DIABETES AND PREGNANCY

Uchenna Nwosu, MD
Professor
Department of OB/GYN
ETSU College of Medicine

DISCLAIMER
NEITHER THE PUBLISHER NOR
THE AUTHORS ASSUME ANY
LIABILITY FOR ANY INJURY
AND OR DAMAGE TO PERSONS
OR PROPERTY ARISING FROM
THIS WEBSITE AND ITS
CONTENT.

DIABETES AND PREGNANCY: OBJECTIVES

❖ Appreciate the role of Priscilla White’s classification in the management of diabetes in pregnancy
❖ Understand the effect of pregnancy on diabetes and effect of diabetes on pregnancy
❖ Appreciate the roles of diet and insulin in the control of blood sugar
❖ Discuss the role of preconception counseling in the management of Type II diabetes

DIABETES IN PREGNANCY: CASE SCENARIO

❖ A 17 year old primigravida is registered at 10 weeks gestation with normal lab results. At 26 weeks a routine urinalysis reveals 2+ glycosuria.
DIABETES IN PREGNANCY:
CASE SCENARIO (CONT'D)

- One hour glucose screen is performed and plasma glucose is reported as 170 mg/dl (Normal <140mg/dl). She has no history of diabetes.

DIABETES & PREGNANCY

- She is prepared for*, and given 3-hr OGTT. Fasting BS and 2 hr values are elevated (110 & 180 respectively).

<table>
<thead>
<tr>
<th>Normal plasma values:</th>
<th>Capillary values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>95</td>
</tr>
<tr>
<td>1 hour</td>
<td>190</td>
</tr>
<tr>
<td>2 hour</td>
<td>165</td>
</tr>
<tr>
<td>3 hour</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>155</td>
</tr>
<tr>
<td></td>
<td>140</td>
</tr>
</tbody>
</table>

* 3 days of high CHO diet (150 gm/day)

GESTATIONAL DIABETES

- Carbohydrate intolerance leading to hyperglycemia with onset or first recognition during pregnancy.

ACOG Committee Opinion #435, June 2009

DEFINITION

ENABLING FACTORS:
PLACENTAL HORMONES

- Human placental lactogen - Diabetogenic
- Increased Progesterone
- Increased Prolactin – Insulin Resistance
- ? Cortisol
ADA CLASSIFICATION

❖ Type I: Diagnosed in childhood, often brittle and difficult to control.
❖ Type II: Adult-onset.
   The diabetic status is then described, e.g., Type II diabetes with mild vascular disease.
❖ Gestational.

Priscilla White’s Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Age at Onset</th>
<th>Duration</th>
<th>Vascular Disease</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Any</td>
<td>Any</td>
<td>None</td>
<td>A1: Diet only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A2: Insulin</td>
</tr>
<tr>
<td>B</td>
<td>&gt;20</td>
<td>&lt;10</td>
<td>None</td>
<td>Insulin</td>
</tr>
<tr>
<td>C</td>
<td>10-19</td>
<td>10-19</td>
<td>None</td>
<td>Insulin</td>
</tr>
<tr>
<td>D</td>
<td>&lt;10</td>
<td>&gt;20</td>
<td>Benign Retinopathy</td>
<td>Insulin</td>
</tr>
<tr>
<td>F</td>
<td>Any</td>
<td>Any</td>
<td>Nephropathy</td>
<td>Insulin</td>
</tr>
<tr>
<td>R</td>
<td>Any</td>
<td>Any</td>
<td>Proliferative Retinopathy</td>
<td>Insulin</td>
</tr>
<tr>
<td>H</td>
<td>Any</td>
<td>Any</td>
<td>Heart Disease</td>
<td>Insulin</td>
</tr>
<tr>
<td>T</td>
<td>Any</td>
<td></td>
<td>Heart or kidney Transplant</td>
<td>Insulin</td>
</tr>
</tbody>
</table>

DIABETES AND PREGNANCY:

❖ SHOULD WE SCREEN?
DIABETES & PREGNANCY

- Maternal age greater than 25
- Previous macrosomic infant
- Previous unexplained fetal demise
- Previous pregnancy with GDM
- Strong immediate family history
- Obesity [greater than 90kg]
- Fasting glucose greater than 140mg/kg
- Hispanic, African, Native American, South or East Asian, Pacific Islands ancestry.

RISK FACTORS FOR GESTATIONAL DIABETES

DIABETES

- Step 1: None Added-Sugar diet
- Target blood sugars
  - FBS 60-100 mg/dl
  - 2 hr pp BS 120 mg/dl

DIABETES & PREGNANCY

Step 2: DIETARY CONTROL

- TIED TO IDEAL BODY WEIGHT (IBW). IBW is 100lb for the first 60 inch. Add 5lb per inch above 60 inch.
- IBW x (36 to 40) /2.2 for low BMI
- Daily caloric need is 100 +0.25(Present weight -IBW) x (36 to 40)/2.2.
- 40% high fiber CHO, 20% protein and 40% fat (polyunsaturated).

DIABETES IN PREGNANCY:

CASE SCENARIO (CONTD)

- Two weeks later both her FBS and 2hr postprandial blood sugars are still elevated.
Diabetes and Pregnancy
Step 3: INSULIN THERAPY
Insulin was discovered by Frederick Banting and Charles Best in 1922

- Species
  - Beef
  - Pork
  - Beef-Pork
  - Human
  - Human Analog (recombinant DNA)
    - Lispro
    - Aspart
    - Glargine

INSULIN

- Types of Insulin
  - Regular
  - NPH
  - Lente
  - Ultralente
  - NPH/R 50/50
  - NPH/R 70/50

Human Insulin Analogs

- Synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that have been genetically altered by gene addition.

Insulin is a polypeptide hormone formed, after elimination of C peptide by hydrolysis, of two chains of 21 and 38 amino acids, connected by two disulfide bridges. It is secreted by the b cells of the islets of Langerhans of the pancreas and exerts an hypoglycemic action.
### C-Peptide

- The pancreas of patients with type 1 diabetes is unable to produce insulin and therefore they will usually have a decreased level of C-peptide, whereas C-peptide levels in type 2 patients are normal or higher than normal.
- Can be used for identifying factitious disorder: Hypoglycemia with low C-peptide level may indicate abuse of insulin.
- C-peptide is easily detected because antibodies that are sensitive to it are readily available, whereas antibodies to insulin are much more difficult to obtain.

### Human Insulin and Analogs

![Diagram of human insulin and analogs]

### Insulin Pharmacodynamics

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset (hr)</th>
<th>Peak (hr)</th>
<th>Duration (hr)</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>½ - 1</td>
<td>2 - 4</td>
<td>5 - 8</td>
<td>Clear</td>
</tr>
<tr>
<td>NPH</td>
<td>1 - 2</td>
<td>4 - 10</td>
<td>14+</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Lente</td>
<td>1 - 3</td>
<td>6 - 14</td>
<td>20+</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Ultra Lente</td>
<td>6</td>
<td>14 - 18</td>
<td>18 - 24</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Insulin Glargine</td>
<td>1½</td>
<td>Flat</td>
<td>24+</td>
<td>Clear</td>
</tr>
</tbody>
</table>
Split dose insulin administration

<table>
<thead>
<tr>
<th>Insulin</th>
<th>FBS</th>
<th>2hr PP Breakfast</th>
<th>2hr PP Lunch</th>
<th>2hr PP Supper</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM Regular</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM NPH</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM Regular</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>PM NPH</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Glibenclamide (Glyburide)

- Sulfonylurea drugs rarely used in pregnancy for fear of teratogenicity and neonatal hypoglycemia
- Recent in vitro and in vivo evidence have determined that glibenclamide does not enter the fetal circulation.
- First-generation sulfonylurea drugs chlorpropamide (Diabenese) and tolbutamide (Orinase) have been shown to cross the placenta

Blood Glucose concentrations Measured At Home and Glycosylated Hemoglobin Values During Treatment in Women with Gestational Diabetes


<table>
<thead>
<tr>
<th>Variable</th>
<th>Glyburide (N = 201)</th>
<th>Insulin (N = 203)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week of onset of blood glucose testing</td>
<td>28 ± 6</td>
<td>27 ± 8</td>
<td>0.22</td>
</tr>
<tr>
<td>No. of weeks of testing</td>
<td>10 ± 6</td>
<td>13 ± 7</td>
<td>0.12</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>98 ± 13</td>
<td>96 ± 16</td>
<td>0.17</td>
</tr>
<tr>
<td>Preprandial</td>
<td>95 ± 15</td>
<td>97 ± 14</td>
<td>0.17</td>
</tr>
<tr>
<td>Postprandial</td>
<td>113 ± 22</td>
<td>112 ± 18</td>
<td>0.60</td>
</tr>
<tr>
<td>Mean</td>
<td>103 ± 16</td>
<td>105 ± 18</td>
<td>0.99</td>
</tr>
<tr>
<td>Glycosylated Hgb (%)</td>
<td>5.5 ± 0.7</td>
<td>5.4 ± 0.6</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Metformin (Glucophage)

- A biguanide hypoglycemic agent
- Does not cross the placenta
- Works in 3 ways
  - Reduces gluconeogenesis in the liver
  - Enhances insulin action
  - Lowers fasting levels of plasma insulin in hyperinsulinemia

Small cohort studies in women with PCOS showed

- Reduced rates of spontaneous abortion
- Normal morbidity and mortality rates in women continuing to use the drug in first trimester or throughout pregnancy
- Reduced subsequent risk of GDM with continued use during pregnancy
- Favorable pregnancy outcome


ACOG Technical Bulletin # 30, 2001, Reaffirmed 2010

- Glyburide should not be prescribed for the treatment of gestational diabetes until additional RCTs support its safety and effectiveness.
- RCTs are needed to demonstrate the safety and effectiveness of metformin in pregnancy before use of this medication is warranted for the treatment of gestational diabetes.

Gestational Diabetes (Obstet Gynecol 2001;98:525-538)
INSULIN: Pharmacodynamics
Absorption from:
- arm
- buttocks
- abdomen
- thighs

Blood Sugars: Pre- or Postprandial?
- Pre meal BS monitoring correlate poorly with fetal morbidity
- Post meal BS monitoring correlate with fetal/neonatal outcome
- 3 – 4 AM BS monitoring permit detection of nocturnal hypoglycemia

DIABETES IN PREGNANCY: CASE SCENARIO (CONTD)
- Once on insulin she has no further problem of hyperglycemia. At 39wk and 4 days she is admitted in labor. The head fails to descend beyond +1 station after full dilatation.
**DIABETES IN PREGNANCY:**

**CASE SCENARIO (CONT'D)**

*Following delivery her blood sugar concentrations return to normal. However she contacts you again 21 yrs later, and tells you that she has been on insulin starting 3 months after her first delivery. She has had no further pregnancy by choice. She is now married, and wishes to be pregnant. Her fasting blood sugar is 118.*

---

**Effect of Maternal Diabetes on the Fetus**

- Maternal insulin release
  - Glucose utilization
    - Hyperglycemia
      - Fetal Hyperglycemia
  - Body mass
  - Delayed lung maturation
  - Hyperinsulinemia
  - Lactate Acidemia
- Congenital malformation

---

**TYPES OF CONGENITAL MALFORMATIONS**

- Fetal cardiac anomalies 5x more common:
  - Transposition of great vessels
  - Mitral and pulmonary atresia
  - Double outlet right ventricle
  - Tetralogy of Fallot
  - Fetal cardiomyopathy
- CNS – Spina Bifida, Anencephaly
- Caudal regression syndrome – Most specific malformation
- Must consider family history of other malformations that are unrelated to DM

---

**GLYCOSYLATED HGB AND MALFORMATIONS**

- Hb A1c <8.5% associated with 3.4% malformations
- Hb A1c > 8.5% associated with 22.4% malformations
Caudal Regression Syndrome:
The ossified spine ends in the mid lumbar region in a 22 week fetus

Radiology 2004;230:229-233

Caudal Regression Syndrome

From Indian Pediatrics Journal

Caudal Regression Syndrome

Twins with caudal regression syndrome
Delivered by a mother with Type 2 Diabetes
X-ray of the twins with caudal regression syndrome delivered by a mother with Type 2 diabetes

**PRE-PREGNANCY COUNSELING**

- Classify her diabetes: determine presence of vasculopathy: ophthalmologic evaluation, EKG, 24hr urine for Cr Cl and protein.
- Obtain Hb A1c
- Educate about management plan in pregnancy.
  - Provide contraceptive counseling.
  - Begin folic acid prophylaxis - Dose: 4 mg/day from 1 month pre-pregnancy to 12 weeks.
  - Improve maternal glucose control to reduce risks of congenital malformation and miscarriage.

**DIABETES IN PREGNANCY: CASE SCENARIO (CONTD)**

- After 3 months she misses her period, and pregnancy test is positive. She has 2+ proteinuria.

**FIRST PRENATAL VISIT**

- Routine prenatal lab
- Baseline 24 hour UA for protein and Cr Clearance
- Baseline retinal exam
- EKG
- Thyroid function tests in Type 1 Diabetics
- Hemoglobin A1C
- Schedule 10-12 week Ultrasound
ASSESSMENT OF FETAL WELL-BEING

- Targeted ultrasound at 17 – 19 weeks
- Fetal echo at 24 – 26 weeks
- Daily fetal movement counting
- Twice weekly NST by 32 weeks
- Weekly BPP or at least weekly assessment of AFV
- Umbilical artery doppler if growth lag detected
- With more advanced disease, earlier testing is recommended

DIABETES IN PREGNANCY:  
CASE SCENARIO (CONTD)

- At 36 weeks the fundal height is 31 cm.

DIABETES & PREGNANCY

- Macrosomia
- IUGR
- Congenital abnormalities

NEONATAL METABOLIC COMPLICATIONS

- Hypoglycemia
- Hypocalcemia
- Hypothermia
- Hypomagnesemia
- Hyperbilirubinemia