Glycemic Patterns in Normal Pregnancy: Determinants of Fetal Growth

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Disclosures

• I have no financial disclosures to report
Objectives

• Why is it important to better define normoglycemia in pregnancy in regards to long-term infant outcomes?
• Do obese women with normal glucose tolerance have different patterns of glycemia in pregnancy compared to normal weight women when diet is controlled?
• Are there other important metabolic determinants of fetal fat accretion other than glucose?
Infant of Woman with Diabetes

Macrosomia (LGA) Shoulder Dystocia, Infant Respiratory Distress Syndrome, Neonatal Hypoglycemia, Hyperbilirubinemia, Polycythemia
Diabetic Effects on the Fetus

Mother

↑ Glucose

Fetus

↑ Glucose → ↑ Insulin → ↑ Growth

Amniotic fluid insulin

Fetal Overgrowth by ↑ AC on US At 29-34 wks

Cord Blood C-peptide

Jorgen Pedersen 1952 PhD Thesis
Copenhagen Danish Science Press: 230

Osler and Pederson: Body Composition of Newborn Infants of Diabetic Mothers: Pediatrics 1960, 26:985

FFA, TG, AA,
Inflammatory Cytokines,
Hormones, GFs,
Placentation
Prevalence of Impaired Glucose Tolerance in Adolescent Offspring of Diabetic Mothers by Amniotic Fluid Insulin

Silverman, Metzger et al., Diabetes Care 1995; 26.
Prevalence of Diabetes in Offspring from Women with Diabetes - Pima Indians

Fetal Origins Hypothesis

Taylor PD  Exp Physiol 2007;92:287

- Metabolic factors in the intrauterine environment (gluc, FFAs, TGs, inflammatory cytokines, insulin, hormones, growth factors, oxidative stress), have a profound effect on prenatal development and enhances susceptibility to later chronic disease
  - Early exposure: embryogenesis or placentation; alters nutrient transport by placenta and gene expression of cytokines, hormones, GFs
  - Mid: Alter number, growth, and function during organogenesis
  - Later: Impact regulatory energy set points on brain and neuronal-metabolic pathways feed back loops, and mitochondrial function. Time when fetal fat accretion is most rapid
Epigenetics
How the intruterine environment alters DNA methylation and histone modification to change gene expression
Role of Genetics & Environment in Body Composition at Birth

Neonatal fat mass = 46% of variability of birth weight

Intrauterine Environment
FAT MASS

12-15%

85-88%

Humans born with highest % fat mass of any species

Studies in human pregnancies necessary

FAT FREE MASS

Genetics

Catalano, AJOG 1995
Long Term Implications to Offspring

Heavier Baby Girls at Higher Risk for Diabetes, Heart Woes as Adults

Study found that as teens, they have larger waist size, higher blood levels of insulin, fat

*JCEM, June 2012*

High birth weight and increased adiposity at age 12 months increases risk of metabolic syndrome at age 17 yrs old in girls

Obese infants are 2-9 times as likely to be obese as adults

*Baird J, BMJ 2005;331:929*

Predictors of 4 yr old OW/Obesity: OW/Obesity at 2 yrs (4.1)

*Kitsantas P Earl Hum Dev 2010;86:563*

25% of obese children age 4-10 have IGT
25,505 pregnant women in 15 centers in 9 countries (Chicago, Rhode Island, California, Belfast Ireland, Bangkok Thailand, Tel-Aviv Israel, Brisbane Australia, Stockholm Sweden, Hong Kong) 9% Hispanics

Objective: clarify risk of adverse outcome with degrees of maternal glucose intolerance less than overt diabetes

75 gm 2 hr OGTT; Blinded if FBG <105; 2hr <200; random <160

Primary outcomes: LGA, Primary C sec, Clinical neonatal hypoglycemia, cord blood C-peptide >90th %
Glucose Values Lower than Current Diagnostic Criteria Associated with Excess Growth

**Primary outcomes**

<table>
<thead>
<tr>
<th>Glucose Category</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.1%</td>
</tr>
<tr>
<td>2</td>
<td>5.3%</td>
</tr>
<tr>
<td>3</td>
<td>13.3%</td>
</tr>
<tr>
<td>4</td>
<td>26.3%</td>
</tr>
<tr>
<td>5</td>
<td>27.9%</td>
</tr>
<tr>
<td>6</td>
<td>32.4%</td>
</tr>
<tr>
<td>7</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

Mean fasting blood glucose 80.9 mg/dl; Mean BMI =28
International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy

Diagnosis and Classification of Diabetes Mellitus

American Diabetes Association

Diabetes Care 2010;33:676-682

Diabetes Care 2011;34 S62-S69
DX of GDM (1 Abnl Value) and Overt DM (likely pre-existing) per IADPSG

Incidence of GDM = 17.8%

Overt DM dx’d by A1C and FBG any time during pregnancy

### Diagnosis of hyperglycemia in pregnancy

#### Table 1—Threshold values for diagnosis of GDM or overt diabetes in pregnancy

<table>
<thead>
<tr>
<th>Glucose measure</th>
<th>Glucose concentration threshold*</th>
<th>Above threshold (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol/l</td>
<td>mg/dl</td>
</tr>
<tr>
<td>FPG</td>
<td>5.1</td>
<td>92</td>
</tr>
<tr>
<td>1-h plasma glucose</td>
<td>10.0</td>
<td>180</td>
</tr>
<tr>
<td>2-h plasma glucose</td>
<td>8.5</td>
<td>153</td>
</tr>
</tbody>
</table>

To diagnose overt diabetes in pregnancy

<table>
<thead>
<tr>
<th>Measure of glycemia</th>
<th>Consensus threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG*</td>
<td>≥7.0 mmol/l (126 mg/dl)</td>
</tr>
<tr>
<td>A1C*</td>
<td>≥6.5% (DCCT/UKPDS standardized)</td>
</tr>
<tr>
<td>Random plasma glucose</td>
<td>≥11.1 mmol/l (200 mg/dl) + confirmation§</td>
</tr>
</tbody>
</table>

*One or more of these values from a 75-g OGTT must be equaled or exceeded for the diagnosis of GDM. †In addition, 1.7% of participants in the initial cohort were unblinded because of FPG >5.8 mmol/l (105 mg/dl) or 2-h OGTT values >11.1 mmol/l (200 mg/dl), bringing the total to 17.8%. ‡One of these must be met to identify the patient as having overt diabetes in pregnancy. §If a random plasma glucose is the initial measure, the tentative diagnosis of overt diabetes in pregnancy should be confirmed by FPG or A1C using a DCCT/UKPDS-standardized assay.
# Initiation of Medical Therapy

 FBG might change based on HAPO

<table>
<thead>
<tr>
<th></th>
<th>FBG</th>
<th>1 hr PP</th>
<th>2 hr PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>*ACOG; 4,5th Int Workshop</td>
<td>&lt;95 mg/ dl</td>
<td>&lt;130-140 mg/ dl</td>
<td>&lt;120 mg/ dl</td>
</tr>
</tbody>
</table>
Where do the Current Therapeutic Targets Come From?

- Historically, the goal for diabetes in pregnancy has been to *mimic* patterns of glycemia in normal pregnancy (Freinkel, N, 1980, *Diabetes*, 29: 1023)
  - Balance between prevention of macrosomia without ↑SGA
- **Current PP targets of <140 and <120 mg/dL come from**
  - Women with pre-gestational and gestational diabetes
    - **Combs, 1992**: Class B-RF diabetes: **1-hour PP target = 130 mg/dL, ↓macrosomia without ↑SGA**
    - **DeVeciana, 1995**: GDM, 1-hour PP target superior than premeal target to ↓macrosomia. Study used 1-hour target of 140 mg/dL, and others followed
    - **Langer, 1988, 1989**: Pre-gestational diabetes, **mean 24-hour BG 87-104 mg/dL** minimizes both SGA and LGA incidence
  - 5th International Workshop on GDM (2007) did not change targets, even though the SMBG study (Parretti, 2001) and one CGMS study (Yogev, 2004) were cited and demonstrated lower values
Patterns of Glycemia in Normal Pregnancy

Should the current therapeutic targets be challenged?

Teri L. Hernandez, PhD, RN
Jacob E. Friedman, PhD
Rachael E. Van Pelt, PhD
Linda A. Barbour, MD, MSPH

Diabetes Care 2011, 34:1660

• 12 studies
  – 5 In-patient
  – 1 SMBG
  – 6 CGMS

• In ~50 years of research, only 255 normal-weight, normal-glucose tolerant women

• Mean gestational week of study
  – 33.8±2.3 weeks (range 24-40.8±0.09-8.1 weeks)

• Most women had a BMI <25kg/m²
  – BMI range 22-28 kg/m²
  – Pre-pregnancy BMI vs. BMI at time of study was variably reported
Glycemic Patterns Throughout Day in 12 Studies

Hernandez, Van Pelt, Barbour 2011

- 12 studies
- 1975-2008
- N=168-255
- 33.8±2.3 wks
- BMI 22-28
Weighted Mean Pattern of Glycemia

Hernandez, Van Pelt, Barbour 2011

- 1-hr PP: 109±13 mg/dL
- 2-hr PP: 99±10 mg/dL
- 24-hr Mean BG: 88±10 mg/dL
- FBG: 71±8 mg/dL
### Weighted Mean Glucose Values

*Hernandez, Van Pelt, Barbour 2011*

- Pooled analysis of 12 studies
- Calculated weighted mean values

<table>
<thead>
<tr>
<th></th>
<th>Weighted Mean</th>
<th>±1 SD range</th>
<th>±2 SD range</th>
<th>Current Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG, mg/dL</td>
<td>71±8</td>
<td></td>
<td></td>
<td>&lt;92</td>
</tr>
<tr>
<td>1-hour PP</td>
<td>109±13</td>
<td>96-122</td>
<td>83-135</td>
<td>&lt;140</td>
</tr>
<tr>
<td>2-hour PP</td>
<td>99±10</td>
<td>89-109</td>
<td>79-119</td>
<td>&lt;120</td>
</tr>
<tr>
<td>24-hour mean</td>
<td>88±10</td>
<td></td>
<td></td>
<td>&lt;130* 87-105</td>
</tr>
</tbody>
</table>

*Macrosomia threshold as per Willman SP, 1986, Am J Obstet Gynecol, 154: 470*
Macrosomia is obviously just due to the Sugar...

19 lbs 2oz
Baby Boy; 9/2009
Mother age 41 DM
Medan, North Sumatra Indonesia

- Although it used to be the case, most macrosomic infants are no longer born to mothers without GDM or DM but to obese moms
- In multivariate models, glucose <25% of the total variability in BW percentile  
  Ouzilleau 2003
- Lipids, growth factors, inflammation, amino acids?
Why do obese women without GDM have fatter babies?

Delaney Buzzell
“Big Enchilada”
13 lb 12 oz at 37 wks
Mom without GDM
### Predictive Value of BW and GDM on Metabolic Syndrome Age 6-11

**Boney CM 2005 Peds 115:e290**

#### TABLE 4. Hazard Ratio for the Risk of MS (n = 175)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio</th>
<th>P Value</th>
<th>95% CI for Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGA versus AGA</td>
<td>2.19</td>
<td>.006</td>
<td>1.25–3.82</td>
</tr>
<tr>
<td>Maternal obesity* versus nonobese</td>
<td>1.81</td>
<td>.039</td>
<td>1.03–3.19</td>
</tr>
<tr>
<td>GDM versus control</td>
<td>1.44</td>
<td>.191</td>
<td>0.83–2.50</td>
</tr>
<tr>
<td>Male versus female</td>
<td>1.52</td>
<td>.133</td>
<td>0.88–2.61</td>
</tr>
</tbody>
</table>

* Prepregnancy BMI of >27.3 mg/m²
Perinatal Risk Factors for Childhood Obesity and Metabolic Dysregulation  
*Catalano PM Am J Clin Nutr 2009;90:1303*

89 women with GDM or NGT; Offspring evaluated at birth and 6-11 yrs

Offspring body comp at birth and at ~9 yrs by DXA

No correlation between BW and Child Wt but pos correlation between %Body fat at birth and child % Body fat

**No differences in Wt Percentile or % Body Fat in offspring of GDM vs NGT**

Strongest predictor for offspring upper tertile wt or % body fat wt was **Maternal BMI >30** (OR=3.8 and 5.5 respec). Explained 18% of variance in childhood adiposity

*FIGURE 1. Correlation between percentage body fat in neonates at birth and percentage body fat in children at follow-up. \( r = 0.29, P = 0.02 (n = 63) \).*

*FIGURE 2. Correlation between birth weight and weight at follow-up in the children. \( r = 0.03, P = 0.79 (n = 89) \).*
Continuous Glucose Profiles in Obese and Normal-Weight Pregnant Women on a Controlled Diet

Metabolic determinants of fetal growth

<table>
<thead>
<tr>
<th></th>
<th>LEAN: Early</th>
<th>Late</th>
<th>OBESE: Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (ng/mL)</td>
<td>4.3 ± 0.4</td>
<td>5.0 ± 0.6</td>
<td>15.9 ± 3.3‡</td>
<td>14.9 ± 2.0‡</td>
</tr>
<tr>
<td>C-peptide (ng/mL)</td>
<td>1.1 ± 0.05</td>
<td>1.3 ± 0.06</td>
<td>2.6 ± 0.3‡</td>
<td>2.8 ± 0.2‡</td>
</tr>
<tr>
<td>Tg (mg/dL)</td>
<td>85 ± 5.6</td>
<td>-</td>
<td>152 ± 14.3‡</td>
<td>-</td>
</tr>
<tr>
<td>FFA (µEq/L)</td>
<td>366 ± 52</td>
<td>326 ± 29</td>
<td>535 ± 55*</td>
<td>547 ± 58‡</td>
</tr>
</tbody>
</table>

Diabetes Care 2011 34:2198

22 NW and 16 Obese Pregnant women at 16 weeks and 28 wks gestation
GCMS on both Ad lib and Fixed diet (Eucaloric with 50% carb (<20% simple); 35% fat; 15% protein)
NW: 1 hr PP 102; 2 hr PP 96 (late)
Obese: 1 hr PP 115; 2 hr PP 107 (late)
Much lower that current targets of 140 and 120! Diet had minimal effect!
Late pregnancy, 95% all glucose values NW ≤ 116 vs <133 mg/dl in obese

Time spent glucose >120 mg/dl was only 33 mins NW vs 209 in Obese
Maternal Metabolic Variables Correlating with Infant Body Fat

TG early was strongest correlate of % body fat ($r=0.67$); FFA late ($r=0.54$)

Early Maternal BMI $r=0.55$

Nothing added to TG in regression model

BW not correlated with any metabolic variables
150 “well controlled” GDM women previously reported in study using fetal-based strategy (Rx of LGA despite nl glucoses)

After adjustment for confounding variables, only maternal TGs and FFA correlated with LGA

Maternal TGs can be hydrolyzed to FFAs by placenta and cross...
What about Fat???
Regulation of Maternal Fuel Supply and Neonatal Adiposity

• **Hypothesis:** Neonatal adiposity and insulin resistance result from unrecognized maternal hyperglycemia and excess lipid availability in early and late pregnancy in obese women with or without GDM
Infant DEXA at 2 wks of Age

Mother: Obese & GDM

- B.W. = 2893 grams; body fat = 16.8%

Mother: Lean Normal GT

- B.W. = 3370 grams; body fat 7.7%
PEA POD of Claire (Air Displacement Plethysmography)
Comparison of 24-Hour Maternal Glycemia at 27-28 weeks Based on Level of Infant Adiposity
Change in Fasting TG from 16-28 weeks Gestation Predicts Infant Adiposity

Barbour, LA et al, Preliminary Data 2009. Regulation of Maternal Fuels and Neonatal Adiposity, R01DK 078645
Feeding mother macaques high fat diet indep of mat wt gain:

Fetal NAFLD in liver; Gene expression assoc with lipotoxicity

Alters fetal serum metabolome

↑Anxiety in female and Aggression in male offspring by Intruder tests, Mr. Potato Head and rubber snake
Neonatal Body Fat: It's Not Just Mom’s Glucose

**Mom**
- Genetics
- Ethnicity
- Placentation
- BMI
- Body Composition
- Glucose
- Lipids
- AAs
- Inflammatory Cytokines
- Hormones
- Mat and Fetal Growth Factors
- Oxidative Stress

**Fetus**
- High Insulin
- Excess Fat
- Pancreas enlargement
- Increases in Appetite
- Change in Energy Balance
- Obesity and Pancreatic Failure
- Glucose Intolerance and Diabetes
Medical Nutrition Therapy

- NO adequate RCT’s on ideal macronutrient intake
- Macronutrient percentages dropped (min 175 g carbs)
- Concern about substituting high fat; worsens insulin resistance and ↑ risk of DM in offspring in animal models
- Maternal TG and FFA may independently ↑ LGA
- Avoid simple carbs; limit saturated fats to <7% calories
- Increase fiber (28 gms/day)
- Avoid excessive weight gain (Used IOM guidelines)
  - Speaker would argue that IOM guidelines are too generous for obese women
**NIH RCT GDM Diet Study**

**Challenging the Current Dogma of Low Carb Diet**

*Hernandez, Barbour, Friedman (NIH R21) Contact: 303-724-3943*

- **Low-Carb/Higher-Fat “Usual Care”**
  - 40% carb
  - 45% fat
  - 15% protein
- **Higher-Carb/Low-Fat “Complex Carb Diet”**
  - 60% carb, mostly complex
  - 25% fat
  - 15% protein

**Both diets**

- SFA- 35-45%; MUFA- 35-45%; PUFA- 15-20%
- Simple Sugars less than or equal to 18% to Total Daily Calories

- **Hypothesis:** Low carb/higher fat diet will have lower PP excursions but glucoses will stay elevated longer; Lipid and inflammatory profiles will be worse
- **RCT cross over X 3 days each diet with 2 day wash out between; Subjects remain on last randomized diet throughout pregnancy**
- **CGMS, TG, FFA, gluc, insulin excursions after breakfast meal; lipoprotein and inflammatory cytokine profiles, adipose biopsy, RBC membrane FA profile, oxidized LDL**
- **Infant oxidized LDL, RBC membrane FA profile, PEAPOD**
• ADA (IADPSG), ACOG, and a representative of IADPSG who disagreed on the adoption of the proposed guidelines to present their positions

• Adopting ADA Diagnostic Criteria may increase prevalence of GDM to 25% in high risk populations

• No one on the panel who has ever published in the area of GDM allowed on panel
1/3 of children in high risk populations are obese (>95%)
7% boys and 5% girls extremely obese

“These kids face 10-20 years shorter life span and will develop health problems in their 20s that we typically see in 40-60 yr olds”

Heaviest: Black teenage girls and Hispanic teenage boys

Primary Prevention of Pediatric Obesity Begins in Pregnancy
In my beginning, is my end.

* T.S. Eliot, *Four Quartlets, The Dry Salvages*

Pregnancy norms are lower than recognized but glucose is only part of the puzzle to excess fetal fat accretion

Adopting the new ADA guidelines will ~triple the prevalence of GDM and assoc costs, may miss early GDM, and only modestly ↓LGA

Lowering therapeutic targets will markedly ↑ women requiring medical Rx but may not ↓LGA

Targeting maternal BMI, GWG, and possibly maternal TG may be valuable

Avoid both a high fat and simple carb in diet

Oral hypoglycemics likely to gain acceptance given ↑ prevalence of GDM but less efficacious and long term risks of Metformin not yet clear

*More questions than answers……*