# Gestational Diabetes Update

## What is Gestational Diabetes?

- Impaired glucose intolerance due to insulin resistance coupled with beta-cell insufficiency
- Associated with:
  - ⇧BMI
  - ⇧maternal age
  - Known glucose intolerance
  - Type II DM in 1st degree relative(s)
  - Certain racial backgrounds

## What is Gestational Diabetes?

- A multigenic condition that may involve abnormalities in genes of:
  - Insulin secretion
  - Insulin or insulin signaling
  - Lipid and glucose metabolism
  - Other pathways

## What is Gestational Diabetes?

- Similar in nature to type II DM
  - "GDM is a window to reveal a predisposition to type II DM"
  - 17% to 63% of women with GDM develop type II DM over 5-16 years

## Gestational Diabetes and Perinatal Morbidity

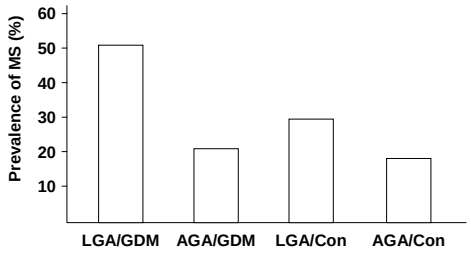
- Worsening glucose tolerance associated with increasing rates of:
  - Preeclampsia
  - Macrosomia >4,000 g
  - Birth trauma
  - Hyperbilirubinemia
  - Neonatal hypoglycemia
  - Cesarean delivery

## Metabolic Syndrome in Children of Women with GDM

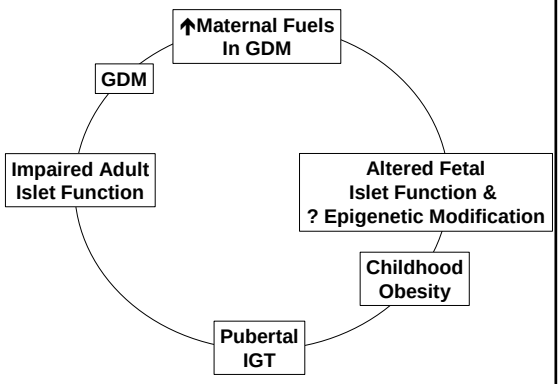
- Longitudinal cohort study of children at ages 6, 7, 9 and 11 years
  - LGA offspring of control mothers
  - LGA offspring of mothers with GDM
  - AGA offspring of control mothers
  - AGA offspring of mothers with GDM
- Obtained biometric and anthropomorphic measurements, postprandial glucose and insulin levels, triglyceride and HDL cholesterol

Boney et al, Pediatr 2005; 115: 290

## Metabolic Syndrome in Children of Women with GDM




Boney et al, Pediatr 2005; 115: 290




## Gestational Diabetes and Morbidity

- Worsening glucose intolerance associated with increasing rates of:
  - Preeclampsia
  - Macrosomia >4,000 g
  - Birth trauma
  - Hyperbilirubinemia
  - Neonatal hypoglycemia
  - Cesarean delivery
  - DM and metabolic syndrome in offspring
- But… there have been doubts about the effectiveness of diagnosis and treatment!

## Gestational Diabetes
### Effect of Treatment

- Randomized clinical trial in 18 centers (ACHOIS)
- Women with GDM, 24-34 weeks'
  - Singletons or twins
  - Risk factor(s) for GDM, or
  - Positive 50 g OGCT (≥ 140 mg/dL), and
  - 75 g GTT with FBG < 140 mg/dL and 2 hour BG < 198 mg/dL

Crowther et al, N Engl J Med 2005;352:2477

## Gestational Diabetes
### Effect of Treatment

- Intervention group
  - Dietary counseling
  - Self monitoring of BGs
    - 4 times daily until BGs in acceptable range for 2 weeks
    - Insulin treatment as necessary
- Routine care group
  - OGCT and GTT results not made available

Crowther et al, N Engl J Med 2005;352:2477

## Gestational Diabetes
### Effect of Treatment

- Outcome variables
  - Infant: Primary – a composite
    - One or more "serious" perinatal events
      - Perinatal death, shoulder dystocia, bone fracture, nerve palsy
    - Admission to NICU
    - Jaundice requiring phototherapy
  - Maternal
    - Need for induction and cesarean
    - Maternal health status (physical and psychological)

Crowther et al, N Engl J Med 2005;352:2477

## Gestational Diabetes
### Effect of Treatment

| Outcome | Treated (N=506) | Routine Care (N=524) | P value |
|---|---|---|---|
| Birthweight | 3,335 ± 551 | 3,482 ± 660 | <0.001 |
| LGA | 68 (13%) | 115 (22%) | <0.001 |
| Macrosomia | 49 (10%) | 110 (21%) | <0.001 |

Crowther et al, N Engl J Med 2005;352:2477

## Gestational Diabetes
### Effect of Treatment

| Outcome | Treated (N=506) | Routine Care (N= 524) | Adj P value |
|---|---|---|---|
| Death | 0 | 5 (1%) | 0.07 |
| Shoulder dystocia | 7 (1%) | 16 (3%) | 0.08 |
| Bone fx | 0 | 1 (<1%) | 0.38 |
| Nerve palsy | 0 | 3 (1%) | 0.11 |
| Composite | 7 (1%) | 23 (4%) | 0.01 |

Crowther et al, N Engl J Med 2005;352:2477

## MFMU Network Randomized Treatment Trial of Mild GDM

- Multicenter randomized trial of women with
  - Abnormal 50 g OGC
  - 3-hr GTT → GDM, but
  - Normal FBS on 3-hr GTT
- Subjects randomized to
  - Usual care (GTT results not available)
  - Dietary intervention, SBGM, and insulin if required

Landon et al, N Engl J Med 2009; 361:1339

## MFMU Network Randomized Treatment Trial of Mild GDM

- Primary outcome – composite
  - Perinatal death
  - Hyperbilirubinemia
  - Hypoglycemia
  - Hyperinsulinemia
  - Birth trauma
- Multiple secondary outcomes
  - LGA
  - SD
  - Neonatal adiposity
  - CS
  - Preeclampsia/GHTN

Landon et al, Am J Obstet Gynecol 2009; 199:S2

## Gestational Diabetes
### Effect of Treatment

| Outcome | Treated (N=485) | Routine Care (N=473) | P value |
|---|---|---|---|
| Birthweight | 3,302 ± 502 | 3,408 ± 589 | <0.001 |
| LGA | 34 (7.1%) | 66 (14.5%) | <0.001 |
| Macrosomia | 28 (5.9%) | 65 (14.3%) | <0.001 |
| Fat Mass (g) | 427 ± 198 | 464 ± 222 | <0.003 |

Landon et al, N Engl J Med 2009; 361:1339

## Gestational Diabetes
### Effect of Treatment

| Outcome | Treated (N=485) | Routine Care (N= 473) | P value |
|---|---|---|---|
| Death | 0 | 0 | |
| Hyperbili-rubinemia | 43 (10%) | 54 (13%) | 0.12 |
| Hypoglycemia | 62 (16%) | 55 (15%) | 0.75 |
| Elevated cord C-peptide | 75 (18%) | 92 (23%) | 0.07 |
| Birth trauma | 3 (<1%) | 6 (1%) | 0.33 |
| Composite | 149 (32%) | 163 (37%) | 0.14 |

Landon et al, N Engl J Med 2009; 361:1339

## Gestational Diabetes
### Effect of Treatment

| Outcome | Treated (N=485) | Routine Care (N= 473) | P value |
|---|---|---|---|
| GHTN - PE | 41 (9%) | 62 (14%) | 0.01 |
| Cesarean | 128 (27%) | 154 (34%) | 0.02 |
| Shoulder dystocia | 7 (1.5%) | 18 (4%) | 0.02 |

Landon et al, N Engl J Med 2009; 361:1339

## MFMU Network Randomized Treatment Trial of Mild GDM

| Outcome | Number Needed to Treat |
|---|---|
| Macrosomia | 12 |
| Cesarean Delivery | 14 |
| Shoulder Dystocia | 40 |
| PE+GHTN | 20 |

Landon et al, Am J Obstet Gynecol 2009; 199:S2

## The Treatment of GDM

- The best studies of GDM treatment included self blood glucose monitoring; " you manage what you measure."

## Daily Home Blood Glucose Monitoring in Diet-controlled GDM

- Retrospective cohort study of diet controlled GDM patients at a single institution (UT Southwestern)
  - 675 women tested weekly in the office (1991-1997)
  - 315 women tested 4 times daily at home with a glucose monitor
  - Women with FBS >105 given insulin and excluded from study
- Primary outcomes – birthweight >4000 g and LGA

Hawkins et al, Obstet Gynecol 2009; 1307

## Daily Home Blood Glucose Monitoring in Diet-controlled GDM

| Outcome | Weekly (N=675) | Daily x 4 (N=315) | P value |
|---|---|---|---|
| BW>4000 g | 199 (30%) | 69 (22%) | 0.013 |
| LGA | 232 (34%) | 73 (23%) | <0.001 |
| Cesarean | 222 (33%) | 116 (37%) | 0.22 |
| Erb's palsy | 3 (0.4%) | 2 (0.6%) | 0.69 |

Hawkins et al, Obstet Gynecol 2009; 1307

## Gestational Diabetes

- GDM diagnosis and treatment has a beneficial effect on
  - LGA/Macrosomia
  - Cesarean delivery
  - Shoulder dystocia
  - PE+GHTN

## Screening and Diagnosis of GDM in the U.S.

- Use the 50 g oral glucose challenge with BS taken 1 hour later
  - Screen all pregnant women @ 24-28 weeks
    - Test earlier in selected patients
  - Threshold of 140 mg/dL or greater

## Screening and Diagnosis of GDM in the U.S.

- Use the 100 g oral glucose tolerance test for the diagnosis of GDM
  - No need to test women with 50 g OCT results of 200 mg/dL or greater
  - Experts recommend against using a capillary glucose meter
  - Use either NDDG or Carpenter & Coustan modification for diagnosis

## Diagnosis of Gestational Diabetes using 100 g OGTT

| Time of BS | NDDG (mg/dL) | Carpenter/Coustan (mg/dL) |
|---|---|---|
| Fasting | 105 | 95 |
| 1 h | 190 | 180 |
| 2 h | 165 | 155 |
| 3 h | 145 | 140 |

## Screening and Diagnosis of GDM in the U.S.

- Women with one abnormal value on the 3 h OGTT are at increased risk for
  - Preeclampsia
  - Macrosomia
  - ? CS
- Treat as GDM versus repeat testing in 4 weeks?

## Treatment of GDM
### Diet

- Diet based on ideal prepregnancy weight
  - 30 kcal/kg for average weight
  - 35 kcal/kg for underweight
  - 25 kcal/kg for overweight
- Generally, 2000-2200 calories per day
  - Avoid concentrated sweets – utilize complex, high-fiber carbohydrates

## Treatment of GDM
### Diet

- Experts recommend checking FBS and 1 or 2 h postprandial BSs
  - Normals:
    - FBS 95 or less
    - 1 h pp 130-140 or less
    - 2 h pp 120 or less
  - Decrease monitoring (number of BS per day) if BSs are normal after several days of testing

## Treatment of GDM
### Medications

- Insulin
- Glyburide
- Metformin

Original Article

## Metformin versus Insulin for the Treatment of Gestational Diabetes

Janet A. Rowan, M.B., Ch.B., William M. Hague, M.D., Wanzhen Gao, Ph.D., Malcolm R. Battin, M.B., Ch.B., M. Peter Moore, M.B., Ch.B., for the MiG Trial Investigators

N Engl J Med
Volume 358(19):2003-2015
May 8, 2008

The NEW ENGLAND JOURNAL of MEDICINE

## Metformin for the Treatment of GDM

- Randomized, open-label trial comparing metformin to insulin for the treatment of GDM
  - 363 → metformin
  - 370 → insulin
- Primary outcome a composite
  - Neonatal hypoglycemia, RDS, need for phototherapy, birth trauma, 5 min AS <7, prematurity

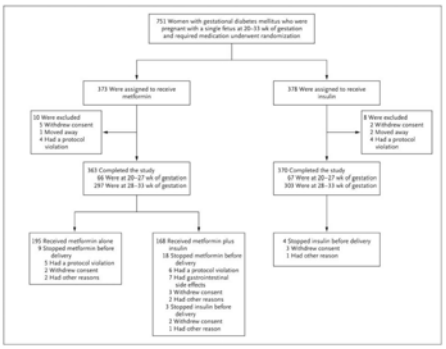
Rowan et al, N Engl J Med 2008; 358:19

## Metformin for the Treatment of GDM

- Metformin started at 500 mg once or twice daily and increased over 2 weeks as needed to a max dose of 2500 mg daily
  - Supplemental insulin eventually required in 46% of metformin patients

Rowan et al, N Engl J Med 2008; 358:19

**Enrollment of Subjects**




Rowan JA et al. N Engl J Med 2008;358:2003-2015

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## Metformin for the Treatment of GDM

| Outcome | Metformin (N=363) | Insulin (N=370) | Relative Risk (95% CI) |
|---|---|---|---|
| Primary outcome | 116 (32%) | 119 (32%) | 0.99 (0.80-1.23) |
| Neon BS <28.8 | 12 (3%) | 30 (8%) | 0.41 (0.21-0.78) |
| Birth trauma | 16 (4%) | 17 (5%) | 0.96 (0.49-1.87) |
| Preterm birth | 44 (12%) | 28 (8%) | 1.60 (1.02-2.52) |
| Adm to NICU | 68 (19%) | 78 (21%) | 0.89 (0.66-1.19) |

Rowan et al, N Engl J Med 2008; 358:19

## Metformin for the Treatment of GDM

| Outcome | Metformin (N=363) | Insulin (N=370) | P Value |
|---|---|---|---|
| GA at birth | 38.3±1.4 | 38.5±1.3 | 0.02 |
| Birth weight | 3372±572 | 3413±569 | 0.33 |
| Birth weight >90th | 70 (19%) | 69 (19%) | 0.83 |
| Maternal glycated Hgb 36-37 week | 5.6±0.5 | 5.7±0.6 | 0.25 |

Rowan et al, N Engl J Med 2008; 358:19

## Metformin for the Treatment of GDM

- In women with gestational diabetes mellitus, metformin (alone or with supplemental insulin) is not associated with increased perinatal complications as compared with insulin
- Patients prefer metformin over insulin

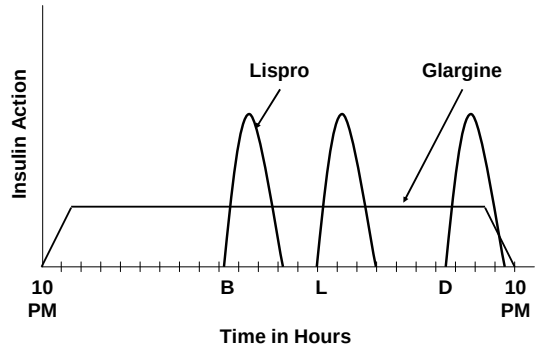
Rowan et al, N Engl J Med 2008; 358:19

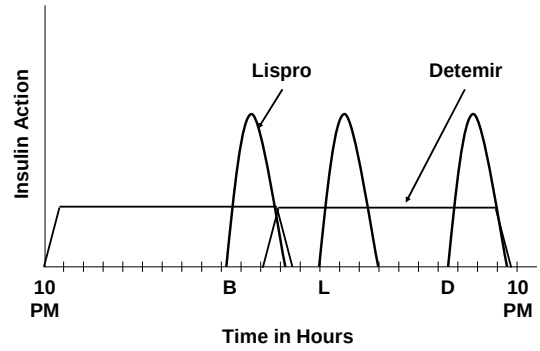
## Metformin for the Treatment of GDM

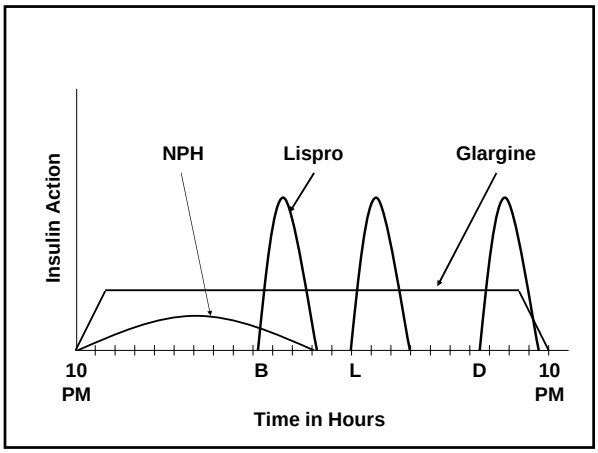
- Start with 500 mg once or twice daily
- Increase by 500 mg per week
- Maximum dose 2000 mg per day

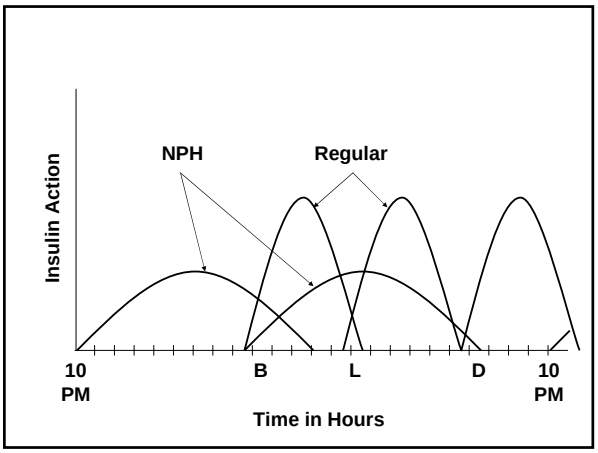
## Potential Adverse Effects of Metformin

- Lactic acidosis: Occurs in 1:30,000 cases; predispositions include renal or liver compromise, heart failure, serious illness, dehydration
- Nausea, bloating, diarrhea: dose dependent
- Drug interactions: cimetadine



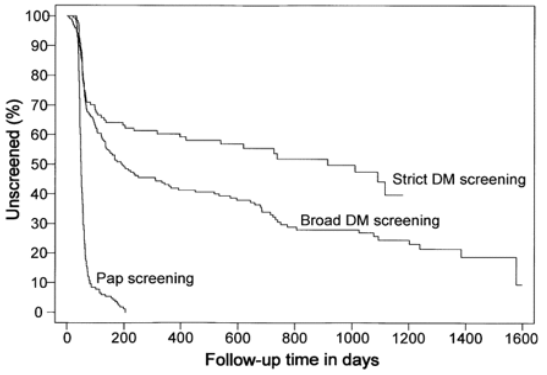



## Postpartum Management of GDM

- ~15% of women with GDM have impaired glucose tolerance or diabetes after delivery
  - Greater likelihood if
    - Obese
    - GDM diagnosed early in pregnancy
    - Treatment required
- ADA recommends that all women with GDM be evaluated postpartum for diabetes

Kaplan-Meier estimates of the time to screening in women with GDM




Smirnakis et al, Obstet Gynecol 2005;106:1297

## Postpartum Evaluation for Diabetes

| Method | Normal | Impaired Glucose Tolerance | Diabetes |
|---|---|---|---|
| Continued home monitoring | FBS < 110 | FBS 110-125 | FBS >125 |
| 75 g oral glucose load | 2 h < 140 | 2 h 140-199 | 2 h >199 |