Gestational diabetes (GDM) is a common complication of pregnancy that increases maternal and infant risk. GDM is associated with infant macrosomia, shoulder dystocia and birth trauma, and stillbirth. Women with GDM are at increased risk for cesarean section and gestational hypertension/preeclampsia. Achieving maternal glycemic control is the key to optimizing infant and maternal outcomes. When diet and lifestyle changes fail to achieve maternal euglycemia, pharmacotherapy is used, with insulin considered the mainstay of GDM treatment. However, oral hypoglycemic agents such as glyburide and metformin have emerged as potential alternatives to insulin for GDM pharmacotherapy. Early studies of oral agents for GDM treatment demonstrated that glyburide and metformin were comparable to insulin with regard to infant birth weight. More recent data suggest that metformin may be preferred to glyburide. Long term maternal and infant outcome data, and large studies examining safety, are lacking.

References:

Gestational Diabetes: Is Insulin Necessary?

Kim A. Boggess MD
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Learning Objectives

- To understand rationale and choices for pharmacologic treatment of gestational diabetes (GDM)
- To identify knowledge gaps regarding use of oral hypoglycemic agents for GDM treatment

Gestational Diabetes

- 3-5% of pregnant women
- ‘Abnormal GTT which is diagnosed or first recognized during gestation’
- Screening for all pregnant women at 24-28 weeks
- 1 or 2 step method for diagnosis

GDM Diagnostic Criteria

- 1 step: 75 gm GTT
- 2-step: 50 gm GTT (>135 gm/dl) then 100 gm GTT

<table>
<thead>
<tr>
<th>Oral GTT</th>
<th>Intravenous GTT</th>
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<tbody>
<tr>
<td>Venous plasma (mg/dl)</td>
<td>Venous plasma (mmol/l)</td>
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<tr>
<td>Venous plasma (mg/dl)</td>
<td>Venous plasma (mmol/l)</td>
</tr>
<tr>
<td>8.0</td>
<td>10.0</td>
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<tr>
<td>Venous plasma (mg/dl)</td>
<td>Venous plasma (mmol/l)</td>
</tr>
<tr>
<td>5.5</td>
<td>8.0</td>
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<tr>
<td>Venous plasma (mg/dl)</td>
<td>Venous plasma (mmol/l)</td>
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<tr>
<td>7.0</td>
<td>9.9</td>
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</table>

GDM – What’s the big deal?

- Insulin resistance
- Diminished insulin secretory response
  - Usually normal fasting response
  - Postprandial hyperglycemia
  - Increased time to reach ‘pre-prandial’ glucose levels
GDM Risks

- Macrosomia, LGA
- Shoulder dystocia, birth injury
- Cesarean delivery
- Stillbirth
- Preeclampsia/GHTN

GDM Management

- Maintaining euglycemia is key to optimizing outcomes
- Surveillance with fasting and postprandial capillary blood glucose
- Diet and insulin mainstay of treatment

GDM Management

- Target capillary blood glucose level
  - Fasting 60 - 90 mg/dl
  - 1 hr PP ≤ 140 mg/dl
  - 2 hr PP ≤ 120 mg/dl
- 1 hr PP may be better predictor of glycemic control, infant birth weight
- Continuous glucose monitoring under study

GDM Management

- 50% successfully treated with:
  - Dietary modification
    - 2000 - 2200 cal/day
    - Complex, high fiber carbs
  - Exercise
    - 3 - 4x/weekly, 20 - 30 min

GDM Management

- Historical debate about utility of aggressive treatment
- Pharmacotherapy when diet and lifestyle changes fail to achieve euglycemia
- ACOG and ADA endorse use of oral agents

Effect of GDM Treatment

- ACHOIS trial
  - RCT of insulin vs. usual care
  - ~1000 women 24-34 weeks
- Serious complications
  - RR 0.33 (0.14-0.75)
- Secondary outcomes
  - Birth weight -145 g (-219, -70)
  - LGA 0.62 (0.47-0.81)
  - > 4000 g 0.47 (0.34-0.64)
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Crowther NEJM 2005

Effect of GDM Treatment

- MFMU GDM trial
  - RCT of insulin vs. usual care
  - ~950 women 24-31 weeks
- Composite outcome – no difference
  - RR 0.87 (0.72-1.07)
- Secondary outcomes
  - Birth weight 3302 vs. 3408 g
  - LGA 0.49 (0.32-0.76)
  - > 4000 g 0.41 (0.26-0.66)

Landon NEJM 2009

Effect of GDM Treatment

- Systematic review/meta-analysis of diet and insulin showed treatment reduced
  - Macrosomia and LGA
  - Shoulder dystocia
  - Preeclampsia/CHTN

Horvath BMJ 2010
What is Best Treatment?

- Insulin mainstay until 2000
- Rational for oral hypoglycemic agents
  - Convenience
  - Less discomfort
  - More acceptable
  - Fewer supplies, less cost

GDM Pharmacotherapy

- Oral agents
  - Glyburide-sulfonylurea
  - Metformin-biguanide
  - Others

Glyburide

- 2nd generation sulfonylurea
- Stimulates insulin secretion, decreases hepatic clearance
- Metabolized in liver
- Onset 1 hr, peak 3-4 hrs, ½ life 8-10 hrs
- Primary adverse effect: hypoglycemia

Glyburide vs. Insulin in GDM

- RCT 11-33 weeks n=404
- 1° outcome – glycemic control
  - Comparable outcomes
  - Lower incidence of maternal hypoglycemia
  - Good compliance, less costly

Glyburide in Pregnancy

- Begin 2.5 mg, max 20 mg; QD, BID, or TID
- Fetal level 70% of maternal level

Glyburide ‘Failure’ in GDM

<table>
<thead>
<tr>
<th>Author/year</th>
<th>N</th>
<th>Failure rate (%)</th>
<th>Macrosomia (%)</th>
<th>Predictors</th>
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<tr>
<td>Chmait 2004</td>
<td>69</td>
<td>19</td>
<td>17</td>
<td>Earlier dx Higher BG</td>
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<td>Conway 2004</td>
<td>75</td>
<td>16</td>
<td>11</td>
<td>Earlier tx Higher OGTT</td>
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<td>Kremer 2004</td>
<td>73</td>
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<td>95</td>
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<td>7</td>
<td>Earlier dx</td>
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<tr>
<td>Yogev 2011</td>
<td>124</td>
<td>25</td>
<td>8.5</td>
<td>Higher GWG GTT &gt; 200</td>
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</tbody>
</table>
Glyburide in GDM
• Marketscan database of >110,000 women
  – 2000-2011: glyburide use increased from 7 to 64%
  – Compared to insulin, glyburide higher risk for
    • NICU admission (RR 1.41; 95% CI 1.23-1.62)
    • RDS (RR 1.63; 95% CI, 1.23-2.15),
    • Hypoglycemia (RR 1.40; 95% CI, 1.00-1.95)
    • Birth injury (RR 1.35; 95% CI, 1.00-1.82)
    • LGA (RR 1.43; 95% CI, 1.16-1.76)

Camelo Castillo Obstet Gynecol 2014
Camelo Castillo JAMA Pediatr 2015

In Summary...
Metformin in GDM

- Biguanide, from French lilac
  - Reduces gluconeogenesis in the liver
  - Limits glucose absorption in the gut
  - Increases insulin receptor sensitivity
- Does not increase insulin production
  - Less likely than insulin to cause hypoglycemia
  - Favorable weight effects
- Dosing start at 500 mg BID increase to 1000 mg BID

Metformin in GDM

- GI upset (diarrhea, nausea, vomiting)
- Lactic acidosis ~ 1/10-30,000
- Crosses the placenta
- Fetal levels exceed maternal levels
- Small amount in breast milk
- Not a teratogen

Metformin in GDM

- RCT of metformin vs. insulin N=733
  - No difference in 1° composite outcome
    - Less neo hypoglycemia (3 vs 8%, p=.008)
    - LGA rate comparable (18 vs. 19%)
    - Less weight gain (0.4 vs. 2.0 kg, p<.001)
    - Metformin preferred by women

Rowan NEJM 2008

Metformin in GDM

- Systematic review/meta-analysis of metformin in GDM and T2DM
- 16 RCT, N=2165
- Metformin lower risk of
  - Neo hypoglycemia (RR 0.63, 0.45-0.87)
  - LGA rate (RR 0.56, 0.37-0.85)
- No long term data

Butalia Diabet Med 2017
Metformin vs. Insulin
• Systematic review/meta analysis
• 6 RCT, 1420 subjects
• No differences in primary outcomes
• Less maternal weight gain
  – (-1.49 kg, -2.66-0.31)
• ? Increase in PTB
  – (RR 1.56, 1.06-2.30)

Glyburide vs. Metformin
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Failure (%)</th>
<th>BW (g)</th>
<th>Neo hypogly (%)</th>
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<tr>
<td>Moore</td>
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<td>74</td>
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<td>Silva</td>
<td>2012</td>
<td>96</td>
<td>29, 21</td>
<td>3387±512, 3193±521</td>
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</table>

What Do We Know (or Think)?
• Treatment of GDM improves outcomes
• Choice of oral agent versus insulin
• Choice of glyburide versus metformin

“I’m making a decision! Stop confusing me with facts!”
Which Agent?

• Systematic review/meta-analysis
• 2509 subjects, 15 studies
• As monotherapy, glyburide inferior to both insulin and metformin
• Metformin (plus insulin when required) slightly better than insulin

Balsells BMJ 2015

Are There Other Options?

• Older sulfonylureas (tolbutamide, chlorpropamide) not used due to fetal hyperinsulinemia and neonatal hypoglycemia
• Acarbose (alpha glucosidase inhibitor) only 2 small studies
• Thiazolidinediones, meglitinides, DPP-4 inhibitors considered experimental
• Inositol

Summary

• Glycemic control reduces perinatal morbidity
• When diet and lifestyle fail pharmacologic therapy indicated
• Oral agents reasonable alternative to insulin; metformin preferred to glyburide
• Long term outcome data lacking