Pharmacotherapy of Gestational Diabetes Mellitus

National Maternal Nutrition Intense Course

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October 9, 2014

Objectives

Discuss epidemiology and current guidelines for screening and diagnosis of gestational diabetes (GDM)

Discuss current evidence-based literature for insulin therapies, and oral antihyperglycemics

Apply evidence based approaches to patient scenarios

Background

Epidemiology

- Approximately 7% of all pregnancies
- >200,000 cases annually

Definition

- Any degree of glucose intolerance with onset or initial recognition during pregnancy

Pathophysiology

- Pancreatic beta cell function
- Genetics of GDM
- Placenta

Complications

- Fetal
  - Macrosomia
  - Hypoglycemia
  - Hyperbilirubinemia
  - Hypocalcemia
  - Dystocia

HAPO Study

- Objective: Compare associations of maternal glucose and A1c with adverse outcomes
- 75 gm OGTT between 24-32 weeks gestation (close to 28 weeks as possible)
  - Fasting, 1 hour and 2 hours post glucose load and A1c
- Outcomes
  - Primary: Birth weight > 90th percentile, C-section, neonatal hypoglycemia, C-peptide > 90th percentile
  - Secondary: Pre-eclampsia, preterm delivery
- Results: OGTT is recommended test
Background

- Screening and Diagnosis
  - High risk women at initial prenatal visit
  - Standard diagnostic criteria
    - FPG ≥ 6.53
    - Two hour plasma glucose ≥ 200 mg/dL during OGTT
    - Patient with classic symptoms of hyperglycemia or hyperglycemic crisis, random plasma glucose ≥ 200 mg/dL
    - Receive diagnosis of overt diabetes (Type 2 DM)

Screening and Diagnosis
- “Two-Step” (NIH consensus)
  - 50 gm GTT (nonfasting) at 24–28 weeks gestation in women not previously diagnosed with overt diabetes (Step 1)
  - If plasma glucose level at 1 hour after load is ≥ 140 mg/dL, then proceed to 100 gm OGTT (Step 2) (administered when patient is fasting)

Screening and Diagnosis
- “One-Step” (IADPSG consensus)
  - 75 gm OGTT at 24–28 weeks gestation in women not previously diagnosed with overt diabetes
  - Diagnosis: when ≥ 2 values exceeded
    - Fasting ≥ 92 mg/dL (5.1 mmol/L)
    - 1 hour ≥ 180 mg/dL (10.0 mmol/L)
    - 2 hours ≥ 153 mg/dL (8.5 mmol/L)

Screening and Diagnosis
- “Two-Step” (NIH consensus)
  - Diagnosis: when ≥ 2 values are met or exceeded

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Background

Treatment

- Self Monitoring of Blood Glucose
  - GDM goal maternal capillary blood glucose values
    - Preprandial: ≥ 95 mg/dL (5.3 mmol/L) AND either
      - 1 hr post meal ≥ 140 mg/dL (7.8 mmol/L)
      - 2 hr post meal ≥ 120 mg/dL (6.7 mmol/L)

Screening and Diagnosis
- “Two-Step” (NIH consensus)
  - Diagnosis: when ≥ 2 values are met or exceeded

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Background

Treatment

- Self Monitoring of Blood Glucose
  - Pre-existing Type 1 or 2 diabetes optional glycemic goals
    - Premeal, bedtime and overnight: 60–99 mg/dL (3.3–5.4 mmol/L)
    - Peak postprandial: 100–129 mg/dL (5.5–7.1 mmol/L)
    - A1c < 6.5%
Physical activity
- 30 min/day
Medical Nutritional Therapy
- Culturally appropriate
- Individualized
- Adjusting amount and type of carbohydrate
- Overall healthy food choices, portion choices and cooking practices

Pharmacotherapy
- Insulin
- Metformin
- Glyburide

Megan, 34 year old Caucasian female, presents to GDM clinic 26 weeks gestation
- Second pregnancy with history of GDM controlled with glyburide
- 1 hour 50 gm glucose test: 202 mg/dL
- Fasting BG at visit 148 mg/dL
- Nocturia 5
- +4 glucose in urine
- 5’9” with weight of 195 lbs

Insulin
- Human Insulin
  - Least immunologic
  - Rapid acting analogs
  - Lispro and aspart
  - Clinical effectiveness
  - Minimal transfer across placenta
  - No evidence of teratogenesis
Metabolic and Immunologic Effects of Insulin Lispro in Gestational Diabetes

- No insulin lispro detected in umbilical cord
- No significant difference between anti-insulin antibodies at enrollment and delivery between insulin lispro and regular insulin
- No macrosomia, fetal anomaly or neonatal hypoglycemia


Maternal Metabolic Control and Perinatal Outcome in Women with Gestational Diabetes Treated with Regular or Lispro Insulin: Comparison with Non-Diabetic Women

- GDM higher pre-prandial blood glucose
- 1 hr post prandial glucose similar in insulin lispro and control groups
- No statistically significant difference in neonatal outcomes


Efficacy, Safety and Lack of Immunogenicity of Insulin Aspart Compared with Regular Human Insulin for Women with Gestational Diabetes

- Aspart group had significantly lower change from baseline values for average glucose and C-peptide.
- No major hypoglycemia
- No significant difference between anti-insulin antibodies from baseline in insulin aspart and regular insulin


Megan, 34 year old Caucasian female, presents to GDM clinic 26 weeks gestation

- Second pregnancy with history of GDM controlled with glyburide
- 1 hour 50 gm glucose test: 202 mg/dL
- Fasting BG at visit 148 mg/dL
- Nocturia 5
- 5'9" with weight of 195 lbs

Yolanda, 30 year old African American female with PCOS, presents to GDM clinic 16 weeks gestation

- First pregnancy
- 75 gm OGTT
- Fasting: 97 mg/dL
- 1 hour: 192 mg/dL
- 2 hour: 168 mg/dL
- Fasting BG at visit 93 mg/dL
- Nocturia 3
- No glucose in urine
- 5'6" with weight of 125 lbs
- Current medication: Metformin 850 mg 1 tablet BID
**Metformin**

- *MiG Trial*
  - 751 women randomly assigned
  - Baseline characteristics of the two treatment groups were similar.
  - All sites agreed to aim for capillary BG levels < 99 mg/dL for fasting and <166 mg/dL 2-hr PP.

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**Metformin**

- *MiG Trial*
  - Inclusion Criteria:
    - 18-45 y.o.
    - Diagnosis of GDM per ADIPS criteria
    - Pregnant ≤ single fetus between 20 and 33 weeks of gestation
    - Met hospital’s usual criteria for starting insulin
    - After lifestyle intervention, > 1 fasting capillary BG > 5.3 mmol/L or > 1 h PP BG > 120.6 mmol/L
  - Exclusion Criteria:
    - Pre-pregnancy diagnosis of DM
    - Contraindication to metformin
    - Fetal anomaly
    - Gestational HTN
    - Preclampsia
    - Fetal growth restriction
    - Ruptured membrane

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**Metformin**

- *MiG Trial*
  - Results (Primary Outcome):
    - No significant difference between groups in composite of neonatal complications (p = 0.95)
    - Severe hypoglycemia (BG < 2.2 mg/dL) was less common in metformin group (p = 0.008).
    - No statistically significant difference in number of hypoglycemic episodes at birth (p = 0.13).
    - Prematurity (<37 weeks of gestation) were more common in metformin group (p = 0.04).
    - Statistically insignificant but clinically small difference in the mean birth weight were more common in metformin group (p = 0.03).
    - 38.3 weeks (metformin) vs. 38.5 weeks (insulin)

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**Metformin**

- *MiG Trial*
  - Results (Secondary Outcomes):
    - No statistically significant difference (p values > 0.05) between groups in:
      - Anthropometric measures
      - Measurements of umbilical-cord serum insulin concentration
      - Maternal hypertensive complications
      - Maternal fasting glycemic control
      - Postpartum glucose tolerance
Metformin

- MiG Trial

  - Results (Secondary Outcomes)
    - Mean maternal postprandial glycemic control (from randomization until delivery) is higher in insulin group ($p = 0.003$).
    - No statistically significant difference in maternal postprandial glycemic control during the last 2 weeks before delivery ($p = 0.19$).
    - Authors conclude that this finding suggests that glucose targets are reached sooner in metformin group.
    - More women in metformin group stated that they would choose to receive their assigned treatment again (76.6% vs. 27.2% ($p < 0.001$)).

- Results (Misc.)
  - 46.3% of patients in metformin group received supplemental insulin.
  - No significant difference in serious adverse events
  - Women in metformin group had greater weight loss between time of enrollment and postpartum visit ($p = 0.006$).
  - Women in metformin group had less weight gain between time of enrollment and 36 weeks of gestation ($p = 0.001$).

- Study Conclusion
  - Metformin, alone or with supplemental insulin, is an effective and safe treatment option for women with GDM who meet the usual criteria for starting insulin.
  - Further follow up data is needed to establish long term safety.
  - Metformin is more acceptable to women with GDM than is insulin.

- Weaknesses
  - Open-label
  - Per study, blinding was not considered practical or ethical
  - Study demographics (limited ethnicities, outside the US, etc.)
  - Underpowered
  - Failed to assess treatment adherence
  - Used a superiority design to assess whether insulin was superior to metformin and have accepted rather than proved the null hypothesis

Metformin

- MiG Trial: Body Composition at 2 Years of Age

  - The Offspring Follow-Up to the MiG Trial
  - Patients from two of the sites in Auckland, New Zealand and one in Adelaide, Australia
  - Body composition measurements performed in 318 children (154 from metformin mothers, 164 from insulin mothers).
  - Goal
    - Compare body composition in children of women who participated in the MiG trial and, in particular, to compare measure of adiposity
    - Metformin crossed placenta so it is important to assess potential effects on growth in children

- Differences from MiG Trial:
  - Smaller proportion of Polynesian ethnicity ($p = 0.02$)
  - Shorter crown-rump length at birth ($p = 0.005$)
  - Smaller triceps skinfolds at birth ($p = 0.000$)
  - Smaller subscapular skinfolds at birth ($p = 0.07$)
  - Reported in results, yet $p$ value indicates trending towards statistically significant (not statistically significant)
Metformin

**MiG TOFU Trial**

• Results
  • No differences (p values > 0.05) between follow up groups
  • Significant difference between follow up groups in regards to
    • Higher maternal FFM in metformin group (p = 0.01)
    • Larger infant upper-arm circumference in metformin group (p = 0.002; adjusted p = 0.005*)
    • Larger infant subscapular skinfolds in metformin group (p = 0.02; adjusted p = 0.01*)
    • Larger infant biceps skinfolds in metformin group (p = 0.04; adjusted p = 0.02*)

**MiG TOFU Trial**

**Weaknesses**

• Setting in which assessment was conducted differ between sites.
• Per study
  • Low follow up rate of total MiG cohort
  • Follow-up group had fewer Polynesian children,
  • Follow-up group had shorter crown-rump length, and smaller subscapular and triceps skinfolds at birth.

**Metformin and Insulin in the Management of GDM**

• Prospective, randomized study:
• Goal
  • Compare glycemic control and maternal and neonatal outcomes in women with GDM treated with metformin vs. insulin
• University of Mississippi Medical Center (US)
• Study population: African American (49.2%), Native American (44.4%) and Caucasian (6.4%)
• Conducted over 32 months (2001 – 2004)
• 65 women randomly assigned (32 in metformin group, 33 in insulin group)
• Metformin group had a higher baseline weight (p = 0.01).

### References


Metformin

**MiG TOFU Trial**

• Study Conclusion
  • Findings suggest:
    • Maternal metformin treatment during pregnancy may lead to a more favorable pattern of fat distribution for exposed children.
    • Simple measures of central fat may not be adequate for determining potential effects of in utero exposure to metformin.
    • Further studies will be needed to confirm whether children exposed to metformin have less visceral fat.

Metformin

**MiG TOFU Trial**

• Inclusion criteria
  • Diagnosis of GDM per ADA guidelines
  • 24-30 weeks of gestation
  • No history of renal or hepatic disease, HTN or substance abuse

**Metformin**

• Differences from MiG Trial
  • Max daily dose of metformin (2000 mg vs. 2500mg)
  • Specifies insulin dose
  • BG goals
    • Tighter control
      • Fasting (60-90 mg/dL)
      • 2-hr PP (<130 mg/dL)
  • Lower average age of women
  • Assessed obstetric outcomes
**Metformin**

**Metformin and Insulin in the Management of GDM**

- **Results**
  - No statistically significant difference (p values > 0.05) between the groups in
    - Demographic characteristics (except weight)
    - Fasting and 2 hr PP BG levels
  - Obstetric outcomes
    - Gestational age, cesarean delivery, shoulder dystocia and postpartum hemorrhage
    - Neonatal outcomes
      - Birth weight, Apgar score in 5 minutes, NICU admission, hypoglycemia, respiratory distress syndrome and hyperbilirubinemia
    - No cases of maternal hypoglycemia reported
    - No patient failed metformin required supplemental insulin
    - 2 patients were controlled on initial dose.

**Additional Metformin vs. Insulin Studies**

- Metformin Treatment for Gestational Diabetes.
  - Significantly less maternal weight gain
  - Significant reduction in birth weight centile for gestational age
  - Significant reduction in the incidence of neonatal jaundice
  - 3.9% discontinue metformin because of gastrointestinal adverse effects and 10% of the metformin group required supplemental insulin

- Pregnancy Outcomes in Women with Gestational Diabetes Treated with Metformin or Insulin: A Case-Control Study
  - Women treated with insulin had significantly greater mean weight gain from enrollment to term (p = 0.001).
  - No difference between groups in gestational age, birth weight, mean cord artery pH or neonatal morbidity between the two groups
  - 31.9% of metformin group required supplemental insulin
  - These women were more obese (p = 0.001), had higher fasting BG levels in a oral GTT (p = 0.01) and needed medical treatment for GDM earlier (p = 0.001) than women who were normoglycemic with metformin alone.

**Additional Metformin vs. Insulin Studies**

- Metformin Should be Considered in the Treatment of Gestational Diabetes: A Prospective Randomized Study
  - No statistically significant difference in incidence of large for gestational age, mean birth weight, mean cord artery pH or neonatal morbidity between the two groups
  - 31.9% of metformin group required supplemental insulin
  - These women were more obese (p = 0.001), had higher fasting BG levels in a oral GTT (p = 0.01) and needed medical treatment for GDM earlier (p = 0.001) than women who were normoglycemic with metformin alone.

**Additional Metformin vs. Insulin Studies**

- Metformin—A Convenient Alternative to Insulin for Indian Women with Diabetes in Pregnancy
  - Glycemic control was better with metformin after 1 week of therapy and also throughout gestation (p = 0.007 – 0.05).
  - No major complications or perinatal death
  - No significant difference between groups in mean gestational age and birth weight
  - Significant increase in NICU admission and stay for babies born in the insulin group
  - Cost of treatment tenfold higher in insulin group

- Pregnancy Outcomes in Women with Gestational Diabetes Treated with Metformin or Insulin: A Case-Control Study
  - Women treated with insulin had significantly greater mean weight gain from enrollment to term (p = 0.001).
  - No difference between groups in gestational age, birth weight, mean cord artery pH or neonatal morbidity between the two groups
  - No perinatal loss occurred in either group.
  - Neonatal morbidity was improved in metformin group.
  - Prevalence, neonatal jaundice and NICU admissions were greater in insulin group (p = 0.001).
**Additional Metformin vs. Insulin Studies**

- Comparison of Metformin and Insulin in the Treatment of Gestational Diabetes: A Retrospective, Case-Control Study
- No significant difference between groups in maternal outcomes (pregnancy induced HTN, preeclampsia, etc.), mean birth weights, prevalence of macrosomia and gestational weeks at delivery
- Glucose values were slightly, but significantly higher, in insulin group ($p < 0.003$) for oral GTT.
- $82\%$ of metformin group required supplemental insulin
- Incidence of neonatal hypoglycemia was higher in insulin group ($p = 0.03$).
- No difference between group in other neonatal outcomes (small for gestational age, Apgar scores, umbilical artery pH, base excess, etc.)


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**Case 2**

- Yolanda, 28 year old African American American female with PCOS, presents to GDM clinic 14 weeks gestation.
  - First pregnancy
  - 75 gm OGTT:
    - Fasting: 95 mg/dL
    - 1 hour: 150 mg/dL
    - 2 hour: 165 mg/dL
  - Fasting BG at visit 97 mg/dL
  - Nocturia
  - $5'2''$ with weight of 130 lbs
  - Current medication
  - Metformin 500 mg 1 tablet BID

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**Glyburide**

- Maria, 23 year old Latino female, presents to GDM clinic 30 weeks gestation.
  - First pregnancy
  - Family History (dad) of Type 2 DM
  - 75 gm OGTT:
    - Fasting: 101 mg/dL
    - 1 hour: 186 mg/dL
    - 2 hour: 152 mg/dL
  - Fasting BG at visit 110 mg/dL
  - Nocturia
  - No glucose in urine
  - $5'3''$ with weight of 150 lbs
Glibenclamide (Glyburide) in the Treatment for GDM in a Compared Study to Insulin

- Prospective, randomized, open-label
- Goal
- Evaluate effectiveness of glyburide vs. insulin in treatment of GDM (maternal glycemic control), and observe impact of their use on the neonatal weight and blood glucose
- Darcy Vargas Maternity Hospital (Brazil)
- 10/01/2003 to 03/08/2005
- Measured BG using automated enzymatic method Airomi device 2000, the Winner


Glibenclamide (Glyburide) in the Treatment for GDM in a Compared Study to Insulin

- 32 women randomly assigned
- 4 were excluded during study period
- Birth in another hospital, birth at home, requested exclusion and presented with asthma (needs statins, corticotherapy and being exchanged therapy)
- 32 in glyburide group, 36 in insulin group
- Initial dose of glyburide
- 1mg, 2.5mg in previous study
- BG Goal:
- Fasting <50 mg/dL
- Postprandial <150 mg/dL


Glyburide

A Comparison of Glyburide and Insulin in Women with GDM

- Prospective, randomized
- Maternal health clinics in San Antonio, TX (US)
- 294 women randomly assigned (205 in the glyburide group, 203 in the insulin group)
- Age 18 - 40 years old
- Medicaid recipients
- Study population
  - Hispanic (83%) [mostly Mexican-American], non-Hispanic white (12%), Black (5%)
- Baseline characteristics of the two treatment groups were similar


Glyburide

A Comparison of Glyburide and Insulin in Women with GDM

- Primary outcome
  - Achievement of the desired level of glycemic control
  - Mean BG [90 – 125 mg/dL]
  - Fasting BG (60 – 90 mg/dL)
  - Preprandial BG (80-95 mg/dL)
  - Postprandial BG (120 mg/dL)

- Secondary outcomes
  - Maternal and neonatal complications

Glyburide

A Comparison of Glyburide and Insulin in Women with GDM

- Results
  - No significant difference (p values > 0.05) between the groups in
    - Achievement of BG goal
    - Perinatal outcomes
    - Neonatal outcomes
    - Birth weight, lung complications, admitted to NICU, hypoglycemia or fetal anomalies
    - Degree of glycemic control
    - Rate of cesarean section
    - Rate/Incidence of preeclampsia

Glyburide

A Comparison of Glyburide and Insulin in Women with GDM

- Results
  - Maternal hypoglycemia more common in insulin group (p = 0.03)
  - 4% conversion rate from glyburide to insulin
  - Glyburide was not detected in cord serum of any infant.

- Study Conclusion
  - Glyburide is an effective alternative to insulin in women with GDM.
### Results
- 18.75% conversion rate from glibenclamide to insulin
- No one required hospitalization for hypoglycemia.
- Weights of newborns were higher in glibenclamide group (p = 0.01).
- Incidence of macrosomia (weight > 4,000 g) was higher in glibenclamide group (p = 0.02).
- Neonatal hypoglycemia (< 40 mg/dl) was more common in glibenclamide group (p = 0.01).

### Prospective, Randomized
- **Inclusion Criteria**
  - Diagnosis of GDM based on WHO criteria of BG > 140 mg/dL following 2-hr 75mg oral GTT
  - Singleton pregnancy
  - 2-hr PP BG > 120 mg/dL after 2 weeks of MNT
- **Initial dose of glibenclamide**
  - 0.625mg (different from previous studies)
- **Initial dose of insulin**
  - 0.1mg/kg (< standard dose of 0.7mg/kg)

### Study Population: Asian Indian Women
- 26 women were randomly assigned
- 23 completed study
  - 10 in glibenclamide group and 13 in insulin group
- 3 women were lost to follow up

### Inclusion Criteria
- Diagnosis of GDM based on WHO criteria of BG > 140 mg/dL following 2-hr 75mg oral GTT
- Singleton pregnancy
- 2-hr PP BG > 120 mg/dL after 2 weeks of MNT

### Initial dose of glibenclamide
- 0.625mg (different from previous studies)

### Initial dose of insulin
- 0.1mg/kg (< standard dose of 0.7mg/kg)

### Strengths
- Prospective
- Randomized
- Described method of statistical analysis

### Weaknesses
- Did not describe method of randomization
- Single-center
- Failed to assess statistical power
- Failed to assess treatment adherence
Case 3

- Maria, 23 year old Latino female, presents to GDM clinic 30 weeks gestation.
  - First pregnancy
  - Family history (mom) of Type 2 DM
  - 75 gm OGTT
  - Fasting: 100 mg/dL
  - 1 hour: 178 mg/dL
  - 2 hour: 148 mg/dL
  - Fasting BG at visit 108 mg/dL
  - Nocturia 3
  - No glucose in urine
  - 5'4" with weight of 145 lbs