Pregnancy and Diabetes

Diabetes Symposium, 2019
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Medical University of South Carolina

Conflicts

I have no relevant disclosures or conflict of interest with the material I’m presenting today.
Objectives

• Explain diabetes management in pregnancy.
• Describe the metabolism of normal pregnancy and the alterations that occur in overt and gestational diabetes.
• Describe the diagnostic criteria and screening recommended by the ADA.
• Describe potential maternal and fetal complications.
• Summarize treatment options in GDM.

Diabetes and Pregnancy

• Preconception
  – Effects of diabetes on maternal/fetal outcomes
    • Glycemic Control
    • Diabetes self-care
    • Comorbidities
    • Congenital Malformations
    • Macrosomia
    • Stillbirth
  – Effects of medications on outcomes
Risk factors for pregestational DM II

• Prepregnancy BMI >25 and at least one of the following (ADA 2017 guidelines):
  ➢ Prior history of GDM
  ➢ Prior infant weighing >4000g at birth
  ➢ Chronic hypertension or cardiovascular disease
  ➢ PCOS
  ➢ Non-caucasian race
  ➢ First degree relative with DM
  ➢ A1C ≥ 5.7%
  ➢ Hypercholesterolemia
  ➢ Age >45
  ➢ Physical inactivity

First trimester screening for women at risk for DM II

• American Diabetic Association Criteria for 2017:
  ➢ A1C ≥ 6.5%
  ➢ Fasting glucose of ≥ 126mg/dl
  ➢ Random glucose ≥ 200 mg/dl and hyperglycemia symptoms
  ➢ 2 hour glucose tolerance test (GTT)
    ➢ 75g glucose load
    ➢ 2 hour glucose ≥ 200 mg/dl

• 1 hour screening GTT followed by 3 hour diagnostic GTT

• If a patient passes early GTT, it still must be repeated at 24-28 weeks
Glucose Thresholds & Complications

NORMOGLYCEMIA OF PREGNANCY

Glycemia in Normal Pregnancy

Hernandez. Diabetes Care. 2011
## Glycemic Patterns

### Median Results

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>71</td>
</tr>
<tr>
<td>1 hr</td>
<td>109</td>
</tr>
<tr>
<td>2 hr</td>
<td>99</td>
</tr>
<tr>
<td>24 hr</td>
<td>88</td>
</tr>
</tbody>
</table>

135 average = 2 SD above

### Recommended

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hr</td>
<td>&lt; 122</td>
</tr>
<tr>
<td>2 hr</td>
<td>&lt; 110</td>
</tr>
</tbody>
</table>

### Diabetes During Pregnancy

**MATERNAL COMPLICATIONS**
Maternal Complications- Diabetes

Table 4

<table>
<thead>
<tr>
<th>IDDM</th>
<th>UK</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight &gt; 90th percentile</td>
<td>52%</td>
<td>10%</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>7.9%</td>
<td>3%</td>
</tr>
<tr>
<td>Erb's Palsy</td>
<td>4.5/1000</td>
<td>0.42/1000</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>37%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>67%</td>
<td>24%</td>
</tr>
<tr>
<td>Congenital Malformations</td>
<td>5.5%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>93.1/1000</td>
<td>3.6/1000</td>
</tr>
<tr>
<td>Perinatal Mortality</td>
<td>31.8/1000</td>
<td>8.5/1000</td>
</tr>
</tbody>
</table>

IDDM (baby of mothers with pregestational diabetes mellitus); UK (rate for general UK population). Perinatal mortality: fetal death between 24 weeks and one week after delivery

Diabetic Ketoacidosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Time Interval</th>
<th>n</th>
<th>Incidence (%)</th>
<th>Fetal loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lufkin, et al</td>
<td>1950-1979</td>
<td>228</td>
<td>7.9%</td>
<td>?</td>
</tr>
<tr>
<td>Cousins, et al</td>
<td>1965-1985</td>
<td>1508</td>
<td>9.3%</td>
<td>?</td>
</tr>
<tr>
<td>Kilvert, et al</td>
<td>1971-1990</td>
<td>635</td>
<td>1.7%</td>
<td>14% (2-3rd tri)</td>
</tr>
<tr>
<td>Rogers and Rogers</td>
<td>1980-1990</td>
<td>~3000</td>
<td>1%</td>
<td>?</td>
</tr>
<tr>
<td>Cullen, et al</td>
<td>1985-1995</td>
<td>520</td>
<td>2%</td>
<td>9%</td>
</tr>
<tr>
<td>Schneider, et al</td>
<td>1991-2001</td>
<td>2025</td>
<td>1.2%</td>
<td>27%</td>
</tr>
</tbody>
</table>

McCance, Best Practice & Research Clinical Endocrinology & Metabolism, 2011
How pregnancy affects the disease

• Accelerated starvation
• Insulin antagonistic state
• Lowered buffering capacity
  – pH 7.4/PCo2 30mm Hg/Bicarb 20 mEq/L.
• Emesis
• Infection

How the disease affects pregnancy

• Fetal Loss (9-27%)

Creasy (p963, 6th ed) “…even when fetal status is questionable during the phase of therapeutic volume and plasma glucose correction, emergency cesarean section should be avoided”
Aspirin

TXA2  Prostacyclin

Favor vasoconstrict  Favor vasodilate

LDA inhibits TXA2 > Prostacyclin production = vasodilate
Figure 3. Pooled analysis of preeclampsia from trials of women at risk for preeclampsia, sorted by sample size.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>PE Incidence (Placebo), %</th>
<th>Dose, mg</th>
<th>RR (95% CI)</th>
<th>Events/Total, n/N</th>
<th>Weight, N-*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cusack et al, 2000 (57)</td>
<td>10</td>
<td>100</td>
<td>1.43 (0.27-7.73)</td>
<td>3/22</td>
<td>2/21</td>
</tr>
<tr>
<td>Walleberg et al, 1996 (54)</td>
<td>20</td>
<td>60</td>
<td>0.97 (0.09-1.20)</td>
<td>0/21</td>
<td>7/23</td>
</tr>
<tr>
<td>Caspi et al, 1994 (56)</td>
<td>9</td>
<td>100</td>
<td>0.19 (0.01-3.80)</td>
<td>0/24</td>
<td>2/23</td>
</tr>
<tr>
<td>Schiff et al, 1989 (47)</td>
<td>23</td>
<td>100</td>
<td>0.13 (0.02-1.00)</td>
<td>1/34</td>
<td>7/31</td>
</tr>
<tr>
<td>Vinirio et al, 2002 (41)</td>
<td>23</td>
<td>49</td>
<td>0.20 (0.05-0.86)</td>
<td>2/43</td>
<td>10/43</td>
</tr>
<tr>
<td>Herenda et al, 1997 (39)</td>
<td>14</td>
<td>100</td>
<td>0.43 (0.12-1.56)</td>
<td>3/50</td>
<td>7/50</td>
</tr>
<tr>
<td>Motherfald et al, 1990 (68)</td>
<td>19</td>
<td>75</td>
<td>0.11 (0.01-0.81)</td>
<td>5/48</td>
<td>10/52</td>
</tr>
<tr>
<td>Villa et al, 2013 (50)</td>
<td>18</td>
<td>100</td>
<td>0.72 (0.31-1.46)</td>
<td>8/41</td>
<td>11/40</td>
</tr>
<tr>
<td>Vilsikka et al, 1993 (58)</td>
<td>11</td>
<td>50</td>
<td>0.84 (0.37-1.95)</td>
<td>9/97</td>
<td>11/100</td>
</tr>
<tr>
<td>Ayala et al, 2013 (55)</td>
<td>13</td>
<td>100</td>
<td>0.49 (0.25-0.99)</td>
<td>11/176</td>
<td>22/174</td>
</tr>
<tr>
<td>Ye et al, 2003 (46)</td>
<td>19</td>
<td>150</td>
<td>0.95 (0.67-1.35)</td>
<td>49/276</td>
<td>52/278</td>
</tr>
<tr>
<td>MFNU, 1996 (44)</td>
<td>29</td>
<td>60</td>
<td>0.95 (0.77-1.16)</td>
<td>256/1254</td>
<td>250/1249</td>
</tr>
<tr>
<td>CLASP, 1994 (53)</td>
<td>8</td>
<td>60</td>
<td>0.88 (0.75-1.03)</td>
<td>267/3992</td>
<td>302/3982</td>
</tr>
<tr>
<td><strong>Overall I² = 40.5%; P = 0.064</strong></td>
<td></td>
<td></td>
<td>0.76 (0.62-0.95)</td>
<td>580/6098</td>
<td>895/6086</td>
</tr>
</tbody>
</table>

Fetal Complications
Congenital Anomalies

- Sacral Agenesis
- Spina Bifida
- Anencephaly
- Heart Defects

Fetal Complications

<table>
<thead>
<tr>
<th>Glucose Thresholds</th>
<th>Fetal Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anomalies 140</td>
</tr>
<tr>
<td></td>
<td>Fetal Death 110</td>
</tr>
<tr>
<td></td>
<td>Respiratory Dis 110</td>
</tr>
<tr>
<td></td>
<td>Macrosomia 100</td>
</tr>
<tr>
<td></td>
<td>Growth Restriction</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
</tr>
</tbody>
</table>
Anomalies

<table>
<thead>
<tr>
<th>Anomaly Risk</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diabetic</td>
<td>2%</td>
</tr>
<tr>
<td>HbA1c 7%</td>
<td>3%</td>
</tr>
<tr>
<td>HbA1c 9%</td>
<td>6%</td>
</tr>
<tr>
<td>HbA1c 11%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Guerin. Diabetes Care. 2007

STILLBIRTH

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Years of DM</th>
<th>Smoke</th>
<th>Pre HbA1c</th>
<th>Early HbA1c</th>
<th>Late HbA1c</th>
<th>EGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>27</td>
<td>11 yrs</td>
<td>64%</td>
<td>7.9%</td>
<td>7.9%</td>
<td>8.0%</td>
<td>35 wks</td>
</tr>
<tr>
<td>Reference</td>
<td>30</td>
<td>14 yrs</td>
<td>29%</td>
<td>7.4%</td>
<td>7.0%</td>
<td>6.3%</td>
<td>37 wks</td>
</tr>
</tbody>
</table>

Women who experienced stillbirth were characterized by a high incidence of suboptimal glycemic control, diabetic nephropathy, smoking and low socioeconomic status.
Respiratory Distress

Etiologies:
1. Increased premature delivery
2. Hyperglycemia and Hyperinsulinemia delay glucocorticoid production and lung maturation

The risk of RDS among preterm infants of well-controlled diabetic mothers approaches that of infants born to non-diabetic mothers at similar gestational ages.

GESTATIONAL DIABETES
Cestational Diabetes Screening

*The International Association of the Diabetes and Pregnancy Study Groups Compared With Carpenter-Coustan Screening*

- n=6,066
  - 2,972 (standard)
  - 3,095 (protocol)

- Rate of GDM
  - Standard 17%
  - Protocol 27%

\[ p < 0.001 \]
Incidence

- 3.5-12% in pregnancy
- 30-50% recurrence risk
- 7x increase risk developing DM2
Risks Associated with GDM

• Maternal
  o Preeclampsia
  o C-section
  o Type II DM

• Neonatal
  o Birth weight >4000g
  o Shoulder dystocia
  o Hypoglycemia
  o Stillbirth
  o Increased risk of childhood obesity

Maternal Complications

Gestational
• Gestational HTN/Preeclampsia
• LGA infant
• Traumatic vaginal delivery
• Cesarean delivery
• Type 2 DM

Pre-Gestational
• Gestational HTN/Preeclampsia
• SGA or LGA
• Cesarean delivery
• Worsening end-organ disease
  • Eyes, Kidneys
Management

• Dietary Modification
  – CDE

• Monitoring of Blood Glucose

• Medication

• Other
  – Exercise
    • Blood Glucose ✔
    • Insulin requirements ✗

GDM Diagnostic Options (24-28 weeks)

• Two step:
  ➢ 50g glucose load
    ➢ Glucose threshold of 135 or 140 mg/dl
    ➢ Consider diagnostic if ≥ 200 mg/dl
  ➢ 100g glucose load (one or two abnormal values)
    ➢ Fasting >95
    ➢ 1 hr >180
    ➢ 2 hr >155
    ➢ 3 hr > 140

• One step:
  ➢ 75g glucose load (one abnormal value)
    ➢ Fasting ≥ 92
    ➢ 1hr ≥ 180
    ➢ 2hr ≥ 153
A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes

Landon. NEJM. 2009

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Treatment Group (N=485)</th>
<th>Control Group (N=473)</th>
<th>Relative Risk (97% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight — g</td>
<td>3302±502.4</td>
<td>3408±589.4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Birth weight &gt;4000 g — no./total no. (%)</td>
<td>28/477 (5.9)</td>
<td>65/454 (14.3)</td>
<td>0.41 (0.26–0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large for gestational age — no./total no. (%)†</td>
<td>34/477 (7.1)</td>
<td>66/454 (14.5)</td>
<td>0.49 (0.32–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat mass — g</td>
<td>427±197.9</td>
<td>464±222.3</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Preterm delivery — no./total no. (%)‡</td>
<td>45/477 (9.4)</td>
<td>53/455 (11.6)</td>
<td>0.81 (0.53–1.23)</td>
<td>0.27</td>
</tr>
<tr>
<td>Small for gestational age — no./total no. (%)§</td>
<td>36/477 (7.5)</td>
<td>29/455 (6.4)</td>
<td>1.18 (0.70–1.99)</td>
<td>0.49</td>
</tr>
<tr>
<td>Admission to NICU — no./total no. (%)</td>
<td>43/477 (9.0)</td>
<td>53/455 (11.6)</td>
<td>0.77 (0.51–1.18)</td>
<td>0.19</td>
</tr>
<tr>
<td>Intravenous glucose treatment — no./total no. (%)</td>
<td>25/475 (5.3)</td>
<td>31/455 (6.8)</td>
<td>0.77 (0.44–1.36)</td>
<td>0.32</td>
</tr>
<tr>
<td>Respiratory distress syndrome — no./total no. (%)</td>
<td>9/477 (1.9)</td>
<td>13/455 (2.9)</td>
<td>0.66 (0.26–1.67)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Landon. NEJM. 2009
## Treatment of Mild GDM

### Table 4. Maternal Outcomes

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Treatment Group (N=476)</th>
<th>Control Group (N=455)</th>
<th>Relative Risk (97% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction of labor — no. (%)</td>
<td>130 (27.3)</td>
<td>122 (26.8)</td>
<td>1.02 (0.81–1.29)</td>
<td>0.86</td>
</tr>
<tr>
<td>Cesarean delivery — no. (%)</td>
<td>128 (26.9)</td>
<td>154 (33.8)</td>
<td>0.79 (0.64–0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>Shoulder dystocia — no. (%)</td>
<td>7 (1.5)</td>
<td>18 (4.0)</td>
<td>0.37 (0.14–0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Preeclampsia — no. (%)</td>
<td>12 (2.5)</td>
<td>25 (5.5)</td>
<td>0.46 (0.22–0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Preeclampsia or gestational hypertension — no. (%)</td>
<td>41 (8.6)</td>
<td>62 (13.6)</td>
<td>0.63 (0.42–0.96)</td>
<td>0.01</td>
</tr>
<tr>
<td>Body-mass index at delivery†</td>
<td>31.3±5.2</td>
<td>32.3±5.2</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Weight gain — kg‡</td>
<td>2.8±4.5</td>
<td>5.0±3.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Landon. NEJM. 2009

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Single abnormal value on 3-hour oral glucose tolerance test during pregnancy is associated with adverse maternal and neonatal outcomes: a systematic review and metaanalysis.

Roediker Z†, Sanchez-Ramos L‡, Jhon-Knuip K§, Kaunitz AM*.

- 2016 metaanalysis of 25 studies with 4466 women total
- Women with 1 abnormal on 3 hour GTT vs no abnormal values
- Significant increased risk of:
  - Macrosomia
  - Neonatal hypoglycemia
  - C-section
  - Gestational hypertension
  - NICU admission
  - Neonatal respiratory distress
Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research.

• Metaanalysis of RCTs and cohort studies
• Compared diet modification, glucose monitoring, and insulin with no treatment
• Treatment group with fewer cases of:
  ➢ Preeclampsia
  ➢ Macrosomia
  ➢ Shoulder dystocia
• Treatment group had more office visits

Glycemic control targets

• ADA and ACOG:
  ➢ Fasting <95
  ➢ 1 hour postprandial <140

• MUSC targets:
  ➢ Fasting <90
  ➢ 1 hour postprandial <130
  ➢ A1C under 6%
Treatment Goals

• Achieve euglycemia
• Decrease risk of adverse perinatal outcome

• Insulin only FDA approved treatment

TREATMENT OF GDM

Insulin
Metformin
Glyburide
Long Acting Insulin

Long acting Insulins in Pregnancy

- Avoid peak action
- Less symptomatic hypoglycemia
- Less nocturnal hypoglycemia
- Result in tighter control

Comparison of All agents

Comparative Efficacy and Safety of OADs in Management of GDM: Network Meta-analysis of Randomized Controlled Trials

Yun-Fa Jiang,* Xue-Yan Chen,* Tao Ding, Xiao-Feng Wang, Zhong-Ning Zhu, and Su-Wen Su

- 18 RCT’s comparing efficacy and safety between different OADs or OAD vs Insulin in GDM
- 30-733 pts (10 had < 100 pts and 13 <150 pts)
Comparison of All agents

• No significant difference in
  – Fasting blood glucose
  – Hb A1C
• Metformin
  – Lower maternal weight gain
• Glyburide
  – Higher neonatal birth weight
  – Increased incidence of neonatal hypoglycemia
  – Increased incidence macrosomia

ACOG Practice Bulletin #180, July 2017

• Recommendation for insulin as first line therapy
• Treatment with glyburide compared with insulin demonstrated worse neonatal outcomes:
  ➢ Respiratory distress syndrome
  ➢ Hypoglycemia
  ➢ Macrosomia
  ➢ Birth injury
• Treatment with metformin compared with insulin:
  ➢ Lower rate of gestational hypertension
  ➢ Less maternal weight gain
• 20-40% of women will fail therapy with metformin or glyburide alone:
  ➢ Both cross placenta
  ➢ Lack of long term follow up of exposed neonates
• Metformin is second line therapy if the patient is unable to comply with insulin
First line GDMA2 treatment: Insulin

- NPH (Novalin, Humalin): **Cloudy**
  - Intermediate acting insulin
  - To control fasting glucose, begin bedtime NPH at 0.2 unit/kg
  - Onset of action 1-3 hours
  - Peak 5-7 hours
  - Duration 13-18 hours

- Novolog(aspart)/Humalog (lispro): **Clear**
  - Short acting insulin for meal coverage
  - Can be targeted for abnormal values at single time of day
  - Onset of action 1-15 minutes
  - Peak 1-2 hours
  - Duration 4-5 hours

---

GDMA2

- Antenatal testing beginning at 32 weeks
- EFW every 4 weeks
- Recommend A1C q4-6 weeks to confirm compliance
- Serial assessment of amniotic fluid
- Well controlled: delivery between 39 0/7-39 6/7
- Consideration of primary c-section if EFW > 4500g
Postpartum 2 hour GTT

Take home points:

- Preconception counseling- Goal A1C <6%
- DM 1 – must take basal insulin
- Screen all women at risk diabetes at the initial Ob visit or in the first trimester
- The risk of recurrent GDM in a subsequent pregnancy is 40%
- Insulin is the first line treatment to achieve glucose targets
  - To control fasting glucose, begin bedtime NPH at 0.2 unit/kg
  - If insulin is not an option, the first line oral treatment is metformin
  - Extended release metformin such as 1000mg ER qday is preferred to decrease GI side effects
- Patients with GDM need postpartum screening for DMII
Learning Assessment Question #1

Which of the following does **NOT** describe a physiologic change that occurs during pregnancy which can have a negative impact on diabetes?

a) Fetal and placental use of maternal glucose
b) Impaired action of maternal insulin
!

**c) Compensated maternal respiratory acidosis**

\[ \text{Compensated maternal respiratory acidosis} \]

d) Dehydration caused by emesis

Learning Assessment Question #2

• True/False: A pregnant woman passes the first trimester early glucose tolerance test. She is no longer required to undergo a glucose tolerance test at 24-28 weeks gestation.

**FALSE**
Learning Assessment Question #3

• True/False: The risk of fetal anomalies increases with increasing maternal HbA1C.

TRUE

Learning Assessment Question #4

The first-line treatment option for gestational diabetes is:
   a) Glyburide
   b) Metformin
   c) Insulin
   d) Exenatide
References


McCance, DR. Best Practice & Research Clinical Endocrinology & Metabolism 25 (2011) 945–958.


References


ACOG Practice Bulletin #180, July 2017