DIAGNOSIS AND MANAGEMENT OF DIABETES DURING PREGNANCY

DONALD R COUSTAN, MD
15 OCTOBER 2011
FACULTY DISCLOSURE

I have no conflict of interest relevant to the content of this presentation.

Donald R. Coustan, MD
LEARNING OBJECTIVES

At the conclusion of this presentation, the participant will be able to...

- Describe the new IADPSG recommendations for diagnosing gestational diabetes
- Describe the rationale for using oral agents and insulin in the treatment of diabetes in pregnancy.
- Formulate a plan for self monitoring of blood glucose for managing diabetes in pregnancy.
International Association of Diabetes in Pregnancy Study Groups (IADPSG): Recommendations on Diagnosis & Classification of Hyperglycemia in Pregnancy

Diabetes Care 33(3):676-682, 2010
International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy

International Association of Diabetes and Pregnancy Study Groups Consensus Panel
Corresponding author: Boyd E. Metzger, bem@northwestern.edu.

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) was formed in 1998 as an umbrella organization to facilitate collaboration between the various regional and national groups that have a primary or significant focus on diabetes and pregnancy. The principal objectives of IADPSG are to foster an international approach to enhancing the quality of care, facilitating research, and advancing education in the field of diabetes in pregnancy.

During 11-12 June 2008, the IADPSG sponsored an International Workshop-Conference on Gestational Diabetes Diagnosis and Classification in Pasadena, California. More than 225 conference attendees from 40
NEW RECOMMENDATIONS FOR DIAGNOSIS OF GESTATIONAL DIABETES.

WHAT IS THE PROBLEM?
HAPO STUDY
WHAT ARE THE RECOMMENDATIONS?
WHAT ARE THE IMPLICATIONS?
WHAT’ S THE PROBLEM?

- THIRD INTERNATIONAL WORKSHOP/CONFERENCE ON GDM (1991):
  - LACK OF INTERNATIONAL AGREEMENT ON TESTING: 50, 75 AND 100 GRAM CHALLENGES; IMPOSSIBLE TO COMPARE PREVALENCES
  - 75 GRAM CHALLENGE WILL EVENTUALLY BECOME UNIVERSALLY EMPLOYED

WHAT’S THE PROBLEM?

- THIRD INTERNATIONAL WORKSHOP/CONFERENCE ON GDM (1991):
  - O’SULLIVAN CRITERIA BASED ON 2 STD DEVS IN POPULATION OF PREGNANT WOMEN (2 CATEGORIES)
  - WHO CRITERIA BASED ON VALUES FOR NONPREGNANT ADULTS (3 CATEGORIES)
  - NONE ARE BASED ON PREGNANCY OUTCOME

DEVELOPING NEW DIAGNOSTIC THRESHOLDS

HYPERGLYCEMIA AND ADVERSE PREGNANCY OUTCOMES

THE HAPO STUDY
HAPO Study Rationale

- Overt diabetes clearly increases the risk of adverse pregnancy outcome.
- What level of glucose intolerance during pregnancy, short of diabetes, is associated with the risk of adverse outcome?
HAPO Protocol

75 gm OGTT 24-32 weeks
Fasting, 1 & 2 hr venous plasma

25,505

Unblinded at Field Center if
OGTT Fasting > 105 &/or 2 hr > 200
or random glucose > 160 ~ 36 wks
or < 45 mg/dl

746 (2.9%) unblinded for treatment

1,443 (5.7%) incomplete

23,316
Standard care for Field Center
Cord glucose & C-peptide
Neonatal glucose: 1-2 hrs of age
Anthropometrics by 72 hrs:
Length, head circ, weight, skin folds x3
# Blinded Participants At Each Field Center

- Bellflower - 1903
- Chicago - 738
- Providence - 746
- Cleveland - 784
- Toronto - 1988
- Belfast - 1634
- Manchester - 2250
- Barbados - 2034

- Petah-Tiqva - 1798
- Beersheba - 1610
- Bangkok - 2426
- Brisbane - 1437
- Newcastle - 653
- Singapore - 1695
- Hong Kong - 1620
HAPO Study Outcomes

◆ Primary outcomes
  - Newborn birth weight > 90th percentile
  - Delivery by primary Cesarean section
  - Clinical neonatal hypoglycemia
  - Neonatal hyperinsulinemia (cord serum C-peptide > 90th percentile)

◆ Secondary outcomes
  - Newborn % body fat > 90th percentile
  - Preterm delivery (< 37 weeks gestation)
  - Preeclampsia
  - Shoulder dystocia/birth injury
  - NICU admit or hyperbilirubinemia
Associations: Glucose & 1° Outcomes

- **Birth Weight > 90th Percentile**
- **Primary C-Section**
- **Clinical Hypoglycemia**
- **Cord C-Peptide >90th Percentile**
Data Analysis: Confounders

- Analyses included adjustments for:
  - Field center
  - Variables at OGTT: age, BMI, MAP, height
  - Gender
  - Parity
  - Smoking & alcohol consumption
  - Hospitalization prior to delivery
  - 1st degree family history of diabetes
  - Gestational age at OGTT
Maternal glucose – perinatal outcome associations are independent of maternal age, BMI and family history of diabetes.

Associations did not differ among centers.

The results are applicable to all centers.

Results can be used globally to develop “outcome based” criteria for classifying glucose metabolism in pregnancy.
From Associations to Diagnostic Criteria

◆ Appoint a committee of “experts” to resolve issues
  ○ A task for the International Association of Diabetes in Pregnancy Study Groups (IADPSG)
From Associations to Diagnostic Criteria: What Is the IADPSG?

◆ **Affiliated Organizations**
  - DPSG of EASD
  - JAPD (Japan)
  - ADIPS (Australasia)
  - West Coast USA DPSG
  - DPSI (India)
  - Canadian Special Interest Group for Diabetes and Pregnancy

◆ **Associated Groups**
  - European Association of Perinatal Medicine; Society of Maternal Fetal Medicine (USA); ADA Pregnancy Council; SAREDIA
IADPSG Workshop Conference

◆ Days 1 & 2
  □ Presentations of data & discussion
    ❖ 220 delegates from ~40 countries
  □ Post conference regional caucuses

◆ Day 3
  □ Consensus development session
    ❖ ~50 delegates: representing IADPSG groups or organizations including ACOG, ADA, EASD, WHO, IDF, CDC, or “at large”
    ❖ Steering Committee/“Writing Group” appointed
IADPSG Consensus Panel
Activities After Pasadena

- **Steering Committee/Writing Group**
  - Conference calls
    - Review Additional data & analyses
    - Reports to parent “Consensus Panel”
  - Prepare draft of *Diabetes Care* manuscript

- **Consensus Panel**
  - Reports from the Writing Group
    - Review additional data analyses & provide feedback
    - Questionnaire X 3
  - Meeting #2: Sorrento, Italy, March 25, 2009
From Associations to Diagnostic Criteria

◆ IADPSG Consensus Panel considerations

☐ Choose outcomes for defining thresholds
  ❖ Relative importance of study outcomes
  ❖ Some outcomes are related
  ❖ Thresholds based on OR for LGA, fat, &/or hyperinsulinemic babies

☐ How much risk is too much?
  ❖ Statistical evidence & outcome frequencies considered in combination

☐ Importance of specific glucose measures:
  ❖ FPG, 1-hr & 2-hr OGTT

☐ Results of RCTs of treating “mild GDM”
Fasting Plasma Glucose and Outcomes

- Birthweight
- % Body fat
- Cord C-peptide

Concentration (mg/dl)

Frequency (%) >90th Percentile

<75 75-79 80-84 85-89 90-94 95-99 ≥100
1-Hour Plasma Glucose and Outcomes
2-Hour Plasma Glucose and Outcomes

![Graph showing frequency (% >90th Percentile) vs. concentration (mg/dl) for Birthweight, % Body fat, and Cord C-peptide.]
From Associations to Diagnostic Criteria

◆ IADPSG Consensus Panel considerations
  Choose outcomes for defining thresholds
  Relative importance of study outcomes
  Some outcomes are related
  Thresholds based on OR for LGA, fat, &/or hyperinsulinemic babies

☐ How much risk is too much?
  ◆ Statistical evidence & outcome frequencies considered in combination

☐ Importance of specific glucose measures:
  ◆ FPG, 1-hr & 2-hr OGTT

☐ Results of RCTs of treating “mild GDM”
Plasma Glucose Concentrations at Specified OR

<table>
<thead>
<tr>
<th>Glucose</th>
<th>mg/dl*</th>
<th>1.5</th>
<th>1.75</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>90</td>
<td>92</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>1-Hr PG</td>
<td>167</td>
<td>180</td>
<td>191</td>
<td></td>
</tr>
<tr>
<td>2-Hr PG</td>
<td>142</td>
<td>153</td>
<td>162</td>
<td></td>
</tr>
</tbody>
</table>

*Mean of threshold values for †: birthweight, cord serum C-peptide, % body fat >90th percentile
### Adjusted Odds Ratios: Maternal Glycemia as Continuous Variable & Primary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fasting</th>
<th>1-Hour</th>
<th>2-Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight &gt;90%</td>
<td>1.68 (1.56-1.80)*</td>
<td>1.75 (1.63-1.87)</td>
<td>1.77 (1.63-1.92)</td>
</tr>
<tr>
<td>Primary C-section</td>
<td>1.18 (1.11-1.26)</td>
<td>1.16 (1.09-1.23)</td>
<td>1.14 (1.06-1.22)</td>
</tr>
<tr>
<td>Clinical neo hypo</td>
<td>1.24¶ (1.05-1.46)</td>
<td>1.21 (1.03-1.40)</td>
<td>1.18 (0.99-1.41)</td>
</tr>
<tr>
<td>Cord serum C-peptide &gt;90%</td>
<td>2.02 (1.85-2.21)</td>
<td>1.76 (1.62-1.91)</td>
<td>1.75 (1.59-1.92)</td>
</tr>
</tbody>
</table>

*Odds ratios for glucose level ↑ (F=10.8; 1-hr=46.8; 2-hr=41.4 mg/dl), the difference between the cohort mean and the threshold

¶Quadratic (nonlinear association)
## Adjusted Odds Ratios: Maternal Glycemia as Continuous Variable & Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fasting</th>
<th>1-Hour</th>
<th>2-Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-term delivery (&lt;37 wks)</td>
<td>1.16 (1.05-1.28)*</td>
<td>1.29 (1.18-1.40)</td>
<td>1.31 (1.19-1.44)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1.40 (1.26-1.56)</td>
<td>1.45 (1.31-1.60)</td>
<td>1.57 (1.40-1.77)</td>
</tr>
<tr>
<td>Shoulder dystocia/birth injury</td>
<td>1.30 (1.07-1.58)</td>
<td>1.36 (1.14-1.62)</td>
<td>1.43 (1.16-1.76)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1.00 (0.92-1.09)</td>
<td>1.17 (1.08-1.26)</td>
<td>1.14 (1.04-1.25)</td>
</tr>
<tr>
<td>Intensive neonatal care</td>
<td>0.99 (0.91-1.08)</td>
<td>1.11 (1.03-1.20)</td>
<td>1.16 (1.05-1.27)</td>
</tr>
</tbody>
</table>

*Odds ratios for glucose level (F=10.8; 1-hr=46.8; 2-hr=41.4 mg/dl), the difference between the cohort mean and the threshold*
From Associations to Diagnostic Criteria

◆ IADPSG Consensus Panel considerations

Choose outcomes for defining thresholds
  Relative importance of study outcomes
  Some outcomes are related
  Thresholds based on OR for LGA, fat, &/or hyperinsulinemic babies

How much risk is too much?
  Statistical evidence & outcome frequencies considered in combination

- Importance of specific glucose measures:
  - FPG, 1-hr & 2-hr OGTT

- Results of RCTs of treating “mild GDM”
Correlations Among OGTT Glucose Measurements

<table>
<thead>
<tr>
<th>OGTT Measures</th>
<th>FPG</th>
<th>1 - hour</th>
<th>2 - hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>------</td>
<td>0.392*</td>
<td>0.317*</td>
</tr>
<tr>
<td>1 - hour</td>
<td>0.377</td>
<td>------</td>
<td>0.626*</td>
</tr>
<tr>
<td>2 - hour</td>
<td>0.300</td>
<td>0.642</td>
<td>------</td>
</tr>
</tbody>
</table>

*Indicates partial correlations adjusted for field center
From Associations to Diagnostic Criteria for GDM

- IADPSG recommendations
  - Threshold values for GDM as follows*
    - Fasting: $\geq 92$ mg/dl (5.1 mmol)
    - 1-hr post 75 gm: $\geq 180$ mg/dl (10.0 mmol)
    - 2-hr post 75 gm: $\geq 153$ mg/dl (8.5 mmol)

*One or more abnormal value = GDM
From Associations to Diagnostic Criteria

◆ **IADPSG Consensus Panel considerations**

Choose outcomes for defining thresholds
- Relative importance of study outcomes
- Some outcomes are related
- Thresholds based on OR for LGA, fat, &/or hyperinsulinemic babies

How much risk is too much?
- Statistical evidence & outcome frequencies considered in combination

Importance of specific glucose measures:
- FPG, 1-hr & 2-hr OGTT

Results of RCTs of treating “mild GDM”
ACHOIS: Participants

- 16-30 weeks gestation
- 18 centers (16 Australia, 2 U.K.)
- GDM risk factor OR abnormal glucose screen
  - THEN
- BLINDED 2-hour, 75-g OGTT
  - Fasting <140 mg/dL (7.8 mmol/L)
  - 2-hour 140-198 mg/dL (7.8-11.0 mmol/L)
- Excluded prior GDM
- Enrolled prior to OGTT, randomized after abnormal result (intervention, “routine care”)
## Treatment of GDM Reduces Adverse Outcome*

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>ROUTINE CARE (N = 510)</th>
<th>INTERVENTION (N = 490)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight</td>
<td>3482 ± 660</td>
<td>3335 ± 551</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>LGA</td>
<td>22%</td>
<td>13%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>21%</td>
<td>10%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>18%</td>
<td>12%</td>
<td>0.02</td>
</tr>
<tr>
<td>SGA</td>
<td>7%</td>
<td>7%</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Crowther CA, et al. NEJM 352:2477-86, 2005*
# Treatment of GDM Reduces Adverse Outcome*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NICHD RCT</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not treated</td>
<td>Treated</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>BW &gt;90th percentile</td>
<td>14.5</td>
<td>7.1</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>C-peptide &gt;95th percentile</td>
<td>22.8</td>
<td>17.7</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>NICU admission</td>
<td>11.6</td>
<td>9.0</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Shoulder Dystocia</td>
<td>4.0</td>
<td>1.5</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>5.5</td>
<td>2.5</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

*Landon MB et al. NEJM 361:1339-48, 2009*
## Frequencies of Outcomes: Comparison of RCT & HAPO

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NICHD RCT</th>
<th>FPG &lt;95 (1-hr ≥180; 2-hr ≥155)</th>
<th>FPG &lt;95 (1-hr &lt;180; 2-hr &lt;155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW &gt;90th percentile</td>
<td>14.5</td>
<td>14.0</td>
<td>9.0</td>
</tr>
<tr>
<td>C-peptide &gt;95th percentile</td>
<td>22.8</td>
<td>18.2 (≥90th %)</td>
<td>7.5 (≥90th %)</td>
</tr>
<tr>
<td>NICU admission</td>
<td>11.6</td>
<td>11.4</td>
<td>7.9</td>
</tr>
<tr>
<td>Shoulder Dystocia</td>
<td>4.0</td>
<td>1.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>5.5</td>
<td>8.3</td>
<td>4.9</td>
</tr>
</tbody>
</table>
Other Considerations

- **Measurement of glucose**
  - Frequencies and OR for outcomes increase substantially over relatively small changes in glucose
  - Measure venous plasma or serum using an enzymatic method with high accuracy/precision
  - Capillary sampling should not be used for diagnosis
Other Considerations

✦ Easy-to-remember thresholds

- Not feasible

- Arbitrarily choosing e.g. FPG ≥ 90 mg/dl (5.0 mmol/l) would substantially affect the proportion of women meeting a diagnostic threshold

- Both SI and standard units are widely used and the numbers are not equally easy or difficult to remember for both units of measure
### Frequencies of Outcomes: Glucose Values < or ≥ Threshold

<table>
<thead>
<tr>
<th>Outcome</th>
<th>% All Values &lt; Threshold</th>
<th>% Any ≥ 92/180/153</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight &gt;90th percentile</td>
<td>8.3</td>
<td>16.2</td>
</tr>
<tr>
<td>Cord C-peptide &gt;90th percentile</td>
<td>6.7</td>
<td>17.5</td>
</tr>
<tr>
<td>% Body fat &gt;90th percentile</td>
<td>8.5</td>
<td>16.6</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>4.5</td>
<td>9.1</td>
</tr>
<tr>
<td>Preterm birth (&lt;37 weeks)</td>
<td>6.4</td>
<td>9.4</td>
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<td>1.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Primary Cesarean section</td>
<td>16.8</td>
<td>24.4</td>
</tr>
</tbody>
</table>
WHY NOT USE HAPO RESULTS AS BASIS FOR CHANGE?

IT DOESN’T SEEM REASONABLE TO RECOMMEND THRESHOLDS THAT IDENTIFY 16+% OF THE POPULATION
WHY ARE WE SURPRISED THAT THE PROPOSED THRESHOLDS IDENTIFY SUCH A HIGH PROPORTION OF THE POPULATION?

GDM HAS BEEN INCREASING IN US
US RATES OF GDM, 1989-2004

Getahun et al AJOG 2008;525e1-e5
US NATIONAL DELIVERY DISCHARGES, 1994-2004

Albrecht et al, Diabetes Care 2010:768
UNDIAGNOSED AND DIAGNOSED DIABETES, USA

Adults >20 years
10.2% and rising
2003-2006
11.3% in 2010

PREDIABETES

79 MILLION PEOPLE IN 2010
25% OF POPULATION

American Diabetes Association:
DIABETES (DIAGNOSED AND UNDIAGNOSED) AND PREDIABETES

- 11.3% DIABETES + 25% PREDIABETES = APPROXIMATELY 36% OF ADULT US POPULATION
- SO IS 17-18% GDM RATE OUTRAGEOUSLY HIGH?
WHY USE HAPO AS BASIS FOR CHANGE?

- 75 GRAM CHALLENGE
- MULTI-NATIONAL DATA; MULTINATIONAL CONSENSUS
- BASED ON PREGNANCY OUTCOMES
- SINGLE ABNORMAL VALUE
- TREATMENT DEMONSTRATED TO BE EFFICACIOUS AT SIMILAR GLUCOSE LEVELS
IADPSG RECOMMENDATION: DIAGNOSIS OF OVERT DIABETES DURING PREGNANCY

GRAVIDAS WITH PRE-EXISTING DIABETES ARE AT RISK FOR:
- INCREASED CONGENITAL MALFORMATIONS
- RETINOPATHY, NEPHROPATHY, ETC.
- NEED FOR RAPID NORMALIZATION

THEY WILL NEED ASSURANCE OF FOLLOWUP POST PARTUM
IADPSG RECOMMENDATION: DIAGNOSIS OF OVERT DIABETES DURING PREGNANCY

ASSIGN DIAGNOSIS OF PRE-EXISTING DIABETES IF, AT FIRST VISIT, ANY OF THE FOLLOWING:

- FASTING PLASMA GLUCOSE ≥ 126 MG/DL
- HEMOGLOBIN A1C ≥ 6.5%
- RANDOM PLASMA GLUCOSE ≥ 200 MG/DL
  (CONFIRMED BY FPG OR HBA1C)

IADPSG RECOMMENDATION. DIABETES CARE 2010;33:676
AMERICAN DIABETES ASSOCIATION

ENDORSED
IADPSG RECOMMENDATIONS
IN JANUARY 2011

ACOG

HAS NOT ENDORSED IADPSG RECOMMENDATIONS

ACOG: COMMITTEE OPINION: SCREENING AND DIAGNOSIS OF GDM.
COMM OPIN #504; SEPT 2011
Frequency of Testing

Daily self glucose monitoring
Glycemia Goals

- Fasting Plasma Glucose <95 mg/dl
- 1 hr PP Glucose <130-140 mg/dl
- 2 hr PP Glucose <120 mg/dl
Preprandial vs postprandial glucose monitoring

- Randomized trial
  - Preprandial (N=33)
  - 1-hr postprandial (N=33)
- GDMs requiring insulin by 30 wks
- Preprandial goal 60-105 mg/dl
- Postprandial goal <140 mg/dl

DeVeciana et al, NEJM, 1995
Preprandial vs postprandial glucose monitoring

- Postprandial group had:
  - Greater fall in glycohemoglobin
  - Fewer LGAs (12% vs 42%)
  - Fewer C/S for CPD (12% vs 36%)
  - Less neonatal hypoglycemia (3% vs 21%)

DeVeciana et al, NEJM, 1995
Metformin and Glyburide in the Treatment of GDM
When diet and exercise are not enough....

- Human insulin – *the gold standard*
  - Requires intensive patient education
  - Must be given as injection
  - Risk for maternal hypoglycemia
When diet and exercise are not enough....glyburide?

- **Glyburide** – similar success to insulin in GDM
  - Insulin secretogogue = risk for maternal hypoglycemia
  - Originally did not appear to cross the placenta
  - Recent study from NICHD Fetal Pharmacology Network found fetal levels 70% of maternal levels
  - Risk and/or benefit to fetus unknown

When diet and exercise are not enough.... metformin?

- Improves insulin sensitivity
- Does not cause hypoglycemia
- Crosses the placenta
DOES METFORMIN CROSS THE PLACENTA?

METFORMIN DETECTABLE IN SERUM OF 13 MOTHERS AT DELIVERY

ALL 13 CORD BLOODS CONTAINED METFORMIN

MEDIAN CONCENTRATIONS (μmol/L)

<table>
<thead>
<tr>
<th></th>
<th>MATERNAL</th>
<th>CORD VEIN</th>
<th>CORD ARTERY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.50</td>
<td>2.81</td>
<td>3.16</td>
</tr>
</tbody>
</table>

FETAL METFORMIN LEVELS EXCEED MATERNAL LEVELS!

VANKY ET AL: FERTIL STERIL 83:1575, 2005
When MNT and exercise are not enough.... metformin?

- Fetal levels twice maternal levels
- Series’ have not demonstrated harm, but numbers are small and reports generally non-randomized
Metformin versus Insulin for the Treatment of Gestational Diabetes

- The “MiG” Trial:
  - “M”etformin
  - “i”n
  - “G”estational Diabetes

MiG Hypotheses

- Perinatal outcomes are similar in women with GDM treated with metformin or insulin
- Women with GDM favor treatment with metformin over treatment with insulin
MiG: Participants

- 20-33 weeks gestation
- 10 centers (Australia and NZ)
- GDM requiring insulin after diet and exercise
  - Two fasting values >97 mg/dL (5.4 mmol/L) OR
  - Two 2-hour postprandial value > 121 mg/dL (6.7 mmol/L)
MiG: Treatments

- Randomized, open-label: insulin vs metformin
- Glycemic targets:
  - Fasting <99 mg/dL (5.5 mmol/L)
  - 2-hour postprandial <126 mg/dL (7.0 mmol/L)
- Metformin dosing:
  - 500 mg daily-twelce daily, up to 2500 mg
- Insulin started if targets not met
MiG: Primary Outcome

- Composite of neonatal complications
  - Hypoglycemia (at least 2 readings <46.8 mg/dL)
  - Respiratory distress
  - Phototherapy
  - Birth trauma
  - 5-minute Apgar < 7
  - Premature birth
MiG Results:

- **No Difference in:**
  - Composite outcome
  - LGA
  - SGA
  - C/S
  - Hypertensive disorders
  - Neonatal hypoglycemia
MiG Results: Metformin Use

- Insulin was required in addition to metformin in 46.3% of the metformin group (168/363).
- Metformin was stopped in 7.4% (27) of women:
  - OB complications (9)
  - Sepsis (1)
  - Worsening LFTs (1)
  - GI side effects (7)
  - Elective/advice (9)
- Dose reduced due to GI side effects in 8.8%
HOW LONG SHOULD PCO PATIENTS CONCEIVING ON METFORMIN CONTINUE THE DRUG TO PREVENT SPONTANEOUS ABORTION?
Randomized blinded trial of metformin (N=45) vs clomiphene (N=47) to treat nonobese anovlulatory PCO patients

- Ovulation rates similar
- Pregnancy rate higher in metformin (15%) than clomiphene group (7.2%)

Palomba et al: *JCEM* 90:4068, 2005
METFORMIN & SPONTANEOUS AB

- Randomized blinded trial (continued)
  - Spontaneous abortion rate lower (3/31, 10%) in metformin than clomiphene group (6/16, 38%), p=0.045
  - METFORMIN WAS STOPPED AS SOON AS PREGNANCY DIAGNOSED!

Palomba et al: JCEM 90:4068, 2005
METFORMIN & SPONTANEOUS AB

• Randomized blinded trial of metformin (N=60) vs laparoscopic ovarian diathermy (N=60) to treat obese anovulatory PCO patients
  - Ovulation rates similar
  - Pregnancy rate higher in metformin (22%) than placebo (13%) group

Palomba et al: JCEM 89:4801, 2004
Randomized blinded trial (continued)

- Spontaneous abortion rate lower (4/43, 9%) in metformin than placebo group (6/16, 29%), p<0.05
- METFORMIN WAS STOPPED AS SOON AS PREGNANCY DIAGNOSED!

Palomba et al: JCEM 89:4801, 2004
METFORMIN & SPONTANEOUS AB

• BOTTOM LINE:
  - Metformin may reduce the rate of spontaneous abortion.
  - This effect is seen even when metformin is D/C’d as soon as pregnancy diagnosed.
  - There is no need to continue metformin once pregnancy occurs.

Palomba et al: JCEM 89:4801, 2004
METFORMIN & SPONTANEOUS AB

RCT METFORMIN VS CLOMIPHENE

• NIH REPRODUCTIVE MEDICINE NETWORK
• 626 INFERTILE PCOS SUBJECTS
• THREE TREATMENT ARMS
  ➢ METFORMIN/PLACEBO (n=208)
  ➢ CLOMIPHENE/PLACEBO (n=209)
  ➢ METFORMIN/CLOMIPHENE (n=209)

METFORMIN & SPONTANEOUS AB

RANDOMIZED TRIAL METFORMIN VS CLOMIPHENE

• LIVE BIRTH RATE
  - METFORMIN 7.2% (15/208) (P<0.001 VS EACH GROUP)
  - CLOMIPHENE 22.5% (47/209)
  - COMBINED 26.8% (56/209)

• SPONTANEOUS ABORTION RATES
  - METFORMIN 21% (NS)
  - CLOMIPHENE 8%
  - COMBINED 9%

• MULTIPLES METFORMIN 0%, CLOMIPHENE 6%, COMBINED 3%

Legro RS et al, 2006
METFORMIN

Conclusions

- Metformin crosses the placenta
- Fetal effects of metformin not known; could be good or bad; animal studies would be helpful
- Preliminary data suggest that metformin:
  - Improves early pregnancy loss rate in PCOS - even if discontinued at time of diagnosis of pregnancy
  - May or may not prevent GDM in PCOS
- No need to continue metformin once pregnancy is diagnosed
METFORMIN AND GLYBURIDE

- BOTH CROSS PLACENTA
- FETAL EFFECTS NOT KNOWN
- COUNSEL PATIENTS IF PRESCRIBING
- INSULIN REMAINS GOLD STANDARD