Disclosure to Participants

- Notice of Requirements For Successful Completion
  - Please refer to learning goals and objectives
  - Learners must attend the full activity and complete the evaluation in order to claim continuing education credit/hours
- Conflict of Interest (COI) and Financial Relationship Disclosures:
  - None to report
- Non-Endorsement of Products:
  - Accredited status does not imply endorsement by AADE, ANCC, ACPE or CDR of any commercial products displayed in conjunction with this educational activity
- Off-Label Use:
  - Participants will be notified by speakers to any product used for a purpose other than for which it was approved by the Food and Drug Administration.

Learning Objectives

- Discuss current guidelines for treatment of pregestational and gestational diabetes
- Discuss current evidence-based literature for insulin therapies, and oral antihyperglycemics during pregnancy
- Apply evidence based approaches to patient scenarios
Introduction

- Diabetes During Pregnancy
  - Gestational Diabetes Mellitus (GDM)
  - Preexisting Type 1 or Type 2 Diabetes Mellitus

Treatment Guidelines

- Glycemic Targets in Pregnancy
  - GDM
    - Preprandial ≤ 95 mg/dL and either
    - 1-hour postprandial ≤ 140 mg/dL
    - 2-hour postprandial ≤ 120 mg/dL

- Women with Preexisting Type 1 or 2 in Pregnancy
  - Premeal, bedtime, overnight 60 – 99 mg/dL
  - Peak postprandial 100 - 129 mg/dL
  - A1c < 6%

- Management of Diabetes in Pregnancy
  - GDM: start with lifestyle modifications then add medications as needed
  - Preexisting diabetes: baseline ophthalmology exam in first trimester and every trimester as needed
  - A1c target in pregnancy < 6%
  - Screen GDM for persistent diabetes at 6 – 12 weeks postpartum, and every 1-3 years

- Insulin Use During Pregnancy
  - Insulin is preferred
  - Insulin management during pregnancy is complex
Insulin

Pregnancy Category B
• Insulin Lispro (Humalog)
• Insulin Aspart (Novolog)
• Insulin Human Recombinant (Humulin R)
• Recombinant R origin (Novolin R)
• Insulin Lispro (Humalog 50/50 and 75/25)
• Human Insulin Isophane and Insulin Regular (Humulin and Novolin 70/30)

Pregnancy Category C
• Insulin Glulisine (Apidra)
• Insulin Glargine (Lantus)
• Insulin Aspart Protamine (Novolog 70/30)

HAPO Study2 (Hyperglycemia and Adverse Pregnancy Outcomes Study)
• Objective:
  – Compared associations of maternal glucose and A1c with adverse outcomes
  – Determine if A1c measurement can provide an alternative to oral glucose tolerance test in pregnant women
• Methods:
  – 15 field centers with >20,000 participants
  – Underwent 75g OGTT between 24-32 weeks’ gestation (as close to 28 weeks as possible)
  – Sample collections at fasting, 1h and 2h post glucose load and A1c

HAPO Study
• Primary Outcomes:
  – Birth weight > 90th percentile
  – Cesarean section
  – Neonatal hypoglycemia
  – C-peptide > 90th percentile

• Secondary Outcomes:
  – Pre-eclampsia
  – Preterm delivery
  – Birth injury
  – Hyperbilirubinemia
  – Placed into the NICU

HAPO Study
• Conclusion:
  – “Our results indicate strong, continuous associations of maternal glucose levels below those diagnostic of diabetes with increased birth weight and increased cord-blood serum C-peptide levels.”
  – Overall OGTT is the recommended test
  – A1c levels did not provide assistance with finding out overall risk compared to OGTT
  – A1c levels are associated with preterm birth

Patient Case
• Blanca, 40 year old Hispanic female with T2DM, presents to clinic 12 weeks gestation
  – Has been on metformin and glipizide therapy
  – A1c 8.5% and fasting BG at visit 160 mg/dL
  – Nocturia 4
  – +3 glucose in urine
  – 5’2” with weight of 150 lbs.
Historical Use of Human Insulin

- Timeline
  - 1921: porcine and bovine insulin
  - Recombinant technology: human insulin
- Type 1 and GDM
- Regular Human Insulin (Humulin and Novolin R and N) (NPH)
- Least immunologic

More Recent Use of Insulin Analogs

- Aspart and lispro
  - Clinical effectiveness
  - Minimal transfer across placenta
  - No evidence of teratogenesis
- Glargine
- Detemir

Aspart

- Type 1
  - Randomized controlled trial
    - 412 women at 63 sites in 18 countries
    - Fewer episodes of maternal nocturnal hypoglycemia and severe hypoglycemia
    - Treatment satisfaction higher in aspart group
    - No difference in fetal outcomes between groups

Lispro

- Type 1
  - Randomized controlled trial
    - Persson et al
      - Progression of retinopathy more frequently in human insulin group
      - Fetal outcomes similar in both groups
    - Loukovaara et al
      - No difference in rates of maternal hypoglycemia or progression of retinopathy

Aspart

- GDM
  - Randomized controlled trial
    - Pettitt et al
      - Significantly lower mean peak glucose at 60 min in aspart group
      - Similar incidence of maternal symptomatic hypoglycemia
    - Di Cianni et al
      - Birth weight and incidence of macrosomia higher in human insulin group

Lispro

- GDM
  - Randomized controlled trial
    - Mecacci et al
      - 1 hr PP blood glucose significantly higher in human insulin group
      - Neonatal outcomes similar
    - Jovanovic et al
      - More hypoglycemia before breakfast in human insulin group
      - No differences in rate of severe hypoglycemia or fetal outcomes
Glargine
• Type 1
  – Observational
    • Gallen et al13
      – Twenty two percent severe hypoglycemia
    • Leperecq et al14
      – Forty seven percent neonatal hypoglycemia
    • Di Cianni et al15
      – Two congenital abnormalities
  – No significant difference in maternal and fetal outcomes

Glargine
• Type 1 and 2, and GDM
  – Observational
    • Smith et al17
      – No difference in maternal or fetal outcomes
    • Egerman et al18
      – Higher incidence of should dystocia with NPH insulin
    • Fang et al19
      – Pre-existing diabetes with NPH insulin
        – More frequent hypoglycemia and large for gestational age babies
  – No significant difference in neonatal hypoglycemia

Glargine
• Type 1
  – Observational16
    • No significant difference in maternal or fetal outcomes

Detemir
• Type 1
  – Randomized controlled trial21-22
    • 470 women at 79 sites in 17 countries
    • No difference in HbA1c between groups
    • No difference in incidence of hypoglycemic events
    • Similar adverse event profiles
    • Total insulin doses similar

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• Type 1
  – Randomized controlled trial21-22
    • 470 women at 79 sites in 17 countries
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    • No difference in incidence of hypoglycemic events
    • Similar adverse event profiles
    • Total insulin doses similar
Patient Case

- Blanca, 40 year old Hispanic female with T2DM, presents to clinic 12 weeks gestation
  - Has been on metformin and glipizide therapy
  - A1c 8.5% and fasting BG at visit 160 mg/dL
  - Nocturia 4
  - +3 glucose in urine
  - 5’2” with weight of 150 lbs.

Oral Anti-Hyperglycemic Agents

- Metformin
  - 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 99 mg/dL
  - Nocturia 3
  - No glucose in urine
  - 5’6” with weight of 125 lbs.
  - Current medication
    - Metformin 850 mg 1 tablet BID

Metformin

- Metformin versus Insulin for Treatment of GDM (MiG Trial)
  - Goal: Rule out 33% increase in a composite of perinatal complications in infants of women treated with metformin as compared to insulin
  - Routine clinical setting
  - Study population: primarily European/white (45 - 48%)

- 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 <126 mg/dL 2 hr PEP.

Metformin Inclusion Criteria
- 18-45 y.o.
- Diagnosis of GDM per ADIPS criteria
- Pregnant w/ single fetus between 20 and 33 weeks of gestation
- Met hospital’s usual criteria for starting insulin
- After dietary intervention, > 1 fasting capillary BG > 97.2 mg/dL or > 1 2-hr PP BG > 120.6 mg/dL

Exclusion Criteria
- Pre-pregnancy diagnosis of DM
- Contraindication to metformin
- Fetal anomaly
- Gestational HTN
- Preeclampsia
- Fetal growth restriction
- Ruptured membrane

Primary Outcome
- Composite of neonatal complications
- Components:
  - Hypoglycemia
  - Respiratory distress
  - Need for phototherapy
  - Birth trauma
  - 5-minute Apgar score below 7
  - Premature birth

Secondary Outcomes
- Neonatal anthropometric measurements
- Maternal glycemic control
- Maternal hypertensive complications
- Postpartum glucose tolerance
- Acceptability of treatment

Results (Primary Outcome):
- No significant difference between groups in composite of neonatal complications (p = 0.95)
- Severe hypoglycemia (BG < 28.8 mg/dL) was less common in metformin group (p = 0.008).
- No statistically significant difference in number of hypoglycemic episodes at birth (p = 0.21).
- Preterm births (<37 weeks of gestation) were more common in metformin group (p = 0.04).
- Statistically insignificant but clinically small difference in the mean group gestational age at delivery between two groups (p = 0.02)
  - 38.3 weeks (metformin) vs. 38.5 weeks (insulin)

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

More women in metformin group stated that they would choose to receive their assigned treatment again [76.6% vs. 27.2% (p < 0.001)].
Metformin

• MiG Trial

• 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.

**MiG TOFU 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 measures of adiposity.

**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 = 0.0002)
- Smaller subscapular skinfolds at birth (p = 0.07)

**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*)

**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

Strengths
- Multi-center
- Describes method of data collection and statistical analysis
- Sufficiently powered
- Uniform training of study personnel
- Per study:
  - Offspring were well matched
- Valid comparison between treatment groups
  - Body composition was measured by several methods.
  - Difference found were consistent with a biologically plausible effect of metformin.

Weaknesses
- Setting in which assessment was conducted differed 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.

MiG TOFU Trial
- Prospective, randomized
- 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 (6.3%)
- Conducted over 32 months (2001 – 2004)
- 63 women randomly assigned (32 in metformin group, 31 in insulin group).
  - Metformin group had a higher baseline weight (p = 0.01).

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

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, hyperbilirubinemia
- No cases of maternal hypoglycemia reported.
- No patient failed metformin required supplemental insulin.
- 27 patients were controlled on initial dose.

Metformin and Insulin in the Management of GDM
- 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 (<120 mg/dL)
  - Lower average age of women
  - Assessed obstetric outcomes

- 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, hyperbilirubinemia
- No cases of maternal hypoglycemia reported.
- No patient failed metformin required supplemental insulin.
- 27 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


- 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 = 0.000), had higher fasting BG levels in a oral GTT (p = 0.001) and needed medical treatment for GDM earlier (p = 0.002) than women who were normoglycemic with metformin alone.


- 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 – 0.03).
  - 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 tertiled 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 = 0.003).
  - No difference between groups in gestational HTN (p = 0.5), pre-eclampsia (p = 0.6), induction of labor (p = 0.57), incidence of macrosomia (p = 0.7) or rate of Cesarean section (p = 0.57).
  - No perinatal loss occurred in either group.
  - Neonatal morbidity was improved in metformin group.
    - Pretermly, neonatal jaundice and NICU admissions were greater in insulin group (p < 0.01).


- 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 one GTT.
  - 18% 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.)


- Randomized Trial of Metformin vs. Insulin in the Management of Gestational Diabetes
  - Metformin group lower mean glucose levels, less weight gain and lower frequency of neonatal hypoglycemia
  - Supplemental insulin required by 26% of metformin group

**Metformin + Pregnancy + Polycystic Ovary Syndrome (PCOS)**

- The efficacy of metformin in pregnant women with polycystic ovary syndrome: A meta-analysis of clinical trials
  - Objective: Whether the use of metformin during pregnancy in women with PCOS could reduce pregnancy-related complications
  - Methods: Meta-analysis
  - Conclusions: Metformin therapy throughout pregnancy decreased the Odds Ratio of early pregnancy loss, gestational diabetes, pre-eclampsia, and pre-term delivery in pregnant PCOS women with no serious detrimental side effects

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**Metformin**

- 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 99 mg/dL
  - Nocturia 3
  - No glucose in urine
  - 5’6” with weight of 125 lbs.
  - Current medication
    - Metformin 850 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: 102 mg/dL
    - 1 hour: 180 mg/dL
    - 2 hour: 152 mg/dL
  - Fasting BG at visit 110 mg/dL
  - Nocturia 2
  - No glucose in urine
  - 5’5” with weight of 150 lbs.
Glyburide
A Comparison of Glyburide and Insulin in Women with GDM

- **Primary outcome**
  - Achievement of the desired level of glycemic control
    - Mean BG (90 – 105 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

**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

**Study Conclusion**
- Glyburide is an effective alternative to insulin in women with GDM.
Glyburide

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

• Results
  – Significant difference between groups in average peripheral capillary BG of newborns just at the 6th hour (p = 0.03)
  – No newborn suffered perinatal death
  – No obstetrical trauma
  – No statistically significant difference (p values > 0.05) between groups in
    • Average maternal fasting and postprandial BG
    • Incidence of newborns large at gestational age

Glyburide

A Prospective Study Comparing Insulin and Glibenclamide in GDM in Asian Indian Women

• 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)

• Results
  – No statistically significant difference between two groups in terms of mean age, BMI and gestational weeks (p > 0.05)
  – No statistically significant difference between groups in the mean birth weight, cord blood insulin level, blood glucose of neonates and glycemic control
  – None of patients developed hypoglycemia during study period

• Study Conclusion
  – Glibenclamide and insulin were equally effective in achieving good glycemic control and no difference in perinatal outcomes

Glyburide

A Prospective Study Comparing Insulin and Glibenclamide in GDM in Asian Indian Women

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

Glyburide

• New Evidence!!!
  – Association of Adverse Pregnancy Outcomes with Glyburide vs. Insulin in Women with Gestational Diabetes
  • March 30, 2015 – JAMA Pediatrics
Glyburide

Objective: To estimate the risk of adverse maternal and neonatal outcomes in women with GDM treated with glyburide compared with insulin.

Methods:
- Retrospective cohort study from insurance claims database from January 1, 2000 to December 31, 2011.
- Women with GDM between 15-45 (excluded: Type 1 and 2 diabetics).
- Treatment with glyburide or insulin during pregnancy within 150 days before delivery.

Results:
- Women treated with glyburide were at increased risk for:
  - Neonatal intensive care unit admission, respiratory distress, hypoglycemia, birth injury, and large for gestational age.
- Women treated with glyburide were not at increased risk for:
  - Obstetric trauma, preterm birth, or jaundice.

Conclusion:
Newborns from privately insured mothers treated with glyburide were more likely to experience adverse outcomes.
Further investigation needs to be done.

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: 105 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.

Other Anti-Hyperglycemic Agents
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones (TZDs)</td>
<td>C</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>B</td>
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<tr>
<td>GLP-1 Receptor Agonists</td>
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References

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