Risk of Obesity/Metabolic Syndrome in Offspring of Women with Gestational Diabetes

2013

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Offspring of Moms with GDM-Risks for Obesity/Metabolic syndrome:

• Degree of risk related to:
  * Maternal blood sugar control before, during and at delivery;

  * Genetic factors

  * Environmental /Population Norms e.g. diet activity cultural norms
Definition metabolic syndrome:

- Obesity = BMI >85% for age
- Hypertension (systolic or diastolic>95% for age
- Postprandial glucose > 140 mg%
- Fasting glucose > 110 mg%
- Triglycerides > 95% for age
- HDL < 5% for age
What follows?

Independent studies by a wide variety of investigators that contribute to supporting this statement follow.... The studies reflect data from diverse populations around the globe.

- “IDM’s from all cases of GDM are
- Predisposed to later life risks of
  - obesity
  - diabetes mellitus
  - cardiovascular disease.”

- Hay, WW Jr “Care of the Infant of the Diabetic Mother"
  Current Dab Rep , 2012  Feb 12(1) 4-16
Parental Transmission of T2 Diabetes
The Framingham Offspring Study
J.B.Meigs, A. Cupples, and P.W.F.Wilson
Diabetes V.49, Dec. 2000; 2201-2207

*Majority of subjects were Caucasian
Data collected over 2-4 decades

*Criteria for DM tight:
  - fbs $\geq 6.1$ mmol/l (>110mg%)
  - 2 hr Gtt value $\geq 7.8$ mmol/l (>140mg%)
  - also dx’d if on diabetes oral medication

*2527 offspring from 1303 families were studied

*Prevalence Dm mothers 23.6%; fathers 25.6% (mean age onset 60+/-10yrs)
Framingham Offspring study (cont.)

• Offspring : 76.3% no parental DM
• \((n=1929)\) 10.5% maternal diabetes
• 11.5% paternal diabetes
• 1.7% bilineal diabetes
• Parental effects similar among male and female offspring

• Incidence of offspring diagnosed with DM 5.1% at age 60 yrs. and 14.0% at age 70 years
Framingham offspring study (#3)

- **Prevalence (parents):**
  
<table>
<thead>
<tr>
<th>Gender</th>
<th>Abnormal GTT (DM)</th>
<th>Abnormal Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>7.2%</td>
<td>21.5%</td>
</tr>
<tr>
<td>Males</td>
<td>10.0%</td>
<td>24.9%</td>
</tr>
</tbody>
</table>

- **Offspring with abnormal fasting blood sugar (fbs) (>110mg%):**
  
  - 43% Bilineal DM
  - 29% Maternal DM
  - 16% Paternal DM
  - 11% Without parental DM

- **Offspring age adjusted risk of having DM with:**
  
  - Maternal DM: 2.5-3.5x
  - Paternal DM: 1.4-3.5x
  - Bilineal DM: 3-6x

  (compared to those without parental DM).
Framingham Offspring study (#4):

- Offspring with parental DM were more obese at baseline than those without parental DM
  - Greater offspring baseline BMI increased risk for subsequent DM

Maternal and paternal DM conferred equal risk for t2DM in offspring.

- Early onset maternal Dm (< 50 yrs) → 7-10x risk of abn glucose tolerance in offspring
- With older maternal age of onset risk only 2-3x that of nondiabetic parentage.

Early maternal onset of Dm correlated with early offspring onset of Dm (47 yrs vs >54 yrs in later onset Dm or paternal dm.)
Framingham study: authors’ conclusions:

- **Offspring risk ratios appear additive** i.e. when both parents affected transmission of DM is the sum of the individual parental risks.
- This risk data is compatible with 2 different non-interactive genes or closely allied sets of genes from each parent.
- If **environmental factors** affect this genetic risk then they may do so equally in both parents.

- **Similar risk data** has been reported among **Pima Indians**
  - risk 2.3 with one diabetic parent and 4.5 with 2 diabetic parents

**  
Framingham authors’ further observations:

- The increased **risk in offspring** delivered to mothers with earlier onset of DM may be associated with an increase in fetal exposure in the **perinatal** period to **hyperglycemia**. This fetal **environmental** factor may be a factor in T2Dm predisposition.

- Other studies have associated **paternally transferred alleles** associated with **SGA** infants that may predispose to development of t2DM in offspring later in life. (INS-VNTR –regulates polymorphism of the insulin gene and lies near the INS-IGF2 locus that mediates fetal growth ). (1,2)

- Thus the gene(s) from the father and the maternal hyperglycemia at delivery may **independently increase risk** in the child for t2Dm and may be responsible for the nearly equal offspring risk associated with maternal and paternal diabetes.

1. Huxtable, SJ et al; Diabetes 49: 975-980 2000
2. DeChiara, TM; Nature 345:78-80 1999
Metabolic Syndrome in childhood: Association with birth weight, maternal obesity and gestational diabetes mellitus

- Conflicting results in different studies.

- Maternal high BMI appears to be a separate risk factor from gestational diabetes for MS in offspring.

- Other risk factors LGA, SGA with insulin resistance +/- hyperglycemia.
Metabolic Syndrome: Association with Birth Weight, Maternal Obesity and Gestational DM

- MS- looked at obesity, hypertension, dyslipidemia and glucose intolerance
- Subjects: children 6, 7, 9 and 11 yrs old:
  - LGA (84) AGA(95)—with and without GDM
- No difference in gender, socioeconomic status, race, maternal weight gain during pregnancy
- Results:
  - Higher maternal weight gain before pregnancy in LGA/GDM group
  - Obesity (BMI>85%) at 11 years present in 25-35%-same rate for SGA and AGA offspring
  - Higher glucose/insulin ratio of <7 in LGA/GDM group at 11 yrs

* Boney, C.M. etal Pediatrics Vol 115 #3 March 1, 2005 ppe290-e295
MS in Childhood Associations (cont.)

- Childhood obesity, hyperinsulinism and LGA 4.3 OR
- Childhood obesity, hyperinsulinism and GDM 10.3 OR

- **Prevalence** of 2 elements of **MS at age 11**;
  - 50% for LGA/GDM group and >
  - 21% for AGA/GDM group
  - 18% for /control group

- Prevalence of 3 elements of MS at age 11:
  - 15% for LGA/GDM group and 3%-5.3% for other groups

- **Maternal obesity** increased risk of **MS 2x** indep. of GDM Risk

- With age increase from 6->11 yrs **MS risk** not changed in AGA nor LGA control groups **but increased 3.6x in GDM /LGA group** (not for AGA/GDM group).

  Boney, et al
Cardiovascular concerns as part of MS in Childhood:

- Hyperglycemia, hyperinsulinism → septal thickening and decreased ventricular contractility in utero.
- Systolic BP is elevated in offspring of DM
- Diabetic intrauterine environment →
  - dyslipidemia
  - subclinical vascular inflammation
  - endothelial dysfunction
  - Markers: PAI-1
    - VCAM and ICAM
    - e selectin, IGF 1, etc

Level of dysfunction correlates with levels of hyperglycemia

**Leptin** increased in placenta? Possible leptin resistant state (usually suppresses insulin)-may reflect adipocyte or pancreatic dysfunction
CV dysfunction fetus $\rightarrow$ child (cont.)

- **Leptin is proinflammatory**, produced by adipose tissue and may in part cause macrosomia.

- **Leptin** may interact with neuropeptide Y in the hypothalamus; intrauterine hyperglycemia affects hypothalamus $\rightarrow$ “metabolic memory” $\rightarrow$ obesity and metabolic syndrome in childhood,

- Tools for measuring CV risk factors associated with hyperlipidemia, hypertension, inflammation:
  - measurement of aortic intima-media thickness (AIMT)
  - carotid intima – media thickness (> 2yrs)(cIMT)
  - echocardiography
  - retinal photography

ref: Vrachnis, N, etal International Journal of Endocrinology; 2012; Role of adipokines in gestational DM and previous GDM
Intrahepatic Fat Increased in Obese GDM Mothers

- **Use MRI**: 13 infants ages 1-3 weeks born to normal weight mothers
  12 infants ages 1-3 weeks born to obese/GDM mothers

  - **Results**: Infants born to obese GDM mothers had mean **68% increase in** IHCL (intrahepatocellular lipid) compared to normal weight mothers

  - **IHCL correlated** with maternal pre-pregnancy BMI but not with sc adiposity

  - Findings may be relevant to development of nonalcoholic fatty liver disease (NASH) of childhood

  BraumbaughmDE, et al
  J Pediatr 2013 May; 162(5) 930-6
Gut hormone activity of children born to women with and without gestational DM:

- Children of GDm have greater risk for obesity
- Obesity in children and adults is associated with blunted post prandial gut hormone responses
- Studied 5-10 yo (n=42) offspring of DM and of nondiabetic mothers

**Study confirmed children of women with Dm have postprandial GLP1 suppression** and high fasting Pyy levels.

- Postprandial blunted gut hormone response may impair satiety and contribute to weight gain.

Influence of GDM on children’s circadian rhythms and their association with fetal adiposity:

• Studied 21 children of GDM and 23 control children
• Measured: *fetal abdominal circ. Ecographically during gestation
  * skin temperature and rest-activity rhythms were monitored for 3 consecutive days in children at 15 days, 1,3, and 6 months
  * anthropometrical parameters of the children were evaluated during first year of life.

Conclusions: fetal adiposity correlated with worse circadian rhythm regulation on offspring of DM; these children also showed a disturbed pattern of circadian function temperature activity at 6 months of age.

ZamoZa-Moreno.M., etal Diabetes Metab Res.Rev 2013, Apr 8 doi 10 1002/dmrr 2417
(E pub)
Metabolic syndrome: public health concern

- Address pre-pregnancy weight
- Assess glucose tolerance in at risk populations:
  - obese
  - family hx of diabetes
  - previous pregnancy with LGA, SGA or glucose abn.
  - predisposed population: South and East Asian
    - African American
    - Pacific Islanders
    - Latino
    - Middle Eastern
- Intervene with diet, lifestyle, monitoring and education as needed from before, through, and after pregnancy

Encourage breast feeding x 7 months or longer as of delivery

Note: It is estimated 30% of T2Dm patients are undiagnosed.
By 2025 current trends would imply 300 million Dm patients world wide (estimated 140 million-200 million at this time.

Williams, Textbook Endocrinology 11th edition
Chapter 30, 2008
Recommendations for treatment and prevention of Metabolic Syndrome:

• Exercise-moderate 30 minutes a day:
  - brisk walk 3+mph
  - bicycling 5 mild in 30 minutes
  - dancing(social)
  - swimming laps (20 minutes)

  Goal; burn 3-7 kcal/min=3-7METS (working/resting metabolic rate. (1 met =3.5ml/kg/O2 consumption of seated adult at rest)

  Effect: *lower triglycerides and raises HDL*

Adapted from CDC and American College of Sports Medicine
Metabolic Syndrome treatment and Prevention

- Maintain or achieve near **normal weight**: 5-10 lbs weight loss can lower triglycerides

  For most patients involves 200 less calories food intake a day and appx 300 cal lost through increased activity to lose 1 lb a week

  Limit alcohol intake; 1 per day 3-5x a week
Metabolic Syndrome: Food choices:

- Fiber CHO: wheat, oat, bran
- Limit simple sugars: 2x a week, ake, syrups, jams, liquids
- 4-6 solid fruit and vegetables daily
- Use Good fats: liquid oils, nuts, reduced fat PB
- AVOID: animal fat, coconut and palm oils

ADD: omega 3 fatty acids 2-3x a week 3 ounces salmon, tuna, etc.

consider: flax seed oil fish oil capsules
consider per MD: niacin, lipid lowering medications, and medications for glucose control +/- insulin sensitivity