Short - and Long-Term Effects of Gestational Diabetes Mellitus (GDM) on the Mother and the Newborn

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Gestational Diabetes Mellitus (GDM)

- Definition & Diagnosis of GDM
- Molecular Pathogenesis of GDM
- Effects of GDM on the Mother
- Short Term Effects of GDM on the Offspring
- Long Term Effects of GDM on the Offspring
Gestational Diabetes (GDM)

• Definition: Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy.

• Prevalence: 1-14% of all pregnancies

• Chance of recurrence in future pregnancies: 30-84%
GDM prevalence linked to background IGT rates

<table>
<thead>
<tr>
<th>Decade</th>
<th>GDM Rate</th>
<th>IGT Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980s</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>1990s</td>
<td>7.6%</td>
<td>8.2%</td>
</tr>
<tr>
<td>2000s</td>
<td>16.6%</td>
<td>14.5%</td>
</tr>
</tbody>
</table>

**1980s**

**1990s**

**2000s**
GDM: Risk factors

• Maternal age >25 years
• Body mass index >25 kg/m²
• Race/Ethnicity
  – Latina
  – Native American
  – South or East Asian, Pacific Island ancestry
• Personal/Family history of DM
• History of macrosomia
Diagnosis

A fasting plasma glucose level $>126\text{ mg/dl (7.0 mmol/l)}$ or
a casual plasma glucose $>200\text{ mg/dl (11.1 mmol/l)}$

In the absence of this degree of hyperglycemia, evaluation for GDM in women with average or high-risk characteristics should get an oral glucose test.
Diagnosis of GDM with a 75-g oral glucose load

<table>
<thead>
<tr>
<th></th>
<th>mg/dl</th>
<th>mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>92</td>
<td>5.1</td>
</tr>
<tr>
<td>1-h</td>
<td>180</td>
<td>10.0</td>
</tr>
<tr>
<td>2-h</td>
<td>153</td>
<td>8.5</td>
</tr>
</tbody>
</table>

One or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of between 8 and 14 h and after at least 3 days of unrestricted diet and unlimited physical activity. The subject should remain seated and should not smoke throughout the test.

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Metabolic changes in pregnancy

• Caloric requirement for a pregnant woman is 300 kcal higher than the non-pregnant woman’s basal needs
• Increased insulin resistance
  – *Due to hormones secreted by the placenta that are “diabetogenic”*:
    • *Growth hormone*
    • *Human placental lactogen*
    • *Progesterone*
    • *Corticotropin releasing hormone*
  – Transient maternal *hyperglycemia* occurs after meals because of increased insulin resistance
Metabolic changes in pregnancy

Relative baseline hypoglycemia

- *Proliferation of pancreatic beta cells (insulin-secreting cells) leads to increased insulin secretion*
  - Insulin levels are higher in pregnant than in nonpregnant women in fasting and postprandial states
- *Hypoglycemia* between meals and at night because of continuous fetal draw
  - Blood glucose levels are 10-20% lower
Metabolic changes in pregnancy

- Lipid metabolism
  - Increased serum triglyceride (300%) and cholesterol (50%) levels
  - Spares glucose for fetus, since lipids do not cross the placenta
  - Increased lipolysis (preferential use of fat for fuel, in order to preserve glucose and protein)
The Feto-Materal Interaction may cause GDM

Placental hormones affect glucose and lipid metabolism to ensure that fetus has ample supply of nutrients
Factors Associated With Preterm Delivery in Mothers of Children With Beckwith–Wiedemann Syndrome: A Case Cohort Study From the BWS Registry

Michael F. Wangler,1 Aimee S. Chang,2 Kelle H. Moley,2 Andrew P. Feinberg,3 and Michael R. DeBaun4:

1Doris Duke Clinical Research Fellowship Washington University School of Medicine and the University of New Mexico School of Medicine, Albuquerque, New Mexico
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3Institute of Genetic Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland
4Department of Pediatrics and Biostatistics Washington University School of Medicine in St. Louis, Missouri

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Polyhydramnios</td>
<td>3.0</td>
<td>1.6–5.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>2.6</td>
<td>1.3–5.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>5.3</td>
<td>2.3–12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1.0</td>
<td>0.4–2.3</td>
<td>0.985</td>
</tr>
<tr>
<td>Infection</td>
<td>0.4</td>
<td>0.2–1.1</td>
<td>0.071</td>
</tr>
<tr>
<td>Maternal age</td>
<td>1.0</td>
<td>0.9–1.1</td>
<td>0.818</td>
</tr>
<tr>
<td>Fetal macrosomia</td>
<td>1.7</td>
<td>0.9–3.4</td>
<td>0.105</td>
</tr>
<tr>
<td>Constant</td>
<td>0.2</td>
<td>—</td>
<td>0.057</td>
</tr>
</tbody>
</table>
Fetal Gender determines Impact of maternal PROGINS Progesterone Receptor Polymorphism on maternal Physiology during Pregnancy

Maternal PROGINS progesterone receptor (AA) genotype affects maternal total glycated hemoglobin (p=0.008) at birth in an offspring gender dependent manner. Hocher et al., Pharmacogenetics (2009)
Fetal Gender determines Impact of maternal PROGINS Progesterone Receptor Polymorphism on maternal Physiology during Pregnancy

Systolic blood pressure values of mothers are provided as arithmetic means ± SD. Blood pressure values were significantly different (p<0.05 at all trimesters; unpaired t-test) between mothers carrying the AA alleles delivering either boys or girls. Hocher et al., Pharmacogenetics (2009)
Magnesium and GDM

The pathway of insulin and glucose metabolism correlated with intracellular magnesium. A low intracellular magnesium concentration, as found in type 2 DM and in hypertensive patients, may result in defective tyrosine-kinase activity at the insulin receptor level. Altered intracellular magnesium may also lead to decreased cellular glucose utilization and thus promote peripheral insulin resistance to a postreceptor mechanism.
Loss of insulin-induced activation of TRPM6 magnesium channels results in impaired glucose tolerance during pregnancy

Hypomagnesemia affects insulin resistance. We show using patch clamp analysis and total internal reflection fluorescence microscopy, that insulin stimulates TRPM6 activity via a phosphoinositide 3-kinase and Rac1-mediated elevation of cell surface expression of TRPM6. Interestingly, insulin failed to activate the genetic variants TRPM6(V(1393)I) and TRPM6(K(1584)E), which is likely due to the inability of the insulin signaling pathway to phosphorylate TRPM6(T(1391)) and TRPM6(S(1583)).

Moreover, by measuring total glycosylated hemoglobin (TGH) in 997 pregnant women as a measure of glucose control, we demonstrate that TRPM6(V(1393)I) and TRPM6(K(1584)E) are associated with higher TGH and confer a higher likelihood of developing GDM. The impaired response of TRPM6(V(1393)I) and TRPM6(K(1584)E) to insulin represents a unique molecular pathway leading to GDM where the defect is located in TRPM6.

Nair, Hocher et al., PNAS 2012
Renin-Angiotensin-Aldosteron-System and GDM
Renin Angiotensin Aldosterone System and Glycemia in Pregnancy

This study demonstrated that fasting blood glucose in pregnant women is inversely correlated with the PRA, whereas plasma aldosterone showed a highly significant positive correlation with fasting blood glucose during pregnancy. Moreover, plasma aldosterone is significantly higher in pregnant women with GDM as compared to those women with normal glucose tolerance during pregnancy. Although causality cannot be proven in association studies, these data may indicate that the RAAS during pregnancy contributes to the pathogenesis of insulin resistance/new onset of diabetes during pregnancy.

Chen YP et al., Clin Lab, 2012
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Effects of GDM on the mother

- **Pre-eclampsia:** affects 10-25% of all pregnant women with GDM
- **Infections:** high incidence of chorioamnionitis and postpartum endometritis
- **Postpartum bleeding:** high incidence caused by exaggerated uterine distension
- **Cesarian section more common** due to fetal macrosomia and cephalo-pelvic disproportion
- **Weight gain**
- **Hypertension**
- **Miscarriages**
- **Third trimester fetal deaths**
- **Long term risk of type-2 diabetes mellitus**
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Effects of GDM on the fetus

- Congenital abnormalities
- Neonatal hypoglycemia
- Macrosomia (big baby syndrome > 4 Kg or >8 lb 13 oz)
- Jaundice
- Polycythemia / hyperviscosity syndrome
- Hypocalcemia, hypomagnesemia
- Birth trauma (due to macrosmia and shoulder dystocia)
- Prematurity
- Hyaline membrane disease
- Apnea and bradycardia
Effects of GDM on neonates

- Respiratory distress
- Hypoglycemia
- Hypocalcemia
- Hyperbilirubinemia
- Cardiac Hypertrophy
- Long term effects on cognitive development
Congenital abnormalities due to GDM

- Cardiac (most common): transposition of great vessels, Ventricular septal defect, Atrial septal defect
- Central nervous system (7.2%): spina bifida, Anencephaly, hydrocephalus
- Skeletal: cleft lip/palate, caudal regression syndrome
- Genitourinary tract: ureteric duplication
- Gastrointestinal: anorectal atresia
- Renal agenesis, Duplex ureters, Cystic Kidney
- Situs inversus

Poor glycemic control at time of conception: risk factor
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Fetal programming

An event in a "critical", early period which permanently alters structure and function leading to cardiovascular diseases.

David Barker
Standardised mortality ratios for Coronary Heart Disease in 15726 Hertfordshire adults under 65 years of age

What causes Fetal Programming – Mechanisms

- Maternal Undernutrition
- Maternal Overnutrition
- 11-beta HSD Hypothesis
- Advanced Barker Hypothesis
- Nephron number
- Renin-Angiotensin-System
- **Gestational Diabetes Mellitus**
Prevalence of GDM by Birth Weight of Women in New York State (n=23,314)

Innes et al. JAMA, 2002
Prevalence of GDM by Birth Weight in Norwegian Women (n=138,714)

Egeland et al. BMJ, 2000
Prevalence of GDM by Birth Weight of African American Women in Washington State

Williams et al. Ped & Perinat Epi, 1999
Prevalence of Diabetes by Birth Weight in 25-34 year old Pima Women During Pregnancy

Pettitt & Knowler, Diabetes Care, 1998
Diabetes Begets Diabetes

Offspring of women with GDM, have a 4 to 8 fold increased risk of diabetes.

Clausen TD et al., Diabetes Care 2008
DEVELOPMENTAL PROGRAMMING OR THE ‘FETAL ORIGINS’ HYPOTHESIS

Programming’ may be due to DNA modifications independent of alterations of 1 nucleotide sequence

The totality of such marks on the genome is describ as the epigenome and comprises 3 distinct, but close inter-acting, mechanisms including

1. DNA methylation
2. histone modifications
3. non-coding microRNAs
Placental adiponectin gene DNA methylation levels are associated with mothers' blood glucose concentration.

In this study, we tested whether maternal glycemic status is associated with the adiponectin gene (ADIPOQ) DNA methylation profile in placenta tissue, in maternal circulating blood cells, and in cord blood cells.

1. We found that lower DNA methylation levels in the promoter of ADIPOQ on the fetal side of the placenta were correlated with higher maternal glucose levels during the second trimester of pregnancy (2-h glucose after the oral glucose tolerance test; $r(s) \leq -0.21$, $P < 0.05$).

2. Lower DNA methylation levels on the maternal side of the placenta were associated with higher insulin resistance index (homeostasis model assessment of insulin resistance) during the second and third trimesters of pregnancy ($r(s) \leq -0.27$, $P < 0.05$).

3. Finally, lower DNA methylation levels were associated with higher maternal circulating adiponectin levels throughout pregnancy ($r(s) \leq -0.26$, $P < 0.05$).

In conclusion, the ADIPOQ DNA methylation profile was associated with maternal glucose status and with maternal circulating adiponectin concentration. Because adiponectin is suspected to have insulin-sensitizing proprieties, these epigenetic adaptations have the potential to induce sustained glucose metabolism changes in the mother and offspring later in life.

Diabetes in Pregnancy: Vicious Cycle

Mother with Diabetes

Child or Woman With Diabetes

Infant of Diabetic Mother

New Diabetes Sources
Summary/Conclusions 1

- GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.
- The hallmark of GDM is increased insulin resistance (IR).
- Pregnancy hormones and other factors are thought to interfere with the action of insulin on its receptor.
- The RAAS and also magnesium handling regulate IR during pregnancy.
- Insufficient proliferation of pancreatic beta cells may contribute to the pathogenesis of GDM.
Summary/Conclusions 2

• GDM increases maternal morbidity and mortality as well as the risk for DM type 2 in later life.

• Short Term Effects of GDM on the Offspring are:
  Congenital malformations, Neonatal hypoglycemia, Macrosomia, Jaundice, Birth trauma, Prematurity.

• Long Term Effects of GDM on the Offspring are: Obesity, Type 2 DM, metabolic syndrome, cardiovascular diseases in later life.

• Diabetes Begets Diabetes

• Diabetes induced Fetal Programming may be due to epigenetic DNA modifications
• Y. Chen
• M. Dorn
• M. Godes
• S. Herzfeld
• T. Pfäb
• L. Richter
• M. Richter
• N. Schulz
• A. Schwarz
• K. Simon
• T. Slowinski
• S. Sommerfeld
• Ch. Thöne-Reineke
• F. Schweigert, Potsdam
• P. Person, Berlin
• H. Halle, Berlin
• M. Schwab, Stuttgart
• D. Schuppan, Boston, USA
• F. Theuring, Berlin
• J. Jr. Burnett, Rochester, USA
• M. Yanagisawa, Dallas, USA
• D. Webb, Edinburgh, UK
Thank you and enjoy your day!