Gestational Diabetes Mellitus—Diagnosis and Treatment

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Outline / Objectives
- Epidemiology of GDM
- Screening of GDM
  - Universal vs. selective screening
  - Screening thresholds
- Diagnosis of GDM
  - GTT: diagnostic thresholds
- Management of GDM
  - Diet and exercise
  - Oral hypoglycemic agents vs. insulin injections
- Postpartum follow-up

Disclosures
No association with private industry
Funded by:
NIH/NICHD Women's Reproductive Health Research (WRHR)
NIH 12HD001262

Epidemiology of Diabetes during Pregnancy in the U.S.
- 154,000 (4%) of all pregnancies
  - 135,000 (88%) due to GDM
  - 12,000 (8%) due to Type 2 DM
  - 7,000 (4%) due to Type 1 DM

ADA position statement. Standards of Medical Care in Diabetes. Diabetes Care 2006;29:S4-S2
**Age-adjusted Percentage of U.S. Adults with:**

- **Obesity (BMI ≥30 kg/m²)**
  - 1994
  - 2000
  - 2009

- **Diagnosis of DM**
  - 1994
  - 2000
  - 2009

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**Obstetric Considerations**

- GDM associated with:
  - Gestational hypertension
  - Preeclampsia
  - Operative deliveries
  - Postpartum development of Type 2 DM

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**Perinatal Considerations**

- GDM associated with:
  - Fetal macrosomia / birth trauma
  - Metabolic abnormalities
    - Hypoglycemia, hypocalcemia
    - Hyperbilirubinemia/polycythemia
  - Respiratory distress syndrome
  - Preterm delivery
  - Perinatal mortality

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Postnatal Considerations

- Metabolic syndrome: a longitudinal cohort of 179 children (at age 6, 7, 9, 11)

Diabetes in Pregnancy

- GDM: insulin resistance first recognized during pregnancy
  - Prevalence: 4-14% of all pregnancies
- T2DM dx in pregnancy
  - HgbA1c >6.5%
  - FPG >125
  - Random BG >200

Risk Factors for GDM

- Maternal age >25 years
- Body mass index >25 kg/m²
- Race/Ethnicity
  - Latina
  - Native American
  - South or East Asian, Pacific Island ancestry
  - ? African American
- Personal/Family history of DM
- History of macrosomia
Screening for GDM

- ACOG: Universal screening
  - Clinical history
  - Laboratory testing
- ADA: Selective screening
  - Risk assessment at first visit
    - High risk: GCT as soon as feasible
    - Average risk: GCT at 24-28 weeks GA
    - Low risk: No GCT

ADA position statement. Standards of Medical Care in Diabetes. Diabetes Care 2006;29:S4-42

Low Risk for GDM

- Maternal age < 25 years
- Weight normal before pregnancy
- Members of an ethnic group with a low prevalence of GDM
- No known DM in 1st degree relatives
- No history of abnormal glucose tolerance
- No history of poor obstetric outcome

ADA position statement. Standards of Medical Care in Diabetes. Diabetes Care 2006;29:S4-42

Universal vs. Selective Screening

- 94% obstetricians reported universal testing
- Danilenko-Dixon, AJOG, 1999
  - Age > 25 identifies 90% with GDM
  - High-risk criteria would identify 97% GDM
  - Only 10% go unscreened


Screening for GDM

- Screening test
  - 50gm 1-hour glucose challenge test (GCT)
- Screening thresholds
  - 130mg/dL: 90% sensitivity (23% screen +)
  - 140mg/dL: 80% sensitivity (14% screen +)
Diagnosis of GDM

- **Diagnostic test**
  - 100gm 3-hour glucose tolerance test (GTT)
    - 2 or more abnormal values

<table>
<thead>
<tr>
<th></th>
<th>Carpenter and Coustan</th>
<th>National Diabetes and Data Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>95 mg/dL</td>
<td>105 mg/dL</td>
</tr>
<tr>
<td>1hr</td>
<td>180 mg/dL</td>
<td>190 mg/dL</td>
</tr>
<tr>
<td>2hr</td>
<td>155 mg/dL</td>
<td>165 mg/dL</td>
</tr>
<tr>
<td>3hr</td>
<td>140 mg/dL</td>
<td>145 mg/dL</td>
</tr>
</tbody>
</table>

ADA position statement. Standards of Medical Care in Diabetes. Diabetes Care 2006;29:S4-42

Diagnosis of GDM

- Women with 1 elevated value on GTT:
  - Retrospective cohort studies:
    - Cesarean delivery
    - Preeclampsia
    - Macrosomia
    - Shoulder dystocia
    - ICN admission

Stamilio et al. False positive 1-hour GCT and adverse perinatal outcomes. Obstet Gynecol 2004

Diagnosis of GDM

- ADA and the 4th International Workshop-Conference on GDM:
  - Carpenter & Coustan diagnostic criteria
- Carpenter & Coustan vs. NDDG:
  - GDM by Carpenter & Coustan only:
  - Macrosomia
  - Hypoglycemia
  - Hyperbilirubinemia

ADA position statement. Standards of Medical Care in Diabetes. Diabetes Care 2008
Ferrara A et al. Diabetologia 2006
Cheng YW, et al. Carpenter-Coustan criteria compared with the national diabetes data group thresholds for GDM. Obstet Gynecol 2009

Diagnosis of GDM

- Continuous relationship between carbohydrate intolerance and adverse outcome
- No single cutoff can separate
  - those with high risk
  - those with no risk at all
- Diagnostic criteria appropriate but arbitrary

Hyperglycemia & Adverse Pregnancy Outcomes

- Whether maternal hyperglycemia less severe than DM → adverse pregnancy outcome
- 25,505 pregnant women at 15 centers, 9 countries
  - 75-g oral glucose tolerance testing at 24-32 weeks GA
  - Data blinded if fasting <105mg/dL or 2-hr <200mg/dL

Hyperglycemia & Adverse Pregnancy Outcomes

- Birthweight >90th centile
  - Adjusted odds ratio (95% CI)

<table>
<thead>
<tr>
<th>Glucose category</th>
<th>Fasting</th>
<th>1-hour</th>
<th>2-hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Category 2</td>
<td>1.37 (1.16-1.62)</td>
<td>1.21 (1.04-1.41)</td>
<td>1.11 (0.96-1.30)</td>
</tr>
<tr>
<td>Category 3</td>
<td>1.72 (1.46-2.03)</td>
<td>1.65 (1.41-1.93)</td>
<td>1.51 (1.30-1.75)</td>
</tr>
<tr>
<td>Category 4</td>
<td>1.95 (1.62-2.35)</td>
<td>2.27 (1.91-2.71)</td>
<td>2.15 (1.82-2.54)</td>
</tr>
<tr>
<td>Category 5</td>
<td>2.73 (2.25-3.31)</td>
<td>2.66 (2.19-3.21)</td>
<td>2.10 (1.73-2.56)</td>
</tr>
<tr>
<td>Category 6</td>
<td>3.00 (2.43-3.86)</td>
<td>3.50 (2.72-4.50)</td>
<td>2.68 (2.08-3.45)</td>
</tr>
<tr>
<td>Category 7</td>
<td>5.01 (3.54-7.00)</td>
<td>4.40 (3.16-6.30)</td>
<td>4.46 (3.35-6.33)</td>
</tr>
</tbody>
</table>

Hyperglycemia & Adverse Pregnancy Outcomes

- Primary outcomes associated with maternal hyperglycemia
  - Adjusted odds ratio (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>1-hour</th>
<th>2-hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth wt &gt;90th centile</td>
<td>1.38 (1.32-1.44)</td>
<td>1.46 (1.39-1.53)</td>
<td>1.38 (1.32-1.44)</td>
</tr>
<tr>
<td>Primary CD</td>
<td>1.11 (1.06-1.15)</td>
<td>1.10 (1.06-1.15)</td>
<td>1.08 (1.03-1.12)</td>
</tr>
<tr>
<td>Neo. Hypoglycemia</td>
<td>1.08 (0.98-1.19)</td>
<td>1.13 (1.03-1.26)</td>
<td>1.10 (1.00-1.12)</td>
</tr>
<tr>
<td>Cord-blood serum C peptide &gt;90th centile</td>
<td>1.55 (1.47-1.64)</td>
<td>1.46 (1.38-1.54)</td>
<td>1.37 (1.30-1.44)</td>
</tr>
</tbody>
</table>
Screening/Diagnosis of GDM

- WHO / IADPSG / ADA
- No screening test
- First trimester FPG in all high risk patients
- 24-28 wks 2 hr-OGTT – 75 gm load
  - Fasting ≥ 92
  - 1 hr ≥ 180
  - 2 hr ≥ 153
- One elevated value
- 15-25% of population

Screening/Diagnosis of GDM

- 24-28 wks 2 hr-OGTT – 75 gm load
  - Fasting ≥ 92
  - 1 hr ≥ 180
  - 2 hr ≥ 153

- Diagnostic cut-points: conveyed an aOR ≥ 1.75 for adverse pregnancy outcomes compared with mean glucose levels in the HAPO study

Screening/Diagnosis of GDM

Worldwide, controversy exists:

<table>
<thead>
<tr>
<th>50g glucose Screen</th>
<th>Oral glucose tolerance test (OGTT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose load</td>
<td>Fasting (mg/dL)</td>
</tr>
<tr>
<td>ACOG (Carpen-ter-Coustan)</td>
<td>130 or 140 mg/dL</td>
</tr>
<tr>
<td>ACOG (NDDG)</td>
<td>140 mg/dL</td>
</tr>
<tr>
<td>CDA</td>
<td>140 mg/dL</td>
</tr>
<tr>
<td>WHO</td>
<td>none</td>
</tr>
<tr>
<td>ADA/WHO</td>
<td>None</td>
</tr>
</tbody>
</table>

Screening/Diagnosis of GDM

RCT: Canada 2001-2004 (n=1594)
- Group 1: 2-step (50g GS + 3-hr 100g OGTT)
- Group 2: 2-step (50g GS + 2-hr 75g OGTT)
- Group 3: 1-step (75g OGTT alone)

GDM diagnosis by CDA or NDDG criteria

Cost of screening:
- Direct: visits, glucose drinks, blood draws, exam fees
- Indirect: Productivity time lost, transportation,

Meltzer et al., GDM screening and diagnosis: RCT comparing 1-step and 2-step tests. BJOG 2010

Diabetes Care 2011;34:676-82
ANZJOG 2011;51:22-25
Screening/Diagnosis of GDM

- RCT: Canada 2001-2004 (n=1594)
  - Group 1: 2-step (50g GS + 3-hr 100g OGTT)
  - Group 2: 2-step (50g GS + 2-hr 75g OGTT)
  - Group 3: 1-step (75g OGTT alone)

<table>
<thead>
<tr>
<th></th>
<th>Cost (CA$) per woman screened</th>
<th>% GDM diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>$91.61</td>
<td>3.7%</td>
</tr>
<tr>
<td>Group 2</td>
<td>$89.03</td>
<td>3.7%</td>
</tr>
<tr>
<td>Group 3</td>
<td>$108.38</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

Meltzer et al, GDM screening and diagnosis: RCT comparing 1-step and 2-step tests. BJOG 2010

ACOG Committee Opinion (Sept 2011):
- All women should be screened for GDM
- Diagnosis of GDM based on 100-g OGTT
- 1-step screening/diagnosis of GDM not yet recommended
- NIH planning a Consensus Development Conference

Management of GDM

- Nutrition therapy
- Home self glucose monitoring
- Medical therapy if glycemic control not achieved with diet/exercise
  - Subcutaneous insulin
  - Oral hypoglycemic agents
    - Glyburide
    - Metformin
- Antenatal monitoring


Goals of Glycemic Control

- Blood glucose goals during pregnancy
  - Fasting < 95mg/dL
  - 1-hr postprandial < 130-140mg/dL
  - 2-hr postprandial am < 120mg/dL
  - 2am < 120mg/dL
Treatment of GDM

- Multi-centered RCT comparing treatment of GDM vs. routine care

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=506)</th>
<th>Routine Care (n=524)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>3335 g</td>
<td>3482 g</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat-mass (g)</td>
<td>422.0 g</td>
<td>464.3 g</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large-for-gestational age</td>
<td>13 %</td>
<td>22 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Macrosomia (&gt;4kg)</td>
<td>10 %</td>
<td>21 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-minute Apgar&lt;7</td>
<td>1 %</td>
<td>4 %</td>
<td>0.26</td>
</tr>
<tr>
<td>Any serious perinatal complication*</td>
<td>1 %</td>
<td>4 %</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* death, shoulder dystocia, bone fracture, nerve palsy


Treatment of Mild GDM

- Multi-centered RCT comparing treatment of mild GDM vs. routine care: MFMU

<table>
<thead>
<tr>
<th></th>
<th>Tx mild GDM (n=485)</th>
<th>Routine Care (n=470)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA at birth</td>
<td>39.0 ± 1.8</td>
<td>38.9 ± 1.8</td>
<td>0.87</td>
</tr>
<tr>
<td>Composite end point*</td>
<td>32.4 %</td>
<td>37.0 %</td>
<td>0.14</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>3302 ± 502</td>
<td>3408 ± 489</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Macrosomia (&gt;4kg)</td>
<td>5.9 %</td>
<td>14.3 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>1.5 %</td>
<td>4.0 %</td>
<td>0.02</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>26.9 %</td>
<td>33.8 %</td>
<td>0.02</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>8.6 %</td>
<td>13.6 %</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* hypoglycemia, hyperbilirubinemia, birth trauma, elevated C-peptide, stillbirth/death

Landon et al. A multicenter, randomized trial of treatment for mild GDM. NEJM 2009;361:1339-48

Treatment of GDM

- Diet
  - Carbohydrate Controlled (not kcals)
  - Meals: 30-45gms / 45-60 gms / 45-60 gms
  - Snacks: 15-30 gms

- Exercise
  - Daily per routine
  - Also, 15 minute walks after each meal

Question

After three weeks of suboptimal blood sugars – 5/7 fasting values 95-110 and 4/7 post breakfast values 140-150 what would you recommend?

a) Exercise and diet
b) Insulin
c) Glyburide
d) Metformin
Treatment of GDM

Adapted from ADA: Clinical Education Program “Insulin Therapy for the 21st Century”

Oral Agents

- Glitazones - Decrease insulin resistance
- 1st gen sulfonylureas - Augment insulin release
  - Concentrated in the neonate - hypoglycemia
- Glyburide (2nd gen sulfonylurea)
  - Low transplacental transfer
- Metformin – decreases insulin resistance
  - Crosses placenta

Insulin vs. Glyburide

- Langer et al. 2000
  - Randomized controlled trial (n=404)
  - Similar glycemic control
  - “Similar” neonatal outcomes

<table>
<thead>
<tr>
<th>Neonatal Outcome</th>
<th>Glyburide % (n)</th>
<th>Insulin % (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight &gt; 4000 gms</td>
<td>7% (14)</td>
<td>4% (9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Lung complications</td>
<td>8% (16)</td>
<td>6% (12)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>9% (18)</td>
<td>6% (12)</td>
<td>0.25</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>6% (12)</td>
<td>4% (8)</td>
<td>0.36</td>
</tr>
<tr>
<td>- Composite</td>
<td>30%</td>
<td>20%</td>
<td>0.05</td>
</tr>
</tbody>
</table>


Insulin vs. Metformin

- Rowan et al. NEJM, 2008
- Prospective RCT – New Zealand / Australia
- 363 metformin vs. 370 insulin
- 46.3% of metformin arm required insulin
- 8.8% had GI side effects – 1.9% stopped

Rowan et al. NEJM, 2008
Insulin vs. Metformin

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Metformin (n=363)</th>
<th>Insulin (n=370)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent BG &lt;46.8mg/dL</td>
<td>32 %</td>
<td>32.2 %</td>
<td>0.95</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>3.3 %</td>
<td>4.3 %</td>
<td>0.47</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>8.0 %</td>
<td>8.4 %</td>
<td>0.85</td>
</tr>
<tr>
<td>Birth trauma</td>
<td>4.4 %</td>
<td>4.6 %</td>
<td>0.90</td>
</tr>
<tr>
<td>Preterm birth &lt;37wks</td>
<td>12.1 %</td>
<td>7.6 %</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Rowan et al. NEJM, 2008

Potential Management of GDM

- Begin with diet / walk after each meal
- Behavioral approaches
- If borderline/mild elevations, consider metformin (start 500 qd)
- Counsel about increased PTD rates
- Pt diagnosed in third trimester 26-32 wks
- Unlikely pre-existing DM
- Otherwise, or if metformin fails, insulin
- Insulin NPH and humalog/novalog

Postpartum Follow-up

- Diagnosis of DM in non-pregnant state:

<table>
<thead>
<tr>
<th>75g 2-hr OGTT</th>
<th>Normal</th>
<th>Impaired fasting glucose or impaired glucose tolerance</th>
<th>Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>&lt;100</td>
<td>100-125</td>
<td>≥126</td>
</tr>
<tr>
<td>2-hr plasma glucose</td>
<td>&lt;140</td>
<td>140-199</td>
<td>≥200 OR Symptoms of DM &amp; random PG ≥200 mg/dL</td>
</tr>
</tbody>
</table>


Postpartum Follow-up

<table>
<thead>
<tr>
<th></th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counseling Intervention</td>
<td>2.06</td>
<td>1.49-2.85</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>0.67</td>
<td>0.34-1.31</td>
</tr>
<tr>
<td>Latina</td>
<td>0.89</td>
<td>0.41-1.16</td>
</tr>
<tr>
<td>Asian</td>
<td>1.72</td>
<td>1.21-2.43</td>
</tr>
<tr>
<td>Insulin Use</td>
<td>2.13</td>
<td>1.54-2.95</td>
</tr>
<tr>
<td>Preterm Birth</td>
<td>0.80</td>
<td>0.68-0.94</td>
</tr>
</tbody>
</table>

Stasenno et al. Postpartum follow up of GDM AJOG, 2011
GDM: Summary

Screening and Diagnosis
- Universal screening
- ACOG: 50-g glucose screen + 100gm OGTT
  - GTT diagnostic criteria: Carpenter and Coustan
  - Is the IADPSG going to be the new standard?

Management
- Diet/exercise, nutrition consult, glucose monitoring
  - Insulin is first line
  - Consider Metformin
- Postpartum screening

Hyperglycemia & Adverse Pregnancy Outcomes

Glucose values (mg/dL)

<table>
<thead>
<tr>
<th>Glucose category</th>
<th>Fasting</th>
<th>1-hour</th>
<th>2-hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>&lt; 75</td>
<td>&lt; 105</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>Category 2</td>
<td>75-79</td>
<td>106-132</td>
<td>91-108</td>
</tr>
<tr>
<td>Category 3</td>
<td>80-84</td>
<td>133-155</td>
<td>109-125</td>
</tr>
<tr>
<td>Category 4</td>
<td>85-89</td>
<td>156-171</td>
<td>126-139</td>
</tr>
<tr>
<td>Category 5</td>
<td>90-94</td>
<td>172-193</td>
<td>140-157</td>
</tr>
<tr>
<td>Category 6</td>
<td>95-99</td>
<td>194-211</td>
<td>158-177</td>
</tr>
<tr>
<td>Category 7</td>
<td>&gt;=100</td>
<td>&gt;=212</td>
<td>&gt;=178</td>
</tr>
</tbody>
</table>