Diabetes and Obesity in Pregnancy. Health Impact for the mother and child

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Objectives

• Review physiologic changes in pregnancy
• Review the risks associated with diabetes and obesity in pregnancy
  – Fetal
  – Obstetric
  – Maternal
  – Offspring
• Management of Diabetes and Obesity
  – Preconception
  – Throughout pregnancy
  – Post pregnancy

Pregnancy:
Physiologic changes

• Insulin sensitivity
  – Increase in early pregnancy
  – Rapid decrease by 40-50% during the course of pregnancy (greater in obese women)
  – Hyperinsulinemia
  – Lower fasting glucose
  – Lipolysis stimulation (placental hormones vs insulin)
  – Increased triglycerides by 260% and fasting TC by 61%
  – Human placenta is responsive to insulin levels
• Increase inflammatory makers

Diabetes in Pregnancy

• Pre-gestational
  – 13-21% of all pregnant diabetic
  – Increasing prevalence
• Gestational
  – 87%
  – Increasing prevalence

In Diabetes

• Placental glucose transport and metabolism are normal
• There is glucose fluxes from mother to fetus that result from increased glucose concentrations on the maternal side.
HbA1c in early pregnancy in women with type 1 Diabetes and risk of major fatal malformations

<table>
<thead>
<tr>
<th>HbA1c &lt;14 weeks %</th>
<th>HbA1c &gt;14 weeks SD</th>
<th>Malformations/all</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Not known</td>
<td>4/49</td>
<td>6.0</td>
</tr>
<tr>
<td>&gt;=9.4</td>
<td>&gt;=14</td>
<td>4/61</td>
<td>4.88</td>
</tr>
<tr>
<td>8.1-9.3</td>
<td>10-13.9</td>
<td>6/133</td>
<td>3.3</td>
</tr>
<tr>
<td>6.9-8.0</td>
<td>6-9.9</td>
<td>8/252</td>
<td>2.3</td>
</tr>
<tr>
<td>5.6-6.8</td>
<td>2-5.9</td>
<td>7/170</td>
<td>3.0</td>
</tr>
<tr>
<td>&lt;5.6</td>
<td>&lt;2.0</td>
<td>1/47</td>
<td>1.6</td>
</tr>
</tbody>
</table>

- All offspring of Diabetic women
  - No. of malformation 30/709
  - Relative risk 3.1
- Control offspring
  - 10/735
  - Relative risk 1.0

Diabetes Care 2000;62(1):79

Risk during pregnancy

- Miscarriages
- Pre-eclampsia/HTN
- Polyhydramnios
- Pre-term delivery
- C-Sections

Effect of Pregnancy in Diabetes

- Worsening DR
- Nephropathy
- Cardiovascular Disease
- DKA
- Higher risk of hypoglycemia

Pregestational Counseling

- In type 1 should start in puberty
- Risks and importance of good control
- Medications (ACEI)
- Contraception
  - Barrier
  - Rhythm
  - OCP
  - Intrauterine devices

Management of Diabetes: monitoring

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>Every 4-6 weeks</td>
</tr>
<tr>
<td>Glucose</td>
<td>SMBG 4 a 8 per day each visit</td>
</tr>
<tr>
<td>Urine ketones</td>
<td>During illness, any BG ≥200mg/dl</td>
</tr>
<tr>
<td>UA</td>
<td>Every 1-2 weeks</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Each trimester</td>
</tr>
<tr>
<td>TFT</td>
<td>Initial visit</td>
</tr>
<tr>
<td>Eye exam</td>
<td>Initial visit and as needed</td>
</tr>
</tbody>
</table>

Glucose Targets

| Fasting       | ≤ 95                                          |
| 1 hr          | <140                                         |
| 2 hr          | <120                                         |
| Overnight     | No less than 60                               |

ADA Standards of Care in Diabetes 2017. © Care 2017/A15 Supp C, 1136
Treatment:
Insulin

• 0.7 – 2 units/Kg
• Basal insulin 50% given as NPH (three/day)/Detemir
• Bolus insulin 50% (Lispro, Aspart)

Treatment:
Insulin

• No data demonstrating superiority of a particular insulin or insulin analog regimen
• Lispro and aspart
  – Clinically effective
  – No evidence of teratogenesis.
• Human NPH insulin as part of a multiple injection regimen should be used for intermediate acting insulin
• Detemir is FDA approved to be used during pregnancy

Treatment:
Oral Hypoglycemic agents

• No oral hypoglycemic agent has been endorsed either by ADA or ACOG to be used in pregnancy

• Are not approved by FDA

Nutritional

• Caloric requirements:
  • 30-32 kcal/kg early in pregnancy, advance to 35kcal/kg
  • Varies 25 a 30% depending on maternal wt
• Severe caloric restriction (>33%) is associated with increase FFA and cetoacids.
• Caloric distribution
• 6 meals: 10-30-30; 10-10-10

Labor and Delivery

• Insulin
  • Keep glucose 70-90mg/dl
  • 15u regular insulin en 150ml de SSN a 1-3u/h
• In active labor the insulin resistance decrease
  • Glucose infusion 2.5mg/kg-min
  • Q1hr FS, give insulin IV if > 120; double the glucose infusion if <60
  • Avoid glucose bolus

GESTATIONAL DIABETES
Gestational Diabetes

- Any degree of glucose intolerance that appears for first time or is first recognize during pregnancy

Physiopathology

- Pregnancy is a physiologic challenge to the insulin reserve
- Phenotypic and genotypic heterogeneity
- There is evidence of impairment in β cells
- Is considered a form of type 2
- Some patients have HLA DR3, DR4 and antibodies against islet cells

Risks

- Congenital abnormalities - no
- Increase morbidity and peri-natal mortality when treatment has been inadequate
- Increase risk of macrosomia and obstetric complications
- Increase risk of maternal hypertensive disease

Risks

- Maternal risk of future diabetes (2.6-70%)
- The risk is higher in the first 5 years, stabilize after 10 years
- The offspring has increase risk of obesity and glucose intolerance

Risk Factors

- Obesity
- Age
- Family or personal history of DM/GDM
- Ethnicity: Hispanic, Afro-Americans, native Americans, south east Asians

Diagnosis

- There are no uniform international standards for the diagnosis of gestational diabetes mellitus
- Women with risk factors for type 2 diabetes should be tested at the initial pre-natal visit using standard criteria
Diagnostic Criteria

<table>
<thead>
<tr>
<th>National Diabetes Data Group</th>
<th>Modified Carpenter Coustan</th>
<th>75-g glucose ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>105 mg/dL</td>
<td>95 mg/dL</td>
</tr>
<tr>
<td>1 hour</td>
<td>190 mg/dL</td>
<td>180 mg/dL</td>
</tr>
<tr>
<td>2 hours</td>
<td>165 mg/dL</td>
<td>155 mg/dL</td>
</tr>
<tr>
<td>3 hours</td>
<td>145 mg/dL</td>
<td>140 mg/dL</td>
</tr>
</tbody>
</table>

Two step: 50 g GLT- 1 hr glucose 130-135-140 mg/dL

Hyperglycemia and Adverse Pregnancy Outcomes (HAPO)

- Objective:
  - Evaluate the risk of adverse outcomes associated with various degrees of maternal glucose intolerance less severe that in overt diabetes mellitus
  - 23K participants with blinded data (2000-2006)
  - OGTT using 75g glucose between 24 and 32 weeks
  - Un-blind data if:
    - 2 hour glucose >200 mg/dL
    - FPG >105 mg/dL
    - Any random glucose < 45mg/dL or > 160 mg/dL
- Outcomes
  - Primary: birth weight above 90th percentile, primary cesarean delivery, clinical neonatal hypoglycemia and fetal hyperinsulinaemia
  - Secondary: premature delivery, birth injury, need for neonatal intensive care, hyperbilirubinemia, preeclampsia

HAPO: Maternal blood sugars were associated with

- Association in primary outcome
  - Birth weight above the 90th percentile
  - Cord blood serum C-peptide above the 90th percentile
  - Primary cesarean delivery (weak)
- Clinical neonatal hypoglycemia (weak)
- Positive associations with secondary outcomes
  - Premature delivery
  - Shoulder dystocia
  - Intensive neonatal care
  - Hyperbilirubinemia
  - Preeclampsia

Treatment Gestational Diabetes

- According to the US Preventive Services Task Force Review, treating Gestational Diabetes
  - More prenatal visits
  - Less Pre-eclampsia
  - Less shoulder dystocia
  - Less macrosomia
  - Insufficient evidence for maternal weight gain, birth injury, long term offspring outcomes
- No significant risk by treating

<table>
<thead>
<tr>
<th>FPG</th>
<th>1 hour</th>
<th>2 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; 75</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>2</td>
<td>75-109</td>
<td>90-132</td>
</tr>
<tr>
<td>3</td>
<td>109-144</td>
<td>133-145</td>
</tr>
<tr>
<td>4</td>
<td>145-157</td>
<td>158-193</td>
</tr>
<tr>
<td>5</td>
<td>194-205</td>
<td>206-244</td>
</tr>
<tr>
<td>6</td>
<td>&gt; 245</td>
<td>&gt; 245</td>
</tr>
</tbody>
</table>


Treatment

- There is very little time for intervention, most patients are diagnosed between 28 and 32 weeks with delivery around 37 – 39 weeks
## Treatment

- One important aspect of the treatment is intensive dietary education and monitoring and weight monitoring
- Severity of GDM is associated with gestational weight gain and can be modified by nutritional education, dietary changes and exercise

### Treatment: MNT Recommendations

- **Objectives**
  - Achieve normoglycemia
  - Prevent ketosis
  - Provide adequate weight gain
  - Promote fetal well-being
- **Caloric intake**
  - 12–40 kcal/Kg depending on BMI (33–40% from carbs)
- **Target postprandial glucose**
  - Better glycemic control and lower incidence of LGA
- **Carbohydrate counting**
- **Planned physical activity**

- It is reasonable to give a diet trial of 2 weeks for patients not obese with FPG <95 before starting pharmacologic treatment

### Insulin

- Hyperglycemia in diabetic range (≥126 mg/dl)
- After nutritional therapy if:
  - Fasting > 95–105 mg/dl
  - 1-hr post-prandial > 140–155 mg/dl
  - 2-hr post-prandial > 120–130 mg/dl

### Treatment: Insulin

- No data demonstrating superiority of a particular insulin or insulin analog regimen in GDM
- Lispro and aspart
  - Clinically effective
  - Minimal transfer across the placenta
  - No evidence of teratogenesis.
- Human NPH insulin as part of a multiple injection regimen should be used for intermediate acting insulin effect in GDM.

### Treatment: Oral Hypoglycemic agents

- No oral hypoglycemic agent has been endorsed either by ADA or ACOG to be used in pregnancy
- Are not approved by FDA
Post-Delivery

- Retest at 6 weeks
- Re-evaluate every 3 years if normal
- Re-evaluate every year if intolerant

Prevalence of obesity among adults aged 20 and over, by sex and age: United States, 2015-2016

WHO BMI Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>Less than 18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
</tr>
<tr>
<td>Obesity Class I</td>
<td>30.0-34.9</td>
</tr>
<tr>
<td>Obesity Class II</td>
<td>35.0-39.9</td>
</tr>
<tr>
<td>Obesity Class III</td>
<td>40 or greater</td>
</tr>
</tbody>
</table>

Effects of Obesity in Pregnancy

- Miscarriages
- Pre-eclampsia/HTN
- Occult type 2 DM
- GDM
  - OR 2.14 overweight
  - OR 8.56 severe obese
- C-Sections
- DVT
- ASD

Effect of Obesity in offspring

- Congenital anomalies
- Nephropathy
- LGA
- Shoulder dystocia
- Asphyxiation and death
- Childhood obesity

Institute of Medicine Recommendations for weight gain during Pregnancy

<table>
<thead>
<tr>
<th>Initial BMI</th>
<th>Weight Gain (lb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;19.8</td>
<td>26-40</td>
</tr>
<tr>
<td>19.8-26</td>
<td>25-35</td>
</tr>
<tr>
<td>26.1-29</td>
<td>15-25</td>
</tr>
<tr>
<td>&gt;29.1</td>
<td>At least 15</td>
</tr>
</tbody>
</table>
Maternal and Neonatal Outcomes Associated with the Amount of Gestational Wt Gain

Maternal weight gain modify the relationship between maternal glucose and fetal macrosomia

• Life Style Modifications during pregnancy may reduce the gestational weight gain, but have little effect on adverse pregnancy outcomes
• Interventions should begin before conception due to the effects on early placental development

Recommendations

• Pre-conception management
  – Education on adverse effects of obesity on fertility and possible complications in pregnancy
  – Evaluate for co-morbid conditions associated with obesity
    • Diabetes
    • HTN
  – Weight loss and LSM before conception
• Pregnancy Management
  – Appropriate referrals
  – US surveillance
  – Assessment of fetal wellbeing
  – DVT antibiotic prophylaxis

EFFECT OFFSPRING
LONG TERM
Metabolic programming (Epigenetics)

- A stimulus or an insult at a critical and sensitive period of early life permanently alters the organism’s physiology and metabolism
- Programming may be induced by nutritional, metabolic and hormonal events
- Mechanisms as reduced organ mass, altered angiogenesis and hyperinsulinemia may reflect how the fetus exposed to maternal diabetes/obesity is programmed to display abnormal glucose tolerance/insulin resistance in later life

High risk of diabetes and obesity in offspring of GDM

- Diabetes during pregnancy predisposes offspring to develop obesity and abnormal glucose tolerance later in life independently from genetic transmission
- In Pima nuclear families study was found that offspring born after their mother displayed diabetes had a 3.7–fold higher risk of diabetes and higher BMI than their full siblings born before their mother developed diabetes

The predisposing effect of intrauterine exposure to a diabetic environment has major public health implications in the presence context of the growing diabetes epidemic along with the tendency to develop diabetes at younger ages, by inducing a vicious circle.
Published studies show that after GDM, 35–60% of women develop type 2 diabetes within 10 years.

Women with GDM may manifest short-term endothelial dysfunction during late pregnancy that is manifested as transient hypertension.

Long-term endothelial dysfunction may be associated later in life with increased risk of chronic hypertension and CVD—90K US women with h/o GDM had 43% greater risk of CVD after adjustment for age, pre-pregnancy BMI and other variables. LS factors attenuated the association.

If only FPG was used in post-partum screening, 40% of Pre-diabetes and 75% of diabetes would have been missed.

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A diagnosis of GDM identifies women at high risk for diabetes.

This routine clinical identification represents a unique opportunity and a responsibility for caregivers to educate the patient and health care system for the need for primary diabetes prevention.
Summary

- Pre-existing diabetes (type 1 and type 2) are associated with significant risk to the mother and child
  - Preconception counseling should emphasize the importance of glycemic control to reduce the risk of congenital abnormalities
  - Strict fasting and post-prandial targets are desirable if they can be achieved safely
  - In the second and third trimester A1c of <6% have the lowest risk of LGA infants
  - Women should be counseled in regards to the risk of development and/or progression of Diabetic Retinopathy

Summary

- Gestational Diabetes is associated with substantial rates of maternal and perinatal complications
  - The risk of perinatal mortality is not increased, but the risk of macrosomia is
  - Macrosomia risk is increased across the spectrum of maternal glucose
  - This relationship is further modified by maternal weight gain
  - Long term adverse health outcomes are reported among infants born to mothers with gestational diabetes (impairment of glucose tolerance, obesity)
  - Treatment of Gestational Diabetes reduces serious perinatal morbidity and may also improve the woman’s health-related quality of life
  - Postpartum screening might detect diabetes preceding pregnancy and therefore enabling early treatment of hyperglycemia reducing the risk of adverse fetal outcomes in subsequent pregnancies and maternal microvascular complications
  - Identified women that benefit of diabetes prevention interventions

Summary

- Obesity in pregnancy is associated with increased risk of adverse outcomes to mother and child
  - Obese women should discuss reproductive planning well before conception with their health care providers and they should be counseled about the benefits of weight loss before attempting to conceive
  - Prompt evaluation of co-morbid conditions and modifications to routine pre-natal care are necessary

- Evidence from Nurses Health Study showed
  - Healthy dietary patterns in patients with previous GDM inversely associated with type 2 DM risk
  - Physical activity decreased the risk of type 2 DM
    - 100 min moderate intensity per week 9% lower risk
    - 150 min moderate intensity per week 47% lower risk