Infant of Diabetic Mother — Not just Glucose

Declan O’Riordan, MD
Neonatologist
St. Luke’s Children’s Hospital
Boise, Idaho
Speaker Disclosure

• I have no financial interest in the topic discussed.

• I will not discuss therapies which are not FDA approved.
Learning Points

• Maternal diabetes causes an abnormal intrauterine environment

• Abnormal intrauterine environment may cause malformations and growth problems

• In addition to well-known hypoglycemia, infants of diabetics are at risk for other difficulties, including feeding and neurologic problems.
Historical Aspects

• Symptoms of DM recognized for thousands of years (as early as 1500 BC)

• Until insulin, no effective treatment for childhood DM—caloric restriction to 450 kcal/day could prolong life

• Frederick Banting and Charles Herbert Best developed insulin in 1921 and 1922—.injected pancreatic extracts into a diabetic dog, then into a child dying of ketoacidosis
Type of Diabetes Mellitus

• Type 1—old term “Juvenile-onset DM”
  – 5-10% of cases of diabetes
  – Onset mostly in childhood (15 to 30% of cases occur after age 30 yr) with autoimmune attack on β-cell

• Type 2 DM—”Adult Onset”
  – About 90% of cases—insulin resistance and deficiency
  – Onset in adolescence to adulthood

• Gestational DM—5% of pregnancies
  – Abnormal glucose tolerance during pregnancy
  – Higher rates in older women, overweight, minorities
DM and Pregnancy

• Pre-gestational v Gestational DM
  – Pre-gestational
    • Type 1 — “Childhood Onset”
    • Type 2 — “Adult Onset”
  – Gestational: onset of insulin resistance in pregnancy — *assumed to have normal glucose level early in pregnancy*
Hyperglycemia Early in Pregnancy

- Hyperglycemia ➔ Teratogenic
- IDM risk for congenital malformation: 5-6% overall
- Risk if mother requires insulin: 10-12%
- Congenital malformations cause of death in 50% of IDM perinatal deaths
Fetus and Diabetic Pregnancy

- Increased risk for stillbirth — fetal loss after 20 wk
- Perinatal mortality rate: Stillbirths + infant deaths up to 28 days/1000 births
- Prior to discovery of insulin
  - Successful pregnancy was rare
  - Perinatal mortality rate 65% (1909)
  - Maternal death rate almost 30%
Decline in IDM Perinatal Mortality Rate 1920-2000

Fig. 1. Estimated rate of stillbirth in diabetic women: 1920-2000. These estimates of the stillbirth rate in diabetic women are based on a summary of the reported literature.

Dudley Clin Perinat 2007
Stillbirth—General Concepts

- National Center for Health Statistics (2003): 6.23/1000 births (overall rate for all pregnancies)
- Rate has been declining for past 50 years
- Most of improvement in rate is for > 28 wks
- Higher stillbirth rates for some groups
  - Non-Hispanic black women: 11.56/1000 births
  - Single women: 8.25/1000
  - Teens, Women > 35 y at higher risk
  - Twins: 16.52/1000
  - Fetal growth restriction with maternal DM
Stillbirth: Type 1 and Type 2 DM

• Type 1:
  – Denmark 1990-2000: \textbf{18}/1000 pregnancies
  – Denmark 1993-1999: \textbf{28}/1000 pregnancies (RR 6.2)
  – Scotland 1979-1995: \textbf{25}/1000 births (RR 4.7)
  – Scotland 1998-1999: \textbf{18.5}/1000 (RR 3.6)
  – UK 2002-2003: \textbf{25.8}/1000 births (RR 4.5)

• Type 2:
  – New Zealand (Cundy 2000): \textbf{34}/1000 v \textbf{12}/1000 in Type 1—Much worse glucose control in Type 2
  – UK 2002-2003: \textbf{29.2} (RR 5.1)
Stillbirth and Gestational DM

• Numbers not as clear as with Type 1 and 2
• Girz (1992): Intensive monitoring
  – 7.7/1000 births
  – Controls: 4.8/1000

• Overall likely some increased risk for stillbirth in GDM, but not to degree of Type 1 or Type 2 DM pregnancies
Causes of Fetal Deaths

• Many cases unexplained
• Fetal hyperglycemia believed to cause acidosis
  – Increased fetal metabolic rate
  – Lactic acidosis (Bradley 1991)
  – Animals: ↑ acidosis and ↑ oxidative damage lead to ↑ fetal deaths and ↑ malformations
• Possibly undetected ketoacidosis (DKA)
  – Perinatal mortality rate 50-90%
• Congenital malformations, infection, vascular insufficiency
Risk for Anomalies (2008 NBDPS study)

- 13,030 infants with anomalies v 4895 controls
  - Risk for Multiple anomalies: highest in mothers with pre-gestational DM (OR 8.62 95% CI 5.27-14.1) — reflects teratogenic effect of hyperglycemia
  - Risk for Single anomaly: higher in pre-gestational DM (OR 3.17 95% CI 2.2 to 4.99)
  - Risk for anomalies higher even in those with Gestational DM (OR 1.42 and 1.5 for single and multiple anomalies)
### Pre-gestational DM and CHD

<table>
<thead>
<tr>
<th>Defect</th>
<th>Isolated Defect Odd Ratio</th>
<th>Multiple Defect Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetralogy of Fallot</td>
<td>4.89 (2.18-10.95)</td>
<td>6.0 (1.67-21.58)</td>
</tr>
<tr>
<td>dTGA</td>
<td>3.34 (1.11-10.07)</td>
<td>71.97 (7.43-696)</td>
</tr>
<tr>
<td>AV Canal</td>
<td>12.36 (3.68-41.49)</td>
<td>25.28 (4.2-152.1)</td>
</tr>
<tr>
<td>TAPVR</td>
<td>7.12 (1.99-25.42)</td>
<td>Not estimated</td>
</tr>
<tr>
<td>Aortic Stenosis</td>
<td>5.01 (1.09-22.9)</td>
<td>Not estimated</td>
</tr>
<tr>
<td>LV Outflow tract problems</td>
<td>4.58 (1.3-16.1)</td>
<td>Not estimated</td>
</tr>
<tr>
<td>RV Outflow tract problems</td>
<td>9.61 (3.53-26.15)</td>
<td>9.83 (1.05-91.85)</td>
</tr>
<tr>
<td>Perimembranous VSD</td>
<td>2.89 (1.27-6.56)</td>
<td>7.70 (2.37-25.04)</td>
</tr>
<tr>
<td>ASD (secundum)</td>
<td>8.47 (4.37-16.42)</td>
<td>13.46 (5.23-34.6)</td>
</tr>
<tr>
<td>ASD (unspecified)</td>
<td>5.32 (1.44-19.68)</td>
<td>Not significant</td>
</tr>
<tr>
<td>VSD + ASD</td>
<td>5.83 (2.48-13.70)</td>
<td>9.62 (2.95-31.35)</td>
</tr>
<tr>
<td>OVERALL</td>
<td>4.64 (2.87-7.51)</td>
<td>10.77 (6.23-18.62)</td>
</tr>
</tbody>
</table>
Congenital Cardiac Malformations

- Overall risk 8.5 per 100 live births to DM
- Defects seen: AV Canals, common atrium, situs inversus, TGA, DORV, VSD, truncus arteriosus, tricuspid atresia, PDA

- Overall incidence of congenital heart disease in all newborns is 1 per 100.
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<th>Defect</th>
<th>Isolated Defect Odds Ratio</th>
<th>Multiple Defect Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All non-cardiac defects</td>
<td>2.34 (1.44-3.81)</td>
<td>7.80 (4.66-13.05)</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>3.39 (1.11-10.31)</td>
<td>Not estimated</td>
</tr>
<tr>
<td>Spina Bifida</td>
<td>NS</td>
<td>7.99 (1.61-39.70)</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>NS</td>
<td>16.16 (1.59-163.88)</td>
</tr>
<tr>
<td>Anotia/Microtia</td>
<td>3.75 (1.04-13.51)</td>
<td>18.50 (6.95-49.24)</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>8.8 (3.39-22.84)</td>
<td>12.13 (3.68-39.98)</td>
</tr>
<tr>
<td>Cleft Lip ± Palate</td>
<td>2.92 (1.45-5.87)</td>
<td>8.07 (3.05-21.39)</td>
</tr>
<tr>
<td>Imperforate Anus</td>
<td>4.70 (1.55-14.26)</td>
<td>8.22 (3.62-18.66)</td>
</tr>
<tr>
<td>Biliary Atresia</td>
<td>NS</td>
<td>18.40 (1.84-183.79)</td>
</tr>
<tr>
<td>Longitudinal Limb Defic.</td>
<td>6.47 (1.83-22.9)</td>
<td>7.01 (1.91-25.68)</td>
</tr>
<tr>
<td>Sacral Agenesis</td>
<td>Not estimated</td>
<td><strong>130.17 (33.8-501)</strong></td>
</tr>
</tbody>
</table>
Birth Defects and Gestational DM

• Weaker odds ratios for birth defects seen in gestational DM
  – overall isolated and overall multiple cardiac defects (OR 1.59 and 1.65).
  – Significant for ToF, Pulmonary Stenosis, and Secundum ASDs

• Association of GDM to isolated non-cardiac defects still significant (OR 1.3 (1.05-1.60))

• Why ↑ risk in gestational DM???
Birth Defects in Gestational DM

• Probably a reflection of pre-pregnancy elevation of glucose
• Birth defects seen more often with maternal obesity
• “Gestational DM” in some may actually represent latent Type 2 DM
Effect of Maternal Wt on Defect Risk in DM in Pregnancy (NBDPS)

<table>
<thead>
<tr>
<th></th>
<th>OR for Isolated Birth Defect</th>
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</thead>
<tbody>
<tr>
<td><strong>Pre-gestational</strong></td>
<td></td>
</tr>
<tr>
<td>Average Wt</td>
<td>2.61 (1.22-5.58)</td>
</tr>
<tr>
<td>Overweight</td>
<td>3.53 (1.24-10.08)</td>
</tr>
<tr>
<td>Obese</td>
<td>3.92 (2.02-7.62)</td>
</tr>
<tr>
<td><strong>Gestational</strong></td>
<td></td>
</tr>
<tr>
<td>Average Wt</td>
<td>1.07 (0.78-1.45)</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.90 (1.28-2.82)</td>
</tr>
<tr>
<td>Obese</td>
<td>1.90 (1.38-2.63)</td>
</tr>
</tbody>
</table>

Gestational Diabetics with normal pre-pregnancy wt did not have increased risk for isolated defects.

Risk for multiple defects also showed ↑ risk w/obesity
Specific Birth Defects

Small Left Colon Syndrome

- Rare
- Bowel obstruction
- Narrow caliber of distal colon beyond splenic flexure
- Usually resolves time
- DDx: Hirschsprung disease

Ellis et al J Ped Surgery 2009
Caudal Regression Syndrome

- Caudal end of spinal cord ends abruptly
- Sacrum hypoplastic
- GU and Lower extremity abnormalities
- Legs may be fused (sirenomelia)
- Rare— but associated with infants of DM

Sharma and Jana, Neurology, 2011
Sacral Agenesis/Caudal Regression

Gabbe: Obstetrics: Normal and Problem Pregnancies, 6th ed
Macrosomia—"big baby"

- Maternal hyperglycemia → fetal hyperglycemia
- Fetal insulin stimulates growth
  - Hyperplasia and hypertrophy of adipocytes
  - Hypertrophy of organs (liver, heart), skeleton
  - Growth acceleration begins at 25 to 28 wks
  - Brain and renal growth are normal
  - Increased shoulder size due to fat accumulation — risk ↑ shoulder dystocia
  - 50% increase in fat stores compared to controls
- Other substances may also affect growth
Macrosomia – Difficult labor

- Increased shoulder size and abdominal circumference → more difficult delivery
- ↑ risk for shoulder dystocia
- ↑ risk for injuries (brachial plexus, clavicular fracture, cephalohematoma, phrenic nerve injury, others)
- ↑ risk for asphyxia
  - 27% of 162 infants born to White class B-R-T mothers had signs of asphyxia (nephropathy, prematurity, hyperglycemia before delivery ↑ risk)
But…..they’re not always big….

- About 5% of IDMs are IUGR (small)
- Uteroplacental insufficiency
  - Maternal vascular disease (Class F, Class R)
  - Hypertension
  - Protein/Energy malnutrition + hypoxia
  - Need to watch for compromise in delivery
IDM: Polycythemia

• Venous HCT > 65%
  – Mimouni (1993)
    • 29% in IDM
    • 5.9% in controls

• Relative hypoxia in utero from hyperglycemia

• One-third of IDMs had elevated umbilical cord EPO levels

• Direct effects of insulin on RBC precursors may contribute

Polycythemia Evaluation

- Follow venous hematocrit
- Viscosity rises with HCT > 65%
- Monitor for complications of *Hyperviscosity*
  - Hypoglycemia
  - Thrombocytopenia
  - Systemic thrombosis (renal vein, stroke, etc)
  - PPHN
  - Altered neurologic function
Hyperviscosity: Therapy

• Balance risk of therapy with benefit
• IV fluids: low risk, avoids excessive wt loss
• Partial volume exchange transfusion:
  – Sequentially replace blood with Normal Saline to decrease HCT to 55 to 60 range
  – Invasive — requires either UVC, UAC, or peripheral art line
  – Increased risk for necrotising enterocolitis (NEC)
  – Does not improve neurologic outcome
Renal Vein Thrombosis

- Rare, but associated with maternal DM
- Post mortem review of 16 cases
  - 5 were in infants of DM
  - 7 other infants were macrosomic with β-cell hypertrophy and hyperplasia (very suggestive of fetal hyperinsulinemia)
- Presentation: Hypertension, flank mass, hematuria, thrombocytopenia
- DX: renal doppler US
Altered Iron Stores

- ↑ HCT requires ↑ iron
- Limited Placental transport
- Reduced iron in:
  - Heart: ↓55%
  - Brain: ↓40%
- 65% have low ferritin at birth
- May affect neuro-development (iron deficiency)

- 95% of LGA IDM have altered iron metabolism
  - Low ferritin
  - ↑TIBC
  - ↓Transferrin saturation

- Post-natal iron therapy not clearly beneficial as this is an altered distribution not total body deficiency
Hyperbilirubinemia

• Jaundice reflects RBC turnover
• ↑ RBC mass in IDM
• Bruising at delivery
• Ineffective erythropoiesis may also contribute
• Phototherapy usually sufficient, but need to be careful regarding bruising and subsequent jaundice
Respiratory Distress Syndrome

• Robert (NEJM, 1976)
  – ↑ risk RDS in IDM
  – RR 5.6 after controlling for confounders
  – Confined to ≤ 38 wk

• Hyperinsulinemia
  – ↓ surfactant due to ↓ substrate availability
  – ↓ fibroblast-pneumocyte factor activity leads to ↓ Type II pneumocyte activity

• Late preterm infants seem at high risk

• Good maternal control, Modern OB methods ↓ risk
RDS: Clinical Features

- Hypoxia due to diffuse microatelectasis
- Retractions
- Grunting and flaring
- DDx: TTN, pneumonia, sepsis, TAPVR
- Mostly in infants < 39 wk

Kliegman: Nelson Textbook of Pediatrics, 19th ed
RDS: Therapy

- Stabilize lung volumes with CPAP
- Intubation and surfactant often required
- Watch for Pneumos!!!
  - Needle aspiration
  - Chest tube
  - Incidence higher with CPAP than ETT/Surfactant
Myocardial Hypertrophy

- Myocyte glycogen ↑
- Septal hypertrophy
- Can be obstructive but is usually temporary
- Avoid hypovolemia, pressors
- ± cardiomyopathy (=? ↓ iron)
Metabolic Problems: Hypocalcemia

• ↓calcium $\rightarrow$ PTH secretion
  – ↑ bone resorption
  – ↑ Ca absorption from gut
  – ↑ Ca resorption from urine

• Calcium usually falls during first 24h (placenta shut off)
• PTH secretion then ↑ Ca
• DM appears to blunt PTH secretion and neonatal bone turnover
Hypocalcemia: Clinical Symptoms

• Often asymptomatic
• Jitteriness common
• Can prolong QTc
• Less likely
  – Seizures
  – Poor contractility
• Measure total and ionized calcium
• Consider DiGeorge if cardiac defect, abnormal lymphocytes (send FISH or microarray)
Hypocalcemia: Therapy

- Balance Risks/Benefits
- Usually can follow without therapy
- Calcium IV infiltration
  - Severe
  - May require plastic surgery
- Calcium gluconate 100 mg/kg/dose slowly
- Central lines preferred
- Oral therapy possible if stable
Hypomagnesemia

- May be as high as 33% of IDMs
- Symptoms similar to hypocalcemia
- Need to fix magnesium to fix the calcium
- Unclear etiology, may be related to maternal hypermagnesemia
Hypomagnesemia: Treatment

• Magnesium Sulfate:
  – 25 to 50 mg/kg/dose IV q4-6h x 3 to 4 doses
  – Max single 2 grams (well below neonatal levels)
  – Enteral: 100-200 mg/kg/dose PO QID

• Cardiac side effects — need to monitor
  – Bradycardia
  – Heart block
  – Hypotension
  – Calcium gluconate is antidote
Hypoglycemia

• Extremely common among infants of diabetics

• Chronic intrauterine hyperglycemia \(\rightarrow\) robust pancreatic insulin secretion by fetus

• Clamping of cord \(\rightarrow\) shut off of glucose

• Continued insulin secretion causes glucose to drop soon after birth

• Therapy: early feeding (may need a bottle)
  – IV support with dextrose (D10, D12.5 via PIV)
  – Glucagon if needed
“Current evidence does not support a specific concentration of glucose that can discriminate normal from abnormal or can potentially result in acute or chronic irreversible neurologic damage.” *Pediatrics* 127:3, March 2011.

- Glucose levels as low as 30 mg/dL are common in first 1 to 2 hr and usually are transient and asymptomatic.
- “No studies have demonstrated harm from a few hours of asymptomatic hypoglycemia during this normal postnatal period…”
## Screening and Management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDM/LGA Infants

((LPT) infants 34 – 36\(^{07}\) weeks and SGA (screen 0-24 hrs); IDM and LGA ≥34 weeks (screen 0-12 hrs))

### Symptomatic and <40 mg/dL — IV glucose

<table>
<thead>
<tr>
<th><strong>Birth to 4 hours of age</strong></th>
<th><strong>4 to 24 hours of age</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INITIAL FEED WITHIN 1 hour</strong></td>
<td><strong>Continue feeds q 2-3 hours</strong></td>
</tr>
<tr>
<td><strong>Screen glucose 30 minutes after 1(^{st}) feed</strong></td>
<td><strong>Screen glucose prior to each feed</strong></td>
</tr>
<tr>
<td><strong>Initial screen &lt;25 mg/dL</strong></td>
<td><strong>Screen &lt;35 mg/dL</strong></td>
</tr>
<tr>
<td><strong>Feed and check in 1 hour</strong></td>
<td><strong>Feed and check in 1 hour</strong></td>
</tr>
<tr>
<td><strong>&lt;25 mg/dL</strong></td>
<td><strong>&lt;35 mg/dL</strong></td>
</tr>
<tr>
<td><strong>IV glucose(^{*})</strong></td>
<td><strong>IV glucose(^{*})</strong></td>
</tr>
<tr>
<td><strong>25–40 mg/dL</strong></td>
<td><strong>Refeed/IV glucose(^{*}) as needed</strong></td>
</tr>
<tr>
<td><strong>Refeed/IV glucose(^{*}) as needed</strong></td>
<td><strong>35 – 45 mg/dL</strong></td>
</tr>
<tr>
<td><strong>Refeed/IV glucose(^{*}) as needed</strong></td>
<td><strong>Refeed/IV glucose(^{*}) as needed</strong></td>
</tr>
</tbody>
</table>

**Target glucose screen ≥45 mg/dL prior to routine feeds**

\(^*\) Glucose dose = 200 mg/kg (dextrose 10\% at 2 mL/kg) and/or IV infusion at 5–8 mg/kg per min (80–100 mL/kg per d). Achieve plasma glucose level of 40-50 mg/dL.

Symptoms of hypoglycemia include: Irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding.
IV Support of Glucose

• If significantly hypoglycemic: **D10W 2 ml/kg bolus followed by constant infusion of D10W at about 80 to 100 ml/kg/day**
• May need D12.5 or even higher dextrose
• Central line needed for > D12.5 (PICC or UVC)
• Glucose infusion rate ➔ useful to track
• GIR = \( \% \text{ Dextrose} \times \text{ Fluid Rate} \times 0.167 \)
  \[
  \text{Infant Wt}
  \]
GIR Calculations

• 5 kg Baby
• Stabilized on D10W at 21 ml/hr (100 ml/kg/day)
• GIR = \(\frac{10 \times 21 \times 0.167}{5} = 7 \text{ mg/kg/min}\)
• Knowing the GIR allows adjustment of dextrose concentration to maintain euglycemia while adjusting total fluids
Hypoglycemia tidbits

• Excessive fluid administration can cause fluid overload → hyponatremia → seizures

So.....

• Follow BMP and follow mL/kg/Day of IVF

• If needing to persistently increase IV rate, then increase dextrose concentration and place central line if needed
Glucagon

- Stimulates gluconeogenesis
- Dose: 200 mcg/kg/dose IV push, IM, or SC
- Continuous: 10-20 mcg/kg/hour
- Max dose 1 mg (1000 mcg)
- Lasts 2 hours
- Indications:
  - Hypoglycemia refractory to IV infusions
  - No IV access
Feeding Difficulties

• Feeding difficulties are **poorly described in literature**

• Periods of intrauterine hypoglycemia may cause secretion of glucagon, which slows intestinal motility (other theory behind Small Left Colon Syndrome)

• Late preterm infants of DM may stay in NICU weeks learning to PO feed or be discharged with home gavage feeds (NG or PEG)
Fetal effects: the long term view

• Is adult health influenced by fetal environment???
• Fetal Origins of Adult Diseases
• “Barker Hypothesis”
• Studies in US, UK, and elsewhere in Europe show fetal growth restriction increases risk for adult cardiac disease
• Fetal metabolic “programming” may not adapt well to post natal circumstances
Barker: Infant wt and Adult Cardiac Disease (1993)

• Lower birth weight and wt at 1 year were associated with increased risk for adult death from cardiovascular disease
• Lowest risk was for infants born at 9.5 lbs
• Risk then rose with advancing BW
Fetal Programming

- Hales and Barker (1992) **Thrifty Phenotype**
  - Fetus adapts to poor intrauterine nutrition by concentrating growth on vital organs (brain)
  - Physiologic response to enhance post-natal survival in environment of questionable nutrition
- Physiologic problems may arise if adaptive response is challenged by abundance of nutrition post natally.
- Concern for excessive post natal growth in growth restricted infants may lead to HTN, insulin resistance, obesity later.
Infant of DM: Uterine Environment

- Intrauterine environment of IDM:
  - Hyperglycemia
  - Chronic increased pancreatic insulin secretion
  - Intermittent hypoglycemia??
  - Increased metabolic rate
  - Increased anabolic rate
  - Increased acidosis
  - Increased growth fat mass, hypertrophy of organs (heart, liver)
  - Increased oxidative stress
Gestational DM: HTN in Offspring

• Mixed results:
  – Jerusalem perinatal study: GDM mothers and > 60,000 singleton offspring at 17 yr → no association of GDM to hypertension in offspring (born between 1964-1976).
  – Retrospective Pima Indian study showed GDM significantly increased systolic BP in children at 7-11 yr. (Still significant after adjusting for BW and childhood obesity).
  – Third Study (Cho, et al J Pediatrics, 2000) —SBP and MBP was significantly higher in children born to GDM mothers
GDM: Overweight and Obesity in Offspring

• Evidence exists showing GDM is linked to overweight/obesity in offspring:
  – UK study showed
    • ↑ risk for obesity/overweight in 9-11 yo offspring of mothers with GDM, but not Type II DM
    • Higher BMI at 17 yr is significantly associated with GDM
  – Prospective study of over 280,000 Swedish men found maternal GDM during pregnancy was associated with higher BMI at 18 yr.
Type 2 DM in Offspring of DM

• **Pima Indian study: Sibling study**
  – higher rates of Type 2 DM in those born after mother developed DM (Dabelea, Hanson, et al, Diabetes 2000)

• **Pima Indian Study:**
  – Offspring of mothers with impaired 3rd trimester glucose tolerance
    • Young adults had ↑ risk (30% at 24 yr) for type 2 DM and risk was directly correlated to degree of hyperglycemia after GTT.
    • If mother had Type 2 DM, 51% risk of type 2 DM for 24 yo offspring.
DM in Offspring of Diabetic Mothers

• Danish Study (Clausen et al Diabetes Care, 2008):
  – Offspring of mothers with DM had 8 fold ↑ risk for diabetes or pre-DM of any type compared to controls
  – Intrauterine hyperglycemia (GDM or Type 1 DM)
    • Increased risk for type 2 DM or pre-DM in offspring
    • At 22 yr, offspring had
      – 21% risk for type 2 DM or pre-DM if mother had GDM
      – 11% risk for type 2 DM or pre-DM if mother had Type 1 DM
      – 4% risk if mother had no DM
  – 3rd Trimester hyperglycemia in Type 1 DM associated risk for diabetes in offspring.
How does this happen??

• Mechanisms unclear—may involve Epigenetic modifications

• Epigenetic Modifications are *environmental changes* to gene expression involving DNA methylation, post-translational histone modifications, and other mechanisms that can be passed down between cell generations.

• Interesting field with widespread applications
Infant of Diabetic: Summary

• Watch for congenital anomalies—even if gestational DM
• Often large for gestational age—but may be small if mother has vascular disease
• At risk for hypoglycemia due to insulin secretion “overshooting” cutoff of glucose with clamping of cord
• May also see hypocalcemia, hypomagnesemia, jaundice, polycythemia/hyperviscosity, birth injuries, asphyxia.
• Often feed poorly as neonates.
• Infants of DM appear to be at higher risk for elevated BP, higher weight in late childhood and as adults, and adult DM.