DIABETES, PREGNANCY, AND THE HEART
I have no financial disclosures
DEFINING DIABETES IN PREGNANCY

- Pregestational
  - Type 1 Diabetes
    - Immune mediated
    - Auto-antibodies destroying beta-cells in the pancreas
    - Leads to insulin deficiency
    - Accounts 5 – 10% of those with diabetes
  - Type 2 Diabetes
    - Insulin resistance
    - Accounts for 90 – 95% of DM
- Other
- Gestational Diabetes (GDM)
  - Any degree of glucose intolerance first recognized in pregnancy
  - Prevalence mirrors that of type 2 diabetes
CASE 1:

- 23 yo G0 with type 1 DM desires pregnancy. She has had diabetes since 10 years old. She has already started taking prenatal vitamins, but has not yet stopped her contraception. Her BMI is 20 and her HgbA1c is 8.2%. What do you advise her?
CASE 2:

- 35 year old African American female with obesity (BMI of 40), chronic hypertension, smoker, and type 2 DM, currently on metformin and lisinopril comes into your office. She has diabetic gastroparesis, a history of a toe-amputation, two PE’s during previous hospitalizations. Her hemoglobin A1c is 14%. An in-office pregnancy test is positive, and a preliminary ultrasound shows twins. What should you advise her about risks to her and her fetuses?
OUTLINE

- The Epidemic of Obesity and Diabetes
- Maternal diabetes and cardiovascular risks to the mother
- Maternal diabetes and risks to the fetus
- Preconceptually preventing complications
The Obesity Epidemic

"Obesity is neither contagious or genetic, and yet, it is passed on from parents to children."
OBESITY TRENDS* AMONG U.S. ADULTS
BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
OBESITY TRENDS* AMONG U.S. ADULTS
BRFSS, 1990

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
OBESITY TRENDS* AMONG U.S. ADULTS
BRFSS, 1995
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
OBESITY TRENDS* AMONG U.S. ADULTS
BRFSS, 2000

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
OBESITY TRENDS* AMONG U.S. ADULTS
BRFSS, 2005

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
OBESITY TRENDS* AMONG U.S. ADULTS
BRFSS, 2010

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Prevalence by Gender & Age

CDC/NCHS, National Health and Nutrition Examination Survey, 2009-10

NHES and NHANES: Flegal e al., JAMA 2002 Ogden et al. JAMA 2006; Ogden et al., NCHS Data brief #1, 2007
County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years:
United States 2004

Percent
0 - 6.5
6.6 - 8.0
8.1 - 9.4
9.5 - 11.1
>11.2
County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years: United States 2005
County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years:
United States 2006
County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years: United States 2007
County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years: United States 2009
Cardiovascular Complications
- Chronic Hypertension
- Preeclampsia
- Heart Disease
- Myocardial Infarction in pregnancy

Worsening of diabetic complications
- Retinopathy
- Nephropathy
- Hypoglycemia
CHRONIC HYPERTENSION

- **Incidence**
  - Hypertensive disorders affects 15 – 30% of pregnancies complicated by diabetes
  - 4-fold over that for non-diabetic population
  - Likely reflects underlying renal compromise

- **Definition**
  - BP $\geq 140/90$ mm Hg before 20 weeks GA

- **Complications**
  - Maternal stroke
  - Growth restriction of the fetus
  - Preeclampsia
  - Placental abruption
Preeclampsia

- Pregnancy-associated disease characterized by high blood pressure and proteinuria
- Other important potential complications:
  - eclampsia (seizure)
  - stroke
  - hepatic dysfunction
  - thrombocytopenia
  - growth restriction
  - Abruption
  - Maternal death
- Affects 5 – 10% of pregnancies at baseline
- 4 times more common in women with pregestational diabetes
- Risk of getting preeclampsia is related to severity and duration of preexisting diabetes
LIKELIHOOD OR PREECLAMPSIA IN DIABETIC PREGNANCY

Eclampsia in the first pregnancy
- Increased mortality two-fold to five-fold higher

Preeclampsia
- Increased mortality from CV mortality 2-8 fold
- Persistent hypertension
- Metabolic syndrome
Is pregnancy a risk factor for acute MI?
Pregnancy offers a glimpse into the future
Pregnancy physiology
  - Increased plasma volume expansion
  - Altered hemodynamics (increased heart rate and stroke volume)
  - Increased estrogen and progesterone
Epidemiology of myocardial infarction in pregnancy
  - 3 – 10 per 100,000 pregnancies
  - Case fatality rate is 5 – 37%
Other factors
  - Increasing proportion of first-time mothers who are advanced maternal age
  - Increasing incidence of obesity

Roth et al. Acute MI Associated with Pregnancy. JACC 2008
FREQUENCY OF PREGNANCY-RELATED MYOCARDIAL INFARCTION

- Nationwide Inpatient Survey
  - 2000 – 2002
  - Over 12 million deliveries
- Goal:
  - Ascertain the incidence, risk factors, and mortality associated with myocardial infarction in pregnancy

<table>
<thead>
<tr>
<th>Timing of AMI</th>
<th>Population size (n)</th>
<th>No. with AMI</th>
<th>Percent of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy admission</td>
<td>13,687,131</td>
<td>626</td>
<td>73</td>
</tr>
<tr>
<td>Postpartum readmission</td>
<td>114,368</td>
<td>233</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>13,801,499</td>
<td>859</td>
<td>100</td>
</tr>
</tbody>
</table>

Overall risk of pregnancy-related AMI: 6.2 per 100,000 deliveries

44 deaths out of 859: all-cause mortality rate of 5.1%

Mortality rate of 0.35 per 100,000 deliveries

Risk of AMI increased with age, and was higher in women who were Black or Hispanic

<table>
<thead>
<tr>
<th>Age and Race</th>
<th>No. of cases</th>
<th>Rate per 100,000</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>White &lt;35 y</td>
<td>185</td>
<td>4.5</td>
<td>1</td>
</tr>
<tr>
<td>White ≥ 35 y</td>
<td>192</td>
<td>22.5</td>
<td>5.1*</td>
</tr>
<tr>
<td>Black &lt; 35 y</td>
<td>87</td>
<td>7.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Black ≥ 35 y</td>
<td>56</td>
<td>40.9</td>
<td>8.4*</td>
</tr>
<tr>
<td>Hispanic &lt; 35</td>
<td>56</td>
<td>3</td>
<td>0.7</td>
</tr>
<tr>
<td>Hispanic ≥ 35</td>
<td>30</td>
<td>14.6</td>
<td>3.2*</td>
</tr>
</tbody>
</table>
## RISK ACCORDING TO MEDICAL COMORBIDITIES AND OB COMPLICATIONS

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>21.7</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>25.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.6</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>3.6</td>
</tr>
<tr>
<td>Smoking</td>
<td>8.4</td>
</tr>
<tr>
<td>Pregnancy or Delivery Complication</td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1.6</td>
</tr>
<tr>
<td>Postpartum Hemorrhage</td>
<td>1.8</td>
</tr>
<tr>
<td>Transfusion</td>
<td>5.1</td>
</tr>
<tr>
<td>Postpartum Infection</td>
<td>3.2</td>
</tr>
</tbody>
</table>
OTHER MATERNAL COMPLICATIONS

- Retinopathy can progress
- Hypoglycemia
- Nephropathy:
  - GFR during pregnancy can decrease (normal GFR should increase by 50 – 100% in pregnancy). Protein excretion can increase
MATERNAL DIABETES AND THE FETUS
PREGNANCY OUTCOMES

Source: Confidential Enquiry into Maternal and Child Health (CEMACH) Diabetes Audit
Risk of a major or minor congenital anomaly according to HbA1c measured periconceptionally.
HEMOGLOBIN A1C AND MAJOR FETAL ANOMALIES

% Risk of Fetal Malformation

- 7
- 7.1 - 9.1
- 9.2 - 11.1
- 11.2
TERATOGEN

- "IS AN AGENT THAT HAS THE POTENTIAL TO INTERFERE WITH THE NORMAL FUNCTIONAL OR STRUCTURAL DEVELOPMENT OF AN EMBRYO OR FETUS"

- HYPERGLYCEMIA IS TERATOGENIC
DIABETES AND FETAL CONGENITAL ANOMALIES: MECHANISM?

HYPERGLYCEMIA

Neural crest cells
Important in development
Of cardiac muscle cells

Formation of:
Free oxygen radicals

TGF-beta
BMP4
MSX4
Pax3

Altered metabolism of:
Inositol
Prostaglandins
Arachidonic acid

Altered gene expression
CONGENITAL HEART DISEASE (CHD)

- EUROCAT
- Conducted from 2000 – 2005
- 29 databases and registries from 16 countries
- Findings:
  - 3,336,209 total births (13% of all European births)
  - 26,598 cases of congenital heart disease → 8 per 1000
  - 23,348 were NOT chromosomal → 7 per 1000

# CHD ASSOCIATED WITH MATERNAL DM

<table>
<thead>
<tr>
<th>Condition</th>
<th>General Population (%)</th>
<th>Diabetic Population (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent Truncus</td>
<td>0.9</td>
<td>3.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Transposition</td>
<td>4.8</td>
<td>12.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Conotruncal</td>
<td>10.7</td>
<td>24</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Single ventricle</td>
<td>0.3</td>
<td>5.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>11.2</td>
<td>6.5</td>
<td>0.012</td>
</tr>
<tr>
<td>Aorta anomalies</td>
<td>4.8</td>
<td>1.9</td>
<td>0.024</td>
</tr>
<tr>
<td>Pulm artery anomalies</td>
<td>2.1</td>
<td>5.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Heterotaxia</td>
<td>0.4</td>
<td>2.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Aortic Valve Anomalies</td>
<td>3.3</td>
<td>0.6</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Lisowski et al. CHD in Pregnancies complicated by maternal DM. Herz 2010
Infants of Insulin dependent diabetic mothers are at increased risk of all CNS anomalies

- Risk: 5.3% (RR is 16)
- Anencephaly: RR = 13
- Spina bifida RR = 20
- Sacral agenesis is rare, but pathognomonic of diabetes
OTHER FETAL COMPLICATIONS

- Increased rate of fetal and neonatal mortality
- Increased risk of miscarriage
- Intrauterine growth restriction (asymmetric)
- Fetal obesity
- Birth Injury
LONG TERM SEQUELAE

- Long-term studies followed children born to diabetic mothers
- Found increased risks of:
  - Obesity at 25 years
  - Adolescent obesity
  - Obesity at ages 2 – 4 years
  - Increased type 2 diabetes in adolescents
  - Adolescent metabolic syndrome (obesity, hypertension, glucose intolerance, and dyslipidemia)
- All findings were independent of maternal obesity
HOW CAN WE PREVENT THIS VICIOUS CYCLE?

"Look out, it's a vicious circle!"
Unplanned pregnancies occur in two thirds of women with preexisting diabetes
Prevents adequate preconception care
Leads to excessively high rate of malformations
In a reproductive aged woman:
- Counseling about the risk of malformations associated with unplanned pregnancies and poor metabolic control
- Use of effective contraception at all times unless the patient is in good metabolic control and actively trying to conceive
• Diabetes is not a contraindication to any form of contraception
PREVENTION OF COMPLICATIONS: PRECONCEPTION CARE PROGRAM

- **Goals**
  - Patient education and counseling

- **Multidisciplinary team**
  - Diabetologist, internist or FP physician skilled in diabetes management
  - Diabetes educators (Nurse, dietician, social worker)
  - OB familiar with managing high-risk pregnancies
  - The patient
### SPECIFIC GOALS

<table>
<thead>
<tr>
<th>HbA1c Upper Target</th>
<th>UK</th>
<th>USA</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT</td>
<td>&lt;6.1% if safely possible</td>
<td>&lt;7%</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>IFC</td>
<td>&lt;43 mmol/mol</td>
<td>&lt;53 mmol/mol</td>
<td>&lt;53 mmol/mol</td>
</tr>
</tbody>
</table>
Duration and type of DM

Acute complications
- Infections
- DKA
- Hypoglycemia

Chronic complications
- Retinopathy
- Nephropathy
- HTN
- Neuropathy

DM management
- Oral medications
- Insulin
- Medical nutrition
- Physical activity

Other medical conditions

Menstrual/pregnancy history and contraception

Support system
PHYSICAL EXAM

- BP measurements (including orthostatics to assess for autonomic neuropathy)
- Retinal exam
- CV exam
- Neurologic exam
LABORATORY EVALUATION

- Hemoglobin A1c
- Serum creatinine
- Protein:Cr ratio or 24 hour urine protein
- +/- TSH and/or FT4 (in Type 1 DM)
MANAGEMENT PLAN

- Counseling
- Antihyperglyemic therapy

Establishing Goals
- HgbA1c <1% above the normal range, lower if possible
- Fasting and before meals meals <95 and 70 – 100 mg/dl
- 2 hour postprandial < 140 mg/dl (no role in preconception, but important in management during pregnancy)

Monitoring
- A1c levels q 1 – 2 months until achieved goals
<table>
<thead>
<tr>
<th>Medications</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>Basal insulin is considered safe and is the insulin of choice</td>
</tr>
<tr>
<td>Fast acting analogue insulin</td>
<td>Widely used without evidence of harm</td>
</tr>
<tr>
<td>Glyburide/Glibenclamide</td>
<td>Safe in pregnancy and lactation</td>
</tr>
<tr>
<td>Metformin</td>
<td>Safe in pregnancy and lactation</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Safe</td>
</tr>
<tr>
<td>Nifedipine, amlodipine</td>
<td>Safe in pregnancy and lactation</td>
</tr>
<tr>
<td>Hydralazine, labetalol</td>
<td>Safe in pregnancy and lactation</td>
</tr>
<tr>
<td>Statins</td>
<td>Discontinue before pregnancy and restart after breastfeeding</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Discontinue before conception – can be teratogenic</td>
</tr>
<tr>
<td>ARB</td>
<td>Avoid, as there is little information available in pregnancy</td>
</tr>
</tbody>
</table>
CASE 1:

- 23 yo G0 with type 1 DM desires pregnancy. She has had diabetes since 10 years old. She has already started taking prenatal vitamins, but has not yet stopped her contraception. Her BMI is 20 and her HgbA1c is 8.2%. What do you advise her?
35 year old African American female with obesity (BMI of 40), chronic hypertension, smoker, and type 2 DM, currently on metformin and lisinopril comes into your office. She has diabetic gastroparesis, a history of a toe-amputation, two PE’s during previous hospitalizations. Her hemoglobin A1c is 14%. An in-office pregnancy test is positive, and a preliminary ultrasound shows twins. What should you advise her about risks to her and her fetuses?
Diabetes and obesity are affecting the reproductive aged population

Diabetes poses many risks to the pregnant woman
Risk of miscarriage increases with worsening glycemic control
There is a fivefold higher risk of stillbirth and other adverse pregnancy outcomes
Fetal macrosomia increases with poor control and obesity
Abnormalities of the heart and CNS are increased 3-fold. Sacral agenesis is uncommon but pathognomonic of DM
Good glycemic control prior to conception is key to avoiding maternal, fetal, and obstetric complications
Encourage the use of effective contraception while optimizing medical problems
THANK YOU