NORMAL GLUCOSE IN PREGNANCY

LEWIS ET AL, 1976

PEDERSEN HYPOTHESIS

MATERNAL HYPERGLYCEMIA

FETAL HYPERGLYCEMIA

FETAL HYPERINSULINEMIA

DIABETIC FETOPATHY

OUTLINE

– PREPRANDIAL VS POSTPRANDIAL GLUCOSE MONITORING
– NEW INSULINS IN PREGNANCY
– ORAL ANTIDIABETIC AGENTS IN GDM
– ANTEPARTUM TESTING
– TIMING AND MODE OF DELIVERY
– POSTPARTUM FOLLOW-UP

DIABETES SYMPOSIUM
BAPTIST HEALTH SOUTH
FLORIDA
MANAGEMENT OF GESTATIONAL DIABETES

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17 OCTOBER, 2015
GOALS FOR METABOLIC CONTROL

FASTING <100 MG/DL
2-HR POST MEALS <120 MG/DL, OR
1-HR POST MEALS <130-140 MG/DL
IDEAL RANGE 70-110 MG/DL

SELF GLUCOSE MONITORING

• FASTING
• 1 OR 2 HOUR POST MEALS
• EVERY DAY

Preprandial or postprandial monitoring?

• Jovanovic-Peterson et al, 1991:
  • DIEP study of gravidas with type 1 diabetes
  • One-hour postprandial better predictor of adverse fetal outcomes than preprandial

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

NEWER INSULIN ANALOGS

- **Short-acting analogs**
  - Lispro insulin:
    - Does not appear in cord blood (Jovanovic et al: Diab Care 22:1422, 1999)
  - Aspart insulin: similar to lispro

INSULIN ANALOGS

**LONG-ACTING**

- Glargine insulin: appears not to cross placenta
- Detemir insulin: large study found similar A1c and incidence of adverse outcomes compared to NPH, better control of fasting (Diab Care 35:2012, 2012). Appears not to cross the placenta (Suffecool et al, Diab Care 38:2015, e20).

When diet and exercise are not enough in GDM...

- Human insulin – the gold standard
  - Requires intensive patient education
  - Must be given as injection
  - Risk for maternal hypoglycemia
**ORAL ANTIDIABETIC AGENTS**

- Classes of agents
- Use in pregnancy

**SULFONYLUREAS**

- Bind to sulfonylurea receptors in β-cells, stimulating insulin secretion at all blood glucose levels
- Patient must have residual β-cell function
  - Not effective in type 1 diabetes
- Side effect: hypoglycemia

**SULFONYLUREAS**

- Suppress hepatic glucose production
- Diminish glucotoxicity
- Improve insulin secretion after meals
- Usually lower blood glucose by ~20%
- Work best in patients of normal or slightly increased body weight

**ORAL AGENTS IN PREGNANCY**

- Sulfonylureas: if they stimulate insulin production in fetus, would make diabetic fetopathy worse
- Mainly case series’ and anecdotes with first generation agents
ORAL AGENTS IN PREGNANCY

• Glyburide study:
  – Randomized trial glyburide vs insulin
  – 404 GDMs FPG >95 but <140 mg/dl or 2-hr pp >120 on diet
  – Similar success of glucose control in both groups

  Langer et al: NEJM 200:343:1134

ORAL AGENTS IN PREGNANCY

• Glyburide study:
  – 4% of glyburide group had to go on insulin
  – Rates of C/S, macrosomia, neonatal hypoglycemia all similar
  – No glyburide detected in cord blood despite measurable levels in moms’ blood

  Langer et al: NEJM 200:343:1134

ORAL AGENTS IN PREGNANCY

Subsequent glyburide study:
  – 16% of 75 glyburide treated women had to go on insulin
  – Risk factors not very predictable, although if fasting plasma glucose ≥110 mg/dl, 24% needed insulin

  Conway et al: J MF-Neo Med 2004 15:51

DOES GLYBURIDE CROSS THE PLACENTA?

• Originally did not appear to cross the placenta
• Subsequent study from NICHD Fetal Pharmacology Network found fetal levels 70% of maternal levels (Hebert 2009)
• Second study found fetal levels 77% of maternal levels (Schwartz 2013)
**DOES GLYBURIDE CROSS THE PLACENTA?**

• Yes it does.
• Is this good or bad for fetus?

**BIGUANIDES**

• Enhance insulin action, stimulating glucose uptake in liver and periphery, and suppressing hepatic glucose output
• Only work when insulin is present
• Do not stimulate insulin secretion and release, nor cause hypoglycemia

**BIGUANIDES**

• Used for type 2 diabetes when diet and exercise are not successful
• Useful in insulin resistance syndrome
• Patients do not tend to gain weight
• Metformin is the only available biguanide

**METFORMIN**

• How about metformin in pregnancy?
  – Small molecule, if it crosses placenta; might enhance insulin action in fetus
  – Could this cause macrosomia and other aspects of diabetic fetopathy?
METFORMIN

- Is metformin teratogenic?
- Not teratogenic in rats and rabbits at doses 2-6X maximum recommended daily exposure

DOES METFORMIN CROSS THE PLACENTA?

- 15 PREGNANCIES IN PCOS PATIENTS
- 12 MOTHERS TOOK 850 MG METFORMIN BID THROUGHOUT PREGNANCY; 3 ON LOWER DOSE
- MATERNAL SERUM, CORD ARTERY AND VEIN METFORMIN LEVELS MEASURED SIMULTANEOUSLY

VANKY ET AL: FERTIL STERIL 83:1575, 2005

<table>
<thead>
<tr>
<th>MATERNAL</th>
<th>CORD VEIN</th>
<th>CORD ARTERY</th>
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<td>1.50</td>
<td>2.81</td>
<td>3.16</td>
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FETAL METFORMIN LEVELS EXCEED MATERNAL LEVELS!

VANKY ET AL: FERTIL STERIL 83:1575, 2005

DOES METFORMIN PREVENT SPONTANEOUS ABORTION?

- Open label case series
- 22 PCOS patients conceived on metformin
- Control group: previous pregnancy outcomes among 125 PCOS patients who did not take metformin during the pregnancies

Gluek et al, Fertil Steril 2001;75:46
DOES METFORMIN PREVENT SPONTANEOUS ABORTION?

- Bottom line:
  - 16 completed pregnancies where metformin used at least through 4-6 wks gestation
  - 3/16 (19%) spontaneous abortions
  - 10 had 22 previous pregnancies without metformin; 73% ended in spontaneous abortion
  - Among 125 women in “control group” there were 265 previous pregnancies without metformin
  - 103/265 (39%) spontaneous abortions

Gluek et al, Fertil Steril 2001;75:46

METFORMIN IN PREGNANCY

- Problems
  - Small sample size (16 completed pregnancies)
  - Not randomized
  - Not even a contemporaneous control group (regression toward the mean)

Gluek et al, Fertil Steril 2001;75:46

METFORMIN & SPONTANEOUS AB

- Case series of 48 anovulatory PCO patients treated with metformin
  - 20 conceived; metformin continued for first 12 weeks
  - 35% (7/20) spontaneous abortions

Heard MJ et al Fert Steril 2002;77:669

METFORMIN & SPONTANEOUS AB

- Randomized blinded trial of metformin (N=45) vs clomiphene (N=47) to treat nonobese anovulatory 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

METFORMIN & SPONTANEOUS AB

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

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 EXTENDED RELEASE (2 g/d)
• METFORMIN D/C’D AT DX OF CONCEPTION
• CLOMIPHENE 50-150 MG/D x 5 DAYS

Legro RS et al, 2006
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

DOES METFORMIN PREVENT GDM?

- RANDOMIZED TRIAL OF METFORMIN VS PLACEBO STARTED ≈10 WKS, CONTINUED THROUGHOUT PREGNANCY, IN PCOS PATIENTS
  - N = 135 IN EACH GROUP
  - OUTCOME: COMPOSITE OF GDM, PRETERM DELIVERY, PREECLAMPSIA
  - COMPOSITE: METFORMIN 25.9%; PLACEBO 24.4%
  - GDM: METFORMIN 17.6%; PLACEBO 16.9%

Vanky E et al: J Clin Endocrinol Metab 2010; 95: E448-E455

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: 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-twice 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)
Conclusions

- Metformin crosses the placenta
  - Fetal effects of metformin not known; could be good or bad; animal studies would be helpful
  - Available data suggest that metformin:
    • May improve early pregnancy loss rate in PCOS - even if discontinued at time of diagnosis of pregnancy; largest RCT was negative
    • Does not prevent GDM in PCOS
  - No need to continue metformin once pregnancy is diagnosed

α-GLUCOSIDASE INHIBITORS

- Slow the absorption of sugars in the upper GI tract, decreasing postprandial glucose excursions
- Major side effects are GI, including flatulence – start at low dosage and work up
- Don’t depend on presence of endogenous insulin

α-glucosidase inhibitors

- Miglitol – highly absorbed from GI tract
- Acarbose – very little is absorbed from GI tract
**α-GLUCOSIDASE INHIBITORS**

- **CASE SERIES OF 6 GDMs IN MEXICO CITY**
- **ACARBOSE 50MG TID WITH MEALS**

Zarate et al: Ginec Obstet Mex 68:42-5, 2000

**RESULTS:**
- GLUCOSE NORMALIZED
- ALL BABIES NORMAL
- ALL MOMS HAD GI DISCOMFORT

Zarate et al: Ginec Obstet Mex 68:42-5, 2000

**α-GLUCOSIDASE INHIBITORS**

- **RANDOMIZED TRIAL**
- **91 GDMs FAILED DIET >20 WKS**
- **45 RECEIVED ACARBOSE, START AT 25 MG TID; MAX 100 MG TID**
- **46 RECEIVED INSULIN (NPH/LISPRO)**

de Veciana et al: ObGyn 99(suppl): 5s

- **6% OF ACARBOSE GROUP REQUIRED INSULIN (GI SIDE EFFECTS)**
- **GLUCOSE CONTROL, HbA1c RESULTS SIMILAR**

de Veciana et al: ObGyn 99(suppl): 5s
**α-GLUCOSIDASE INHIBITORS**  
- ACARBOSE NOT WELL ABSORBED SYSTEMICALLY  
- THEORETICALLY, LITTLE SHOULD REACH FETUS  
- SHOWS PROMISE (ALTHOUGH 15% PREVALENCE OF TRANSAMINASE ELEVATION IS WORRISOME)

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

**Obstetric Management**

**ANTEPARTUM FETAL TESTING**  
- ACOG NON-DIRECTIVE  
- OUR APPROACH:  
  - WELL CONTROLLED ON DIET: 1x WKLY BEGINNING AT 36 WEEKS  
  - WELL CONTROLLED ON INSULIN: 2x WKLY BEGINNING AT 36 WEEKS  
  - NOT WELL CONTROLLED: TREAT AS PREEXISTING DIABETES
TIMING OF DELIVERY IN GDM

- GOOD CONTROL, NO PROBLEMS: ≥39 WKS
- POOR CONTROL: 34-39 WKS, NO AMNIO


SHOULD WE DELIVER BY EDC?

- POPULATION-BASED RETROSPECTIVE COHORT STUDY OF ALL 193,028 GDMS DELIVERING IN CALIFORNIA IN 1997-2006.
- COMPARED INFANT MORTALITY RATE IF DELIVERED AT A GIVEN GESTATIONAL AGE VERSUS STILLBIRTH RATE OVER THE FOLLOWING WEEK PLUS INFANT MORTALITY IF DELIVERED 1 WEEK LATER.

Rosenstein MG et al: The risk of stillbirth and infant death stratified by Gestational age in women with GDM. AJOG 2012; 206: 309.e1-7

TIMING OF DELIVERY IN GDM

Mode of Delivery

- GDM is not an indication for cesarean, but its complications may be:
  - CPD
  - Need to induce with unripe cervix
  - Fetal compromise
- What EFW should prompt cesarean section without labor?

Rosenstein MG et al: The risk of stillbirth and infant death stratified by Gestational age in women with GDM. AJOG 2012; 206: 309.e1-7
Elective Cesarean Section for Macrosomia Dx’d by U/S

- How many elective cesarean sections would it take to prevent one permanent brachial plexus injury?
  - C/S for all EFW >4.5 kg
    - 3,695 nondiabetic women ($8.7 million)
    - 443 diabetic women ($930,000)
  - C/S for all EFW >4 kg
    - 2,345 nondiabetic women ($4.9 million)
    - 489 diabetic women ($880,000)

Rouse et al. *JAMA* 276:1480, 1996

Postpartum Followup

- 75 gram, 2-hour oral GTT
- Around the time of 6 week checkup

Non-pregnant Diagnostic Criteria

- **DIABETES**
  - Fasting plasma glucose ≥126 mg/dl (X2), or
  - 2-hr after 75 gm load ≥200 mg/dl, or
  - Glycohemoglobin ≥ 6.5%

Non-pregnant Diagnostic Criteria

- **PREDIABETES:**
  - **IMPAIRED FASTING GLUCOSE**
    - FPG 100-125 mg/dl
  - **IGT**
    - 2-hr 75 gram OGTT value 140-199 mg/dl
  - **A1c**
    - 5.7-6.4%
REFERENCES

• ACOG: Gestational Diabetes Mellitus. *ACOG Practice Bulletin* #137 August 2013.


• Gluek et al: Continuing metformin throughout pregnancy in women with PCOS appears to safely reduce first trimester Sab. *Fertil Steril* 2001;75:46-52


• Glueck et al: Metformin throughout pregnancy reduces the development of GDM in women with PCOS. *Fertil Steril* 2002;75:46-52

REFERENCES


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• Stadtmauer LA et al: Metformin treatment of patients with PCOS undergoing IVF improves outcomes and is associated with modulation of the IGFs. Fertil Steril 2001; 75:505-509


• Vanky E, Zahlsen K, Spigset O, Carlsen SM: Placental passage of metformin in women with polycystic ovary syndrome. Fertility Sterility 2005;83:1575-1578

RECOMMENDED READING
