Pt. 1
Medical Management of Diabetes in Pregnancy
Concepts & Treatment Strategies
(the basis of why we do what we do)

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What’s new in GDM diagnosis and treatment

Part 1: The basis of medical management
1. Who is the New GDM patient diagnosed by the new criteria?
2. Evidence that treatment prevents Obstetrical and Neonatal complications
   – RCT’s showing benefit of treatment of mild GDM vs placebo
   – Obesity and Weight targets

Part 2: Clinical approaches to Medication
1. When and How to treat: “Glycemic Therapy”
   – Diet, exercise, lifestyle changes
   – RCT’s showing efficacy of treatment of GDM with glyburide and with metformin
   – RCT’s showing efficacy of modified therapy based on fetal growth and glycemia
Old criteria for GDM and New Recommendations IADPSG: Based on Perinatal Morbidity (HAPO)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Old Criteria</th>
<th>New Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>3H oGTT (100 g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th &amp; 5th IWCGDM mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>1 Hour</td>
<td>180</td>
<td>180</td>
</tr>
<tr>
<td>2 Hour</td>
<td>155</td>
<td>153</td>
</tr>
<tr>
<td>3 Hour</td>
<td>140</td>
<td></td>
</tr>
</tbody>
</table>

*Require ≥ 2 abnormal values

*IADPSG Consensus Panel, Diabetes Care 2010, 33:676-82
How many and who will be “diabetic” using the new diagnostic criteria for GDM?
Basis of New Recommendations from IADPSG Consensus Panel

Thresholds are the average glucose values at which the odds for:

• birth weight >90\textsuperscript{th} percentile
• cord C-peptide >90\textsuperscript{th} percentile and
• percent body fat >90\textsuperscript{th} percentile

Reached 1.75 times the estimated odds of these outcomes at mean glucose values, based on fully adjusted logistic regression models.

At least one of these threshold values must be equal to or exceed to diagnosis GDM
Recommended Diagnostic Criteria for GDM and Overt Diabetes During Pregnancy IADPSG Consensus Panel
Diabetes Care 2010, 33:676

To diagnose GDM and Cumulative proportion of HAPO cohort equaling or Exceeding those thresholds

<table>
<thead>
<tr>
<th>Glucose measure</th>
<th>Glucose Concentration mmol/l</th>
<th>Threshold* mg/ml</th>
<th>Above threshold (%) Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG</td>
<td>5.1</td>
<td>92</td>
<td>8.3</td>
</tr>
<tr>
<td>1-h plasma glucose</td>
<td>10.0</td>
<td>180</td>
<td>14.0</td>
</tr>
<tr>
<td>2-h plasma glucose</td>
<td>8.5</td>
<td>153</td>
<td>16.1+</td>
</tr>
</tbody>
</table>

Total Incidence GDM: 17.8%

- Will not only treat women with high risk of developing diabetes
- Expand GDM to include “Metabolic Syndrome”
- Will just glucose control be the best treatment?
- No evidence of best treatment strategies to follow with new criteria

**Threshold values for diagnosis of GDM**
* One or more of these values from a 75-g OGTT must be equaled or exceeded for the diagnosis of GDM.
+ In addition, 1.7% of participants in the initial cohort were unblinded because of FPG >5.8 mmol/l (105 mg/dl) or 2-h OGTT values >11.1 mmol/l (200 mg/dl), bringing the total to 17.8%.
Recommended Diagnostic Criteria for GDM and Overt Diabetes During Pregnancy
IADPSG Consensus Panel, Diabetes Care 2010, 33:676

<table>
<thead>
<tr>
<th>Measure of Glycemia</th>
<th>Consensus Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG*</td>
<td>≥ 7.0 mmol/l (126 mg/dl)</td>
</tr>
<tr>
<td>HBA1C*</td>
<td>≥ 6.5% (DCCT/UKPDS standardized)</td>
</tr>
<tr>
<td>Random Plasma Glucose</td>
<td>≥ 11.1 mmol/l (200 mg/dl) + confirmation**</td>
</tr>
</tbody>
</table>

* One of these must be met to identify the patient as having overt diabetes in pregnancy.

** If a random plasma glucose is the initial measure, the tentative diagnosis of overt diabetes in pregnancy should be confirmed by FPG or Hba1C using a DCCT/UKPDS-standardized assay.
Recommended Diagnostic Criteria for GDM and Overt Diabetes During Pregnancy, IADPSG Consensus Panel

Diabetes Care 2010, 33:676

• First prenatal visit Measure FPG, HbA$_{1C}$, or random plasma glucose on all or only high-risk women†
  – If results indicate overt diabetes
    • Treatment and follow-up as for preexisting diabetes
  If not diabetes and FPG $\geq$ 92 mg/dl and <126 mg/dl
    ($\geq$5.1 mmol/l and <7.0 mmol/l)
    • Diagnose as GDM
  – If fasting plasma glucose <5.1 mmol/l (92 mg/dl),
    • test for GDM from 24 to 28 weeks' gestation with a 75-gOGTT‡

What if HbA$_{1C}$ 5.7-6.4%? Can you treat as GDM?
Early diagnosis of GDM/Overt DM

prenatal visit Measure FPG, A1C, or random plasma glucose on all or only high-risk women

Dx by FPG

<92 mg/dl  
No GDM

92-125 mg/dl  
GDM

> 126 mg/dl  
Overt DM

75g oGTT at 24-28 wk

IADPSG Consensus Panel Diabetes Care 2010, 33:676
Early diagnosis of GDM/Overt DM using A1c

First prenatal visit Measure A1C on all or only high-risk women

Dx by A1c

- <5.7%  
  No GDM

- 5.7 – 6.4% mg/dl  
  GDM

- > 6.5%  
  Overt DM

75g oGTT at 24-28 wk

Sweet Success Express
Evidence for treatment of mild gestational diabetes
Multicenter RCT for Treatment of Mild GDM

**Study:** 958 women diagnosed with GDM and FPG<95 mg/dl, at 24-31 weeks,
Randomized to
- Usual PNC (Control).
- Diet, SMBG, +insulin prn (Treatment)

1° Outcomes: Composite stillbirth/perinatal death, neonatal hyperbilirubinemia, hypoglycemia, hyperinsulinemia, birth trauma

2° Outcomes weight gain after entry, gestational hypertension, preeclampsia, cesarean delivery, labor induction, shoulder dystocia
Multicenter RCT for Treatment of Mild GDM
Primary Perinatal Outcome

<table>
<thead>
<tr>
<th>Outcome</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>GA at birth (wk)</td>
<td>39.0 ± 1.8</td>
<td>39.0 ± 1.8</td>
<td>0.87 (0.72-1.07)</td>
<td>0.14</td>
</tr>
<tr>
<td>Composite Endpoint</td>
<td>149/460 (32.4%)</td>
<td>163/440 (37.0%)</td>
<td>0.87 (0.72-1.07)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>62/381 (16.3%)</td>
<td>55/357 (15.4%)</td>
<td>1.06 (0.73-1.53)</td>
<td>0.75</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>43/450 (9.6%)</td>
<td>54/418 (12.9%)</td>
<td>0.74 (0.49-1.12)</td>
<td>0.12</td>
</tr>
<tr>
<td>↑ Cord C-Peptide</td>
<td>75/423 (17.7%)</td>
<td>92/403 (22.8%)</td>
<td>0.78 (0.57-1.05)</td>
<td>0.07</td>
</tr>
<tr>
<td>Stillbirth/NND</td>
<td>3/476 (0.6%)</td>
<td>6/455 (1.3%)</td>
<td>0.48 (0.10-2.20)</td>
<td>0.33</td>
</tr>
<tr>
<td>Birth Trauma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Multicenter RCT for Treatment of Mild GDM
### Secondary Neonatal Outcome


<table>
<thead>
<tr>
<th>Outcome</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) (SD)</td>
<td>3302 (502)</td>
<td>3408 (N=473)</td>
<td>0.41 (0.26-0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BW &gt;4000g</td>
<td>28/477 (5.9%)</td>
<td>65/454 (14.3%)</td>
<td>0.49 (0.32-0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large for GA</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) (SD)</td>
<td>427.0 (198)</td>
<td>464.3 (222)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Preterm delivery</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 GA</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>NICU admission</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>IV glucose Rx</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</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>
# Multicenter RCT for Treatment of Mild GDM

**Secondary Maternal Outcome**


<table>
<thead>
<tr>
<th>Outcome</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>Labor induction</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</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</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</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 HTN</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>BMI at delivery (SD)</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) (SD)</td>
<td>2.8 (4.5)</td>
<td>5.0 (3.3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion**

- Treatment of mild GDM did not significantly reduce frequency of composite outcome (stillbirth, NND, several neonatal complications).
- Treatment did reduce risks of fetal overgrowth, shoulder dystocia, cesarean delivery, hypertensive disorders.

ACHOIS: Effect of Treatment of GDM on Pregnancy Outcomes


**Study:** 1000 women diagnosed with GDM (by 75g oGTT, at 24-34 weeks with FPG<140 and 2H<200 mg/dl)

Randomized to

- **Control:** Routine PNC, patient and provider (N=510)
- **Intervention:** Diet, SMBG, +insulin prn ↑glucose (N=490)
- **1° Outcomes:** Serious perinatal complication (stillbirth/perinatal death, shoulder dystocia, nerve palsy, bone fracture), neonatal hyperbilirubinemia, hypoglycemia, hyperinsulinemia, labor induction, cesarean delivery, maternal anxiety, depression, health status
## ACHOIS: Treatment of GDM on Pregnancy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>Relative Risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious Perinatal Complication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>5 (1%)</td>
<td>0.33 (0.14-0.75)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0</td>
<td>3 (1%)</td>
<td>0.48 (0.10-2.20)</td>
<td>0.07</td>
</tr>
<tr>
<td>NND</td>
<td>0</td>
<td>2 (&lt;1%)</td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Shoulder Dystocia</strong></td>
<td>7 (1%)</td>
<td>16 (3%)</td>
<td>0.46 (0.19-1.10)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Bone Fracture</strong></td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td>0.46 (0.19-1.10)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Nerve Palsy</strong></td>
<td>0</td>
<td>3 (1%)</td>
<td>0.46 (0.19-1.10)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Admission to NICU</strong></td>
<td>357 (71%)</td>
<td>321 (61%)</td>
<td>1.13 (1.03-1.23)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Jaundice</strong></td>
<td>44 (9%)</td>
<td>48 (9%)</td>
<td>0.93 (0.63-1.37)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Labor induction</strong></td>
<td>189 (39%)</td>
<td>150 (29%)</td>
<td>1.36 (1.15-1.62)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Cesarean</strong></td>
<td>152 (31%)</td>
<td>164 (32%)</td>
<td>0.97 (0.81-1.16)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Elective</strong></td>
<td>72 (15%)</td>
<td>61 (12%)</td>
<td>1.17 (0.85-1.60)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Emergent</strong></td>
<td>80 (16%)</td>
<td>103 (20%)</td>
<td>0.87 (0.68-1.13)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

**Perinatal deaths**
- **Intervention Group:** none
- **Control:**
  - 2 unexplained stillbirths at term
  - 1 intrapartum stillbirth with IUGR, preeclampsia
  - 1 NND with lethal congenital anomaly
  - 1 NND with birth asphyxia

mpsia @ 35 weeks
### Conclusion

- Treatment of gestational diabetes reduces serious perinatal morbidity and
- May also improve the woman’s health-related quality of life.
Effects of Diabetes on Fetus in Later Pregnancy

• Abnormal Growth
  – abnormal adipose deposition & distribution
  – visceral organ hypertrophy & hyperplasia
  – acceleration of skeletal growth

• Pederson Hypothesis (1952)
  – Stimulated by elevated fetal glucose

• Freinkel (1980)
  – Stimulated by altered levels of free fatty acids, amino acids, ketones and glucose

• Failure of strict metabolic control to correlate with the risk of macrosomia
Accelerated Fetal Growth

Diabetes

↓ Insulin

Plasma

↑ Glucose

↑ Lipids

↑ Amino acids

Mother

Placenta

↑ Insulin

↑ “Mixed Nutrients”

↑ “Growth Factors”

Fetus

Insulin Sensitive & Insensitive

↑ Fetal Growth
Reducing Macrosomia risk Identifying Diabetic LGA Infants in Early 3\textsuperscript{rd} Trimester

*Sonographic evaluation of Fetal Abdominal Growth*

- Growth Curve of LGA and AGA infants of diabetic mother from serial ultrasound:
  - LGA infants (n=31): appropriate growth of
    - Femur Length & Head Circumference.
  - Accelerated Abdominal Circumference (AC) growth in LGA infants by 32 weeks:
    - AC growth $> 1.2$ cm/w predicted LGA growth:
      - Sensitivity 84%; Specificity 85%
      - Better than term US

Pathophysiology of macrosomia Hyperinsulinemia & Diabetic Fetopathy

• Amniotic fluid insulin levels correlate with diabetic-associated complications in newborn
• “Biochemical Fetopathy”
  – AFI >17 µU/ml¹
• “Somatic Fetopathy” e.g. LGA
  – AFI >18-20 µU/ml¹,²
• Long term diabetes risk³
  – childhood obesity: AFI >150pmol/l (~20 µU/ml)
  – Impaired glucose tolerance (age 6): (~14 µU/ml)

Amniotic fluid insulin levels and fetal AC at time of amniocentesis in women with Type 1 diabetes:

↑AC measurements correlated with pathologically elevated AFI (AFI >20 µU/ml)¹

¹Kainer F, Early Hum Dev 1997, 49:113-21

Effects of Maternal GDM on Offspring Adiposity at 4-7 yrs

• 3 critical time periods for development of childhood obesity:
  – gestation/early infancy, 5-7 yrs, adolescence

• Rates of BMI >90\textsuperscript{th} % in 7 y/o’s:
  – 38% of LGA Offspring of GDM
  – 6% AGA Offspring of GDM

• Child BMI at 7 yrs correlated with maternal BMI, maternal FBG and Birthweight in OGDM but not in controls

Vohr 1999 Diabetes Care; 22: 1284
It is not just Glucose! The effect of maternal weight and weight gain

- By lowering the glucose cut-points for GDM, we include metabolic syndrome and obesity
- Controlling glucose may not be what is needed to decrease morbidity measures of the newborn
- Limiting weight gain through lifestyle, diet and exercise may be more important
  - Eating healthier: less fats, less simple carbs, less processed foods, more veges
<table>
<thead>
<tr>
<th>Pre-Pregnancy BMI</th>
<th>BMI (Kg/m^2) (WHO)</th>
<th>Total Weight Gain Range lbs (kg)</th>
<th>2^{nd}, 3^{rd} Trimester Weight Gain (lbs/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>28-40</td>
<td>1 (1-1.3)</td>
</tr>
<tr>
<td>Normal Weight</td>
<td>18.5 – 24.9</td>
<td>25-35</td>
<td>1 (0.8-1)</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 – 29.9</td>
<td>15-25</td>
<td>0.6 (0.5-0.7)</td>
</tr>
<tr>
<td>Obese (all classes)</td>
<td>≥30.0</td>
<td>11-20</td>
<td>0.5 (0.4-0.6)</td>
</tr>
</tbody>
</table>

“Weight Gain During Pregnancy: Reexamining the Guidelines”: National Academy Sciences, Washington DC, May 2009,
Pregnancy Weight Gain in Obese Women:

Adjusted OR for Risk of HIGH & LOW BIRTH

Risk of LBW in Obese women
• Only $\geq 10$ lb below IOM weight (weight gain $< 5$ lb.) was significantly associated with LBW:
  White 1.6 (1.04-2.4), Black 2.6 (1.5-4.5), Hispanic 1.0 (0.4-2.5)
  Additional weight gain above IOM did not lower LBW risk

Risk of HBW
  Weight gain above IOM increased HBW risk
  Weight gain below IOM decreased HBW risk
    Each increase in weight category associated with increase in HBW risk
  Similar trend in White, Black, and Hispanic
Gestational weight gain in obese women Population study

- **Design:** Population based cohort (n=120,251) of obese women (BMI>30)
  - delivering full term infants in Missouri 1990-2001
- **Goal:** examine effect of GWG on pregnancy outcome by weight gain < or ≥15 lb according to Obesity class I (BMI 30-34.9), II (35-39.9) and III (BMI ≥40)
- **Outcome Measures:** Preeclampsia, Cesarean delivery, LGA and SGA infant

<table>
<thead>
<tr>
<th>Pregnancy Outcome</th>
<th>Class I N=70,536</th>
<th>Class II N=30,609</th>
<th>Class III N=19,025</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Preeclampsia</td>
<td>7%</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Ceasarean</td>
<td>28%</td>
<td>34%</td>
<td>41%</td>
</tr>
<tr>
<td>SGA Infant</td>
<td>7%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>LGA Infant</td>
<td>13%</td>
<td>16%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Kiel DW, Obstet Gynecol 2007, 110:752
Absolute risk of Adverse Pregnancy Outcome by GWG Category according to Class I, Class II or Class III Obesity using 1990 IOM Recommendations (15 lb minimum) for Obese Women

**Class I Obesity**
- Optimal Wt Gain
  - 10-25 lb

**Class II Obesity**
- Optimal Wt Gain
  - 0-9 lb

**Class III Obesity**
- Optimal Wt loss
  - 0-9 lb
Gestational weight gain in obese women: Population study
Recommend different GWG Targets based on Obesity Class

<table>
<thead>
<tr>
<th>Suggested target GWG to minimize risk</th>
<th>Class I BMI 30-34.9</th>
<th>Class II BMI 35-39.9</th>
<th>Class III BMI ≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-25 lbs gain</td>
<td>0-9 lbs gain</td>
<td>0-9 lbs loss</td>
<td></td>
</tr>
</tbody>
</table>

- Gestational weight gain incidence for overweight or obese pregnant women, less than 15 lbs, was associated with significantly lower risk of preeclampsia, cesarean, LGA and a higher risk of SGA.
- Results were similar for each obesity class I, II or III
- Limited weight or no weight gain in obese pregnant women has a favorable pregnancy outcome.

Absolute effect of GWG <15 lb on Pregnancy Outcomes: Number needed to treat to avoid one case

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Class I BMI 30-34.9</th>
<th>Class II BMI 35-39.9</th>
<th>Class III BMI ≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>29</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>Cesarean</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>SGA</td>
<td>21</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>LGA</td>
<td>14</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>
HAPO:
Associations with Maternal Body Mass Index

**Design:** Of 23,316 study participants, 75g oGTT at 24-32 wk, pregnancy BMI calculated from Wt, Ht at oGTT

**Analysis:** Logistic regression to assess relationship of maternal BMI with:

- **Primary Outcome:** Birthweight >90\textsuperscript{th}, Cord C-peptide >90\textsuperscript{th}, NN hypoglycemia, primary CD
- **Secondary Outcome:** pre-eclampsia, Preterm delivery, percent body fat >90\textsuperscript{th}

Model 1: Adjusted for age, parity, Height, gestational age at delivery, baby sex, smoking, alcohol, FH of HTN, FH of DM

Model 2: Added fasting glucose and mean arterial pressure

HAPO Study. BJOG 2010:117:575-84
HAPO: Associations with Maternal Body Mass Index: Model II OR (95% CI) adjusted for FPG & MAP

<table>
<thead>
<tr>
<th>BMI (Kg/m²)</th>
<th>Birth weight &gt;90th perc.</th>
<th>Primary CD</th>
<th>Cord C-Peptide &gt;90th perc.</th>
<th>Preeclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;22.6</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>22.6-28.4</td>
<td>2.17 (1.78-2.65)</td>
<td>1.17 (1.03-1.33)</td>
<td>1.29 (1.05-1.58)</td>
<td>1.56 (1.17-20.8)</td>
</tr>
<tr>
<td>28.5-32.9</td>
<td>3.31 (2.68-4.10)</td>
<td>1.48 (1.28-1.71)</td>
<td>1.66 (1.32-2.08)</td>
<td>2.85 (2.11-3.85)</td>
</tr>
<tr>
<td>33.0-37.4</td>
<td>3.89 (3.07-4.93)</td>
<td>1.75 (1.47-2.08)</td>
<td>2.13 (1.65-2.75)</td>
<td>5.01 (3.64-6.89)</td>
</tr>
<tr>
<td>37.5-41.9</td>
<td>3.80 (2.84-5.08)</td>
<td>1.78 (1.41-2.25)</td>
<td>1.90 (1.37-2.63)</td>
<td>8.92 (6.25-12.73)</td>
</tr>
<tr>
<td>≥ 42.0</td>
<td>3.52 (2.48-5.00)</td>
<td>2.23 (1.66-2.99)</td>
<td>2.33 (1.58-3.43)</td>
<td>14.14 (9.44-21.17)</td>
</tr>
</tbody>
</table>

- No significant association w/ increasing BMI: neonatal hypoglycemia, hyperbilirubinemia, NICU admit
- ↑ OR of Shoulder dystocia with BMI 33.0-41.9 2-fold (low numbers of cases)
- ↑ OR of Preterm Delivery with Lowest BMI <22.6 compared to all other BMI categories

HAPO Study. BJOG 2010:117:575-84
### HAPO: Associations with Maternal Body Mass Index: Model II OR (95% CI) adjusted for FPG & MAP

<table>
<thead>
<tr>
<th>BMI (Kg/m²)</th>
<th>Birth weight &gt;90&lt;sup&gt;th&lt;/sup&gt; perc.</th>
<th>Percent Body Fat &gt;90&lt;sup&gt;th&lt;/sup&gt; perc.</th>
<th>Sum skinfolds &gt;90&lt;sup&gt;th&lt;/sup&gt; perc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;22.6</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>22.6-28.4</td>
<td>2.17 (1.78-2.65)</td>
<td>1.81 (1.48-2.23)</td>
<td>1.70 (1.38-2.08)</td>
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<tr>
<td>28.5-32.9</td>
<td>3.31 (2.68-4.10)</td>
<td>2.77 (2.22-3.44)</td>
<td>2.42 (1.95-3.01)</td>
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<tr>
<td>33.0-37.4</td>
<td>3.89 (3.07-4.93)</td>
<td>3.19 (2.50-4.08)</td>
<td>2.94 (2.30-3.75)</td>
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<tr>
<td>37.5-41.9</td>
<td>3.80 (2.84-5.08)</td>
<td>3.51 (2.61-4.74)</td>
<td>2.36 (1.72-3.23)</td>
</tr>
<tr>
<td>≥ 42.0</td>
<td>3.52 (2.48-5.00)</td>
<td>3.28 (2.28-4.71)</td>
<td>2.63 (1.82-3.81)</td>
</tr>
</tbody>
</table>
Pt 2: Glycemic Therapy: Clinical Approaches to Medication
Are these patients different?

A: 30 y/o G3 P2
- 1H GCT: 195 mg/dl
- GTT: 103/215/169/145
- 30 weeks
- prepregnancy wt: 120
  ht: 64; BMI: 20
- white
- no family history of DM
- no prior GD
- Prior BW: 3000g,3400 g

B: 30 y/o G3 P2
- 1H GCT: 195 mg/dl
- GTT: 103/215/169/145
- GA: 23 weeks
- prepregnancy wt: 220
  ht: 64; BMI: 38.5
- Native American
- DM: Mother & sister
- prior GD: diet treated
- Prior BW: 4000g,4500 g

Same diagnostic glucose values!
Gestational Weight Gain In GDM California Sweet Success Program

Study: Retrospective (2001-4), n=31,704, GDM singletons pregnancies Predelivery-prepregnancy weight, Referent weight gain 15-35 lb

Mean gestational age enrollment 27.9 wk
Mean weight gain/wk:
• Before SS enrollment: 0.64 lb
• After SS enrollment: 0.41 lb

Cheng YW, Obstet Gynecol
Prevention of Diabetes: Achieving Healthy Weight Strategy: Limit weight gain during pregnancy

1. 15 yr follow-up of Swedish 2345 women categorizing weight gain during pregnancy (high/low/normal) and weight retention (SPAWN)

   High weight *gainers* retained more weight @ 1Y after 1\textsuperscript{st} & 2\textsuperscript{nd} Pregnancy
   
   High weight *retainers* gained more during pregnancy, and into the 2\textsuperscript{nd} pregnancy; and gained/retained more during 2\textsuperscript{nd} pregnancy


2. Children (n=1739) followed (age 2 to 12), ≥3 visits

   Categorized as early onset (<8Y, 10.9%) & late onset (>8Y, 5.2%) Overweight (BMI>95\textsuperscript{th} % for age/gender) and normal weight (83.9%, referant)

   Prediction of Early onset overweight (adjusted model):
   
   • Male, OR 1.5, Black, OR 1.7
   • Mat BMI ≥30, OR 2.2
   • Mat Weight gain during pregnancy >20Kg, OR 1.7
   • Birth weight >4000g, OR 2.0
   
   – Breastfeeding protective: Early(OR 0.7) & Late overweight (OR 0.7)


Limit weight gain during pregnancy!

- Better control of glucose during pregnancy
- Decrease risk weight retention post-pregnancy
  
- Decrease LGA risk
- Decrease childhood obesity
Are these patients different?

A: 30 y/o G3 P2
- Start 1800 cal diet
- Self glucose monitoring
- Daily walking 3x’s/d

2 weeks later
- fasting: 90-102
- 1HPP: 124-158
- 2HPP: 104-135

B: 30 y/o G3 P2
- Start 2200 cal diet
- Self glucose monitoring
- Daily walking 3x’s/d

2 weeks later
- fasting: 90-102
- 1HPP: 124-158
- 2HPP: 104-135

Same glycemic control Do you treat them the same?
Treatment Goals in Diabetic Pregnancies:

Questions

1. Should treatment of Gestational Diabetes be the same as for Pregestational Diabetes?
   - Based on maternal glycemia
   - Insulin

2. What is the Goal of therapy? Maternal Euglycemia or ↓ Neonatal Morbidity?

ACHOIS, NIH MFM trial, HAPO
Medical Management of GDM

When to initiate intensive therapy?

**Strategy #1: Monitoring maternal glycemia:**

– To detect pre- and post-meal hyperglycemia
  - Primary treatment goal with greatest clinical experience
  - Demonstrated normalization of neonatal outcomes

**Goal:** Non-diabetic range glucose levels in all women with GDM
Many Therapeutic Modalities

• Diet:
  – Moderate caloric restriction, low glycemic index, limit CHO intake & distribute during day

• Exercise
  – Small pilot studies: Suggest exercise ~ insulin

• Self-blood glucose monitoring
  – Memory meters improve diet compliance

• Oral Anti-hyperglycemics
  – Glyburide: 1 RCT suggest glyburide ~ insulin
  – Metformin: 1 RCT comparing metformin ~ insulin

• Insulin:
  – Normalizes glucose and improves outcome
  – Debate over thresholds of when to treat

Few RCT’s for evidence-based guidelines
Initial FPG GDM Glycemic Management: Fasting & Post-prandial

- **F: 92 - 125**
  - HPP: ≥140
  - Monitor BG SBGM + insulin

- **F: < 92**
  - 1 HPP: <140
  - Diet and Exercise Therapy
  - Monitor BG
  - All FCG < 90
  - 1HPP < 140
  - 2HPP < 120

- **F: ≥ 125**
  - 1 HPP ≥ 200
  - SBGM + insulin

- **SBGM**
  - FCG 95-126
  - 1HPP 140-200
  - 2HPP 120-200

- **Insulin or Glyburide?**
- **Metformin?**

New Fasting Glucose diagnostic level recommended ≥92 mg/dl
How to assess effectiveness of Oral Anti-Diabetic Agents in Pregnancy: the Mother?

- Lowers maternal glucose levels
  - Easiest but likely oversimplistic

- Improve pathophysiology of GDM
  - ↓Insulin resistance, ↑insulin sensitivity
  - Lower risk of subsequent maternal diabetes
  - Therapy not associated with large weight gain
    - Target: obese <15 lbs, overweight 15-25 lbs

Theoretical best choice: Insulin-sensitizing agent
How to assess effectiveness of Oral Anti-Diabetic Agents in Pregnancy: the Fetus?

- Normal in utero growth pattern
- Prevent fetal hyperinsulinemia
  - Proxy measures: Amniotic fluid insulin, fetal abdominal circumference growth
- Placental transfer?
  - If no: should only effect fetus through maternal metabolism, transfer nutrients/hormones across placenta
  - If yes: drug in fetus should not cause hyperinsulinemia
- What is long-term effect of in utero changes in insulin resistance/ sensitivity?
How to assess effectiveness of Oral Anti-Diabetic Agents in Pregnancy: the Offspring?

- Normal newborn growth: not LGA or SGA
- no ↑Stillbirth, morbidity
- No excess NN morbidity?
  - Biochemical: RDS
    - Hypoglycemia: no requirement for IV glucose
    - Polycythemia, hyperbilirubinemia, hypocalcemia
- Pathophysiology: ↓hyperinsulinemia
  - NN Insulin levels (C peptide): cord blood, amniotic fluid
  - NN obesity: ↑skin-fold thickness, Ponderal Index
Options for therapy for GDM
Many Classes of Oral Anti-diabetics

- **Insulin Secretagogues**
  - **Sulfonylureas**: stimulates insulin secretion \(\rightarrow\) improves postprandial glucose. Must have residual β-cell function, Cat B in pregnancy
  - suppresses hepatic glucose production via insulin secretion
    (newer class—not studied in pregnancy: Meglitinides)

- **Biguanides**
  - Metformin

- **α-Glucosidase Inhibitors**
  - Acarbose, Mitglitol

- **Thiazolidinediones**

- **Incretin Mimetics** (potentiate insulin & inhibit glucagon secretion, slow gastric emptying)
  - GLIP-1 Agonists (Glucagon like Peptide-1: Exentide), GIP (glucose dependent insulinotropic polypeptide, DPP-4 Inhibitor (Dipeptidyl Peptidase 4 —Sinagliptin), GK Activators (glucose kinase)
Placental Transfer & effect on fetus: Why it matters & what would be ideal? Recent Studies


Recent Studies

Human placenta has capacity to:

• Oxidatively biotransform glyburide to its multiple metabolites and
• Transport glyburide across the placenta by various transporter proteins (including BCRP)
• Using ultrasensitive assays (detection limit=0.13ng/ml cf. older assays with DL=10ng/dl)
• Observed lower mat [glyburide] 0=32.7 ng/ml and
• Cord venous [glyburide] 0-12.5ng/ml
• Levels were 0.7 (+ 0.4) of simultaneous

Biguanides

**Metformin***

**Action:** requires insulin

- Enhance insulin action via post-receptor effect, primarily on the liver & muscle
- ↑ Hepatic sensitivity to insulin: Suppress hepatic glucose output
  - ↓ Glucagon production and ↓ Gluconeogenesis
  - ↓ Glucogenolysis, ↓ Fatty acid oxidation
  - Stimulating glucose uptake in liver
- ↑ Glucose uptake in skeletal muscle (↑ glucose disposal)
  - **Does not stimulate insulin secretion/release**
  - **Does not cause hypoglycemia**

**Side effect:** GI upset--nausea, abdominal discomfort, metallic taste, diarrhea **Placental transfer:** ~50%

Metformin recommended as 1st line therapy in newly diagnosed T2DM by ADA/EASD Consensus Conference (Diabetes Care 29:1963, 2006)

*only biguanide available—Phenformin off market*
Preconception Care:

No Evidence that Oral Anti-diabetic Medications Cause Birth Defects

• Meta-analysis of Metformin exposure during 1st trimester (Gilbert C, Fert Steril 86:658, 2006)
  – 8 studies included (65 rejected): 1st trimester exposure in women with T2DM (n=28) or PCOS (n=139) with disease-matched control group
  – Outcome: OR 0.50 (98%CI: 0.15, 1.60)
    • After adjustment: 57% protective effect
    • Pooled malformation rate:
      – control 7.2% vs. metformin 1.7%
• Sulfonylureas: No evidence of teratogenicity,
  – minimal transport across placenta (in vivo & in vitro)
  – Retrospective studies controlling for glucose show no increase risk
• Thiazolidinediones: no data, category C
# Randomized Trial of Glyburide vs. Insulin*


<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Glyburide (n=201)</th>
<th>Insulin (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA entry (wk)</td>
<td>24 (7)</td>
<td>25 (7)</td>
</tr>
<tr>
<td>GTT FPG (mg/dl)</td>
<td>97 (14)</td>
<td>98 (16)</td>
</tr>
<tr>
<td>Mean cbg (mg/dl)</td>
<td>114 (19)</td>
<td>116 (22)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.7 (1.3)</td>
<td>5.6 (1.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-treatment</th>
<th>Glyburide (n=201)</th>
<th>Insulin (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy dose</td>
<td>9 (6) mg</td>
<td>85 (48) U</td>
</tr>
<tr>
<td>Fasting (mg/dl)</td>
<td>98 (13)</td>
<td>96 (16)</td>
</tr>
<tr>
<td>Mean cbg</td>
<td>105 (16)</td>
<td>105 (16)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.5 (0.7)</td>
<td>5.4 (0.6)</td>
</tr>
</tbody>
</table>
## Randomized Trial of Glyburide vs. Insulin


<table>
<thead>
<tr>
<th>Neonatal Outcome</th>
<th>Glyburide (n=201)</th>
<th>Insulin (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGA n(%)</td>
<td>24 (12)</td>
<td>26 (13)</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>3256 (543)</td>
<td>3194 (598)</td>
</tr>
<tr>
<td>Macrosomia n (%)</td>
<td>14 (7)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Cord Insulin</td>
<td>15 (13)</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>18 (9)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>IV Glucose</td>
<td>28 (14)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>2 (1)</td>
<td>22 (11)</td>
</tr>
</tbody>
</table>

No cord glyburide detected in 12 tested subjects
Randomized Trial of Glyburide vs. Insulin

Summary

• Mild GDM: Mean FSG at dx: <100 mg/dl
  • mean CBG achieved: ~105 mg/dl
• No difference in C/S, macrosomia, NN hypoglycemia
• No glyburide detected in cord blood (measurable levels in moms’blood, n=12)
• 4% of glyburide group had to go on insulin

• Subsequent comparison of disease severity:
  – Low-dose glyburide ≤10 mg vs High-dose >10 mg to control BS
  – LGA rate: 8% vs. 22%; Macrosomia: 5% vs 16% with higher dose
  – No differences in PI, NN morbidity

## Summary Glyburide vs. Insulin Studies: Part

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Subjects Gly / Ins</th>
<th>LGA%</th>
<th>Macro %</th>
<th>Require insulin%</th>
<th>NN hypoglycemia%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langer 2000</td>
<td>RCT</td>
<td>201 / 203</td>
<td>12 / 13</td>
<td>7 / 4</td>
<td>4%</td>
<td>9 / 6</td>
</tr>
<tr>
<td>Chmait 2004</td>
<td>Retrospective</td>
<td>69 Rx failure</td>
<td>No info</td>
<td>No info</td>
<td>19%</td>
<td>No info</td>
</tr>
<tr>
<td>Conway 2004</td>
<td>Retrospective</td>
<td>75 Rx failure</td>
<td>11% Gly 8.3% failed glyburide Rx</td>
<td>16%</td>
<td>12.7% gly 25% failed glyburide</td>
<td></td>
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<tr>
<td>Kremer 2004</td>
<td>Retrospective</td>
<td>73 Rx failure</td>
<td>No info</td>
<td>No info</td>
<td>19%</td>
<td>No info</td>
</tr>
<tr>
<td>Fines VL 2004</td>
<td>Case Control</td>
<td>51 / 32</td>
<td>No info</td>
<td>9.5 / 28</td>
<td>NA</td>
<td>No info</td>
</tr>
<tr>
<td>Mudhaliar 2007</td>
<td>RCT</td>
<td>10 / 13</td>
<td>No info</td>
<td>BW n.s.</td>
<td>No info</td>
<td>NN cap BS n.s.</td>
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# Summary Glyburide vs. Insulin Studies: Part 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Subjects Gly / Ins</th>
<th>LGA%</th>
<th>Macro%</th>
<th>Require insulin%</th>
<th>NN hypoglycemia%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobson 2005*</td>
<td>Retrospective Historical control</td>
<td>236 / 268</td>
<td>25 / 24</td>
<td>25 / 24</td>
<td>12%</td>
<td>31 / 27*</td>
</tr>
<tr>
<td>Bertini 2005</td>
<td>RCT: Gly/Insulin/Acarbose</td>
<td>24 / 27 / 19 acarb</td>
<td>25 / 3.7 / 10.5</td>
<td>16 / 0 / 0</td>
<td>21% glyb 42% acarb</td>
<td>33 / 3.7 / 5.3</td>
</tr>
<tr>
<td>Rochon 2006</td>
<td>Retro Rx failure</td>
<td>101</td>
<td>16% Gly 11% Fail</td>
<td>21%</td>
<td>12.5% Gly 9.5% Fail</td>
<td></td>
</tr>
<tr>
<td>Ramos 2007</td>
<td>Retro:Hx Control FSG&gt;105G CT&gt;200</td>
<td>44 / 78</td>
<td>Gly use: ↑OR 3.5 (1.1,11.4)</td>
<td>23/19</td>
<td>16%</td>
<td>34/ 14</td>
</tr>
</tbody>
</table>

*Preeclampsia: 12% vs 6% (p=0.02); PhotoRx: 9% vs 5% (p<0.05)
Summary Glyburide vs. Insulin Studies

• Failure of glyburide: ~15-20%; associated w/
  • ↑Severe hyperglycemia: ↑entry FPG or ↑GCT
  • More obese (↑BMI or ↑Prepregnancy weight)

• Ramos (2007) analyzed subset women with initial FPG 105-139 mg/dl or 1H GCT ≥200 mg/dl:
  – 16% failure with Glyburide
  – ↑Macrosomia OR 3.5 (95% CI 1.1, 11.4)
  – ↑Hypoglycemia: 34% vs. 14% (p=0.01)

• Bertini (2005); RCT with glyburide, insulin, acarbose
  – 21% glyburide failure, 42% acarbose failure
  – ↑LGA w/ glyburide (25%) of insulin (3.7%) & acarbose (10.5%)
  – ↑NN Hypoglycemia w/ glyburide (33%) cf insulin (3.7%)
MiG Study Design

Women with GDM: 20-33 weeks’, singleton pregnancy, clinic criteria for insulin

Recruitment into MiG (750)

Stratified by site/gestation

Metformin (375) Insulin (375)

Baseline data, fasting maternal blood, Fetal U/S
Pregnancy data and all capillary glucose measures
Delivery data, 6-8 week postpartum data
TOFU : the offspring follow up

# MiG Study Primary Outcome

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>Insulin</th>
<th>RR (95th CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Perinatal</td>
<td>32.0%</td>
<td>32.2%</td>
<td>1.0 (0.90-1.10)</td>
<td>0.95</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MiG Study Neonatal Outcome

No significant difference in birthweight, measures of adiposity or growth
Conclusion
• Treatment of women with GDM with metformin (alone or with supplemental insulin is not associated with increased perinatal morbidity.
• Women preferred metformin therapy to insulin therapy.
Glyburide Info

Glyburide (DiaBeta®):
• Initial: 2.5-5 mg/day, administered with breakfast or the first main meal of the day.
  – Increase 2.5 mg/day at weekly intervals based on the patient's blood glucose response
• Maintenance: 1.25-20 mg/day given as single or divided doses.
• Some patients (especially those receiving >10 mg/day) may have a more satisfactory response with twice-daily dosing. Maximum: 20 mg/day

Micronized tablets (Glynase® PresTab®):
• Initial: 1.5-3 mg/day, administered with breakfast or the first main meal of the day
  – Increase in increments of no more than 1.5 mg/day in weekly intervals based on the patient's blood glucose response.
• Maintenance: 0.75-12 mg/day given as a single dose or in divided doses. Some patients (especially those receiving >6 mg/day) may have a more satisfactory response with twice-daily dosing. Maximum: 12 mg/day

Time to peak, serum: Adults: 2-4 hours – risk of hypoglycemia > 2h after meal
• Excretion: Feces (50%) and urine (50%) as metabolites

Glyburide has been evaluated as an alternative for the treatment of GDM.
• Most pregnancy outcome information from pregnant women with GDM when therapy was started after the period of organogenesis (> 13 weeks).
• Severe hypoglycemia lasting 4-10 days has been noted in infants born to mothers taking a sulfonylurea at the time of delivery.
• Due to the potential for neonatal hypoglycemia, the manufacturer recommends that if glyburide is used during pregnancy, it should be discontinued at least 2 weeks before the expected delivery date.
• Insulin is the drug of choice for the control of type 1 or type 2 diabetes mellitus during pregnancy (ACOG, 2005; ADA, 2013; Kitzmiller, 2008; Metzger, 2007)
Metformin Info

Dosing
• Allow 1-2 weeks between dose titrations: Generally, clinically significant responses are not seen at doses <1500 mg daily;
• Start lower dose, gradually increase to minimize gastrointestinal symptoms (12-57%)

Immediate release tablet:
• Start: 500 mg twice daily or 850 mg once daily;
• Titrate in increments of 500 mg weekly or 850 mg every other week
• If a dose >2000 mg daily is required, it may be better tolerated in 3 divided doses.
  Maximum recommended dose (850 mg tid): 2550 mg daily.

Extended release tablet:
• Fortamet®: Initial: 500-1000 mg once daily; dosage may be increased by 500 mg weekly; maximum dose: 2500 mg once daily
• Glucophage® XR & Glumetza®: Initial: 500 mg once daily; dosage may be increased by 500 mg weekly; maximum dose: 2000 mg once daily

Contraindications
• Renal Impairment: Do not use if serum creatinine ≥ 1.4 mg/dL and in patients with abnormal Creatinine clearance.
• Hepatic Impairment Avoid metformin; can develop lactic acidosis during metformin therapy.
• Breast-Feeding: Low amounts of metformin (generally ≤1% of the weight-adjusted maternal dose) are excreted into breast milk.
• Breast milk concentrations of metformin stay relatively constant
• Growth and development were not affected in infants born to mothers with PCOS and who took metformin while breast-feeding (Glueck, 2006)
My Experience with Oral Agents

- Greatly preferred by patients: **Only in T2DM or GDM:**
  - No measuring, no injection, no refrigeration, no pain
- **1st line preference: Metformin**
  - 1st line oral agent in obese T2DM: protective for MI, improves IR, does not cause hypoglycemia
  - Pts often on metformin before pregnancy (T2, PCOS)
  - Dosing: better experience with higher dose
    - Week 1: 500 mg bid (w/ breakfast/dinner)
    - Week 2: 500 mg tid or 500 mg AM/1000 mg PM
    - Week 3: 1000 mg bid (can increase to 2550 mg total)
    - Not really very time dependent—but total dose seems more impt
    - Can use once day extended release forms
- **Glyburide:** can use as timed medicine—e.g. qhs for fasting hyperglycemia
  - more hypoglycemia, less effective in obese,
  - Dosing
    - Start at 2.5 mg to 5.0 mg per day—usually give bid with food
    - Higher doses (20 mg) have more newborn hypoglycemia
My Experience with Oral Agents: Metformin and Insulin

Studies in nonpregnant T2DM adults support use of metformin + insulin. Helpful in very insulin resistant patients, poor compliance. Patients often on metformin at conception.

Embryogenesis complete at 8 weeks of gestation (Use >12wk)

Protocol

– Start initially on insulin and titrate to normalize dose (insulin sensitivity improves after period poor control).
– If total insulin dose >0.9 U/kg in first tri, or >1.0 in 2nd tri: add metformin by
– Decreasing short-acting insulin, maintaining NPH
– Can titrate down short acting to only use NPH (possibly daytime NPH)
– See weekly to titrate and decrease insulin until stable.

• Also can add metformin to poorly controlled diabetics, or in those who have difficulty with insulin use

– If using metformin and past conception (>8 weeks) and under good control (A1c < 6.5%) many pts ask to continue. Recommend counsel wit MFM to possibly continue. Likely to need insulin later in pregnancy.
Summary: Effectiveness of Oral Anti-Diabetic Therapy to treat GDM

• Using oral agents still requires diabetes education, glucose monitoring, fetal growth and well being assessment.
  – Recommend using a protocol
  – Need more prospective studies—tend to treat the “mild” GDM with oral agents

• All future trials should consider pregnancy outcome and the long term risks:
  – To mother (weight gain, risk of developing diabetes)
  – To offspring (intrauterine programming, metabolism, obesity, diabetes, metabolic syndrome)

One size will not likely fit all—

GDM is a heterogenesis disorder
Modified therapy for gestational diabetes using high-risk and low-risk fetal abdominal circumference growth to select strict vs. relaxed glycemic targets
Medical Management of GDM
When to initiate intensive therapy?

**Strategy #1: Monitoring maternal glycemia:**
- To detect pre- and post-meal hyperglycemia
  - Primary treatment goal with greatest clinical experience
  - Demonstrated normalization of neonatal outcomes

⇒ **Goal:** Non-diabetic range glucose levels in all women with GDM
How tight is tight enough? or How low do you have to go to eliminate all “excess growth”?

- Study: 334 GDM c.f. 334 matched Controls
  - Insulin started if:
    - Fasting or Preprandial > 80 mg/dl
    - Bedtime > 90 mg/dl or Postprandial > 120 mg/dl
- Achieved Normal neonatal growth c.f. controls:
  - When mean glucose levels were 87-104 mg/dl
- To achieve “tight” control:
  - 68% treated with insulin therapy
  - Overall: AGA: 79%  SGA 11%  LGA 10%

*Normalized distribution of growth!*

Intensive Insulin Therapy, How tight is tight enough?

Mean Pregnancy Blood Glucose (mg/dl)

SMBG performed 7x's--fasting, premeal, postmeal, at bedtime


- Lowest levels of glucose, while reducing LGA rates, can result in excess SGA rates.
- Not all infants benefit from strict control
Assessing risk for diabetic fetopathy to guide medical therapy

**Maternal Glycemia + Fetal Measurements:**
- To identify fetuses at risk for diabetic fetopathy
  
  - Amniotic Fluid Insulin
  - Ultrasound AC (percentile for g.a.)

**Strategy:** Limit Intensive therapy for at-risk fetuses
Pathophysiology of Diabetic Effects on the Fetus

Mother  Fetus

↑ Glucose  ↑ $\rightarrow$ Glucose  ↑ $\rightarrow$ Insulin  $\rightarrow$  ↑ Growth

Self Blood Glucose Monitoring

Amniotic fluid insulin

Biochemical measure of Fetal Hyperinsulinism

Fetal AC

Clinical measure of Somatic Fetopathy
#1: Randomized Insulin vs. Diet Therapy in Mild GDM

Use of Ultrasound: AC > 75th Percentile

1. Can US identify a fetus at high-risk for macrosomia in early 3rd trimester?
2. Can insulin therapy reduce that risk?

Study

- 303 consecutive women screened 29-33 wk g.a.
- Eligible: AC ≥ 75th %: n=98 (32%)
- Randomized:
  - Diet & HGM (n=30)
  - Diet & HGM + insulin (n=29)

Buchanan, Diabetes Care 1994; 17:275-83
#1: Randomized Insulin vs. Diet Therapy in mild GDM: Guided by AC measurement

GDM on Diet Therapy

Summary: Intensive insulin therapy reduced

- Birth weight: (3647 vs. 3878 g)
- LGA rate (13% vs. 45%)
- Neonatal skin-fold thickness

Conclusion:
- US in early 3rd trimester identified infants at risk for LGA in pregnancies Complicated by mild GDM
- Intensive insulin therapy reduced GLA risk:

<table>
<thead>
<tr>
<th>Weight</th>
<th>3444</th>
<th>3878*</th>
<th>3647</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean</td>
<td>14%</td>
<td>18%</td>
<td>43%*</td>
</tr>
</tbody>
</table>

Buchanan, Diabetes Care 1994; 17:275-83
#2: Moderate Hyperglycemia in GDM: 
*Insulin Rx based on Fetal AC & Maternal Glycemia*

1. Can US identify a fetus at *low-macrosomic risk* in GDM with moderate hyperglycemia?
2. Can *relaxed glycemic goals* for starting insulin therapy be used if fetal growth continues to be low-risk?

**Study**: Eligible: FPG 105-120 mg/dl, US exam
- 98 randomized after diagnosis of GDM
- **Standard Therapy**: Insulin
- **Experimental Therapy**: Serial AC measurements and relaxed glycemic thresholds

Kjos SL, Diabetes Care Nov 2001
#2: Moderate Gestational Diabetes
(Initial FPG 105 - 120 mg/gl)

Diabetes Self-management Education
(diet, daily exercise, glucose self-monitoring, insulin injection)

RANDOMIZATION

<table>
<thead>
<tr>
<th>Standard Management</th>
<th>Experimental Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin therapy</td>
<td>Monthly ultrasound</td>
</tr>
<tr>
<td></td>
<td>FPG every 1-2 weeks</td>
</tr>
</tbody>
</table>

AC≥70th &/or
FPG >120mg/dl

AC<70th &
FPG <120mg/dl

Insulin therapy

Diet therapy

PERINATAL OUTCOME

Kjos, Diabetes Care 24:1904-10, 2001
#2: GDM with Moderate Hyperglycemia: Insulin vs. Diet Rx based on Fetal Growth and Maternal Glycemia

Initial FPG 105 - 120 mg/dl  
DM education, SBGM

Infants at low-risk for macrosomia

- Could be identified by AC <70th percentile
  
Protocol using fetal AC & maternal glycemia

- Avoided insulin therapy in 38% without raising morbidity

Similar BW* (3369 vs. 3271), LGA (8.3% vs. 6.3%)

- Newborn morbidity (25% vs. 25%)
- Despite higher fasting and mean CBG

- Intensive insulin therapy may raise risk of SGA in IDM with normal growth patterns

| GA entry GA | 26.9 | 26.9 | 26.9 |
| delivery    | 38.2 | 38.3 | Mean 38.3 |
| Birthweight | 3271 | 3482* | 3369 | 3180 |
| LGA infants | 6.3% | 13% | 8.3% | 0 |
| SGA infants*| 6.3% | 0   | 0     |

*included 1 stillbirth at 37 wk, any newborn morbidity in both group 25%

Kjos, Diabetes Care 24:1904-10, 2001
#3: RCT evaluating Fetal-Growth based Strategy in GDM in Caucasian Women: Background

• 2 RCTs examined targeted intensive insulin therapy based on fetal growth in addition to maternal glycemic
  • – Predominately Latina population
• 1st Trial: Women with normoglycemia + fetal macrosomia
  – LGA rate decreased from 45% to 13% ¹
• 2nd Trial: Women with hyperglycemia + normal growth
  – Insulin therapy could be avoided in 40% without adverse outcome²
• 3rd Trial: Combined both strategies from 2 prior trials
  • Standard management based solely on maternal glycemia
  • Combined management based on fetal growth + maternal glycemia
  • – based on serial 4 week ultrasound measurements of the fetal abdominal circumference

2. Buchanan, Diabetes Care 17:275-83, 2004
Gestational Diabetes
75 g oGTT: 90/165/145 mg/dl*

Diet instruction;
Self-glucose monitoring
(6 x’s pre & post-meal; 2 d/wk)

Inclusion: FCB <120;
2HPP<200 1st US before 20 weeks

Exclusion: Multiple gestation, smoking, hypertension

Block Randomize by GA

Standard: Insulin if
FCG>90 &/or 2HPP>120
2 values/2 profiles or 1 value/4 profiles

US-guided group: Insulin
if AC>75th percentile or
FCG>120 &/or 2HPP >200

N=100

US: Entry, every 4 weeks NST @ 32 weeks
Delivery @ 40/0-41/0

N=99

Schaefer-Graf, Diabetes Care 2004, 27:297
#3 RCT evaluating Fetal-Growth based Strategy in GDM in Caucasian Women

<table>
<thead>
<tr>
<th></th>
<th>Standard N =</th>
<th>Ultrasound N = 99</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA Del (wk)</td>
<td>39.3 (1.3)</td>
<td>39.0 (1.9)</td>
</tr>
<tr>
<td>Induction</td>
<td>23%</td>
<td>32.2%</td>
</tr>
<tr>
<td>Cesarean</td>
<td>19% 3371</td>
<td>18.2%</td>
</tr>
<tr>
<td>BW (g)</td>
<td>(500)</td>
<td>3306 (558)</td>
</tr>
<tr>
<td>SGA</td>
<td>13%</td>
<td>12.1%</td>
</tr>
<tr>
<td>LGA</td>
<td>10% 13.1</td>
<td>12.1%</td>
</tr>
<tr>
<td>Neonatal BMI (Kg/m²)</td>
<td>(1.2)</td>
<td>12.8</td>
</tr>
<tr>
<td>Sum Skinfolds (mm)</td>
<td>13.2 (3.2)</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Hypoglycemia (%)</td>
<td>16%</td>
<td>14.1 (3.4)</td>
</tr>
<tr>
<td>IV glucose</td>
<td>11% 9.1</td>
<td>9.1%</td>
</tr>
<tr>
<td>Cord blood insulin</td>
<td>(6.2)</td>
<td>8.8 (6.8)</td>
</tr>
<tr>
<td>NICU transfer</td>
<td>15%</td>
<td>14.1%</td>
</tr>
</tbody>
</table>

Conclusions
1. No difference in overall outcome between management based 1 degree on fetal growth criteria b. maternal glycemia
2. Fetal US-based management resulted in different therapy in 34% of subjects than if treated based on maternal glycemia
3. Fetal US-based therapy may optimize therapy:
   When insulin was withheld (raised glucose) based on normal growth- reduced SGA by approx. half (35.3% v. 16.6%)
   When insulin was given (lower glucose) based on normal growth- reduced LGA (21.9% v. 8.3%)

<table>
<thead>
<tr>
<th>Fetal AC ever</th>
<th>No insulin</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGA</td>
<td>21.9%</td>
<td>8.3%</td>
</tr>
<tr>
<td>SGA</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Lower glucose</td>
<td>15.6%</td>
<td>8.3%</td>
</tr>
<tr>
<td>NICU</td>
<td>12.5%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Cesarean</td>
<td>25%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LGA</th>
<th>26.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA</td>
<td>4.3%</td>
</tr>
<tr>
<td>Lower glucose</td>
<td>18.2%</td>
</tr>
<tr>
<td>NICU</td>
<td>24.2%</td>
</tr>
<tr>
<td>Cesarean</td>
<td>24.2%</td>
</tr>
</tbody>
</table>

#4: Flexible Treatment of GDM Modulated by US Evaluation of Intrauterine Growth

- RCT of 229 GDM in Italy
- Rx Glycemic goals:
  - Conventional (maternal glycemia)
    - Targets: 90 mg/dl pre-meal; 120 mg/dl post-meal
  - Modified (Measure AC every 2 weeks):
    - AC<75%: Relaxed targets
      - 100 mg/dl pre-meal; 140 mg/dl post-meal;
    - AC>75%: Lower targets
      - 80mg/dl pre-meal; 100 mg/dl post-meal
    - Add insulin when exceed targets

(Bonomo, Diab & Metab 2004;30:237)
#4: Flexible Treatment of GDM Modulated by US Evaluation of Intrauterine Growth: Results

**Insulin Use:** 17\%(C) vs 30\% (M)

<table>
<thead>
<tr>
<th>Group</th>
<th>Fasting/ PP glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>81.5 / 102 mg/dl</td>
</tr>
<tr>
<td>Modified</td>
<td></td>
</tr>
<tr>
<td>• Relaxed</td>
<td>87 / 121 mg/dl</td>
</tr>
<tr>
<td>Modified</td>
<td></td>
</tr>
<tr>
<td>• Strict</td>
<td>79 / 99 mg/dl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Modified</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGA</td>
<td>7.9%</td>
<td>17.9%*</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>3.3%</td>
<td>11.5%*</td>
</tr>
<tr>
<td>SGA</td>
<td>6%</td>
<td>10.3%*</td>
</tr>
</tbody>
</table>

_Bonomo, Diab & Metab 2004;3_
Intensive Therapy in GDM: \textit{Insulin vs. Diet Rx based on Fetal Growth \\& Maternal Glycemia}

4 RCT including 484 women
- Latina \\& Caucasian Fetal Abdominal

--- reliably identifies fetuses at low-risk and high-risk for somatic fetopathy

- Perform earlier after GDM DX
  - to maximize benefit of intensive therapy
  - High-risk: Lower glycemic targets, intensive therapy
  - Low-risk: Relaxed glycemic control
    - may ↓SGA growth by avoiding "too tight" control
## Combined LGA & SGA Rates from 4 RCTs:

<table>
<thead>
<tr>
<th></th>
<th>Conventional RX LGA Rate</th>
<th>Modified RX LGA Rate</th>
<th>P; OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-risk AC</strong></td>
<td>4/123 (3.3%)</td>
<td>6/165 (3.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>+<strong>High-risk AC</strong></td>
<td>38/129 (29.6%)</td>
<td>20/155 (12.9%)</td>
<td>0.003; 0.41 (0.22-0.78)</td>
</tr>
<tr>
<td><strong>Total LGA Rate</strong></td>
<td>42/252 (16.7%)</td>
<td>26/320 (8.1%)</td>
<td>0.002; 0.44 (0.25-0.77)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>SGA Rate</th>
<th>SGA Rate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-risk AC</strong></td>
<td>23/123 (18.7%)</td>
<td>19/165 (11.5%)</td>
<td>0.09; 0.57 (0.28-1.15)</td>
</tr>
<tr>
<td>+<strong>High-risk AC</strong></td>
<td>2/100 (2%)</td>
<td>1/125 (0.8%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Total SGA Rate</strong></td>
<td>25/223 (11.2%)</td>
<td>20/290 (6.9%)</td>
<td>0.09; 0.59 (0.30-1.13)</td>
</tr>
</tbody>
</table>
Gestational Diabetes

Modified Glycemic Therapy using
Low-risk and High-risk Fetal AC Growth

Fetal AC < 75\textsuperscript{th} percentile
Relaxed glycemic targets
Serial fetal AC measurement

Fetal AC ≥ 75\textsuperscript{th} percentile
Lower glycemic targets
Intensive therapy

Modified Therapy utilized fetal AC growth
Are these patients different?

**A:** 30 y/o G3 P2
- Ultrasound @ 32 weeks
- AC ~ 50-70th percentile
  - Low LGA risk
- Continue diet, Exercise, SBGM

**B:** 30 y/o G3 P2
- Ultrasound @ 25 weeks
- AC ≥ 75th percentile High LGA risk
  - Add Insulin with strict glucose targets
    - FSG <80
    - 2HPP <100-110

- Intensive Therapy

Relaxed glycemic targets
Is strict euglycemia necessary in GDM?

- Not in all pregnancies
- Maternal glucose is only part of the answer
  - Low-risk fetus: strict euglycemia may \( \uparrow \) SGA
    - normal growth, relaxed maternal glycemic goals
  - High-risk fetus, normal maternal glucose
    - Intensive insulin therapy, \( \downarrow \) risk of fetal hyperinsulinemia

- Need to identify which pregnancies at risk
- neonatal morbidity and long term diabetes risk
- Develop individualized therapeutic strategies based on evidence based medicine
Summary: Goals for treatment
Diabetic Pregnancy Care

• Most of GDM is can be treated with diet, exercise and lifestyle changes. These changes should be encouraged to become permanent for mother and family.
  • Crucial to identify who needs intensive medical care vs lifestyle changes (also intensive!)
  • All women, especially obese need preventive diet and exercise education from the start of pregnancy

• Differentiate between diabetic and non-diabetic overgrowth
  – Target intensive therapy to high-risk pregnancies

• Reduction in long-term maternal and offspring risk of diabetes
  – prospective cohort follow-up
  – interventions to decrease risk
Heterogeneity of the Diagnosis of GDM

Non-diabetic determinants of LGA growth
- BMI, ↑ weight gain
- Genetic, constitutional

Diabetic fetopathy
- β↑-cell defect, ↓ insulin
- ↑ importance of euglycemia
- ↑ benefit from insulin therapy
## Recommendations for Antepartum Fetal Surveillance in Pregnancies complicated by DM and (GDM)

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preconception</td>
<td>Glycemic Control, review of medications, evaluation of vascular dz</td>
</tr>
<tr>
<td>Initial booking</td>
<td>Glycemic Control, Baseline evaluation (renal, liver, retina, CV)</td>
</tr>
<tr>
<td>10-14/2 wk</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Tri Prenatal screen; US: CRL + nuchal translucency</td>
</tr>
<tr>
<td>16-20 wk</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Tri Prenatal screen</td>
</tr>
<tr>
<td>18-22 wk</td>
<td>US: Detailed anatomy; Fetal cardiac echo (if HbA&lt;sub&gt;1c&lt;/sub&gt; &gt; 7.0-8.5%)</td>
</tr>
<tr>
<td>26-28 wk</td>
<td>US: for growth assessment (or as soon as GDM diagnosed)</td>
</tr>
<tr>
<td>28 wk</td>
<td>Daily fetal kick count, Biophysical testing in women with vascular disease, growth restriction, poor control</td>
</tr>
<tr>
<td>32 wk</td>
<td>US for growth; Biophysical testing (NST/AFI, BPP or CST) (diet-controlled GDM can wait until “Term”)</td>
</tr>
<tr>
<td>37-38½ wk</td>
<td>US for EFW; develop delivery plan; Consider fetal lung maturation determination if early delivery (&lt;38½ wk) for poor control</td>
</tr>
<tr>
<td>38½ - 40 wk</td>
<td>Evaluation for induction vs. expectant management, fetal lung maturation not indicated in good control, reliable dating</td>
</tr>
</tbody>
</table>
# Postpartum Diabetes Testing after GDM

Summary and Recommendations of 5th IWC on GDM.  
Diabetes Care 30(suppl.2) S251

<table>
<thead>
<tr>
<th>Time</th>
<th>Test</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-delivery (1-3 d)</td>
<td>Fasting or random glucose</td>
<td>Detect persistent overt diabetes</td>
</tr>
<tr>
<td>Early postpartum (4-12 wk)</td>
<td>75 g, 2-h oGTT</td>
<td>Postpartum GTT classification</td>
</tr>
<tr>
<td>1 Year postpartum</td>
<td>75 g, 2-h oGTT</td>
<td>Assess glucose metabolism</td>
</tr>
<tr>
<td>Annually</td>
<td>FPG, HbA1c</td>
<td>Assess glucose metabolism</td>
</tr>
<tr>
<td>Tri-annually</td>
<td>75 g, 2-h oGTT</td>
<td>Assess glucose metabolism</td>
</tr>
<tr>
<td>Pre-pregnancy</td>
<td>75 g, 2-h oGTT</td>
<td>Classify glucose metabolism</td>
</tr>
</tbody>
</table>