Insulin vs. Oral Therapy for the Treatment of Gestational Diabetes

Maaya Srinivasa, PharmD
PGY-1 Community Pharmacy Practice Resident
Centro San Vicente Family Health Center
UTEP/UT Austin Cooperative Pharmacy Program
Preceptor: Margie E. Padilla, PharmD, CDE

February 3rd, 2012

Objectives
1. Describe diagnosis of gestational diabetes
2. Review current guidelines for management of gestational diabetes
3. Evaluate existing literature in regards to insulin versus oral therapy for the treatment of gestational diabetes
4. Discuss recommendations regarding pharmacotherapy for gestational diabetes

I. Introduction
A. Definitions
1. Gestational Diabetes Mellitus (GDM): “diabetes diagnosed during pregnancy that is not clearly overt diabetes”¹

B. Epidemiology²³⁴
1. National: reported rates range from 2% to 10%
2. 6% to 7% of pregnancies are complicated by diabetes; 85% of these cases are due to GDM
3. Local: 11.5% of women in Texas reported they had GDM (2009)

Figure 1: Pre-existing vs. Gestational Diabetes, Texas PRAMS 2004-2009 ⁴

C. Pathophysiology⁵
1. Insulin resistance increases as pregnancy progresses; insulin sensitivity falls by ~50% in late pregnancy
2. Increased insulin resistance due to increased maternal adiposity and effects of placental hormones
3. Hormones produced by the placenta: Human chorionic somatomammotropin (HCS), cortisol, estrogen, progesterone
4. As pregnancy progresses and placenta grows, production of hormones increases; thus leading to increased insulin-resistance
5. GDM occurs when insulin secretion is not sufficient to offset the decrease in insulin sensitivity

Figure 2: Pathophysiology of Gestational Diabetes

Adapted from: http://diabetesmellitus-treatments.com/wp-content/uploads/2011/05/imaq.png

² 1987
³ 1997
⁴ 2009
⁵ 2012

(From figure 1: Pre-existing Diabetes, 1.7% in 2004, 3.2% in 2005, etc.)

(From figure 2: Pathophysiology of Gestational Diabetes: Mother and Fetus diagram showing glucose transport and hormone production.)
II. Complications
A. Mother\textsuperscript{2,5}
1. Increased risk of hypertensive disorders
2. Increased risk of developing diabetes later in life
   a. Patients with a history of GDM are 33\% - 50\% more likely to develop GDM with subsequent pregnancies
   b. Immediately after pregnancy, 5\% - 10\% of women are found to have diabetes, usually Type 2
   c. There is a 35\% - 60\% chance of women with a history of GDM developing diabetes in the next 10 – 20 years

B. Baby\textsuperscript{2,5}
1. Macrosomia: birth weight > 4000 g (8 lbs. 13 oz.)
2. Hyperbilirubinemia: infant jaundice
3. Increase in operative delivery, shoulder dystocia, and birth trauma
4. Obesity and diabetes in children has been linked to those who are offspring of mothers with GDM

C. HAPO Study\textsuperscript{7,8}
1. 25,505 women in 9 countries were given 75-g OGTT test between 24-32 weeks gestation
2. Primary Outcomes: Birth weight > 90\textsuperscript{th} percentile, cesarean delivery, neonatal hypoglycemia, cord-blood serum C-peptide > 90\textsuperscript{th} percentile
3. Secondary outcomes: delivery before 37 weeks gestation, shoulder dystocia or birth injury, need for intensive care, hyperbilirubinemia, preeclampsia
4. Odds ratios calculated for 23,616 patients with blinded data for adverse pregnancy outcomes associated with an increase in fasting plasma glucose, 1-hour plasma glucose, and 2-hour plasma glucose
5. Showed that adverse outcomes were associated with hyperglycemia less severe than that found in diabetes
6. Results were used by IADPSG in determining diagnostic criteria for GDM

\textit{Figure 3: Association Between Maternal Glycemia and Primary and Secondary Perinatal Outcomes in the HAPO Study}\textsuperscript{7}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Outcome} & \textbf{Plasma Glucose Level} & \textbf{At 1 Hr} & \textbf{At 2 Hr} \\
& \textit{Fasting} & \textit{odds ratio (95\% CI)} & \textit{odds ratio (95\% CI)} \\
\hline
\textbf{Primary outcome} & & & \\
Birth weight >90th percentile & 1.38 (1.32–1.44) & 1.46 (1.39–1.53) & 1.38 (1.32–1.44) \\
Primary cesarean section\textsuperscript{†} & 1.11 (1.06–1.15) & 1.10 (1.06–1.15) & 1.08 (1.03–1.12) \\
Clinical neonatal hypoglycemia & 1.08 (0.98–1.19)\textsuperscript{‡} & 1.13 (1.03–1.26) & 1.10 (1.00–1.12) \\
Cord-blood serum C peptide >90th percentile & 1.55 (1.47–1.64) & 1.46 (1.38–1.54) & 1.37 (1.30–1.44) \\
\hline
\textbf{Secondary outcome} & & & \\
Premature delivery (before 37 wk) & 1.05 (0.99–1.11) & 1.18 (1.12–1.25) & 1.16 (1.10–1.23) \\
Shoulder dystocia or birth injury & 1.18 (1.04–1.33) & 1.23 (1.09–1.38) & 1.22 (1.09–1.37) \\
Intensive neonatal care & 0.99 (0.94–1.05) & 1.07 (1.02–1.13) & 1.09 (1.03–1.14) \\
Hyperbilirubinemia & 1.00 (0.95–1.05) & 1.11 (1.05–1.17) & 1.08 (1.02–1.13) \\
Preeclampsia & 1.21 (1.13–1.29) & 1.28 (1.20–1.37) & 1.28 (1.20–1.37) \\
\hline
\end{tabular}
\caption{Associations between maternal glycemia and primary and secondary perinatal outcomes in the HAPO Study.}
\end{table}

\textit{Source: HAPO Study, 2008.}
III. Risk Factors

A. Age
   1. Increased risk with increased age; < 25 years old considered low risk

B. Ethnicity
   1. Highest risk: Native Americans, Hispanic, Asian decent
   2. Moderate risk: African women
   3. Lowest risk: Non-Hispanic white women

C. Obesity

D. Family History

E. Past Obstetric History
   1. Women who have previously delivered a large infant
   2. Women with a history of PCOS or previous GDM

IV. Screening and Diagnosis

A. Screening
   1. ACOG: 50-g 1 hour glucose challenge with a threshold of 130 mg/dL or 140 mg/dL
   2. ADA: screen at 24-28 weeks using a 75-g OGTT; use diagnostic cut points listed below

B. Diagnosis
   1. ACOG
      a. Evidence supports 100-g, 3 hour OGTT; positive diagnosis made when two or more thresholds are met
### Figure 5: Two Diagnostic Criteria for GDM

<table>
<thead>
<tr>
<th>Status</th>
<th>Plasma or Serum Glucose Level</th>
<th>Plasma Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carpenter/Coustan Conversion</td>
<td>National Diabetes Data Group Conversion</td>
</tr>
<tr>
<td></td>
<td>mg/dL</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Fasting</td>
<td>95</td>
<td>5.3</td>
</tr>
<tr>
<td>One hour</td>
<td>180</td>
<td>10.0</td>
</tr>
<tr>
<td>Two hours</td>
<td>155</td>
<td>8.6</td>
</tr>
<tr>
<td>Three hours</td>
<td>140</td>
<td>7.8</td>
</tr>
</tbody>
</table>


2. ADA
   - Diagnosis made when fasting blood glucose ≥ 92 mg/dL, OR values after 75-g OGTT are 1 hour ≥ 180 mg/dL or 2 hour ≥ 153 mg/dL

3. IADPSG
   - At first prenatal visit, measure fasting blood glucose, A1c, or random blood glucose for all women or those that are considered high-risk
   - Overt diabetes: fasting blood glucose ≥ 126 mg/dL, A1c ≥ 6.5%, or random blood glucose ≥ 200 mg/dL
   - If not overt diabetes, but fasting blood glucose is ≥ 92 and < 126 mg/dL, diagnose as GDM
   - If not overt diabetes, and fasting blood glucose < 92 mg/dL, test for GDM at 24 – 28 weeks gestation
   - At 24 – 28 weeks, perform 75-g OGTT test; GDM diagnosed if any of the thresholds are met (Fasting blood glucose ≥ 92 mg/dL, 1 hour ≥ 180 mg/dL, 2 hour ≥ 153 mg/dL)

V. Current Recommendations for Treatment


1. Diet
   - Cites ADA recommendations to provide nutritional counseling with individualization based on height and weight
   - For non-obese women, 30 kcal/kg/d recommended
   - Current evidence does not provide recommendation for or against caloric restriction

2. Exercise
   - Randomized trials examining exercise in addition to, or substituted for insulin found no difference in birth of macrosomic infants
   - Randomized trial of diet versus exercise found improvement in fasting plasma glucose; another study found no difference in glucose control
   - “Regular exercise program has clear benefits for all women and may offer additional benefits for women with GDM.”

3. Pharmacologic Therapy
   - Insulin
     - No specific regimen or dose has been shown to be superior for GDM
     - No clear recommendation about how long glucose values should exceed targets before adding insulin. (One study suggests 2 weeks of diet management before adding insulin)
     - May be considered in patients treated with diet therapy when 1-hour post-prandial values > 130-140 mg/dL, 2-hour post-prandial values > 120 mg/dL, or FPG > 95 mg/dL
     - Insulin does not cross the placenta; all types have been used in GDM
4. Oral Agents
   a. Traditionally contraindicated because of risks of crossing the placenta and teratogenic effects
   b. When compared to insulin, glyburide showed similar glucose control and pregnancy outcomes
   c. Glyburide was not detected in infants based on cord blood analyses
   d. No oral agent has been shown to be safe and effective; further study is recommended

B. ADA: Standards of Medical Care in Diabetes (2011, 2012)\textsuperscript{1,10}
   1. Does not provide recommendations for treatment. “Additional well-designed clinical studies are needed to determine the optimal intensity of monitoring and treatment of women with GDM diagnosed by the new criteria.”

C. Perkins et al. Perspectives in Gestational Diabetes Mellitus: A Review of Screening, Diagnosis, and Treatment (2007)\textsuperscript{5}
   1. Diet
      a. Patients should receive nutrition counseling to count carbohydrates and meal planning
      b. Women of normal weight: 30-32 kcal/kg; carbohydrates should be 40% of calories
      c. Overweight women: 25 kcal/kg
   2. Exercise
   3. Pharmacologic Therapy
      a. Insulin
         i. Traditionally, longer acting insulin such as NPH have been used for GDM
         ii. More data is needed regarding newer insulin formulations
         iii. If fasting blood glucose > 90 mg/dL, NPH should be started at a dose of 0.2 units/kg QHS
         iv. If both fasting and preprandial blood glucose is still elevated, a rapid-acting insulin analogue can be added on at mealtimes
      b. Glyburide
         i. Dosing and titration schedule not specified
         ii. Langer et al. found that an average dose of 10 mg daily brought patients to goal
      c. Metformin
         i. Dosing and titration schedule not specified

VI. Pharmacologic Agents\textsuperscript{11,12}
A. Insulin
   1. Mechanism of Action: acts on membrane-bound receptors of target tissues to regulate metabolism of carbohydrate, protein, and fats; lowers blood glucose by enhancing glucose transport into adipose tissue and muscle by recruitment of glucose transporters (GLUT 4) from the interior of the cell to the plasma membrane
   2. Products Available: see Appendix A
   3. Dosing: no specific dosing guidelines recommended
   4. Adverse Effects: hypoglycemia, injection site reactions, weight gain

B. Metformin (Glucophage\textsuperscript{®}, Fortamet\textsuperscript{®}, Glumetza\textsuperscript{®})\textsuperscript{13}
   1. Mechanism of Action: decreases hepatic glucose production, decreases intestinal absorption of glucose, improves insulin sensitivity
   2. Dosing: initiate at 500 mg PO BID with food; increase to 1 g PO BID after 1 week if tolerated
   3. Adverse Effects: GI: diarrhea, N/V, flatulence
   4. Pregnancy Category: B
C. Glyburide (DiaBeta®, Glynase®)\textsuperscript{14}
   1. **Mechanism of Action**: stimulates insulin release, increases insulin sensitivity, reduces hepatic glucose output
   2. **Dosing**: initiate at 2.5 mg PO daily, can increase by 2.5 mg the next week, 5 mg/week thereafter; maximum dose: 20 mg/day
   3. **Adverse Effects**: hypoglycemia, epigastric fullness, nausea, heartburn
   4. **Pregnancy Category**: B/C (varies among manufacturer)

D. Other Agents
   1. See Appendix B

VII. Goals and Monitoring\textsuperscript{3,5}

A. Blood Glucose Goals
   1. Before meals < 95 mg/dL
   2. 1-hour postprandial < 140 mg/dL
   3. 2-hour postprandial < 120 mg/dL

B. Monitoring\textsuperscript{5}
   1. Patients should be taught proper SMBG technique
   2. SMBG should be performed 4 times daily (AM fasting and 2-hour postmeal)
   3. Grams of carbohydrate consumed should be documented as well
   4. Values should be brought into each prenatal visit and can be used to guide therapy adjustment
VIII. Literature Review

| Study Design | Randomized, open-label trial |
| Study Site(s) | New Zealand, Australian urban obstetric hospitals |
| Objective | To rule out an increase in neonatal complications in women being treated with metformin vs. insulin |
| Subjects | 751 women with gestational diabetes mellitus at 20 to 33 weeks of gestation |
| Inclusion Criteria | • Between 18 and 45 years of age, with a diagnosis of GDM  
• Met hospital’s criteria for starting insulin treatment, and after lifestyle intervention, had more than one FBG > 97.2 mg/dL or more than one 2-hour PPG > 120.6 mg/dL  
| Exclusion Criteria | • Previous diagnosis of DM, contraindication to metformin, a fetal anomaly, gestational HTN, preeclampsia, fetal growth restriction, and ruptured membrane |
| Methods | • Randomization occurred with a block size of four and was stratified according to gestational age  
• Goal was FBG < 99 mg/dL and PPG < 126 mg/dL  
• Metformin: started at 500 mg daily or BID with food and increased over 1-2 weeks to a max 2500 mg  
• If targets were not achieved, insulin was added; insulin was prescribed according to usual practice |
| Statistics | • Two-tailed tests used to rule out a significant difference in the incidence of composite neonatal complications in the metformin group  
• Differences between treatment groups were compared using chi-square or Fisher’s exact test for categorical variables and two-sample t-test or Mann–Whitney test for continuous variables  
• Analyses were performed with SAS software  
• Relative risks were reported with 95% confidence intervals |

<table>
<thead>
<tr>
<th>Results</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcomes</td>
<td>Metformin (N=363)</td>
<td>Insulin (N=370)</td>
<td>RR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Recurrent BG &lt; 46.8 mg/dL</td>
<td>55 (15.2%)</td>
<td>69 (18.6%)</td>
<td>0.81 (0.59-1.12)</td>
<td>0.21</td>
</tr>
<tr>
<td>Any BG &lt; 28.8 mg/dL</td>
<td>12 (3.3%)</td>
<td>30 (8.1%)</td>
<td>0.41 (0.21-0.78)</td>
<td>0.008</td>
</tr>
<tr>
<td>Respiratory Distress</td>
<td>12 (3.3%)</td>
<td>16 (4.3%)</td>
<td>0.76 (0.37-1.59)</td>
<td>0.47</td>
</tr>
<tr>
<td>Pre-term Birth</td>
<td>44 (12.1%)</td>
<td>28 (7.6%)</td>
<td>1.60 (1.02-2.52)</td>
<td>0.04</td>
</tr>
<tr>
<td>Neonatal Outcomes</td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Gestational age at birth-week</td>
<td>38.3 ± 1.4</td>
<td>38.5 ± 1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight-g</td>
<td>3372 ± 572</td>
<td>3413 ± 569</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Maternal Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycemic control from randomization until delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM Fasting</td>
<td>93.6 ± 10.8</td>
<td>91.8 ± 12.6</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>Postprandial</td>
<td>111.6 ± 10.8</td>
<td>115.2 ± 16.2</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Hgb A1c at week 36-37</td>
<td>5.6 ± 0.5</td>
<td>5.7 ± 0.6</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Results of 75-g OGTT at 6-8 week post partum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>91.8 ± 14.4</td>
<td>91.8 ± 16.2</td>
<td></td>
<td>0.34</td>
</tr>
</tbody>
</table>
| • Metformin group: 168 women (46.3%) required supplemental insulin  
• 76.6% of women in metformin group would choose it again, compared to 27.2% in insulin group (P<0.001) |

Authors’ Conclusions
Metformin, alone or with supplemental insulin, is an effective and safe treatment option for women with GDM. “Metformin is more acceptable to women with gestational diabetes mellitus than is insulin.”

Comments
Follow up data showed that at 2 years children exposed to metformin had larger measures of subcutaneous fat, but overall body fat was the same in the children of mothers who were treated with insulin.

Weaknesses:
- Some patients received combination of metformin and insulin  
- Study completed in Australia, not generalizable

Strengths:
+ Posthoc inferiority analysis supports conclusion that metformin is noninferior to insulin  
+ Followed standards of practice  
+ Safety measures were monitored

<table>
<thead>
<tr>
<th><strong>Study Design</strong></th>
<th>Randomized, open-label trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Site(s)</strong></td>
<td>Maternal health clinics in San Antonio, Texas</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To establish information on the efficacy of glyburide when used as treatment for gestational diabetes</td>
</tr>
</tbody>
</table>
| **Subjects** | - 404 women with a diagnosis of gestational diabetes  
- Women carrying 1 child with FPG on day of OGTT ≥ 95 mg/dl and < 140 mg/dl at 11-33 weeks gestation  
- If FPG < 95 mg/dl, they were initially treated with diet, but if later they had FPG ≥ 95 mg/dl or their PPG ≥ 120 mg/dl, they were enrolled in the study |
| **Methods** | - Women randomly assigned to receive glyburide or insulin from a computer-generated list  
- Detailed social, medical history was obtained at first visit  
- Women were provided with recommendations for 3 meals and 4 snacks daily (25 kcal/kg for obese women and 35 kcal/kg for non-obese women. 40-45% of calories came from carbohydrates)  
- Adherence to diet was assessed at weekly visits  
- Insulin: started at 0.7 units/kg TID. If necessary, dose was adjusted weekly  
- Glyburide: started at 2.5 mg QAM. If necessary, dose was increased 2.5 mg the following week, and then by 5 mg weekly. Max dose was 20 mg daily.  
- Patients were educated on glucose meter use and instructed to test 7 times daily. This began 1 week before initiation of therapy. Hgb A1c and serum C peptide were also measured at this time. Hgb A1c was repeated in 3rd trimester. |
| **Statistics** | - Intention to treat analysis  
- Chi-squared tests used to compare data between the treatment groups  
- Student’s t-tests were used to compare numerical data |
| **Results** | | **Glyburide Group (N=201)** | **Insulin Group (N=203)** | **P Value** |
| **Outcome** | | | | | |
| FBG (mg/dL) | | 98 ± 13 | 96 ± 16 | 0.17 |
| Postprandial | | 113 ± 22 | 112 ± 15 | 0.60 |
| Hgb A1c | | 5.5 ± 0.7 | 5.4 ± 0.6 | 0.12 |
| **Neonatal Outcomes** | | | | | |
| Large size for gestational age | | 24 (12%) | 26 (13%) | 0.76 |
| Birth weight – g | | 3256 ± 543 | 3194 ± 598 | 0.28 |
| Macrosomia | | 14 (7%) | 9 (4%) | 0.26 |
| Admission to neonatal ICU | | 12 (6%) | 14 (7%) | 0.68 |
| **Authors’ Conclusions** | In women with gestational diabetes, glycemic control and perinatal outcomes were essentially the same for glyburide and insulin treatment groups. |
| **Comments** | **Weaknesses:**  
- Used 50-g OGTT for diagnosis; different screening/diagnosis than current practice  
**Strengths:**  
+ One of the first studies to look at glyburide vs. insulin  
+ Patients were provided with nutrition counseling and assessed for adherence with diet  
+ Relatively large population studied |
C. Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. Obstet Gynecol 2010;115:55-9. 16

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Randomized controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Site(s)</td>
<td>University of New Mexico, Albuquerque, New Mexico</td>
</tr>
<tr>
<td>Objective</td>
<td>To compare the efficacy of glyburide and metformin for glycemic control in gestational diabetes</td>
</tr>
<tr>
<td>Subjects</td>
<td>149 pregnant women receiving prenatal care from the UNM Pregnancy Diabetic group</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>Women were screened with 50-g glucose load; those with 1-hour glucose level ≥ 130 mg/dL were given a 3-hour 100-g glucose load. GDM was diagnosed if 2 or more abnormal values were found. Those diagnosed were provided diet and exercise education. Women who failed to maintain FBG &lt; 105 mg/dL or 2-hour PPG &lt; 120 mg/dL were offered participation in the study</td>
</tr>
<tr>
<td>Exclusion Criteria</td>
<td>History of renal or hepatic disease, chronic HTN needing medication, substance misuse</td>
</tr>
</tbody>
</table>

**Methods**
- Women were randomized between 11 and 33 weeks and received either glyburide or metformin based on a computer-generated random list
- Women advised to eat a diet providing 30 kcal/kg for normal body weight and 25 kcal/kg for obese women. 40% of calories from carbohydrates, 20% from protein, and 30-40% from fats
- Exercise was encouraged, and walking 30 minutes per day was recommended
- Patients instructed on use of glucometer and told to check AM fasting and 2 hours after each meal
- Glyburide: started at 2.5 mg BID, increased as necessary to a max dose of 10 mg BID
- Metformin: started at 500 mg daily; increased as necessary to a max dose of 2 grams in divided doses
- Oral medications were discontinued if insulin was initiated

**Statistics**
- Powered to have 80% probability of detecting 10 mg/dL difference in blood glucose between the treatment groups with a standard deviation of 20 mg/dL and α of 0.05.
- Fisher exact test used for categorical data, Student t-test used for numerical data
- Intent to treat analysis was used

**Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Glyburide Group (N=74)</th>
<th>Metformin Group (N=75)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG (mg/dL)</td>
<td>90.9 ± 13 (88.5)</td>
<td>94.3 ± 15 (88.5)</td>
<td>0.23</td>
</tr>
<tr>
<td>2-hour breakfast</td>
<td>104 ± 17 (104.8)</td>
<td>99 ± 20 (97.7)</td>
<td>0.15</td>
</tr>
<tr>
<td>2-hour lunch</td>
<td>112 ± 22 (108.6)</td>
<td>107 ± 16 (105.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>2-hour dinner</td>
<td>119 ± 19 (117)</td>
<td>123 ± 17 (115)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

**Neonatal Outcomes**
- Est. Gestational Age: 38 ± 1 (38 ± 2) P = 0.49
- Birth weight — g: 3329.6 ± 334 (3103 ± 600) P = 0.02
- NICU Admission: 1 (4) P = 0.37
- Cesarean Delivery: 2 (11) P = 0.02

- Failure to meet glycemic goals, requiring insulin:
  - **Glyburide group: 12 (16.2%), Metformin group: 26 patients (34.7%) P=0.01**

**Authors’ Conclusions**
Metformin had a failure rate of achieving glycemic control 2.1 times higher than glyburide.

**Comments**
Results do not completely coincide with results from previous studies. This may be due to difference in patient population, i.e., ethnicity, BMI.

**Weaknesses:**
- Study had a very small sample size and was underpowered
- Screening/diagnosis did not follow IADPSG recommendations

**Strengths:**
- 1 of 2 trials to compare glyburide to metformin
- Studied high risk population

2012 Srinivasa 10
IX. Other Considerations for Selecting Treatment

A. Provider Preference
   1. Comfort level/experience with insulin versus oral agents
   2. Insulin use requires extensive training

B. Patient Preference
   1. Fears associated with insulin use and injection
   2. Side effect profile

C. Accessibility
   1. Glyburide and metformin are available at a low cost
   2. Oral medications do not require purchase of additional supplies, e.g., syringes

X. Follow-up¹
A. History of GDM increases risk of developing DM later in life
   1. Screen 6 weeks postpartum
   2. Women should be screened for diabetes at least every 3 years thereafter

XI. Summary/Conclusions (See Appendix C for Proposed Algorithm for Treating GDM)
A. Screening/Diagnosis
   1. Patients should be screened for GDM based on risk factors
   2. Screen for GDM and undiagnosed DM at first prenatal visit
   3. At 24-28 weeks gestation, 75-g OGTT should be performed to diagnose GDM

B. Treatment
   1. Avoid complications that can affect both mother and baby by using aggressive therapy
   2. Patient should be given a trial of lifestyle modifications (diet/exercise) for 2 weeks and instructed to SMBG at home
   3. If patient does not meet blood glucose targets, pharmacotherapy should be started
   4. More evidence supports insulin as first line, but glyburide has been used widely and can also be considered first line
   5. Metformin should be considered after insulin and glyburide

C. Monitoring and Follow-up
   1. Patient should continue to SMBG and follow up with provider frequently, so that adjustments to therapy can be made as necessary
   2. After delivery, patient should be screened for diabetes at 6 weeks and then every 3 years thereafter

D. Future Considerations
   1. Well-designed studies are needed to evaluate safety and efficacy of oral antidiabetic drugs, optimal insulin regimens, and to establish current treatment guidelines
## Appendix A: Available Insulin Products

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset (Hours)</th>
<th>Peak (Hours)</th>
<th>Duration (Hours)</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart (Novolog®)</td>
<td>15-30 min</td>
<td>1-2</td>
<td>3-5</td>
<td>B</td>
</tr>
<tr>
<td>Glulisine (Apidra®)</td>
<td>15-30 min</td>
<td>1-2</td>
<td>3-4</td>
<td>C</td>
</tr>
<tr>
<td>Lispro (Humalog®)</td>
<td>15-30 min</td>
<td>1-2</td>
<td>3-4</td>
<td>B</td>
</tr>
<tr>
<td><strong>Short-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular (Humulin®, Novolin®)</td>
<td>0.5-1.0</td>
<td>2-3</td>
<td>4-6</td>
<td>B</td>
</tr>
<tr>
<td><strong>Intermediate-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH (Humulin N®, Novolin N®)</td>
<td>2-4</td>
<td>4-8</td>
<td>8-12</td>
<td>B</td>
</tr>
<tr>
<td><strong>Long-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detemir (Levemir®)</td>
<td>2</td>
<td>---</td>
<td>14-24</td>
<td>C</td>
</tr>
<tr>
<td>Glargine (Lantus®)</td>
<td>4-5</td>
<td>---</td>
<td>22-24</td>
<td>C</td>
</tr>
</tbody>
</table>
### Appendix B: Noninsulin Antidiabetic Agents and Pregnancy Category

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biguanides</strong></td>
<td></td>
</tr>
<tr>
<td>Metformin (Glucophage®, Fortamet®, Glumetza®)</td>
<td>B</td>
</tr>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td></td>
</tr>
<tr>
<td>Glimepiride (Amaryl®)</td>
<td>C</td>
</tr>
<tr>
<td>Glipizide (Glucotrol®)</td>
<td>C</td>
</tr>
<tr>
<td>Glyburide (DiaBeta®, Glynase®)</td>
<td>B/C (varies among manufacturer)</td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone (Actos®)</td>
<td>C</td>
</tr>
<tr>
<td><strong>DPP-4 Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin (Januvia®)</td>
<td>B</td>
</tr>
<tr>
<td>Saxagliptin (Onglyza®)</td>
<td>B</td>
</tr>
<tr>
<td>Linagliptin (Tradjenta®)</td>
<td>B</td>
</tr>
<tr>
<td><strong>α-Glucosidase Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Acarbose (Precose®)</td>
<td>B</td>
</tr>
<tr>
<td>Miglitol (Glyset®)</td>
<td>B</td>
</tr>
<tr>
<td><strong>Short-acting insulin secretagogues</strong></td>
<td></td>
</tr>
<tr>
<td>Nateglinide (Starlix®)</td>
<td>C</td>
</tr>
<tr>
<td>Repaglinide (Prandin®)</td>
<td>C</td>
</tr>
<tr>
<td><strong>GLP-1 Agonists</strong></td>
<td></td>
</tr>
<tr>
<td>Exenatide (Byetta®)</td>
<td>C</td>
</tr>
<tr>
<td>Liraglutide (Victoza®)</td>
<td>C</td>
</tr>
<tr>
<td><strong>Amylinomimetic</strong></td>
<td></td>
</tr>
<tr>
<td>Pramlintide (Symlin®)</td>
<td>C</td>
</tr>
</tbody>
</table>
Appendix C: Proposed Algorithm for Management of GDM

### Risk Factors for GDM

**Low Risk**
- < 25 yo
- No prior hx poor obstetric outcomes
- Low-risk ethnic group
- Normal weight before or throughout pregnancy
- No hx glucose intolerance

**Medium Risk**
- Neither low or high risk

**High Risk**
- Obese
- DM in 1º relative
- Current glycosuria
- Hx GDM/glucose intolerance
- Prior delivery of macrosomic infant

---

+Use IADPSG thresholds to diagnose GDM

| FBG ≥ 92 mg/dL, 1 hour mmol ≥ 180 mg/dL, OR 2 hour ≥ 153 mg/dL |

---

*Adapted from: http://www.uspharmacist.com/CMSImagesContent/2009/9/GestationalFig1.gif*
Appendix D: Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG</td>
<td>American Congress of Obstetricians and Gynecologists</td>
</tr>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>FPG</td>
<td>Fasting plasma glucose</td>
</tr>
<tr>
<td>HAPO</td>
<td>Hyperglycemia Adverse Pregnancy Outcomes</td>
</tr>
<tr>
<td>HCS</td>
<td>Human chorionic somatomammotropin</td>
</tr>
<tr>
<td>IADPSG</td>
<td>International Association of Diabetes in Pregnancy Study Group</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
</tr>
<tr>
<td>PPG</td>
<td>Postprandial glucose</td>
</tr>
<tr>
<td>PRAMS</td>
<td>Pregnancy Risk Assessment Monitoring System</td>
</tr>
<tr>
<td>SMBG</td>
<td>Self-monitoring of blood glucose</td>
</tr>
</tbody>
</table>

Acknowledgments

- Christy Blanco, WHNP, DNP
- Debra Lopez, PharmD, CDE, BCACP
- Jeri Sias, PharmD, MPH
- Margie Padilla, PharmD, CDE
- Tricia Tabor, PharmD, BCPS
References