Metabolic Disorders of Pregnancy: Gestational Diabetes and Hyperlipidemia

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Metabolic Disorders of Pregnancy

I. GDM
   I. GDM Screening & Diagnostic Thresholds
   II. GDM Incidence
   III. Adverse Outcomes associated with GDM
   IV. Mechanisms Underlying GDM
   V. CHO metabolism in normal and GDM pregnancies

II. Hyperlipidemia
   I. Lipid metabolism in normal and GDM pregnancies
   II. Adverse outcomes associated with hyperlipidemia

III. Treatment of hyperlipidemia and GDM
Gestational Diabetes Mellitus

- GDM is defined as glucose intolerance with onset or first recognition during pregnancy
- Caused by reduced pancreatic β-cell function that results in insufficient insulin to meet the increased requirements of late pregnancy
- Nutritional management cornerstone of treatment; when necessary medications
- All pregnant women should be screened for GDM
- Although diagnosing and treating GDM can reduce perinatal complications, only small fraction of pregnancies benefit

American Diabetes Association 2011
GDM Screening & Diagnostic Thresholds

• ACOG (2013) two-step approach at 24-28 wk
  - 50 g 1-h OGTT (1-h 130 to 140 mg/dL) (O’Sullivan and Mahan, 1973)
  - 100 g 3-h OGTT (two abnormal values)
    Fasting  95-105 mg/dL
    1-h  180-190 mg/dL
    2-h  155-165 mg/dL
    3-h  140-145 mg/dL

• International Association of Diabetes and Pregnancy Study Group (IADPSG; Metzger 2010)
  - 75 g, 2-h OGTT (one abnormal value)
    Fasting  92 mg/dL
    1-h  180 mg/dL
    2-h  153 mg/dL
Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study

• N=25,500 women, 9 countries
  75 g OGTT

• Perinatal outcomes (BWT, C-peptide, %FM) to set criteria for GDM rather than future T2D

• No clear threshold identified; risks for adverse perinatal outcomes linearly increased with maternal glucose levels

• OR=1.75 used to set thresholds

<table>
<thead>
<tr>
<th>IADPSG 2010 Diagnosis and test</th>
<th>Glucose (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GDM</strong> (one abnormal value)</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>≥ 5.1</td>
</tr>
<tr>
<td>1 h plasma glucose</td>
<td>≥ 10.0</td>
</tr>
<tr>
<td>2 h plasma glucose</td>
<td>≥ 8.5</td>
</tr>
<tr>
<td><strong>Overt diabetes</strong></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>≥ 7.0</td>
</tr>
<tr>
<td>Random plasma glucose</td>
<td>≥ 11.1</td>
</tr>
<tr>
<td>HbA$_{1C}$</td>
<td>≥ 6.5%</td>
</tr>
</tbody>
</table>

* Overt diabetes = met criteria of DM outside of pregnancy
  High risk for birth defects (that does not occur at lower glucose levels), and hypertension

Metzger 2008
GDM Screening & Diagnostic Thresholds

  - Adoption of the IADPSG criteria would ~double GDM rates
- In US, NICHD and ACOG endorse two step approach, since no evidence that IADPSG criteria leads to clinically significant improvements in maternal or child outcomes, but would increase health care costs
- European Board & College of Obstetrics and Gynaecology (EBCOG) recommends, but has not endorsed, initial screen for overt diabetes and IADPSG criteria (Benhalima, 2015)
GDM Incidence

• United States:
  - Kaiser Permanente 1995-2009 incidence rates overall 10%; Asian 17%, Hispanic 11%, white 7%, black 7% (Xiang 2011)
  - Adoption of the IADPSG criteria would increase prevalence of GDM in US from 10% to 18%

• Europe:
  - Incidence is most often reported as 2–6% of pregnancies (Buckley 2012)
  - May be lower towards Northern Atlantic seaboard and higher in Southern Mediterranean seaboard

• Asia
  Tianjin, China, 2010-2012, 17,808 pregnancies
  GDM incidence 7.7% by IADPSG criteria
Offspring Adverse Outcomes of GDM

- **1st trimester:** spontaneous abortion, major congenital anomalies
- **2nd & 3rd trimester:** modest increases in macrosomia, neonatal hypoglycemia, hyperbilirubinemia, operative delivery, shoulder dystocia, birth trauma, stillbirth
- Increased risk of obesity during childhood and adolescence
- Not shown in all studies (Whitaker 1998; Catalano 2009)
Maternal Adverse Outcomes of GDM

- Gestational hypertension, preeclampsia, C-sec
- High risk of later diabetes mellitus (Sullivan 1991)
  - 10% develop DM soon after delivery
  - Others develop DM at rates of 30-50% within 5-10 years after delivery (Kim 2002)
- Metabolic effects of obesity are important determinants of β-cell deterioration & DM:
  - weight gain, insulin resistance, rising CRP, falling adiponectin

American Diabetes Association 2011; Buchanan 2012
## Perinatal Outcomes in HAPO Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GDM IADPSG (%)</th>
<th>non-GDM (%)</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia</td>
<td>9.1</td>
<td>4.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Delivery at &lt;37 weeks</td>
<td>9.4</td>
<td>6.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Primary c-sec</td>
<td>24.4</td>
<td>16.8</td>
<td>7.6</td>
</tr>
<tr>
<td>Shoulder dystocia or birth injury</td>
<td>1.8</td>
<td>1.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Intensive neonatal care</td>
<td>9.1</td>
<td>7.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Neonatal hypoglycaemia</td>
<td>2.7</td>
<td>1.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Neonatal hyperbilirubinaemia</td>
<td>10.0</td>
<td>8.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Birthweight &gt;90&lt;sup&gt;th&lt;/sup&gt;pct</td>
<td>16.2</td>
<td>8.3</td>
<td>7.9</td>
</tr>
<tr>
<td>Cord C-peptide &gt;90&lt;sup&gt;th&lt;/sup&gt;pct</td>
<td>17.5</td>
<td>6.7</td>
<td>10.8</td>
</tr>
<tr>
<td>% Fat mass &gt;90&lt;sup&gt;th&lt;/sup&gt;pct</td>
<td>16.6</td>
<td>8.5</td>
<td>8.1</td>
</tr>
</tbody>
</table>

GDM is associated excess risk of perinatal complications but absolute risk ≤ 10.8% for any given complication

Metzger 2008
Mechanisms Underlying GDM (β-cell dysfunction)

• Anti-islet antibodies or antibodies to glutamate decarboxylase that are diagnostic of T1DM (<10%)
• Genetic variants diagnostic of monogenic forms DM (1-5%)
• Obesity and chronic insulin resistance
  - Chronic β-cell defect rather than acquired during pregnancy
  - GDM occurs primarily in women over 30 y, multiple pregnancies, and obese
  - GDM happens to be detected during pregnancy, and poses a high risk for T2D later
Inflammation

- Low grade inflammation starts ~7-10 wks, and persists throughout pregnancy
- Placenta also source of adipokines (leptin) and cytokines
- Maternal obesity associated with increased inflammation in adipose tissue, plasma and placenta (IL-6, TNFa, IL-1, CRP)
- Chronic insulin resistance in GDM may be due to inflammation affecting post-receptor insulin signaling cascade
  - TNF-α: factor most strongly associated with decreased insulin sensitivity in pregnancy
- Hyperlipidemia may enhance cytokine expression and IR
Genetics of GDM

• Candidate gene and GWAS studies to identify genes associated with GDM

• Candidate gene studies for GDM (Robitaille 2008; Watanabe 2011; Zhang 2013)

• GWAS for GDM (Kwak 2012)

• All the identified genes associated with increased risk of T2D

• Considerable overlap in genetic architecture of GDM and T2D

Lowe 2014
# Candidate Gene Studies for GDM

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Encoded Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRS1</td>
<td>2</td>
<td>Insulin receptor substrate 1</td>
</tr>
<tr>
<td>IGF2BP2</td>
<td>3</td>
<td>Insulin-like growth factor 2 mRNA binding protein 2</td>
</tr>
<tr>
<td>CDKAL1</td>
<td>6</td>
<td>CDK5 regulatory subunit associated protein 1 like-1</td>
</tr>
<tr>
<td>GCK</td>
<td>7</td>
<td>Glucokinase</td>
</tr>
<tr>
<td>TCF7L2</td>
<td>10</td>
<td>Transcription factor 7-like-2</td>
</tr>
<tr>
<td>MTNR1B</td>
<td>11</td>
<td>Melatonin receptor 1β</td>
</tr>
<tr>
<td>KCNJ11</td>
<td>11</td>
<td>Potassium inwardly rectifying channel, subfamily 3, member 11</td>
</tr>
<tr>
<td>KCNQ1</td>
<td>11</td>
<td>Potassium voltage-gated channel, KQT-like subfamily, member 1</td>
</tr>
</tbody>
</table>

Robitaille 2008; Watanabe 2011; Zhang 2013
## GWAS for GDM

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<td>CDK5 regulatory subunit associated protein 1 like-1</td>
</tr>
<tr>
<td>MTNR1B</td>
<td>11</td>
<td>Melatonin receptor 1β</td>
</tr>
<tr>
<td>IGF2BP2</td>
<td>3</td>
<td>Insulin-like growth factor 2 mRNA binding protein 2</td>
</tr>
</tbody>
</table>

Kwak 2012
Maternal Metabolism

Changes in carbohydrate and lipid metabolism occur during pregnancy to ensure a continuous supply of nutrients to the growing fetus, despite intermittent maternal food intake.
Carbohydrate Metabolism in Normal Pregnancy

• Early Pregnancy:
  - ↑ Estrogen & progesterone
  - ↑ Glucose tolerance - slightly improved
  - ↑ Enhanced insulin secretion
    • ↑ First-phase insulin response - 120%
    • Second-phase insulin response - NS nongravid

• Favors lipogenesis and fat storage
Carbohydrate Metabolism in Normal Pregnancy

• Late Pregnancy:
  - ↑ Human chorionic somatomammotropin, prolactin, cortisol
  - ↓ Insulin sensitivity
  - ↑ Insulin secretion
  - ↑ Hepatic glucose production
  - ↑ Net carbohydrate utilization (oxidation)

• Exaggerated changes in postprandial levels
  - ↑ Glucose
  - ↑ VLDL
  - ↑ Amino acids

• Ensure nutrient flux to fetus
Fasting Plasma Glucose and Insulin in Normal Pregnancy

- Glucose (mmol/L)
- Insulin (mU/L)

Time of Gestation (wks)
Insulin Sensitivity in Normal Pregnancy

- Method: hyperinsulinemic-euglycemic clamp
- Results: peripheral insulin sensitivity decreased markedly in late pregnancy
  - Ryan, 1985 \(\downarrow33\%\)
  - Buchanan, 1990 \(\downarrow67\%\)
  - Catalano, 1991 \(\downarrow57\%\)
Insulin Sensitivity in GDM

- Method: hyperinsulinemia-euglycemic clamp

- Results: ↓ insulin sensitivity evident in lean GDM group prior to conception (similar in obese GDM)

- ↓ ↓ insulin sensitivity in late pregnancy

Catalano, P. Am J Physiol, 1993
Insulin Secretion in Normal Pregnancy

• Method: intravenous glucose tolerance test

• Results: basal and 24-h insulin levels may double in late pregnancy

• First- and second-phase insulin release 3X greater

Insulin Secretion in GDM

- Method: intravenous glucose tolerance test
- Results: increase in first-phase insulin response in lean GDM and controls, however, increase was greater in controls

Catalano, P. Am J Physiol, 1993
Insulin Secretion in Obese GDM

- Method: intravenous glucose tolerance test
- Results: similar increase in first-phase insulin response in obese GDM and controls, however, greater increase in second-phase insulin response in obese GDM

Catalano, P. Am J Obs Gyn 1999
Basal Hepatic Glucose Production in Normal Pregnancy

• Method: glucose production quantified using $^{13}\text{C}\text{glucose}$ or $6,6\text{-}^{2}\text{H}_2\text{glucose}$

• Results: basal hepatic glucose production increased in late pregnancy:
  - Kalhan, 1979 $\uparrow 16\%$
  - Catalano, 1992 $\uparrow 30\%$
  - Assel, 1993 $\uparrow 17\%$
Basal Hepatic Glucose Production in GDM

- Method: $6,6^{-2}\text{H}_2\text{glucose}$
- Results:
  - Basal glucose production increased similarly in lean GDM and controls 0 and 12 wk
  - Increase basal glucose production was greater in controls at 36 wk

![Graph showing Basal Hepatic Glucose Production (mg/min) over Time of Gestation (wks).]
Increased Contribution of Carbohydrate to Oxidative Metabolism in Normal Pregnancy

• In late pregnancy,
  - Basal respiratory quotient (RQ) elevated
    • van Raaij, 1989
    • Denne, 1991
    • Bronstein, 1995
    • Butte, 1998
## Contribution of Carbohydrate to Oxidative Metabolism in Normal Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Pregnancy</th>
<th>3 mo</th>
<th>6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Postpartum</td>
<td>Postpartum</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>NL</td>
<td>L</td>
</tr>
<tr>
<td>24-h RQ</td>
<td>0.87</td>
<td>0.87</td>
<td>0.84</td>
</tr>
<tr>
<td>Basal RQ</td>
<td>0.83</td>
<td>0.84</td>
<td>0.80</td>
</tr>
<tr>
<td>SMR RQ</td>
<td>0.87</td>
<td>0.87</td>
<td>0.84</td>
</tr>
<tr>
<td>CHO oxidation (%NPEE)</td>
<td>64</td>
<td>65</td>
<td>61</td>
</tr>
<tr>
<td>CHO oxidation (g/d)</td>
<td>282</td>
<td>283</td>
<td>226</td>
</tr>
</tbody>
</table>
Carbohydrate Metabolism in GDM

• Late Pregnancy:
  - ↓ ↓ Insulin sensitivity
  - ↑ Insulin secretion
  - ↑ Hepatic glucose production
  - ↑ Net carbohydrate utilization (oxidation)
Lipid Metabolism in Normal Pregnancy

• Early Pregnancy: **Anabolic - fat storage**
  - ↑ Estrogen, progesterone, insulin
  - ↑ Fat synthesis
  - ↑ Fat cell hypertrophy
  - Lipolysis inhibited

• Late Pregnancy: **Catabolic - fat mobilization**
  - ↑ Human chorionic somatomammotropin
  - ↑ Leptin
  - Lipolysis favored
Fasting Plasma Lipid Profile in Normal Pregnancy

- Triglycerides
- Total cholesterol
- HDL-cholesterol
- LDL-cholesterol

Time of Gestation (wks)

(mmol/L)
Lipids: Fetoplacental Unit

- Placental transport
  - Lipids cross the placenta with difficulty
  - NEFA and LCPUFA are transferred to the fetus from maternal circulation to support fetal growth and development
  - Placenta has receptors for plasma lipoproteins, lipases and FA binding proteins

Herrera 2014
Lipid Metabolism in GDM

- State of dyslipidemia
  - ↑↑Triglycerides and VLDL
  - ↑Total cholesterol (or unaltered)
  - ↑small, dense LDL
  - ↑LDL oxidation
  - ↑NEFA due to inability of insulin to suppress lipolysis and delayed clearance
Hyperlipidemia: Risk for Macrosomia

• GDM - disturbances in lipid metabolism even if serum glucose normal
  - Exaggerated changes in serum TG, NEFA and lipoprotein profiles, adipocytokines
  - Maternal TG and NEFA correlate with fetal lipid concentrations and fetal growth

• Maternal TG partially responsible for LGA infants despite good maternal glucose control (Olmos 2014)
  - GDM study: normal weight (n=128), overweight (n=105), obese (n=45)
  - Newborn weight correlated with maternal TG in overweight (r=0.42) and obese GDM (r=0.47)

Olmos 2014
Hyperlipidemia: Risk for Preeclampsia and Preterm Delivery

- Systematic review demonstrated that preeclampsia associated with elevated levels of total cholesterol, non-HDL-C, and TG during all trimesters and lower levels of HDL-C during 3rd trimester (Spracklen 2014)

- Abnormal lipids in mid-pregnancy associated with preterm delivery (Mudd 2012)
  - Extremely low TC, HDL-C, and LDL-C modestly increased risk of medically indicated preterm delivery
  - High TC, LDL-C and TG modestly increased the risk of spontaneous preterm delivery
Hyperlipidemia of Pregnancy: Is It Time To Target Lipids In Diabetic Pregnancy?

Few RCT targeting maternal lipids

- **Metformin in Gestational Diabetes (MiG) Trial (Barrett HL 2013)**
  - TG increased more in women treated with metformin than insulin

- **Cardiovascular Risk Reduction Diet in Pregnancy (CARRDIP) (Khoury J 2005)**
  - Cholesterol lowering diet in uncomplicated pregnancies
  - Total and LDL cholesterol levels were lowered and reduction in preterm delivery

- **Omega-3 Fatty Acids Supplementation Systematic Review (Swska H 2006)**
  - No difference in the rates of GDM

- **DHA/EPA to Optimize Mother Infant Outcome (DOMInO) trial (Zhou J 2012)**
  - No difference in risk of developing GDM or preeclampsia (largely healthy, low risk pregnant women)

No RCT targeting lipids in women with diabetes

Barrett, HL. Diabetes Care 2014
Severe Hyperlipidemia of Pregnancy

- Severe Hypertriglyceridemia = plasma TG >11.4 mmol/L (1000 mg/dL)
- Complications: acute pancreatitis, hyperviscosity syndrome, preeclampsia
- Few, rare mutations (LPL, APOE, APOC2) identified
- Treatment (American College Cardiology 2014):
  - All lipid-lowering medications should be stopped before conception or immediately when pregnancy occurs unexpectedly
  - Appropriate fat-restricted diet (<20% fat; hospitalize if necessary)
  - Omega-3 fatty acids
  - Not recommended
    - Niacin - lowers TG, transient effect
    - Fibrates - decrease TG, increase LDL clearance, increase HDL, not well studied
    - Statins - conflicting reports of teratogenicity and congenital malformations

Wild 2015, Goldberg 2012
Treatment of GDM

- Two RCT evidence that diagnosis and treatment can be beneficial
- **Australian CHO Intolerance Study (ACHOIS) (Crowther 2005)**
  - Design: Usual care vs. nutritional advice, glucose monitoring
  - Results:
    - lower perinatal complications (1% vs. 4%)
    - higher neonatal ICU admit
    - lower birthweight and macrosomia
    - BMI z-score at ages 4-5 y – NS

- **NICHD Maternal-Fetal Medical Unites Network (Landon 2009)**
  - Design: Usual care vs. nutritional advice, glucose monitoring
  - Results:
    - reduced shoulder dystocia (1.5% vs. 4%)
    - reduction in birthweight (~100-150 g), LGA, macrosomia, reduced maternal hypertensive disorders
Treatment of GDM

• Systematic review of diet interventions (Viana, 2014)
  • Low glycemic index (4 RCTs)
  • Total energy restriction (2 RCTs)
  • Low carbohydrate diet (2 RCTs)
  - Only low GI diet affected maternal and newborn outcomes: reduced proportion of women rec. insulin and lowered birth weight

• Systematic review of medication treatments (Li, 2015)
  • 11 RCTs Metformin vs. insulin
  - Metformin reduced several adverse outcomes including PIH rate, incidence of hypoglycemia and NICU admit
  - Effective and safe alternative or additional treatment to insulin for GDM
Recommendations for GDM Treatment

ACOG 2013 Practice Bulletin:
• Nutrition therapy, and medication when necessary

Academy Nutrition and Dietetics, 2013:
• Nutrition therapy
  - Energy Intake: nonpregnant EER plus 340 and 452 kcal/d, 2nd and 3rd trimester (DRI)
  - CHO intake: <45% of calories to prevent hyperglycemia
  - Three meals, 2 to 4 snacks
  - For overweight or obese women, modest energy restriction
    • 70% of DRI calculated energy intake
• Exercise
  - Moderate exercise program is recommended
Recommendations for GDM Treatment

• Medications
  - Insulin, insulin ispro, insulin aspart
  - Antidiabetic meds – sulfonylurea and metformin (not approved by FDA for GDM)

• Blood Glucose Monitoring (4X/d)
  - Fasting
  - 1-h after each meal (<140 mg/dL) OR
  - 2-h after each meal (<120 mg/dL)

• Postpartum Screening
  - At 6-12 wks, and every 3 y afterwards

ACOG 2013
Conclusion

• Nutritional management remains the cornerstone of GDM treatment, and when necessary medications
  - Acknowledge that adherence to dietary and exercise recommendations, medications and avoidance of excessive GWG have had modest success in reducing risk for GDM, preeclampsia or macrosomia

• Women are entering pregnancy with obesity, chronic insulin resistance and inflammation
  - Interventions targeting metabolic dysfunction are needed prior to conception to improve neonatal and maternal outcomes

• Abnormal lipid metabolism in pregnancy appears associated with adverse pregnancy outcomes
  - Further research is needed to address treatments to modify maternal lipids during pregnancy