprecise test with poor reproducibility
- currently recommended by ACOG; two elevated glucose values are needed for a positive test

=>Carbohydrate loading **for three days** has been recommended before this test, but is probably not necessary if the patient is not on a low carbohydrate diet.

	Plasma or serum glucose level Carpenter/Coustan		Plasma level National Diabetes Data Group	
	mg/dL	mmol/L	mg/dL	mmol/L
Fasting	≥95	5.3	≥105	5.8
One hour	≥180	10.0	≥190	10.6
Two hours	≥155	8.6	≥165	9.2
Three hours	≥140	7.8	≥145	8.0



- 100 gram oral glucose load is given to a patient who is fasting. Glucose concentration greater than or equal to these values at **TWO or more time points is a positive test.**
- Two different classification schemes of GDM based upon results of the three-hour GTT results have been proposed. The Fourth International Workshop-Conference on Gestational Diabetes GTT values cited above are based upon the Carpenter and Coustan modification of earlier values. They are lower than those proposed by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus and the National Diabetes Data Group (NDDG), which used cutoff values of 105, 190, 165, and 145 mg/dL (5.8, 10.6, 9.2, and 8.0 mmol/L), respectively.
- The values are lower because the thresholds derived from the older **Somogyi-Nelson** method of glucose analysis were corrected to account for the enzymatic assays currently in use.

## Read

- What is the preparation of this glucose
- What is the difference between capillary Serum and plasma glucose

# One step approach

- 2. One step approach** — The IADPSG felt that the decision to screen/test for diabetes at the first prenatal visit should be based upon the background frequency of abnormal glucose metabolism in the population and on local circumstances. Given the increasing frequency of type 2 diabetes in the US population, universal early testing when routine initial prenatal laboratory tests are drawn is both desirable and convenient.
- We suggest universal testing at the initial prenatal visit by obtaining an A1C, since women are unlikely to be fasting at this visit. This approach has not yet been validated by data from randomized trials. It is endorsed by the ADA , but not by ACOG.
  - ACOG noted that, by the IADPSG estimate, 18 percent of all pregnant women will be diagnosed with gestational diabetes. They opined that the **one step approach would increase health care costs** in the absence of evidence that use of the IADPSG approach and criteria result in improvements in maternal or newborn outcomes

# One step Contd.

- a diagnosis of overt diabetes is made in women who meet any of the following criteria at their initial prenatal visit:
  1. Fasting plasma glucose  $\geq 126$  mg/dL [7.0 mmol/L], or
  2. A1C  $\geq 6.5$  percent using a standardized assay, or
  3. Random plasma glucose  $\geq 200$  mg/dL [11.1 mmol/L] that is subsequently confirmed by elevated fasting plasma glucose or A1C, as noted above
- A diagnosis of gestational diabetes is made at the initial prenatal visit if the fasting plasma glucose is  $\geq 92$  mg/dL [5.1 mmol/L], but  $< 126$  mg/dL [7.0 mmol/L].
- (Fasting plasma glucose  $\geq 126$  mg/dL [7.0 mmol/L] is consistent with overt diabetes). Since most women will not be fasting when their blood is drawn, this diagnosis will rarely be made

# **75 gram two hour oral glucose tolerance test**

- The 75 gram two hour oral GTT as recommended by the IADPSG is more convenient, better tolerated, and more sensitive for identifying the pregnancy at risk for adverse outcome than the 100 gram three hour oral GTT.
- Increased sensitivity is likely related to a
  1. Lower threshold for a positive test
  2. Only one elevated glucose value is needed &
  3. The cut-offs are slightly lower

## World Health Organization

Fasting	$\geq 125$ mg/dL (6.9 mmol/L)
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**OR**

Two hour	$\geq 140$ mg/dL (7.8 mmol/L)
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## International Association of Diabetes and Pregnancy Study Groups (IADPSG) and American Diabetes Association

Fasting	$\geq 92$ mg/dL (5.1 mmol/L)
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**OR**

One hour	$\geq 180$ mg/dL (10.0 mmol/L)
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**OR**

Two hour	$\geq 153$ mg/dL (8.5 mmol/L)
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These values represent the average glucose values at which infant birth weight, cord C-peptide, and percent body fat >90 percentile reached 1.75 times.

**Pregnancy < 24 weeks of gestation**

Draw blood for FBS, RBS or A1C

RBS < 200 mg/dl  
A1C < 6.5 %  
FBS < 92

75 gm 2 hrs GTT at  
24-28 weeks

FBS  $\geq$  92 but < 126 mg/dl

GDM no further  
testing

RBS  $\geq$  200 mg/dl  
A1C  $\geq$  6.5 %  
FBS  $\geq$  92

Overt diabetes no  
further testing

**Pregnancy  $\geq$  24 weeks 75 gm 2 hrs GTT**

# # Patients unable to tolerate oral hyperosmolar glucose

- The highly concentrated hyperosmolar glucose solution can cause gastric irritation, delayed emptying, and gastrointestinal osmotic imbalance leading to nausea and vomiting.
- Other types of oral screening (and glucose tolerance) tests have been proposed and are better tolerated, but appear to be less sensitive and have not been validated in large studies.
- These approaches typically use candy, a predefined meal, or commercial soft drinks instead of a standard glucose monomer or polymer solution
- None have been endorsed by the ADA or ACOG



### **3.Serial glucose monitoring**

**Serial glucose monitoring:** Periodic random fasting and two-hour postprandial blood glucose testing is a monitoring option for women at high risk for gestational diabetes who are unable to take an oral glucose load.

- This approach is also useful for women who have dumping syndrome after a roux-en-Y gastric bypass procedure; these women are unlikely to tolerate a hyperosmolar glucose solution.

## 4. Intravenous GTT

- An alternative for such patients is the intravenous GTT. While it is not a standard approach or widely used, we have found this test to be useful in patients who cannot tolerate the oral glucose load. *The test dose of 25 grams of glucose is rapidly infused intravenously. Plasma glucose is measured prior to the infusion, at 10 minutes and at 60 minutes. The 10-minute plasma glucose value is divided by the 60-minute glucose value to arrive at a quotient (Q) describing the rate of disappearance of glucose from the circulation.*
- Nondiabetic individuals will clear glucose more rapidly than those with diabetes. A table can be used to convert the Q to a k value, which represents the slope of the glucose disappearance curve. The lower limit of normal (mean – 2 standard deviations) k values was found to be 1.37 in the first trimester, 1.18 in the second trimester, and 1.13 in the third trimester.
- While this approach has not been well validated against oral GTT results, nor against pregnancy outcome, we have found it useful in those patients who cannot tolerate the oral glucose load.

## 5.A1C

- There is a large overlap in the distribution of A1C values between women with normal, borderline abnormal, and mildly abnormal blood glucose levels. Therefore, A1C is **not** a suitable test to detect mildly impaired glucose tolerance. An A1C  $\geq 6.5$  percent suggests type 2 diabetes, and is one of the criteria for diagnosis of overt diabetes in pregnancy proposed by the IADPSG and endorsed by the ADA
- In fact, data are accruing that an A1C level greater than two standard deviations above the normal mean during pregnancy, when A1C levels are generally slightly lower than in the nonpregnant state (in most laboratories this level is approximately 5.3 percent), may identify those women at risk for delivering a large for gestational age infant. However, an A1C below this level should not be taken as evidence against the diagnosis of diabetes and cannot substitute for an oral GT

## B.Pregestational diabetes

=>Comprises approximately 13 % of all diabetes in pregnancy,while gestational diabetes comprises the remaining 87%.

# Assessing glycemic control

- **Glycated hemoglobin (A1C)**
- **Physiology** — Red blood cells that have been recently released from the bone marrow into the circulation have a very low concentration of glycated hemoglobin; the concentration increases over time and with increasing exposure to glucose. The total glycated hemoglobin level is reasonably approximated by measurement of hemoglobin A1C since it accounts for approximately 92 percent of all glycated hemoglobin. In nonpregnant individuals, **the A1C level in blood reflects the mean age of the red blood cells and the mean glucose concentration to which they have been exposed over the previous 8 to 12 weeks.** When used clinically to assess glycemic control over time, it is assumed that the mean age of the red blood cells remains constant and that changes in A1C concentration only reflect changes in glucose concentration.

- In pregnant women, however, physiologic changes related to pregnancy also contribute to changes in A1C. In pregnant nondiabetic women, A1C falls to a nadir in the midtrimester and rises in the third trimester. These changes in A1C are caused by physiologic changes in mean glucose concentration during pregnancy and from physiologic changes in mean red blood cell age (mean red blood cell age falls in pregnancy as red blood cell mass increases to meet volume expansion [9]). As a result, pregnant women have lower A1C levels compared with nonpregnant women. For this reason, several investigators have suggested use of a pregnancy specific reference range for A1C [10-13], some have advised against using the A1C during the second and third trimesters [2], while others have proposed that the A1C goal in late pregnancy should be lowered by 0.4 percent [13]. We recommend use of A1C goal <6.0 percent throughout pregnancy, interpreted with an understanding of the physiologic changes in A1C concentration across gestation. Despite the shortcoming of the A1C value in pregnancy, monitoring A1C is still useful as a correlate of mealtime glycemia, as well as neonatal outcomes

- **Measurement and target A1C level —**
- American Diabetes Association (ADA) clinical practice guideline for managing preexisting diabetes in pregnancy that recommends monthly A1C determinations beginning with the initial prenatal visit and an A1C goal <6.0 percent throughout pregnancy , if safely achievable without inducing hypoglycemia.

## Glucose monitoring

- Elevated blood glucose levels are associated with diabetes complications, such as worsening nephropathy and retinopathy, and pregnancy complications, such as preeclampsia, preterm labor, and delivery of a large for gestational age infant
- Several studies have reported the beneficial effects of improved glycemic control on fetal outcome in pregnant women with pregestational diabetes.
- The most consistent effect demonstrated in these studies is a reduction in rate of **macrosomia**, which is desirable because macrosomia increases the risk of shoulder dystocia and cesarean delivery. A reduction in **preeclampsia** appears to be another benefit. The incidence of preeclampsia is lowest in women with optimal glycemic control and increases as A1C increases



# Self-monitoring of blood glucose

- In nonpregnant individuals, the American Diabetes Association (ADA) generally recommends self-monitoring of blood glucose (SMBG) three or more times daily; however, for pregnant women with preexisting diabetes, they suggest SMBG before and one hour after the first bite of each meal, at bedtime, and occasionally between 2 AM and 4 AM  
=>Postprandial glucose concentrations peak 60 to 90 minutes after eating.

# There are several causes of early morning hyperglycemia. The **dawn phenomenon** refers to the increase in blood glucose that usually occurs between 3 AM and 5 AM and **not preceded by hypoglycemia**; it is related to the normal overnight release of hormones associated with insulin resistance. In contrast, the **Somogyi effect** refers to rebound hyperglycemia that occurs 6 to 12 hours after hypoglycemia and thought to be related to release of counter-regulatory hormones in response to low blood glucose levels. High morning blood glucose levels may also result from inadequate insulin management or carbohydrate snack consumption at bedtime. In order to distinguish among these possibilities, early morning blood sugar assessment (between 3 AM and 5 AM) and review of insulin administration and dietary habits are necessary.

