Learning Objectives:

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

1. Describe the metabolic changes in pregnancy which produce a “diabetogenic stress.”

2. Describe the short-term and long-term morbidities for the woman with gestational diabetes mellitus and her infant.
Gestational Diabetes: Detection and Management

Learning Objectives (cont’d):

3. Discuss the need to detect gestational diabetes in pregnancy, and methods presently in use for screening and diagnosis.

4. Explain the use of dietary therapy, the indications for insulin and oral agents (glyburide, metformin), and strategies for monitoring maternal glucose control.

Diabetes Trends Among Delivery Hospitalizations in the U.S., 1994-2004

Figure 1—Trends for all diabetes (C), GDM (Δ), type 1 diabetes (■), and type 2 diabetes (○) among delivery hospitalizations in the U.S., 1994-2004.

“Coming events cast their shadows before. The woman destined to develop diabetes divulges her future fate by producing infants which are dead or large . . . . .”

W.P.U. Jackson, Studies in Pre-diabetes; BMJ (1952)

Pathophysiology of GDM

- Insulin resistance
- Impaired insulin secretion
- Increased hepatic glucose production
Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy. The definition applies whether insulin or diet modification is used for treatment . . . It does exclude the possibility that unrecognized glucose intolerance may leave antedated or begun concomitantly with the pregnancy.

American Diabetes Association
Fifth Int’l Workshop
Conference on GDM 2005
Consequences of Gestational Diabetes: Why Bother to Screen?

Maternal

Subsequent diabetes mellitus, 35-60% with type 2 diabetes mellitus especially in first decade postpartum; shortened life expectancy

Incidence of Type 2 Diabetes Mellitus After Pregnancy Complicated by GDM

Cumulative incidence of diabetes in high-risk and control participants. Yellow squares indicate overweight control subjects; orange triangles, normal-weight control subjects; green squares, overweight high-risk subjects; blue triangles, normal-weight high-risk subjects.

J.B. O'Sullivan, Body Weight and Subsequent Diabetes Mellitus, JAMA 1982;248(6):949-52
Women who have had gestational diabetes have at least a seven-fold increased risk of developing type 2 diabetes mellitus in the future compared with those who have had a normoglycaemic pregnancy.

Consequences of Gestational Diabetes: Why Bother to Screen?

### Fetal and Neonatal

- Maternal hyperglycemia leads to fetal hyperglycemia and hyperinsulinemia.
- Macrosomia and trauma including shoulder dystocia; Hypoglycemia, Hypocalcemia, Hyperbilirubinemia
- Increased perinatal mortality associated with fasting hyperglycemia
- Long term morbidity: obesity, carbohydrate intolerance

### Gestational Diabetes Mellitus

Approaches to Screening and Diagnosis

| Detection: | All pregnant women should be screened for glucose intolerance since selective screening based on clinical attributes or past obstetric history has been shown to be inadequate. |
### Gestational Diabetes Mellitus
#### Approaches to Screening and Diagnosis

<table>
<thead>
<tr>
<th>High Risk:</th>
<th>Clinical characteristics consistent with a high risk of GDM (severe obesity, PCOS, history of GDM or delivery of LGA infant, glycosuria, strong family history of type 2 diabetes), test as soon as possible. If negative, retest at 24-28 weeks gestation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Note:</td>
<td>fasting &gt;120 mg/dL or HbA₁c ≥ 7% indicates need for ultrasound screening for anomalies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average Risk:</th>
<th>Testing at 24-28 weeks gestation</th>
</tr>
</thead>
</table>
# GDM: Approaches to Screening and Diagnosis

<table>
<thead>
<tr>
<th>Low Risk:</th>
<th>Includes women with <strong>all</strong> of the following characteristics:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• &lt;25 years of age</td>
</tr>
<tr>
<td></td>
<td>• Normal weight before pregnancy</td>
</tr>
<tr>
<td></td>
<td>• No first degree relative with diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>• Not a member of an ethnic group an increased risk for type 2 diabetes</td>
</tr>
<tr>
<td></td>
<td>• No history of abnormal glucose metabolism</td>
</tr>
<tr>
<td></td>
<td>• No history of poor obstetric outcome</td>
</tr>
<tr>
<td></td>
<td>• No glucose testing required</td>
</tr>
</tbody>
</table>

### Detection

- Screening with a 50g glucose load or in high risk women, a diagnostic OGTT
- 50g oral glucose load, administered between the 24th and 28th week, without regard to time of day or time of last meal, to all pregnant women who have not been identified as having glucose intolerance before the 24th week
- Venous plasma glucose measured one hour later. Value of 130-140 mg/dL or above in venous plasma indicates the need for a full diagnostic glucose tolerance test
Gestational Diabetes Mellitus Diagnostic Criteria

Two or more of the following venous plasma concentrations must be met or exceeded:

<table>
<thead>
<tr>
<th></th>
<th>O-Sullivan</th>
<th>NDDG</th>
<th>Carpenter/Coustan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>90 mg/dL</td>
<td>105 mg/dL</td>
<td>95 mg/dL</td>
</tr>
<tr>
<td>1-hour</td>
<td>165 mg/dL</td>
<td>190 mg/dL</td>
<td>180 mg/dL</td>
</tr>
<tr>
<td>2-hour</td>
<td>145 mg/dL</td>
<td>165 mg/dL</td>
<td>155 mg/dL</td>
</tr>
<tr>
<td>3-hour</td>
<td>125 mg/dL</td>
<td>145 mg/dL</td>
<td>140 mg/dL</td>
</tr>
</tbody>
</table>

Hyperglycemia and Adverse Pregnancy Outcomes
The HAPO Study Cooperative Research Group

Conclusions
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.

Participants Completing an OGTT and Included in Analyses

- 75 gram, 2-hour OGTT at 24-32 weeks (avg 28 weeks)
- Venous samples at F, 1 hr, 2 hrs
- Total OGTTs: 25,505
- Unblinded: 746 (2.9%)
- Did not complete: 1,443 (5.7%)
- Analytic cohort: 23,316

Major Outcomes

Associations of maternal glycemia with frequency of:
1. Infants with birth weight > 90th percentile for gestational age
2. Delivery by primary cesarean section
3. Clinical neonatal hypoglycemia
4. Cord C-peptide >90th percentile
What is the Nature of the Relationship between Maternal Glucose values and These Three Outcomes?

Fasting plasma glucose

Proposed Definition of GDM

Any one of the following: % GDM

<table>
<thead>
<tr>
<th>Glucose Value</th>
<th>Condition</th>
<th>Fasting</th>
<th>1-hour</th>
<th>2-hour</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>92 mg/dl</td>
<td>alone</td>
<td>8.3%</td>
<td>5.7%</td>
<td>2.1%</td>
<td></td>
</tr>
<tr>
<td>180 mg/dl</td>
<td>plus</td>
<td></td>
<td></td>
<td>2.1%</td>
<td>1.7% = 16.1%</td>
</tr>
<tr>
<td>153 mg/dl</td>
<td>plus</td>
<td></td>
<td></td>
<td></td>
<td>1.7% = 17.8%*</td>
</tr>
</tbody>
</table>

*1.7% were unblinded because of FPG ≥105 mg/dl &/or 2h ≥200 mg/dl

IADPSG
Diab Care. 2010;33:676-682
Gestational Diabetes Mellitus Treatment

Mark Landon, MD
The Ohio State University Medical Center

Visits every 1-2 weeks until 36 weeks; then weekly
Dietary management:
  ✓ 2000-2200 calorie, no-concentrated-sweets diet
  ✓ Capillary blood glucose monitoring
Exercise and GDM

- A program of moderate physical exercise is recommended
- 30 minutes daily or 10 minutes after each meal

Surveillance of Maternal Diabetes

- Check fasting and 1-hour or 2-hour postprandial glucose levels daily to assess efficacy of diet with self monitoring of capillary blood glucose.
- Check fasting urine ketones in patients on caloric restriction.
- If fasting capillary value > 95mg/dL and/or 1-hour value > 140 mg/dL or 2-hour value > 120mg/dL, insulin or glyburide therapy is required.
### Neonatal Outcomes in Women with Weekly Office-Based Glucose Monitoring Compared with Women Using Daily Monitoring

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Weekly (n=675)</th>
<th>Daily (n=315)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>3,690±612</td>
<td>3,536±603</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>More than 4,000 g</td>
<td>199 (29.5)</td>
<td>69 (21.9)</td>
<td>.013</td>
</tr>
<tr>
<td>Large for gestational age*</td>
<td>232 (34.4)</td>
<td>73 (23.1)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>


### Oral Agents for GDM

“Further study is recommended before the use of newer oral hypoglycemic agents can be supported for use in pregnancy.”

ACOG Practice Bull. #30 Sept. 2001

“Glyburide... further studies are needed in a larger patient population to establish its safety.”

ADA, Position Statement

Diabetes Care 26: S103-105, 2003
**Oral Agents for GDM**

“In our experience, glyburide has become the first choice of our patients with GDM who require therapy beyond diet.”

---

**Glyburide vs. Insulin**

- 404 women with GDM randomized to insulin or glyburide (Micronase, DiaBeta)
- Both therapies showed comparable improvement in glucose control
  - 8% of glyburide patients required insulin
- Hypoglycemia (<40 mg/dL) more frequent with insulin (20% vs. 2%, p=0.03)
- No differences in maternal complications, cesarean delivery rate, neonatal outcomes
- Conclusion: In women with GDM, glyburide is a clinically effective alternative to insulin therapy

---

Gabbe and Graves
*Obstet Gynecol* 2003; 102: 857

Langer O et al
Risk Factors for Glyburide Failure

- Diagnosis of GDM before 25 weeks
- Higher baseline fasting glucose 
  \((112 \text{ mg/dL vs. } 102 \text{ mg/dL})\)
- Maternal age \((34 \text{ years vs. } 29 \text{ years})\)
- Higher gravidity \((4.3 \text{ vs. } 2.7)\)
- Higher parity \((2 \text{ vs. } 1)\)
- Obesity

Kahn et al., Obstet Gynecol 2006;107:1303-9

Glyburide vs. Insulin: Summary

- Maternal fasting and postpartum glycemia is improved with glyburide Rx.
- Glyburide failure rate 15-20%.
- Glyburide failures associated with earlier dx of GDM, fasting > 110-115 mg %.
- Comparable neonatal outcomes
- Significant cost savings.
Mean umbilical cord / maternal glyburide concentration ratio was 0.7 ± 0.4

Hebert et al
Clin Pharm Therapeutics; 85:609,2009

Metformin (Glucophage)

- Class B drug, decreases hepatic glucose production, crosses placenta
- In PCOS, use of metformin is associated with a 10-fold reduction in GDM (31% to 3%). (Glueck, et al. Fertil Steril 2002;77:250-5)
- Use in pregnancy controversial. May be continued through 12 weeks to decrease risk of miscarriage in patients with PCOS.
Metformin in Gestational Diabetes Trial (MIG)

- Prospective randomized multicenter trial
- Insulin vs. Metformin (n=750)
- Enrollment 20-33 wks gestation
- Primary outcome – composite neonatal morbidity
- Planned 2 and 5 yr. follow-up of offspring

J. Rowan et al
NEJM 2008; 358:2003

Metformin vs. Insulin for the Treatment of GDM
(Rowan et al, NEJM 2008;358:2003-15)

<table>
<thead>
<tr>
<th>Glycemic Control (mg/dl)</th>
<th>Metformin</th>
<th>Insulin</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>90 ± 10.8</td>
<td>88.2 ± 12.6</td>
<td>0.16</td>
</tr>
<tr>
<td>2 hr pp</td>
<td>109.8 ± 12.6</td>
<td>111.6 ± 18.0</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Metformin vs. Insulin for the Treatment of GDM

<table>
<thead>
<tr>
<th></th>
<th>Metformin (n=363)</th>
<th>Insulin (n=370)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite</td>
<td>116 (32.0)</td>
<td>119 (32.2)</td>
<td>0.95</td>
</tr>
<tr>
<td>NN Hypoglycemia</td>
<td>55 (15.2)</td>
<td>69 (18.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>RDS</td>
<td>12 (3.3)</td>
<td>16 (4.3)</td>
<td>0.47</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>29 (8.0)</td>
<td>31 (8.4)</td>
<td>0.85</td>
</tr>
<tr>
<td>Trauma</td>
<td>16 (4.4)</td>
<td>17 (4.6)</td>
<td>0.90</td>
</tr>
<tr>
<td>Preterm Birth</td>
<td>44 (12.1)</td>
<td>28 (7.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Spontaneous PTB</td>
<td>26 (7.2)</td>
<td>15 (4.1)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

(Rowan et al, NEJM 2008;2003-15)

Metformin Versus Insulin for the Treatment of Gestational Diabetes

Conclusions
In women with gestational diabetes mellitus, metformin (alone or with supplemental insulin) is not associated with increased perinatal complications as compared with insulin. The women preferred metformin to insulin treatment.

Rowan JA, et al.
Benefits and Risks of Oral Diabetic Agents Compared with Insulin in Women with GDM

- Overall strength of evidence from RCTs and observational studies – very low for reported maternal and neonatal outcomes
- No consistent evidence for increase in adverse maternal or neonatal outcomes with oral agents vs. insulin


Benefits and Risks of Oral Diabetic Agents Compared with Insulin in Women with GDM

- Obstetricians now have evidence to support use of glyburide as well as insulin in management of GDM. Metformin also appears to be effective.
- Further studies with sufficient power to detect meaningful differences in maternal and neonatal outcomes are needed.

Delivery

- Allow to go to term
- If undelivered at 40 weeks, begin fetal assessment with twice weekly nonstress tests (NST): Patients who have had a previous stillbirth or have hypertension should be followed with twice weekly NSTs at 32 weeks.
- Clinical estimation of fetal size and ultrasonographic indices should be used to detect fetal macrosomia: Evaluate for cesarean delivery if estimated fetal weight > 4500g

Patients with GDM who require insulin as well as diet to maintain normal glucose levels should be followed with a program of antepartum fetal surveillance identical to that used for women with pre-gestational diabetes, twice weekly NSTs.

- Infant to be observed closely for hypoglycemia, hypocalcemia, hyperbilirubinemia.
GDM: Treatment Benefit?

For the population to benefit from the diagnosis of GDM, there should be an effective treatment for the condition... there is little information regarding the effectiveness of treatment versus no treatment.

ACOG Practice Bulletin No. 30
September 2001

A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes

Mark B. Landon, M.D., Catherine Y. Spong, M.D., Elizabeth Thom, Ph.D., Marshall W. Carpenter, M.D., Susan M. Ramin, M.D., Brian Casey, M.D., Ronald J. Wapner, M.D., Michael W. Varner, M.D., Dwight J. Rouse, M.D., John M. Thorp, Jr., M.D., Anthony Sciscione, D.O., Patrick Catalano, M.D., Margaret Harper, M.D., George Saade, M.D., Kristine Y. Lain, M.D., Yoram Sorokin, M.D., Alan M. Peaceman, M.D., Jorge E. Tolosa, M.D., M.S.C.E., and Garland B. Anderson, M.D., for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network®
Study Design

Women with mild GDM

2 of these abnormal

Fasting <95 mg/dl
1 hour ≥190 mg/dl
2 hour ≥155 mg/dl
3 hour >140 mg/dl

Randomized to:
**Study Design**

### Women with mild GDM

2 of these abnormal

- Fasting <95 mg/dl
- 1 hour ≥190 mg/dl
- 2 hour ≥155 mg/dl
- 3 hour ≥140 mg/dl

Randomized to:

#### Treatment

- Nutrition counseling
- SBGM/memory meter
- Insulin if necessary

#### No Treatment

- Standard OB care

Providers and patients unaware of GTT results
A Prospective Multicenter Randomized Treatment Trial of Mild Gestational Diabetes

Conclusions:
• Whereas treatment of mild GDM does not reduce the frequency of several commonly observed neonatal morbidities associated with diabetic pregnancy, it does lower the risk for fetal overgrowth, shoulder dystocia, and cesarean delivery.


<table>
<thead>
<tr>
<th>RCTs of Treatment of GDM: Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MFMU</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Preeclampsia</td>
</tr>
<tr>
<td>Weight gain</td>
</tr>
<tr>
<td>LGA</td>
</tr>
<tr>
<td>Fetal fat</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
</tr>
</tbody>
</table>

<sup>1</sup>Landon. NEJM 2009;361:1339
<sup>2</sup>Crowther. NEJM 2005;352:2477
Evaluation for Carbohydrate Intolerance Postpartum Care

- Check fasting or random plasma glucose, 1-3 days after delivery
- At 6-12 weeks postpartum, all patients who had carbohydrate intolerance during pregnancy (GDM) should be evaluated and reclassified as follows:

---

<table>
<thead>
<tr>
<th>Normal</th>
<th>Impaired</th>
<th>Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting &lt;100mg/dL</td>
<td>100-125 mg/dL</td>
<td>≥ 126 mg/dL</td>
</tr>
<tr>
<td>and</td>
<td>and</td>
<td>and</td>
</tr>
<tr>
<td>2hr &lt;140mg/dL</td>
<td>2 hr ≥ 140-199mg/dL</td>
<td>2hr ≥ 200mg/dL</td>
</tr>
</tbody>
</table>

---
### Evaluation for Postpartum Carbohydrate Intolerance

- 1 year postpartum
  - 75g 2 hour oral GTT, then every 3 years
- Annual Fasting Glucose

### Gestational Diabetes Mellitus Key Points

1. Pregnancy has been characterized as a diabetogenic state because of increased postprandial glucose levels in late gestation.

2. GDM is an important health care problem affecting approximately 200,000 women annually. Proposed diagnostic criteria would increase this number significantly.

3. Perinatal mortality is not increased in most cases of GDM, although increased morbidity, primarily macrosomia, is found in the offspring of women with GDM.
4. At the present time, universal screening for GDM using measurements of blood glucose should be performed at 24-28 weeks gestation except for women identified as low risk based on clinical attributes.

5. Recent data have helped us define the level of glycemic control which poses a risk for fetal and neonatal complications such as macrosomia.

6. The key element in treating gestational diabetes mellitus is dietary therapy. Moderate exercise is also valuable.

7. Insulin or glyburide are utilized when significant fasting or postprandial hyperglycemia occurs despite dietary treatment. Metformin may also prove to be an acceptable oral agent.

8. A program of fetal surveillance is appropriate for patients with GDM requiring insulin or glyburide, or those with hypertension or a previous stillbirth.

9. Women with GDM are at high risk for developing type 2 diabetes. Regular medical evaluations are therefore recommended.