GESTATIONAL DIABETES MELLITUS UPDATES AND OVERVIEW

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Idaho Perinatal Project Winter Conference 2018

DISCLOSURES

NONE
LEARNING OBJECTIVES

- Gestational Diabetes Mellitus Pathophysiology
- Gestational Diabetes Mellitus Updates & Rationale for Screening /Diagnosis
- Appreciate Fetal and Maternal Morbidity/Mortality Correlated with GDM
- Management Guidelines Updates: Identifying Appropriate 1st and 2nd Line Therapies
- Future Research Considerations in Regards to Screening and Management

PATHOPHYSIOLOGY IN GESTATIONAL DIABETES MELLITUS

Condition in Which Carbohydrate Intolerance Develops During Pregnancy
MATERNAL INSULIN RESISTANCE IN NORMAL PREGNANCY

Maternal Insulin Resistance:
Provides fetus with Glucose and AA’s in 3rd Trimester

Maternal Fuel:
Fatty acids, Ketones & Glycerol

Mediated by Hormones:
Prolactin + Chorionic Somatotropin (HPL), Progesterone, Cortisol

GDM PATHOPHYSIOLOGY

ETIOLOGY: “UNKNOWN”
HYPOTHESIS: OBESITY, AUTOIMMUNE, SINGLE GENE MUTATION

Figure 1: Insulin bind to its receptor on cell membrane (1). Starts many protein activation cascades (2). Includes translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6).
PERINATAL MORBIDITY AND MORTALITY

MATERNAL

• Pre-Eclampsia Association
• Cesarean Section
• Increased Risk of Type 2 Diabetes Mellitus
• Gestational Hypertension

FETAL

• Macrosomia
• Hypoglycemia
• Hyperbilirubinemia
• Shoulder Dystocia
• Birth Trauma

LONG TERM FETAL EFFECTS VIA FETAL PROGRAMMING

"Fetuses exposed to maternal diabetes have a higher risk of abnormal glucose homeostasis in later life beyond that attributable to genetic factors leading to increased rates of future cardiovascular disease, hypertension and T2DM."

In utero diagram showing the effects of fetal programming on metabolic and cardiovascular health.
EPIGENETIC MODIFICATION

DIAGNOSTIC CRITERIA

FIRST TRIMESTER SCREENING

&

UNIVERSAL SCREENING 24-28 WEEKS GESTATION
ACOG FIRST TRIMESTER SCREENING INDICATIONS

OBESE OR OVERWEIGHT WOMEN WITH ONE OF THE FOLLOWING RISK FACTORS

• Physical inactivity
• First-degree relative with diabetes
• High-risk race or ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
• Have previously given birth to an infant weighing 4,000g (approximately 9 lb) or more
• Previous gestational diabetes mellitus
• Hypertension (140/90 mm Hg or on therapy for hypertension)
• High-density lipoprotein cholesterol level less than 35 mg/dL (0.90 mmol/L), a triglyceride level greater than 250 mg/dL (2.82 mmol/L)
• Women with polycystic ovarian syndrome
• A1C greater than or equal to 5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
• Other clinical conditions associated with insulin resistance (e.g., pre-pregnancy body mass index greater than 40 kg/m2, acanthosis nigricans)
• History of cardiovascular Disease

AMERICAN DIABETES ASSOCIATION EARLY SCREENING RECOMMENDATION

Table 2.2—Criteria for the diagnosis of diabetes

<table>
<thead>
<tr>
<th>Fasting PG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
</tr>
<tr>
<td>2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).</td>
</tr>
</tbody>
</table>

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.
ACOG EARLY SCREENING RECOMMENDATION

2 STEP SCREENING PROCESS

<table>
<thead>
<tr>
<th>Step</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 g Glucose Challenge Test</td>
</tr>
<tr>
<td>2</td>
<td>3 hour OGTT</td>
</tr>
</tbody>
</table>

HEMOGLOBIN A1C DURING PREGNANCY

<table>
<thead>
<tr>
<th>BENEFITS</th>
<th>PITFALLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cost effective</td>
<td>• Values vary with age, race, hemoglobinopathies and ethnicity</td>
</tr>
<tr>
<td>• Convenient</td>
<td>• A1C levels fall 2\textsuperscript{nd} and 3\textsuperscript{rd} Trimester</td>
</tr>
<tr>
<td>• Less Daily Variability</td>
<td>• Less sensitive than OGTT</td>
</tr>
<tr>
<td>• Greater Pre-Analytical Stability</td>
<td></td>
</tr>
</tbody>
</table>

Diagram:
- **< 13 weeks**
  - Hgb A1c < 5.7
    - Repeat testing at 24 to 28 weeks
  - Hgb A1c 5.7-6.4
    - Treat as GDM
    - Refer to nutrition & Diabetes Education
  - Hgb A1c ≥ 6.5
    - Treat as gestational Diabetes Mellitus
### Objective:
Examine prevalence of previously diagnosed diabetes and undiagnosed diabetes using suggested A1C criteria in US and compared to other glucose criteria.

### Methods:
Survey sample of 14,611 individuals from National Health and Nutrition Examination Survey.

Participants were classified on glycemic status by interview for diagnosed diabetes and by A1C, fasting, and 2-h glucose challenge values measured in subsamples.

### Results:
Using A1C criteria, prevalence of undiagnosed diabetes and high risk of diabetes were one-third that and one-tenth that, respectively, using glucose criteria.

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**UNIVERSAL SCREENING**

24-28 WEEKS
### Study Design:
- Multinational Cohort Study

### Power:
- 23,000 in 3rd trimester

### Objective:
- Obtain data on associations between Maternal Glycemia and Risk of Adverse Outcomes

### Purpose:
- Derive International Acceptable Criteria for Diagnosis and Classification of GDM

### Results:
- Adverse Outcomes Increase as Function of Maternal Hyperglycemia
# Overview of Screening Recommendations

Recommending body | Criteria | Screening on first antenatal visit | Screening at 24–32 weeks with OGTT | One-step/two-step screening | HbA1c for screening
--- | --- | --- | --- | --- | ---
Endocrine Society, USA | IADPSG | Universal | Universal | One-step | No
World Health Organization | IADPSG | Universal or Risk factor-based | Universal | One-step | No
ACOG | Carpenter and Costan | Risk factor-based | Universal | Two-step | No
ADA | IADPSG/Carpenter and Costan | Risk factor-based | Universal | Either of one | No
ADIPS | IADPSG | Risk factor-based | Universal | One-step | No

**Abbreviations:** ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; ADIPS, Australian Diabetes in Pregnancy Society; IADPSG, International Association of Diabetes and Pregnancy Study Groups; OGTT, oral glucose tolerance test.

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# One Step Screening Process for International Association of Diabetes and Pregnancy

Table 2.6—Screening for and diagnosis of GDM

**One-step strategy**
Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. The OGTT should be performed in the morning after an overnight fast of at least 8 h. The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:
- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)
TWO STEP STRATEGY FOR ACOG

Two-step strategy
Step 1: Perform a 50-g GTT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. If the plasma glucose level measured 1 h after the load is ≥130 mg/dL, 135 mg/dL, or 140 mg/dL,* (7.2 mmol/L, 7.5 mmol/L, or 7.8 mmol/L), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting. The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

<table>
<thead>
<tr>
<th></th>
<th>Carpenter/Countan (59)</th>
<th>or</th>
<th>NDDG (60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>95 mg/dL (5.3 mmol/L)</td>
<td></td>
<td>105 mg/dL (5.8 mmol/L)</td>
</tr>
<tr>
<td>1 h</td>
<td>180 mg/dL (10.0 mmol/L)</td>
<td></td>
<td>190 mg/dL (10.6 mmol/L)</td>
</tr>
<tr>
<td>2 h</td>
<td>155 mg/dL (8.6 mmol/L)</td>
<td></td>
<td>165 mg/dL (9.2 mmol/L)</td>
</tr>
<tr>
<td>3 h</td>
<td>140 mg/dL (7.8 mmol/L)</td>
<td></td>
<td>145 mg/dL (8.0 mmol/L)</td>
</tr>
</tbody>
</table>

NDDG, National Diabetes Data Group. *The ACOG recommends either 135 mg/dL (7.5 mmol/L) or 140 mg/dL (7.8 mmol/L). A systematic review determined that a cutoff of 130 mg/dL (7.2 mmol/L) was more sensitive but less specific than 140 mg/dL (7.8 mmol/L) (55).

PRACTICAL APPROACH

Pragmatic indications for one- and two-step approaches based on biopsychosocial model

**Biological:**
*One-step preferable: high-risk conditions, with likely chances of having GDM, like obesity, PCOS, etc. Missed or delayed diagnosis in such cases could increase the adverse effects.*
*Two-step preferable: Medical or obstetrical complications for frequent travel. Negative GCT can prevent travel (if GCT could be done on routine antenatal visit) and further testing in nearly 75% of women.*

**Psychological:**
*One-step preferable: fear of frequent investigations*

**Social:**
*One-step preferable: chances of not following again for OGTT after GCT*
*Two-step preferable: difficult travel conditions/limited resources to carry out OGTT in every patient (if GCT could be done on routine antenatal visit)*
COMPARISON AND FUTURE CONSIDERATIONS

Management of Gestational Diabetes Mellitus

Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Therapy</th>
</tr>
</thead>
</table>
| Apgar         | Neonatal intensive care unit admission, 
                | for 7-10 days, then 7-10 days |
| Strategies    | 
                | Maternal control, 
                | Ketone monitoring, 
                | Maternal care |
| Diaphragm     | Postoperative management, 
                | to prevent 
                | for 24 hours, 
                | for 48 hours |

PERCENTAGE

2-hour (period 1) vs 1-hour (period 2)
**USPTF SYSTEMATIC REVIEW**

<table>
<thead>
<tr>
<th>Objective</th>
<th>Summarize maternal and neonatal benefits and harms of treating GDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Source</td>
<td>15 electronic databases from 1995-2012</td>
</tr>
<tr>
<td>Study Types</td>
<td>RCT's and Retrospective Cohort Studies</td>
</tr>
<tr>
<td>Summary:</td>
<td>Support for treating mild GDM</td>
</tr>
</tbody>
</table>

**Figure 1.** Effect of treatment for shoulder dystocia, neonatal hypoglycemia, and macrosomia (birthweight >4000 g) based on data from randomized, controlled trials.
MEDICAL NUTRITION THERAPY

GOALS: CLINICAL RECOMMENDATIONS:

Caloric Allotment

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Calories/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>30</td>
</tr>
<tr>
<td>2nd</td>
<td>36</td>
</tr>
<tr>
<td>3rd</td>
<td>38</td>
</tr>
<tr>
<td>Total</td>
<td>2000</td>
</tr>
</tbody>
</table>

Carbohydrate Intake

- Starch Portions: 1 cup, 2 pieces of bread
- Dairy: 1 cup of milk
- Fruit: 1-3 portions fruit daily

Caloric Distribution

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Carbohydrates</th>
<th>Protein</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>40%</td>
<td>20%</td>
<td>40%</td>
</tr>
</tbody>
</table>

CALORIC ALLOTMENT

Women: 12-13 servings of Carbohydrates per Day
1 serving = 15 grams Carbs
Total daily carbs = 15 x 12 = 180 Grams Carbs

Recommend Splitting between:
- 3 small meals: 40 g per meal
- 2 snacks: 30 g per snack

CARBOHYDRATES

15 GRAMS OF CARB SERVINGS

Women: 12-13 servings of Carbohydrates per Day
1 serving = 15 grams Carbs
Total daily carbs = 15 x 12 = 180 Grams Carbs

Recommend Splitting between:
- 3 small meals: 40 g per meal
- 2 snacks: 30 g per snack
WHICH DIET DO I CHOOSE?

The conventional diet approach to gestational diabetes mellitus (GDM) advocates carbohydrate restriction, resulting in higher fat (HF), also a substrate for fetal fat accretion and associated with maternal insulin resistance. Consequently, there is no consensus about the ideal GDM diet.

TRIAL TIME

SURVEILLANCE + DIET + EXERCISE

MONITOR FASTING AND POSTPRANDIAL BG’s:
Fasting < 95
1 hour < 140
2 hour < 120

TRANSITION TO MEDICAL THERAPY if >2/7 Abnormal in 2 WEEKS or if >50 % are BELOW goal.
ACOG PHARMACOLOGIC THERAPY

- INSULIN FIRST LINE
- METFORMIN SECOND LINE
- GLYBURIDE NO LONGER RECOMMENDED

FIRST LINE: INSULIN

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset of Action</th>
<th>Peak of Action (h)</th>
<th>Duration of Action (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin lispro</td>
<td>1–15 min</td>
<td>1–2</td>
<td>4–5</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>1–15 min</td>
<td>1–2</td>
<td>4–5</td>
</tr>
<tr>
<td>Regular insulin</td>
<td>30–60 min</td>
<td>2–4</td>
<td>6–8</td>
</tr>
<tr>
<td>Isophane/insulin suspension (NPH insulin)</td>
<td>1–3 h</td>
<td>5–7</td>
<td>13–18</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>1–2 h</td>
<td>No peak</td>
<td>24</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>1–3 h</td>
<td>Minimal peak at 8–10</td>
<td>18–26</td>
</tr>
</tbody>
</table>


### Basal Insulin
1) NPH
2) Glargine or Detemir

### Short Acting
1) Lispro
2) Aspart

More rapid onset that Regular Insulin.

### Starting Dose
1) 0.7–1.0 Unit/kg
2) Divided into long acting and short

Basal Insulin

Short Acting

Starting Dose
METFORMIN
SECOND LINE TREATMENT

- Mechanism of Action: Inhibits hepatic gluconeogenesis and glucose absorption. Stimulates glucose uptake into tissues.
- Dosing: 500 mg BID. Up to 3000 mg BID in 2 divided doses
- Fetal Concerns: Crosses the placenta with unknown long term fetal outcomes

SUMMARY for PATIENT COUNSELING

- Reasonable Second Line Therapy
- Benefits: Lower risk of neonatal hypoglycemia, gestation hypertension, less visceral fetal fat mass and less maternal weight gain
- Risks: Long term outcomes unknown, Risk of prematurity with RR of 1.5, 1/2 treat with Metformin eventually need insulin

Metformin, the aspirin of the 21st century: its role in gestational diabetes mellitus, prevention of preeclampsia and cancer, and the promotion of longevity
QUESTIONABLE OUTCOMES
WITH METFORMIN

Further studies need to be done to query whether there is:

1) Long term change in neurodevelopmental outcomes

2) Effects on long term insulin-sensitive pattern of growth

Neurodevelopmental outcome at 2 years in offspring of women randomized to metformin or insulin treatment for gestational diabetes

<table>
<thead>
<tr>
<th>Study design</th>
<th>Prospective Study. Mothers assigned to insulin vs metformin at 20-33 weeks gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power</td>
<td>211</td>
</tr>
<tr>
<td>Methods</td>
<td>Neurodevelopment assessment with Bayles Scales of Infant Development to 2 years of age</td>
</tr>
<tr>
<td>Results</td>
<td>No significant developmental differences appreciated</td>
</tr>
</tbody>
</table>

GLYBURIDE
NO LONGER RECOMMENDED

MECHANISM: Binds pancreatic beta cell ATP calcium channel receptors to increase secretion and insulin sensitivity

DOSAGE: 2.5-20 mg Daily

CONCERNS:
1) Concentration in umbilical cord approximately 70% higher than maternal levels.

2) Meta Analyses demonstrated worse neonatal outcomes

Hypoglycemia (RR)

Birthweight (g)
SOCIETY FOR MATERNAL FETAL MEDICINE RECOMMENDATIONS

- INSULIN or METFORMIN FIRST LINE
- GLYBURIDE: DATA INSUFFICIENT for RECOMMENDATION

TRIALS COMPARING METFORMIN TO INSULIN

OUTCOMES
HEALTHCARE DISPARITIES IN GDM

<table>
<thead>
<tr>
<th>FOOD INSECURITY</th>
<th>LANGUAGE BARRIER</th>
<th>HOMELESSNESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Affects 1/7</td>
<td>• GDM/Diabetes more common among non-English speaking individuals</td>
<td>• Associated with literacy and numeracy deficiencies, cog dysfunction and mental health issues</td>
</tr>
<tr>
<td>• Higher rate among minorities</td>
<td></td>
<td>Temporary housing. Secure place to keep supplies</td>
</tr>
<tr>
<td>Find out community resources for your patients</td>
<td>Develop education materials in multiple languages</td>
<td></td>
</tr>
</tbody>
</table>

Community Support can Include: Promotoras, Clinical Pharmacists, Community Health Workers and Dieticians

INTRAPARTUM MANAGEMENT

- Goal is to reduce the risk of transient neonatal hypoglycemia
- NO consensus about optimal glycemic controls during pregnancy
- Endocrine Society Recommends 72-126
- Monitoring: Every 1-2 hours while in active labor
- Consider start IV insulin infusion if Blood Glucoses >120 mg/dl
MATERNAL PROGNOSIS

INCREASED PREVALENCE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent GDM</td>
<td>Obesity</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Stroke</td>
</tr>
<tr>
<td>CHF</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>Renal Disease</td>
<td>Retinopathy</td>
</tr>
</tbody>
</table>

POSTPARTUM MANAGEMENT

Timing: Changed to 4-12 weeks postpartum

75 g OGTT recommended over A1C

Rescreen every 1-3 years based on risk factors

Can use A1C, fasting plasma glucose or 75 g OGTT for screen

*Up to 80% of women affected by GDM will develop T2DM

Figure 3. Management of postpartum screening results. Abbreviations: IPC, fasting plasma glucose; OGGT, oral glucose tolerance test; ICT, impaired glucose tolerance. 41
**PREVENTION OF TYPE 2 DIABETES MELLITUS AFTER GDM**

<table>
<thead>
<tr>
<th>Study:</th>
<th>Prospective Nurse' Health Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation:</td>
<td>GDM and Postpartum weight gain → Adverse Pregnancy Outcome → Early Progression to T2Dm</td>
</tr>
<tr>
<td>Intervention of Lifestyle Modification and Metformin</td>
<td>Delayed progression of Type 2 DM</td>
</tr>
<tr>
<td>NNT: 5-6 to prevent 1 case over 3 years</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 1](image.png)

**CLOSING THE GAP**

![Diagram](image.png)
SUMMARY

- Test for undiagnosed diabetes at the first prenatal visit in those with risk factors, using standard diagnostic criteria
- Test for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant women not previously known to have diabetes.
- Lifestyle Management with Medical Nutrition Therapy and Exercise is Primary Therapeutic Intervention for GDM
- Insulin is the ONLY Appropriate first line therapy. Metformin ONLY 2nd line therapy.
- Screen women with gestational diabetes mellitus for persistent diabetes at 4–12 weeks' postpartum, using the oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria
- Women with history of gestation diabetes should have lifelong screening every 1-3 years
- Women with history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle intervention or metformin to prevent diabetes. Need to ensure follow up with PCP.

REFERENCES


Catherine C. Cowie, Keith F. Rust, Danita D. M. R, Linda S. G. S. Women with history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle intervention or metformin to prevent diabetes. Need to ensure follow up with PCP.


QUESTIONS?