Gestational Diabetes:
Controversies and Challenges

Kirsten E. Salmeen, MD

I have nothing to disclose.

A Brief History of GDM

1880s: Diabetes may appear during pregnancy, then cease at the end of pregnancy

1950s: Prior stillbirth and macrosomia were more likely in women with diabetes

1960s: 30% of women with GDM develop type 2 DM within 5-6 years of incident pregnancy
GDM screening identified as a tool to reduce this risk

1970s: Suggestion to use 1-hour/50gram OGTT as screening tool for GDM

1960s-1990s: GDM is also associated with worse pregnancy outcomes

2008: Publication of Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study – attempting to inform an evidence-based and universal approach to diagnosis of GDM
A Brief History of GDM

2010: IADPSG Consensus Meeting: recommended one-step GDM testing with threshold values based on ORs for poor outcomes of 1.75 (fetal macrosomia, neonatal adiposity, fetal hyperinsulinemia)

2013: NIH Consensus Meeting: recommended two-step testing citing concerns regarding over-medicalization, cost, and inadequate evidence

2014: US Preventative Services Task Force recommends screening for all pregnant woman for GDM at or beyond 24 weeks

2017: ACOG PB 180: “Supports two-step process and recommends that implications of suggested changes be studied before they are proposed at a national level. However, individual practices and institutions may choose to use the IADPSG’s recommendation, if appropriate, for the population they serve.”

Controversies & Challenges:
Who, how and when to test
Who, how and when to treat

Why are these things controversial & challenging?
Disagreement about how to define “disease”
What constitutes disease?

Dichotomization of a continuous process is bound to result in disagreement.

What primary cesarean section rate defines a bad outcome from disease?

One-Step vs. Two-Step Testing

One-Step
- Fasting, 75 g, 1 & 2 hr glucose measurement
- WHO & IADPSG - Supported
- 1+ at value → GDM
- GDM prevalence ~ 20%

Two-Step
- Step 1: Non-Fasting, 50 g, 1 hr glucose measurement
- ≥ 130/140 mg/dL → Step 2
- NIH - Supported
- Fasting, 100 g, 3 hr glucose test
- 2+ abnormal values → GDM
- GDM prevalence ~ 5-10%

Sensitivity vs Specificity

<table>
<thead>
<tr>
<th>One-Step</th>
<th>Two-Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carpenter Coustan</td>
<td>National Diabetes Data Group</td>
</tr>
<tr>
<td>Universal Screening</td>
<td>Risk-Based Screening</td>
</tr>
<tr>
<td>Early Screening</td>
<td>24-28 Week Screening</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>No Hemoglobin A1c</td>
</tr>
<tr>
<td>Testing for 1 abnormal value</td>
<td>No f/u for 1 abnormal value</td>
</tr>
</tbody>
</table>

More Sensitive, Less Specific
- More women with disease test positive
- More women WITHOUT disease test positive
- Diagnosing women who might not actually have clinically important disease

Less Sensitive, More Specific
- Fewer women with disease test positive
- Fewer women WITHOUT disease test positive
- Missing a clinically important diagnosis
Why are these things controversial & challenging?

Different patient populations & available resources

Different Patient Populations & Available Resources

• Variability in rates of GDM (3-50%)
• Variability in overall population health-literacy and health priorities
• Variability in available resources (nutritionists, support staff, diabetes educators)

Why are these things controversial & challenging?

Individual versus population health & concerns about cost of care
Costs v Benefits

1-step screening strategy would:
• Increase frequency of GDM 2-3 fold → 15-20%
• Annually Add:
  – 450,000 patient education visits
  – 1 million prenatal testing appointments
  – 1 million clinic visits
• Increase cost of care for GDM by > $1 billion

Why are these things controversial & challenging?

Worry about over-medicalization of pregnancies without clear data for improved outcomes.

So what do we actually know*?

1 – Increasing blood glucose is associated with worse perinatal outcomes.

Blinded study of ~25,000 women at 15 centers, 9 countries
Primary predictor: Levels of hyperglycemia
Primary outcomes: Birth weight > 90thile, primary CD, neonatal hypoglycemia, cord-blood C-peptide level

* Insomuch as we ever really “know” anything in medicine
HAPO Results

Summary of GDM-Related Risks

<table>
<thead>
<tr>
<th>Overall %</th>
<th>RR/OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrosomia</td>
<td>20</td>
</tr>
<tr>
<td>Pre-Eclampsia</td>
<td>15</td>
</tr>
<tr>
<td>Cesarean Section</td>
<td>Varies</td>
</tr>
<tr>
<td>Shoulder Dystocia</td>
<td>3-5</td>
</tr>
<tr>
<td>IUF D</td>
<td>~ 0.05</td>
</tr>
</tbody>
</table>

Table 3. Adjusted Odds Ratios for Associations Between Maternal Glycemia as a Continuous Variable and Primary and Secondary Perinatal Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fasting</th>
<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.38 (1.32-1.44)</td>
<td>1.46 (1.39-1.53)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>1.11 (1.06-1.13)</td>
<td>1.10 (1.06-1.13)</td>
</tr>
<tr>
<td>Primary cesarean section</td>
<td>1.08 (0.98-1.18)</td>
<td>1.09 (0.94-1.25)</td>
</tr>
<tr>
<td>Maternal risks</td>
<td>1.00 (0.95-1.05)</td>
<td>1.04 (0.98-1.11)</td>
</tr>
<tr>
<td>Prechloralpia</td>
<td>1.21 (1.13-1.29)</td>
<td>1.28 (1.20-1.37)</td>
</tr>
</tbody>
</table>

Maternal Risks

<table>
<thead>
<tr>
<th>Weight (g)</th>
<th>Prolonged Labor (%)</th>
<th>Excess Bleeding (%)</th>
<th>CD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3000 – 3999 g</td>
<td>0.9%</td>
<td>0.5</td>
<td>18</td>
</tr>
<tr>
<td>4000 – 4499 g</td>
<td>1.2</td>
<td>0.7</td>
<td>25.5</td>
</tr>
<tr>
<td>4500 – 4999 g</td>
<td>1.3</td>
<td>0.9</td>
<td>35.6</td>
</tr>
<tr>
<td>&gt; 5000 g</td>
<td>1.5</td>
<td>1.1</td>
<td>50.6</td>
</tr>
</tbody>
</table>
Macrosumia

Neonatal Risks

<table>
<thead>
<tr>
<th>Weight</th>
<th>Shoulder Dystocia</th>
<th>Mechanical Ventilation &gt; 30 min</th>
<th>5 min Apgar &lt; 3</th>
<th>Neonatal Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4000 g</td>
<td>0.6-3.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4000 – 4449 g</td>
<td>4.9 – 23.1%</td>
<td>RR = 1.2 – 1.9</td>
<td>RR = 1.3-5.2</td>
<td>RR = 2.7</td>
</tr>
<tr>
<td>≥ 5000 g</td>
<td>20-50%</td>
<td>RR = 4.0</td>
<td>RR = 5.2</td>
<td></td>
</tr>
</tbody>
</table>

Other Risks:
- Hypoglycemia
- Hypothermia
- Polycythemia
- Birth trauma/asphyxia

Secondary Analysis of HAPO

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Participants in category n</th>
<th>Model</th>
<th>Model II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrosomia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5000 g</td>
<td>255</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value – 95th percentile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-GDM</td>
<td>1173</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM diagnosed based on IADPSG</td>
<td>524</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM based on CC</td>
<td>256</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1953</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-GDM</td>
<td>1173</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM diagnosed based on IADPSG</td>
<td>524</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM based on CC</td>
<td>256</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1953</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Secondary Analysis of HAPO

So what do we actually know*?

2 – Women with GDM by IADPSG criteria have worse pregnancy outcomes than women with normal glucose tolerance

* Insomuch as we ever really “know” anything in medicine
CC vs IADPSG vs NGT


IADPSG vs CC

• Duran et al: 1,750 women screened using CC criteria, 1,526 women screened using IADPSG
• IADPSG screening resulted in:
  – Decreased rates of gestational hypertension (3.5% vs 4.1%)
  – Decreased cesarean rates (19.7% vs 25.4%)
  – Fewer LGA babies (3.7% vs 4.6%)


IADPSG vs. Canadian Diabetes Association Criteria

Mayo et al: 4,183 women with negative CGT, 526 women with negative OGTT, 155 women in the IADPSG group, 385 in the CDA group

Composite outcome: hypertensive complications, shoulder dystocia, third/fourth degree perineal laceration, LGA neonate, NICU admission, neonatal respiratory morbidity, neonatal hypoglycemia, neonatal jaundice


So what do we actually know*?

3 – Screening by IADPSG criteria appear to be cost-effective, at least when postpartum care is included.

* Insomuch as we ever really “know” anything in medicine
Cost Effectiveness

- Werner et al: Cost-effectiveness study
  - One-step testing is cost-effective when post-delivery care reduces diabetes incidence.
  - For every 100,000 women screened, 6,178 quality-adjusted life-years are gained
  - ICER was $20,336 per QALY

- Mission et al: Cost-effectiveness study
  - Testing with IADPSG-criteria is more expensive, but more effective
  - $61,503/quality-adjusted life year

- Duran et al: Estimated cost-savings using IADPSG approach was €14,358

So what do we actually know*?

4 – Treating elevated blood sugars improves outcomes.

* Insomuch as we ever really “know” anything in medicine

Crowther – Trial of Treatment for GDM

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group N=490 (%)</th>
<th>Routine Care N=510 (%)</th>
<th>Adjusted RR or Treatment Effect</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious perinatal complication</td>
<td>1</td>
<td>4</td>
<td>0.33 (0.14 – 0.75)</td>
<td>0.01</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>71</td>
<td>61</td>
<td>1.13 (1.03 – 1.23)</td>
<td>0.04</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>10</td>
<td>21</td>
<td>0.47 (0.34 – 0.64)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neonatal hypoglycemia</td>
<td>7</td>
<td>5</td>
<td>1.42 (0.87 – 2.32)</td>
<td>0.16</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>12</td>
<td>18</td>
<td>0.7 (0.51 – 0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cesarean Delivery</td>
<td>31</td>
<td>32</td>
<td>0.97 (0.81 – 1.16)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

* One or more of: death, shoulder dystocia, bone fracture, nerve palsy
### Landon – Trial of Treatment for GDM

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group N = 485 (%)</th>
<th>Control Group N = 473 (%)</th>
<th>Relative Risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU Admission</td>
<td>9</td>
<td>11.6</td>
<td>0.77</td>
<td>0.51 – 1.18</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>5.9</td>
<td>14.3</td>
<td>0.41</td>
<td>0.26 – 0.66</td>
</tr>
<tr>
<td>Neonatal Hypoglycemia</td>
<td>5.3</td>
<td>6.8</td>
<td>0.77</td>
<td>0.44 – 1.36</td>
</tr>
<tr>
<td>Shoulder Dystocia</td>
<td>1.5</td>
<td>4.0</td>
<td>0.37</td>
<td>0.14 – 0.97</td>
</tr>
<tr>
<td>Cesarean Delivery</td>
<td>26.9</td>
<td>33.8</td>
<td>0.79</td>
<td>0.64 – 0.99</td>
</tr>
<tr>
<td>Preeclampsia or GHTN</td>
<td>8.6</td>
<td>13.6</td>
<td>0.63</td>
<td>0.42 – 0.96</td>
</tr>
</tbody>
</table>


---

### Metformin vs Insulin

**Rowan**

**RCT of 751 women: 373 Metformin, 378 insulin**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metformin (n=373)</th>
<th>Insulin (n=378)</th>
<th>Relative Risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDM events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonates requiring supplemental insulin</td>
<td>46.3%</td>
<td>76.6%</td>
<td>0.60</td>
<td>0.001</td>
</tr>
<tr>
<td>Women stating they would choose their assigned treatment again vs. 27.2% in the insulin group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


---

### So what do we actually know*?

5 – Glyburide, Metformin and insulin all have demonstrated efficacy

* Insomuch as we ever really “know” anything in medicine

---

### Metformin vs Insulin

**Rowan**

• 46.3% of women in the Metformin group required supplemental insulin.
• 76.6% of women in the Metformin group stated that they would choose their assigned treatment again vs. 27.2% in the insulin group
Metformin vs. Insulin
Spaulonci

RCT of ~ 100 women: ~50 insulin, 50 metformin

Table 2: Neonatal outcomes in the metformin and insulin group for continuous variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Metformin group</th>
<th>Insulin group</th>
<th>P  value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at birth</td>
<td>38.33 ± 1.45</td>
<td>38.24 ± 1.53</td>
<td>.776</td>
</tr>
<tr>
<td>1-min Apgar score</td>
<td>9 (4-10)</td>
<td>9 (0-10)</td>
<td>.991</td>
</tr>
<tr>
<td>5-min Apgar score</td>
<td>10 (0-10)</td>
<td>10 (0-10)</td>
<td>.186</td>
</tr>
<tr>
<td>Umbilical artery pH at birth</td>
<td>7.22 ± 0.07</td>
<td>7.22 ± 0.08</td>
<td>.824</td>
</tr>
<tr>
<td>Neoton weight</td>
<td>3143.7 ± 446.6</td>
<td>2377.6 ± 586.8</td>
<td>.390</td>
</tr>
</tbody>
</table>

Results are reported as the mean ± standard deviation for parametric variables and median (min-max) for nonparametric variables.


Metformin vs Glyburide
Moore

- RCT of ~ 150 women – 75 women metformin, 74 women Glyburide

Table 3: Pregnancy and Neonatal Outcomes for the Glyburide Compared With the Metformin Group

<table>
<thead>
<tr>
<th></th>
<th>Glyburide</th>
<th>Metformin</th>
<th>P  value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA at delivery</td>
<td>38.13</td>
<td>38.35</td>
<td>.49</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3155±83.3</td>
<td>3358±82.0</td>
<td>.012</td>
</tr>
<tr>
<td>Birth weight &gt; 4000 g</td>
<td>4 (16.6)</td>
<td>5 (22.2)</td>
<td>.2</td>
</tr>
<tr>
<td>NACG admission</td>
<td>1</td>
<td>1</td>
<td>.37</td>
</tr>
<tr>
<td>Neonatal hypoglycemia</td>
<td>0</td>
<td>1</td>
<td>.32</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>1</td>
<td>1</td>
<td>.56</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>.32</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>2</td>
<td>2</td>
<td>.25</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>3</td>
<td>3</td>
<td>.5</td>
</tr>
</tbody>
</table>

26 patients (34.7%) in the Metformin group and 12 patients (16.2%) in the Glyburide group failed treatment and required insulin therapy.

### Glyburide vs. Insulin

**Langer**

<table>
<thead>
<tr>
<th>Variable/Outcome</th>
<th>Glyburide (N = 201)</th>
<th>Insulin (N = 203)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Dose</td>
<td>9 ± 6 mg/day</td>
<td>85 ± 48 units/day</td>
<td></td>
</tr>
<tr>
<td>Fasting Blood Glucose</td>
<td>98 ± 13 mg/dL</td>
<td>96 ± 16 mg/dL</td>
<td>0.17</td>
</tr>
<tr>
<td>Postprandial Blood Glucose</td>
<td>113 ± 22 mg/dL</td>
<td>112 ± 15 mg/dL</td>
<td>0.6</td>
</tr>
<tr>
<td>LGA</td>
<td>12%</td>
<td>13%</td>
<td>0.76</td>
</tr>
<tr>
<td>Neonatal hypoglycemia</td>
<td>9%</td>
<td>6%</td>
<td>0.25</td>
</tr>
<tr>
<td>Preecclampsia</td>
<td>6%</td>
<td>6%</td>
<td>1</td>
</tr>
</tbody>
</table>

Secondary analysis: No differences when stratified by disease severity.

---

*So what do we actually know*?

6 – Glyburide and Metformin cross the placenta, long-term outcomes are not well known, and may be associated with worse outcomes.

* *Insomuch as we ever really “know” anything in medicine*

---

### Metformin Long-Term Outcomes

2-year olds exposed to metformin or insulin:

No difference in:
- Bayley Scales
- Hammersmith Infant Neurological Examination
- Receptive communication
- Expressive communication
- Fine motor scale
- Gross motor scale

---

### Glyburide Outcomes

- **Jacobson:**
  - Outcomes among 268 women treated with insulin vs. 236 women treated with Glyburide
  - Equivalent: Birthweight, mode of delivery, hyperbilirubinemia, neonatal hypoglycemia
  - Twice as many women in the Glyburide group developed pre-eclampsia (12% vs 6%; p = 0.02)
  - More infants in the Glyburide group required phototherapy (9% vs 5%; p = 0.05)

---


Glyburide Outcomes
Balsells et al: Systematic review & meta-analysis of Glibenclamide (Glyburide), metformin & insulin
Compared to insulin, Glyburide was associated with:
• Macrosomia: RR 2.62 (1.35 – 5.08)
• Neonatal hypoglycemia: RR 2.04 (1.30 – 3.20)
• No difference in pre-eclampsia
• Failure rate for Glyburide = 6.7%

Metformin Outcomes
Balsells et al:
Compared with insulin, Metformin was associated with:
• Less maternal weight gain (-1.14 kg)
• Preterm birth: RR 1.50 (95% CI 1.04 – 2.16)
• Less PIH: RR 0.53 (95% CI 0.31 – 0.90)
• Failure rate for Metformin: 33.8%

Glyburide Outcomes
Poolsup et al: Meta-Analysis of 13 studies, including 2,151 patients
Compared to insulin, Glyburide was associated with:
• Macrosomia: RR 3.07 (95% CI 1.14 – 8.23)
• Neonatal hypoglycemia: RR 2.30 (95% CI 1.28 – 4.11)
• No difference in pre-eclampsia risk

Metformin Outcomes
Poolsup et al:
Compared with insulin, metformin was associated with:
• No difference in risk of macrosomia
• Preterm birth: RR 1.51 (95% CI 1.04 – 2.19)
• Reduced risk of gestational hypertension:
  RR 0.54, 95% CI 0.31 – 0.91
So what do we actually know*?

7 – Women with GDM may benefit from delivery between 39-40 weeks

* Insomuch as we ever really “know” anything in medicine

Induction of Labor

- Rosenstein: Infant mortality rates at 39 weeks are lower than overall mortality risk of expectant management.

Prevention of Diabetes

- Ratner et al - 350 women with history of GDM compared to 1,416 women without GDM randomized to lifestyle intervention, metformin or usual care

* Insomuch as we ever really “know” anything in medicine
So what do we actually KNOW?

1 – Increasing blood glucose is associated with worse perinatal outcomes.
2 – Women with GDM by IADPSG criteria have worse pregnancy outcomes than women with normal glucose tolerance.
3 – Screening by IADPSG criteria appear to be cost-effective, at least when postpartum care is included.
4 – Treating elevated blood sugars improves outcomes.
5 – Glyburide, Metformin and insulin all have demonstrated efficacy.
6 – Glyburide and Metformin cross the placenta, long-term outcomes are not well known, and may be associated with worse outcomes.
7 – Women with GDM may benefit from delivery between 39-40 weeks.
8 – Postpartum interventions reduce long-term risk of type 2 diabetes.

What We Don’t Know

• Optimal diet
• Ideal threshold for initiating medical therapies
• Best medical treatment(s)
• Impact of exercise, optimal exercise regimens

What Is NOT Controversial

Perinatal risks go up with increasing blood sugar.
There is no risk of harm from encouraging women to follow a healthy diet and get regular physical activity.
SOME portion of women will change their behavior after being made aware of an increased risk of disease.

What I Think You Should Do

Determine what testing & treatment strategies generally fit your circumstances best

Be flexible!
Thank You