Improving Outcomes in Pregnancies Complicated by Diabetes Mellitus

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Disclosure Statements
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I have no relevant financial relationships to disclose or conflicts of interest to resolve

I will not discuss any unapproved or off-label, experimental or investigational use of a product, drug or device.
Improving Outcomes in Pregnancies Complicated by Diabetes Mellitus

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

1. Understand the pathophysiology of perinatal complications seen in the pregnancy complicated by diabetes mellitus, especially as they relate to maternal glycemic regulation.

2. Explain the need for preconception counseling and the role of maternal hyperglycemia in the etiology of malformations in type 1 and type 2 diabetes mellitus.
Improving Outcomes in Pregnancies Complicated by Diabetes Mellitus

Learning Objectives (continued):

3. Construct an algorithm to detect gestational diabetes, using methods presently recommended for screening and diagnosis.

4. Describe the techniques available for control of maternal diabetes during the antepartum period and the current techniques used for the assessment of fetal well being.
Diabetes: Trends Among Delivery Hospitalizations in the U.S., 1994 - 2004

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

Carbohydrate Metabolism in Pregnancy

- Postprandial hyperglycemia
- Accelerated starvation
Effect of Maternal Diabetes Mellitus on the Fetus

MATERNAL
- INSULIN RELEASE
- GLUCOSE UTILIZATION
- HYPERGLYCEMIA

Placenta

FETAL
- BIRTHWEIGHT
- HYPERINSULINEMIA
- HYPERGLYCEMIA
- LACTIC ACIDEMIA

DELAYED PULMONARY MATURATION
Perinatal Mortality Rates In Pregnancy Complicated By Type 1 Diabetes Mellitus
Pregnancy Complicated by Diabetes Mellitus
Consequences of Poor Glucose Control and Vasculopathy
Pregnancy Complicated by Diabetes Mellitus
Persistent Problems

- Increased congenital malformations
  - Leading cause of perinatal deaths

- “Difficult” patients

- Patients with vasculopathy
Congenital Malformations and Diabetes

- Incidence of major fetal malformations is 5-10%, 2-4 fold increase over control populations; anomalies of heart, CNS, skeleton most common
  - Risk of spontaneous abortion is also increased
- Patients at risk: poor control during period of organogenesis, 5-8 weeks after LMP; “fuel mediated teratogenesis”
- Associated with increasing hemoglobin A1c level; not hypoglycemia
Major Malformations in Infants of Women with Type 1 Diabetes – 11 Studies

Prepregnancy
31/1264 (2.5%)

Postconception
115/1471 (7.8%)
1. How will pregnancy affect my life expectancy?
2. What effect will pregnancy have on diabetic nephropathy?
3. What effect will pregnancy have on diabetic retinopathy?
4. Will my baby develop diabetes mellitus?
Objectives of Prepregnancy Counseling

- Assess the patient’s fitness for pregnancy, especially vasculopathy
- Discontinue ACE inhibitors, statins, ARBs
- In type 2 patients, discontinue oral agents; start insulin
Pregestational Diabetes
Prepregnancy Planning: Objectives

- Obtain optimum glycemic control before conception; target hemoglobin $A_{1c} < 6.5\%$
- Check immune status against rubella
- Check thyroid function
- Begin folic acid supplementation
Detection and Evaluation of Malformations

- Identification of the population at greatest risk: Maternal glycosylated hemoglobin level in the first trimester
- Ultrasound in first trimester to detect anencephaly
- Aneuploidy screening including Quad screen at 15-20 weeks or maternal serum alpha-fetoprotein alone
- Comprehensive ultrasound including fetal echocardiography at 18-20 weeks
Management of Diabetes Mellitus in Pregnancy

Low-Dose Aspirin

Unless contra-indicated:
Begin low-dose (81mg) aspirin daily in patients with type 1 and type 2 diabetes mellitus after the 1st trimester.

LeFevre M.L., U.S. Preventative Services Task Force
Werner EF, Obstet Gynecol 2015:126:1242-50
Management of Diabetes Mellitus in Pregnancy

“Controlled diabetes is essential to fetal welfare.”

Dr. Priscilla White, 1928
Relationship Between Perinatal Mortality and Maternal Glucose Control

![Graph showing the relationship between perinatal mortality and maternal glucose control. The graph plots perinatal mortality (%) against mean maternal blood glucose (mg/dl). Various studies are marked on the graph, including Joslin (1922-1924), Pedersen (1969), Tyson (1976), Martin (1979), Coustan (1980), Fuhrmann (1980), Karlsson (1972), Joslin (1956-1975), and Essex (1973). There is a trend line indicating a positive correlation between higher glucose levels and higher perinatal mortality.]
Target Plasma Glucose Levels in Pregnancy

Before breakfast: 60-90 mg/dL
Before lunch, supper, Bedtime snack: 60-105 mg/dL
One hour after meal: ≤140 mg/dL
Two hours after meals: ≤120 mg/dL
2:00 a.m. to 6:00 a.m.: >60 mg/dL
Regulation of Maternal Glycemia
Antepartum Care

Maintain mean capillary glucose at ≤ 100 mg/dL

- Self blood glucose monitoring of pre-meal and postprandial glucose levels
  - Glycosylated hemoglobin levels in each trimester;
    - maintain at 6% - 6.5%

- Insulin therapy
  - Multiple insulin injections
  - Subcutaneous insulin infusion (pump therapy)

- May combine metformin and insulin in type 2 patients
Comparison of Equal Amounts of Different Types of Insulin

- Lispro
- Regular
- NPH
- Glargine
Management of Diabetes Mellitus in Pregnancy
Developing Individualized Insulin Regimens

Insulin Effect

<table>
<thead>
<tr>
<th>Time</th>
<th>Insulin Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning</td>
<td>Rapid</td>
</tr>
<tr>
<td>Afternoon</td>
<td>NPH</td>
</tr>
<tr>
<td>Evening</td>
<td>Rapid</td>
</tr>
<tr>
<td>Night</td>
<td>NPH</td>
</tr>
</tbody>
</table>

Meals

B: Breakfast
L: Lunch
S: Snack
HS: Dinner
What Your Patient with Diabetes Should Know

- How much will 1 unit of rapid acting insulin lower my blood glucose?
  - Answer: Approximately 30 mg/dL
- How much will 10 grams of carbohydrate elevate my blood glucose?
  - Answer: Approximately 30 mg/dL
- How many grams of carbohydrate will be covered by one unit of rapid acting insulin?
  - Answer: Approximately 10 grams
Management of Diabetes Mellitus in Pregnancy

Dietary Recommendations

Plan: 3 meals, up to 3 snacks
2000-2400 kcalories daily

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Diet: 35 kcal/kg</th>
<th>Normal 30 kcal/kg</th>
<th>&gt;120% 25 kcal/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Gain:</td>
<td>28-40 lbs</td>
<td>25-35 lbs</td>
<td>15-25 lbs</td>
</tr>
<tr>
<td>Composition:</td>
<td>Carbohydrate:</td>
<td>40-50% (complex high fiber)</td>
<td>200 gm</td>
</tr>
<tr>
<td></td>
<td>Protein:</td>
<td>20%</td>
<td>100 gm</td>
</tr>
<tr>
<td></td>
<td>Fat:</td>
<td>30-40% (&lt;10% saturated)</td>
<td>100 gm</td>
</tr>
</tbody>
</table>
Hypoglycemia in the Pregnancy Complicated by Diabetes Mellitus

Program of Care

- Determine if: patient has hypoglycemic (un)awareness; wears diabetes identification
- Review and adjust diet, insulin regimen, exercise
- Instruct family members in treatment of hypoglycemia including use of glucagon
Neonatal Morbidity and Glycemic Control in Women with Type 1 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Condition</th>
<th>&lt; 100 mg/dL</th>
<th>≥ 100 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGA (90th percentile)</td>
<td>6%</td>
<td>&gt; 20%</td>
</tr>
<tr>
<td>Macrosomia (≥ 4 kg)</td>
<td>3%</td>
<td>&gt; 10%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>7%</td>
<td>38%</td>
</tr>
<tr>
<td>RDS</td>
<td>5%</td>
<td>22%</td>
</tr>
</tbody>
</table>

IMPORTANT: Lessons Learned

- Remember the patient is more than her blood glucose
- Don’t underestimate the patient’s insight. Ask for the patient’s input in determining what changes to make to improve her glucose control
- Keep the insulin program simple and make changes based on patterns
Lessons Learned

- Enlist the support of the patient’s family
- Avoid hypoglycemic reactions
- Work closely with the healthcare team including the nurse educator, nutritionist, and social worker
- When glucose control is poor, it’s often the diet
Lessons Learned

- Weekends are not our “friends”, especially three day weekends
- When changing the insulin regimen, try to change just one insulin and one dose at a time
- Insulin analogues are valuable
- Respond aggressively to nausea and vomiting and fever
Fetal Evaluation

- Assessment of fetal well being:
  - Outpatient testing programs:
    - Daily maternal assessment of fetal activity at 28 weeks
    - Weekly NST at 28-30 weeks
    - Twice weekly testing: NST alternating with BPP at 32 weeks
Pregestational Diabetes Mellitus
Timing of Delivery

Low Risk for Fetal Death
Well-controlled 39 weeks

High Risk for Fetal Death
With vascular disease 37\(0/7\)–38\(6/7\) weeks
Poorly controlled 37\(0/7\)–38\(6/7\) weeks
Pregnancy Complicated by Diabetes Mellitus: Objectives of Care

- Prevent congenital malformations
- Eliminate intrauterine deaths
- Prevent iatrogenic prematurity and RDS
- Prevent immediate neonatal morbidity, including
  - Birth trauma
  - Hypoglycemia
  - Hypocalcemia
  - Hyperbilirubinemia
- Reduce long-term neurologic sequelae
Keys to the Care of the Pregnancy Complicated by Diabetes Mellitus

• Blood glucose

• Blood vessels
References


Gestational diabetes mellitus (GDM) is defined as diabetes that is first diagnosed in the second or third trimester of pregnancy that is not clearly either preexisting type 1 or type 2 diabetes.

- American Diabetes Association 2017
Consequences of Gestational Diabetes: Why Bother to Screen?

*Maternal*

Subsequent diabetes mellitus:
- 50% with type 2 diabetes mellitus especially in first decade postpartum
- Shortened life expectancy
Gestational Diabetes Mellitus
Approaches to Screening and Diagnosis

High Risk: Clinical characteristics consistent with a high risk of GDM:
- Overweight or obese, BMI ≥ 25
- PCOS
- High-risk race/ethnicity
- Hypertension
- History of GDM or glucose intolerance
- Delivery of LGA infant
- First-degree relative with diabetes

Test as soon as possible to detect undiagnosed type 2 diabetes. If negative, retest at 24-28 weeks gestation.
What is the Nature of the Relationship between Maternal Glucose Values and Neonatal Outcomes?

![Graph showing the relationship between fasting plasma glucose concentration (mmol/L) and outcome frequency (%). The graph has concentration categories from <4.2 to >=5.6 and outcome categories like Birthweight, % Body fat, and Cord C-peptide.]

Detection: Two Step Approach

- 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.

- 135 mg/dL used at Ohio State
Gestational Diabetes Mellitus
100 g oral glucose load
Diagnostic Criteria: ADA* and ACOG*

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>
Gestational Diabetes Mellitus Treatment

- Visits every 1-2 weeks until 36 weeks; then weekly
- Dietary management:
  - 2000-2200 calorie, no-concentrated-sweets diet.
  - Utilization of high fiber foods.
  - Blood glucose monitoring
Exercise and GDM

- A program of moderate-intensity physical exercise (brisk walking) is recommended
- Daily for 20-30 minutes

ACOG Committee Opinion, Number 650; December 2015
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.

- If fasting capillary value > 95mg/dL and/or 1-hour value > 140 mg/dL or 2-hour value > 120mg/dL, insulin or an oral hypoglycemic drug is required.

- Approximately 10-20% of patients will need this additional therapy.
Treatment with Insulin and Oral Hypoglycemic Drugs

- Insulin may be started at 0.8-1.2 units/kg actual body weight depending on trimester
- <50% of total dose as NPH at breakfast and/or bedtime
- >50% of total dose as rapid acting insulin (lispro or aspart) before meals
- Glyburide may be started at 2.5 mg twice daily; 30-60 minutes before breakfast and dinner.
- Metformin may be started at 500-1000mg twice daily.
**GDM: Consequences of Not Treating**

Pregnancy Outcomes in Untreated and Treated GDM and Nondiabetic Subjects

Group 1: untreated GDM (n=555); Group 2: treated GDM (n=1110); Group 3: nondiabetic (n=1110)

<table>
<thead>
<tr>
<th></th>
<th>OR (95%CI) Group 1 vs .3</th>
<th>OR (95% CI) Group 2 vs. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrosomia</td>
<td>2.66 (1.93 -3.67)</td>
<td>1.13 (0.82 -1.55)</td>
</tr>
<tr>
<td>LGA</td>
<td>3.28 (2.53 – 4.6)</td>
<td>1.06 (0.81 – 1.38)</td>
</tr>
<tr>
<td>Composite Outcome*</td>
<td>11.20 (8.71 – 14.39)</td>
<td>1.69 (1.33 – 2.15)</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>4.07 (1.63 – 10.16)</td>
<td>1.43 (0.54-3.78)</td>
</tr>
</tbody>
</table>

*One or more of the following stillbirth; macrosomia/LGA; neonatal hypoglycemia; erythrocytosis hyperbilirubinemia

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

\[
\begin{align*}
&\text{Fasting} < 95 \text{ mg/dl} \\
&\text{1 hour} \geq 180 \text{ mg/dl} \\
&\text{2 hour} \geq 155 \text{ mg/dl} \\
&\text{3 hour} > 140 \text{ mg/dl}
\end{align*}
\]

2 of these abnormal

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.

A Prospective Multicenter Randomized Treatment Trial of Mild Gestational Diabetes

### RCTs of Treatment of GDM: Results

<table>
<thead>
<tr>
<th></th>
<th>MFMU(^1)</th>
<th>ACHOIS(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Weight gain</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>LGA</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Fetal fat</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>↓</td>
<td>NS</td>
</tr>
</tbody>
</table>

1-Landon. NEJM 2009;361:1339  
2-Crowther. NEJM 2005;352:2477
Glibenclamide (G), Metformin (M), and Insulin (I) for the treatment of GDM: a systematic review and meta-analysis

G vs. I: ↑ B.W. 109g, ↑macro RR 2.62,
↑ NN hypo RR 2.04; failure rate 6.4%

M vs. I: ↓mat. wt. gain 1.1 kg., ↓GA 0.16 wks,
↑PTB RR 1.5; failure rate 34%

M vs. G: ↓mat. wt. gain 2kg., ↓B.W. 209g,
↓macro RR 0.3, ↓LGA RR .44

Delivery – Class A₁

- 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
Delivery – Class A2

- Patients with GDM who require insulin or an oral hypoglycemic agent 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.

- Suboptimally controlled GDM may require delivery before 39 weeks.

- Infant to be observed closely for hypoglycemia, hypocalcemia, hyperbilirubinemia.

- Encourage breastfeeding
Evaluation for Carbohydrate Intolerance
Postpartum Care

- Check fasting or random plasma glucose, 1-3 days after delivery

- At 6-12 weeks postpartum (ACOG)*, all patients who had GDM should be evaluated and reclassified as follows using a fasting glucose or 75-g 2 hour oral GTT (ACOG)**

*ADA, 4-12 weeks
**ADA, 75-g 2 hour oral GTT
Evaluation for Postpartum Carbohydrate Intolerance:

75g  2 hour oral GTT

<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>
Strategies for Prevention/Delaying Onset of Type 2 Diabetes Mellitus in Women with Prior GDM

- Breast Feeding
- Family Planning
- Weight Loss
- Healthy Diet
- Exercise
- Smoking Cessation
- Metformin
References


