Diabetes in Pregnancy: A Growing Dilemma

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Objectives

- Describe pathophysiologic processes related to diabetes in pregnancy that increase risks for both mother/newborn
- Define current recommendations for screening and treatment of mothers who have diabetes complicating their pregnancies
- Discuss outcomes in infants exposed to maternal hyperglycemia during pregnancy

Disclosure

- The presenter has no conflicts to disclose

Diabetes in the US

- Total: 29.1 million people or 9.3% of the population have diabetes.
- Diagnosed: 21.0 million people.
- Undiagnosed: 8.1 million people (27.8% of people with diabetes are undiagnosed).
  - all ages, 2012

Age-adjusted* percentage of people aged 20 years or older with diagnosed diabetes, by race/ethnicity, United States, 2010–2012

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Rate (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic whites</td>
<td>7.6</td>
</tr>
<tr>
<td>Asian Americans</td>
<td>5.0</td>
</tr>
<tr>
<td>Hispanics</td>
<td>12.8</td>
</tr>
<tr>
<td>Non-Hispanic blacks</td>
<td>15.9</td>
</tr>
<tr>
<td>American Indian/Alaska Natives</td>
<td>15.9</td>
</tr>
</tbody>
</table>

*Based on the 2000 U.S. standard population.

Rate of new cases of type 1 and type 2 diabetes among people younger than 20 years, by age and race/ethnicity, 2008–2009

Source: SEARCH for Diabetes in Youth Study. NHW = non-Hispanic whites; NHB = non-Hispanic blacks; H = Hispanics; API = Asians/Pacific Islanders; AIAN = American Indians/Alaska Natives.

*The American Indian/Alaska Native (AI/AN) youth who participated in the SEARCH study are not representative of all AI/AN youth nationwide. Thus, these rates cannot be generalized to all AI/AN youth nationwide.
Estimated costs- 2012

- Total (direct and indirect) $ 245 billion/year
- Direct
  - medical costs $ 176 billion
  - After adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes were 2.3 times higher than people without diabetes.
- Indirect
  - $ 69 billion (disability, work loss, premature death).

Washington State Diabetes: By County


Physiology of Pregnancy

A continuously feeding fetus in an intermittently feeding mom!
1\textsuperscript{st} half of pregnancy

- Early pregnancy: beta cell hyperplasia $\Rightarrow$ increased insulin production
- Increased tissue sensitivity to insulin
- Hyperinsulinemic state $\Rightarrow$ increased lipogenesis and fat deposition in early pregnancy
- Increased incidence of hypoglycemia in early pregnancy

2\textsuperscript{nd} half of pregnancy

- Accelerated growth of fetus (and placenta)
- $\uparrow$ maternal and placental ‘diabetogenic’ hormones
  - HPL
  - Cortisol
  - Estrogen/progesterone
  - Prolactin

Cont’d

- Increasing insulin requirement as pregnancy progresses
- Progressive increase in insulin secretion
- Pregnancy related insulin resistance
  - Hormonally mediated (as fetus/placenta grow)
  - Cytokine secretion (from fetus/placenta) which modulates the balance between humoral (antibody) and cell based immune responses

- Rapid change to a catabolic phase in 2\textsuperscript{nd} half of pregnancy $\Rightarrow$ Lipolysis (fat breakdown)
- Change from carbohydrate to fat metabolism during \textit{fasting times (overnight)}
  - Fats become fuel source
    - Fatty acids, triglycerides produced
    - Ketones produced (DKA)
  - Accelerated starvation
  - Increase in hepatic glucose production

\begin{tabular}{|c|c|}
\hline
\textbf{MATERNAL} & \textbf{FETAL} \\
\hline
Glucose & \textbullet\textbullet\textbullet \\
Amino Acids & \textbullet\textbullet\textbullet \\
FFA & \textbullet\textbullet\textbullet \\
TGFA & \textbullet\textbullet\textbullet \\
Ketones & \textbullet\textbullet\textbullet \\
Insulin & \textbullet\textbullet\textbullet \\
Glucagon & \textbullet\textbullet\textbullet \\
\hline
\end{tabular}
Maternal Obesity

• ~33% of pregnancies complicated by maternal obesity!

• Metabolic syndrome (choose 3)
  • Hyperlipidemia
  • Hypertension
  • Elevated fasting BS
  • Elevated triglycerides
  • Low HDL
  • Source: NIH

• Impacts quality of oocytes and embryos

• Fetal programming
  • Predisposition begins in utero
  • Susceptibility to adult disease in response to exposure

• Over nutrition during pregnancy
  • Epigenetic changes
    – Changes in the biochemical structure of DNA that alter gene expression
    – Affected by both inherited and environmental triggers

• Origins of adult diseases (HTN, T2D, CVD)
  • Impact both embryonic and fetal development

• Resulting in:
  • permanent structural/functional damage
  • Damage to cellular structures
  • May manipulate cellular responses to stimuli

• Over nutrition:
  • Programs the developing fetus to anticipate excessive nutrient availability after birth
    » Increases adiposity in offspring
    » Increases inflammation in offspring
    » Elevates fasting insulin levels
    » Increases insulin resistance
What if nutrients are appropriate after birth?

• Normal diet postnatally

• Offspring maintained adverse metabolic profile and epigenetic changes into adulthood….

What about pregnancy outcomes after bariatric surgery? (compared with matched controls)

• Lower risk of GDM
  - 1.9% v 6.8%
• Lower risk of LGA babies
  - 8.6% v 22.4%
• Higher risk of SGA babies
  - 15.6% v 7.6%
• Similar risk of “preterm” birth
  - 10% v 7.5%
• Higher risk of stillbirth or NND
  - 1.7% v .7%
• No significant differences in congenital malformations

Johansson K et al. NEJM 2015

Diabetes as a complication of pregnancy

• type 1 - autoimmune destruction of pancreatic islet cells (~10%)
• type 2 – enhanced insulin resistance (β cell dysfunction) (~90%)

  – Limited (or NO) pancreatic reserve
  – Increasing hormonal secretion
  – Increasing insulin resistance

Type 2 Diabetes:

• Can have insulin resistance with normal insulin secretion
• Changes can be seen 10-20 years before onset of overt disease
• Insulin resistance => precursor to β cell dysfunction
• Treating insulin resistance can lower dysfunction and slow the onset of the disease

Risk factors

• history of gestational diabetes, macrosomia, unexplained stillbirth, malformed infant
• family history of overt diabetes among first degree relatives
• high risk ethnic groups: African American, American Indian, Hispanic/Latina, Asian/Pacific Islander, South East Asian, East Indian
• obesity (BMI >30)
• medications that adversely affect normoglycemia
• H/O prediabetes, PCOS
**Gestational Diabetes**

- “Because of the number of pregnant women with undiagnosed type 2 diabetes, it is reasonable to test women with risk factors for type 2 diabetes at their initial prenatal visit, using standard diagnostic criteria.”
- Women with diabetes in the first trimester would be classified as having type 2 diabetes.
- GDM is diabetes diagnosed in the 2nd or 3rd trimester that is not clearly overt diabetes.

ADA Classification and Diagnosis of Diabetes: 2015

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**Patterns of Glycemia in Normal Pregnancy**

Should the current therapeutic targets be challenged?

11 studies reviewed

- Diabetes care, Volume 34, July 2011

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**Screening**

Screen at first visit: EITHER all women or only those with risk factors using FPG, RPG or A1C (not rapid)... include in prenatal labs

- Obtain fasting & 2 hour 75 gm OGTT (or 50 gm)
- Consider ordering with 3rd trimester labs

- Treat GDM if ONE or more values ≥ the following:
  - Fasting: 92, the 180, 2hr: 153
ACOG and ADA recommendations for BS goals (2013)

- Assess BS at either 1 or 2 hours postprandially
  - BS <140 at 1 hour
  - BS <120 at 2 hours

Patterns of Glycemia in Normal Pregnancy

Authors' Recommendation

* Exercise
* Medical nutrition therapy
* Medications
  - Oral
    - Metformin
    - Glyburide
  - insulin

Treatment

Diabetes care, Volume 34, July 2011
**Metformin**

- Crosses the placenta but no apparent adverse fetal effects (MiG trial)
- May decrease pre-eclampsia by decreasing insulin resistance
- May decrease spontaneous abortion in PCOS patients
- Long term, may protect against breast, colon, lung and pancreatic cancer

**Metformin in GDM Trial**

- Centers in Australia and New Zealand
- 751 women with GDM enrolled
  - 733 completed study
  - 363 assigned to Metformin (46.3% with supplemental Insulin)
    - 500 mg bid starting dose
    - 2500 mg/day maximum dose
  - 370 assigned to Insulin

Rowan et al NEJM 2008;358:19

- No differences in Neonatal Primary Composite Outcomes
  - Hypoglycemia, Birth Trauma, Respiratory Distress, Neonatal Depression, Preterm Birth, Phototherapy, etc
- No differences in Neonatal Secondary Outcomes
  - GA at birth, BW, Measurements, UC Insulin Levels, etc
- No clinically significant differences in Maternal Secondary Outcomes
  - Significantly better control with Metformin (but not clinically significant)
- Patients preferred Metformin (77% vs 27%)

**Diet v Insulin v Oral Agents**

- Start medication if ≥ 30\% of CBG levels are above goals while on diet
  - Fasting ≥ 90 mg/dl
  - 1 hour postprandial ≥ 120 mg/dl

*May not have enough time to try a diet or fail on oral agents*

**Metformin**

- Starting dose: 500 mg bid and increase twice weekly. (Rapid increase
  ➔ GI Symptoms)
- Maximum dose: 2500-3000 mg daily
- How supplied: 500, 850, 1000 mg (generic)  (also supplied as SR in
  500 and 750 mg)
- Hypoglycemia minimal concern
**Glyburide**

- Peak: ~4 hours
- Non Pregnant Elimination half life: ~10 hours
- Clearance increases as pregnancy progresses
- Breastfeeding not affected
- Pregnancy category B (Probably will change)
- **Not** detected in cord blood (Langer 2000)
- **Is** detected in cord blood (Hebert 2008)

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**CONCLUSIONS AND RELEVANCE**

Newborns from privately insured mothers treated with glyburide were more likely to experience adverse outcomes than those from mothers treated with insulin. Given the widespread use of glyburide, further investigation of these differences in pregnancy outcomes is a public health priority.

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**Plasma Glucose Variation Over 24 Hrs**

**Pregnant, Normal, Non-Diabetic at 28 and 38 wks**

10AM, 2PM, 6PM, 10PM, 2AM, 6 AM

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**What's on the horizon?**

The gut microbiome… but, that’s another story entirely!
References:


American Diabetes Association.


Smith, C; Ryckman,K. Epigenetic and developmental influences on the risk of obesity, diabetes and metabolic syndrome. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2015: 8 295-302

Obesity and Gestational Diabetes Mellitus Pathways for Programming in Mouse, Monkey and Man- where do we go next? The 2014 Norbert Freinkel Award Lecture. Diabetes Care; 2015; 38: 1402-1411.