Oral-Systemic Links:
Gestational Diabetes Mellitus, Periodontitis and Maternal/Fetal Outcomes

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Interprofessional Collaboration for Collective Impact!

• Dr. Jeff Ebersole, Basic Scientist
• Dr. James E. Ferguson, OB/GYN
• Dr. John Novak, Periodontist and Basic Scientist
• Dr. George Taylor, General Dentist, Epidemiologist
Objectives

• After this presentation participants will be able to:
  – discuss the etiology of gestational diabetes mellitus (GDM),
  – describe how periodontal disease (PD), GDM and negative pregnancy outcomes may be linked.
  – describe data linking PD, GDM and negative pregnancy outcomes.
Gestational Diabetes Mellitus (GDM)

- Diabetes that has onset during pregnancy;
- Occurs in approximately 5-7% of pregnant women;
- Is the most common metabolic disorder of pregnancy.
GDM Etiology

- Women with GDM make sufficient amounts of insulin.
  - Placental hormones block the effect of insulin leading to “insulin resistance.”
  - The larger the placenta grows, the more these hormones are produced, and the greater the insulin resistance becomes.
GDM Risk Factors

• Obesity
• Previous history of GDM
• Family history of diabetes
• Having given birth previously to a very large infant, a still birth or a child with a birth defect
• Having too much amniotic fluid
• Being >25 years of age
• Being African American, Hispanic/Latina American, American Indian
GDM Testing and Diagnosis

• Non-fasting, 50 gm glucose screening test (Glucola)
  – Negative (&lt;140 mg/dL)
    • No further testing
  – Positive (&gt;140 mg/dL)
    • Fasting, 4 hour, 100 gm glucose tolerance test (GTT)
  – Positive (&gt;200 mg/dL)
    • Diagnostic, no further test needed
GDM Testing and Diagnosis

• GTT
  – Overnight fast followed by 100 gm glucose administration
  – Fasting, 1, 2, and 3 hour plasma levels obtained
  – Two values > normal are diagnostic
    • Fasting: 105 mg/dL
    • 1 hour: 190 mg/dL
    • 2 hours: 165 mg/dL
    • 3 hours: 145 mg/dL
GDM Testing and Diagnosis

- Average risk women
  - Tested between 24-28 weeks gestation

- High risk women
  - Tested as soon as possible
GDM Potential Negative Outcomes

• After pregnancy, 5-10% of women with GDM develop type 2 diabetes mellitus.
• Women who have had GDM have a 20-50% chance of developing type 2 diabetes in the next 5-10 years.
Study 1: NHANES III Analysis

Periodontal Disease and GDM

- 4244 women ages 20-59
  - 113 had a history of GDM during pregnancy
- Periodontal disease defined as one or more teeth with one or more sites with PD > 4mm, LOA > 2mm and bleeding on probing.
- There was a trend for women with a history of GDM to have more periodontal disease than women without a history of GDM
Hypothesis

Fig. 1:

Gestational Diabetes Mellitus  →  Periodontal Disease

Combined Effect

→

Negative Maternal and Fetal Outcomes

Periodontal Disease and GDM

• Prior GDM, higher pre-pregnancy BMI, vaginal levels of *Tannerella forsythia* and C-reactive protein were risk factors for developing GDM. Periodontal disease was not statistically significant. Dasanayake et al. 2008
  
  “New Evidence of Periodontal Disease Leading to Gestational Diabetes”

• Further support for the hypothesis that there is an association between periodontal disease and GDM. Xiong et al. 2009

• The presence of periodontal disease was significantly higher in women with either GDM or Type 2 diabetes during their pregnancy. Age, pregestational BMI and HbA1c) were related to clinical attachment loss in these two group. Ruiz et al. 2011

• Women with both prior GDM and periodontal disease showed greater insulin resistance and altered Beta cell function, potentially making them at greater risk for developing Type 2 diabetes. Xiong et al. 2012
Study 2: NIH Cross-Sectional Analysis

NIH/NCRR Center of Biomedical Research Excellence P20 RR020145
University of Kentucky CR-DOC
Study Population

• 306 matched pairs of pregnant women
  – Ages 16-45
  – No history of type 1 or type 2 diabetes mellitus
  – Minimum of 20 teeth

• 153 with GDM, 153 controls without GDM
  – Age, race/ethnicity and gestational age matched

• Categorized by presence/absence of periodontal disease (PD)
Data Collection

• Enrollment
  – Consent and HIPAA authorization
  – Medical and dental histories
  – Comprehensive periodontal examination
    • Plaque index, probing pocket depths, clinical attachment levels, bleeding index, calculus index
  – Periodontitis (PD)
    • At least 4 teeth with PD ≥4mm, LOA ≥2mm, and BOP
Data Collection

● Laboratory samples
  • Serum – assessed by ELISA and Luminex
  • Subgingival plaque – biofilm microbiota assessed by qPCR
Data collection

• Post-delivery maternal and fetal outcomes

  – *Maternal:* pre-eclampsia, premature labor, premature rupture of membranes, urinary tract infections, chorioamnionitis/funisitis, induction of labor, operative vaginal deliveries or unplanned cesarean*

  – *Fetal:* IUGR/LBW, shoulder dystocia, brachial plexus damage, facial nerve injury, fractured bones, other neonatal birth problems, hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, transient tachypnea of the newborn, polycythemia, hypocalcemia, intraventricular hemorrhage, necrotizing enterocolitis, congenital anomaly, stay in NICU, Apgars 1 or Apgars 5 <7’

*Crowther et al. 2005. Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes. NEJM. 352;2477-2486*
Analysis of 306 Matched Subjects
<table>
<thead>
<tr>
<th>Variable</th>
<th>GDM=No</th>
<th>GDM=Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>153</td>
<td>153</td>
</tr>
<tr>
<td>Age (s.d)</td>
<td>28.4 (5.2)</td>
<td>29.3 (5.9)</td>
</tr>
<tr>
<td>Race/ethnicity, number and (column %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian (n=24)</td>
<td>12 (7.8%)</td>
<td>12 (7.8%)</td>
</tr>
<tr>
<td>African American (n=24)</td>
<td>12 (7.8%)</td>
<td>12 (7.8%)</td>
</tr>
<tr>
<td>Caucasian (n=96)</td>
<td>48 (31.4%)</td>
<td>48 (31.4%)</td>
</tr>
<tr>
<td>Hispanic (n=162)</td>
<td>81 (52.9%)</td>
<td>81 (52.9%)</td>
</tr>
<tr>
<td>Gestational age at enrollment</td>
<td>29.0 (8.4)</td>
<td>28.6 (8.5)</td>
</tr>
</tbody>
</table>
## Clinical Characteristics: Periodontal Evaluation

<table>
<thead>
<tr>
<th>Variable</th>
<th>GDM+PD+ N=68</th>
<th>GDM+PD- N=85</th>
<th>GDM-PD+ N=59</th>
<th>GDM-PD- N=94</th>
<th>Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plaque index</strong></td>
<td>0.65 (0.16)</td>
<td>0.47 (0.14)</td>
<td>0.64 (0.16)</td>
<td>0.46 (0.17)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Probing depth</strong></td>
<td>3.26 (0.54)</td>
<td>2.50 (0.33)</td>
<td>3.14 (0.51)</td>
<td>2.47 (0.24)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Clinical attachment loss</strong></td>
<td>1.03 (0.61)</td>
<td>0.36 (0.25)</td>
<td>1.0 (0.65)</td>
<td>0.32 (0.20)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Calculus (0-3)</strong></td>
<td>0.73 (0.32)</td>
<td>0.21 (0.21)</td>
<td>0.74 (0.33)</td>
<td>0.17 (0.19)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Bleeding (0-3)</strong></td>
<td>0.57 (0.30)</td>
<td>0.20 (0.21)</td>
<td>0.45 (0.32)</td>
<td>0.16 (0.15)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Odds Ratios for Adverse Maternal Outcomes

<table>
<thead>
<tr>
<th>Contrasts for PD and GDM status</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD+ GDM+ vs. PD- GDM-</td>
<td>2.3</td>
<td>1.06, 4.8</td>
</tr>
<tr>
<td>PD+ GDM+ vs. PD- GDM+</td>
<td>1.97</td>
<td>0.88, 4.4</td>
</tr>
<tr>
<td>PD+ GDM+ vs. PD+ GDM-</td>
<td>1.77</td>
<td>0.85, 3.7</td>
</tr>
</tbody>
</table>

*Multivariable logistic regression: GEE adjusted for smoking and calculus

Variables used for matching were not used as covariates in the GEE matched analysis regression modeling. These included age, race/ethnicity, and gestational age at enrollment.
Conclusion

• Women in this study with the combination of GDM plus periodontal disease had:
  – a 2.3-fold greater risk for developing adverse maternal outcomes than women with either GDM or periodontal disease alone.

Fig. 1:  
Gestational Diabetes Mellitus  
Periodontal Disease  
Combined Effect  
Negative Maternal and Fetal Outcomes
### Case Control Comparison

<table>
<thead>
<tr>
<th>Periodontal Variable</th>
<th>Adverse pregnancy outcomes n=130</th>
<th>No adverse pregnancy outcomes n=176</th>
<th>P-value (Wilcoxon test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque index</td>
<td>0.56 (0.19)</td>
<td>0.53 (0.17)</td>
<td>0.08</td>
</tr>
<tr>
<td>Probing depth</td>
<td>2.8 (0.51)</td>
<td>2.7 (0.56)</td>
<td>0.01</td>
</tr>
<tr>
<td>Clinical attachment loss</td>
<td>0.63 (0.55)</td>
<td>0.62 (0.55)</td>
<td>0.84</td>
</tr>
<tr>
<td>Calculus (0-3)</td>
<td>0.44 (0.37)</td>
<td>0.39 (0.37)</td>
<td>0.17</td>
</tr>
<tr>
<td>Bleeding (0-3)</td>
<td>0.36 (0.30)</td>
<td>0.33 (0.31)</td>
<td>0.07</td>
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Case Control Comparison

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<thead>
<tr>
<th>Periodontal Variable</th>
<th>GDM + n=153</th>
<th>GDM – n=153</th>
<th>(P- value) (Wilcoxon test)</th>
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<td>0.55 (0.17)</td>
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<td>Probing depth</td>
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<td>2.7 (0.49)</td>
<td>0.08</td>
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<tr>
<td>Clinical attachment loss</td>
<td>0.66 (0.56)</td>
<td>0.58 (0.54)</td>
<td>0.21</td>
</tr>
<tr>
<td>Calculus (0-3)</td>
<td>0.44 (0.37)</td>
<td>0.39 (0.37)</td>
<td>0.20</td>
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<td>Bleeding (0-3)</td>
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<td>0.32 (0.30)</td>
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Conclusions

• Probing pocket depth, independent of GDM status, was a significant predictor of adverse pregnancy outcomes (p=0.01)

• Bleeding on probing was related to adverse pregnancy outcomes (p=0.07)

• GDM status was related to probing pocket depth (p=0.08)
# Odds Ratios for Adverse Fetal Outcomes

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<tr>
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<td>1.42</td>
<td>0.64, 3.14</td>
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<tr>
<td>PD+ GDM+ vs. PD- GDM+</td>
<td>1.47</td>
<td>0.66, 3.27</td>
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• Women in this study with the combination of GDM plus periodontal disease had:
  – no greater risk for adverse fetal outcomes than women with either GDM or periodontal disease alone.
Conclusions

• Women in this study with the combination of GDM plus periodontal disease had:
  – a 2.3-fold greater risk for developing adverse maternal outcomes than women with either GDM or periodontal disease alone.
  • Probing pocket depth, independent of GDM status, was a significant predictor of adverse pregnancy outcomes (p=0.01)
  • Bleeding on probing was related to adverse pregnancy outcomes (p=0.07)
  • GDM status was related to probing pocket depth (p=0.08)
  – no greater risk for adverse fetal outcomes than women with either GDM or periodontal disease alone.
Exploring the possible biology of an oral-systemic link
“Oral health is integral to general health”

A “silent epidemic of oral diseases is affecting our most vulnerable citizens”
Associations between oral and systemic conditions

• type 2 diabetes
• preterm birth
• coronary heart disease, atherosclerosis, stroke

• Alzheimer’s disease
• chronic, obstructive pulmonary disease
• acute respiratory infections
How could periodontal disease contribute to systemic conditions?
Defining periodontal disease

• An **inflammatory disease** that is initiated by the accumulation of **Gram-negative bacteria** around the teeth and gums
Potential mechanisms

- Dissemination of periodontal infection
- Dissemination of periodontal inflammation
Is there evidence that periodontal bacteria play a major role?

• “Guilt by association”
  – Periodontal bacteria rarely found in systemic organs
  – Case of fetal demise due to oral Fusobacterial infection extremely rare
  – No cases of stroke or myocardial infarction due to periodontal infection
Let’s look at inflammation as a potential culprit.
Inflammation

• Initiates the host response to challenge
• Brings immune cells and molecules to the site of challenge
• A tightly regulated mechanism
• When dysregulated leads to pathology
  – Genetic (polymorphisms in gene structure)
  – Environmental (smoking, stress, diet)
  – Systemic (obesity, type 2 diabetes, hormonal)
The secret killer

The surprising link between inflammation and heart attacks, cancer, Alzheimer’s and other diseases

Including periodontal disease

Inflammation is the body’s first defense against infection, but when it goes awry, it can lead to heart attacks, colon cancer, Alzheimer’s and a host of other diseases

Illustration for TIME by Brian Stannher
Periodontal disease and systemic disease

• Risk indicator or risk factor?
  – *Risk indicator* – periodontal disease and the systemic condition share common etiologies
  – *Risk factor* – oral infection/inflammation contributes to the genesis of the systemic condition. Remove periodontal disease and the systemic condition improves.
What is the evidence?

• Cross sectional studies
  – periodontal disease may be a risk indicator for systemic inflammatory conditions in certain populations

• Prospective, multi-center, randomized, controlled, intervention studies
  – failed to show a causal effect suggesting that periodontal disease is not a risk factor for systemic disease.
What is the answer?

• Periodontitis and systemic inflammatory conditions have complex etiologies

• Influenced by:
  – Socio-economic status
  – Lifestyle choices/behaviors
    • Diet, stress, smoking, drug abuse
  – Genetics; family history a good predictor
    • Infection
    • Inflammation
The answer may lie in complex interactions between multiple components of susceptibility.

This may make it very difficult to show a direct causal relationship between periodontal disease and systemic conditions.
Thank you!

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References


