Periodontal Disease and Risk for Preterm Birth

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Health Consequences of Preterm Birth

Short-term:
Respiratory distress syndrome, Intraventricular hemorrhage, Periventricular hemorrhagic infarction, Periventricular leukomalacia, Necrotizing enterocolitis, Bronchopulmonary dysplasia, Sepsis, Patent ductus arteriosus

Long-term:
Cerebral palsy, Attention deficit disorder, Retinopathy of prematurity, Mental retardation, Cardiovascular malformations
Medical costs for infants

The average hospital stay and first-year medical costs for premature and full-term babies:

<table>
<thead>
<tr>
<th>Hospital stay</th>
<th>Medical costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 days</td>
<td>$32,325</td>
</tr>
<tr>
<td>1.5 days</td>
<td>$3,325</td>
</tr>
</tbody>
</table>

Premature | Full-term | Premature | Full-term

Sources: March of Dimes and Institute for Medicine

USA Today, November 14, 2006
Primary Predictors
Black race, Young mother, Domestic violence, Low socioeconomic status, Stress or depression, Cigarette smoking, Cocaine or heroin use, Low Body Mass Index, Low maternal weight gain before pregnancy, Previous preterm birth or second trimester pregnancy loss, Previous induced abortion, Family history/inflammatory gene polymorphisms, Chronic lung disease, Chronic hypertension, Diabetes, Renal disease

Secondary Predictors
No or inadequate prenatal care, In vitro fertilization, Low maternal weight gain late in pregnancy, Iron-deficiency anemia, Pre-eclampsia, Elevated fetal fibronectin, $\alpha$-fetoprotein, alkaline phosphatase, or G-CSF, Early Contractions, Vaginal bleeding in first or second trimester, Short cervical length, Bacterial vaginosis, especially early in pregnancy, Chorioamnionitis, Placental abruption, Placenta previa, Hydramnios, Pre-eclampsia, Multiple fetuses
Gingivitis
Chronic Periodontitis
Periodontal Diagnosis
Fig. 3-5. Prevalence of slight, moderate and severe periodontitis in the U.S.  
(Albandar et al. 1999)
Why periodontal disease and preterm birth?

- Some infections are risk factors for PTB.
- Periodontal pathogens can enter the bloodstream through infected gums.
- Chronic periodontal inflammation involves mediators that are associated with PTB (e.g., PGE2, IL-1, IL-6).
- Supporting evidence in animal models.
**Periodontitis has been associated with:**

- Smoking
- CVD
- PAD
- Stroke/TIA
- Diabetes
- Pre-eclampsia
- Low birth weight
- Preterm birth
- COPD
- Gastric cancer

- Bacterial pneumonia
- Osteoporosis
- Poor physical fitness
- Foot balance
- Rheumatoid arthritis
- Obesity (young adults)
- Vitamin C intake
- Oral Cancer
- Gastric cancer
Offenbacher et al, 1996

- 124 women examined either at pre-natal visit or within 72 hours post-partum
- Cases (n=93): current or previous LBW baby (< 2,500 g) and spontaneous abortion < 12 wks, pre-term labor, PROM with resultant delivery < 36 wks, or delivery < 36 wks
- Controls (n=31): all birth weights ≥ 2,500 g and no PTL or PROM
Mean CAL (mm) in cases and controls

* P = 0.04 compared to NBW controls
Offenbacher et al, 1996

• Adjusted* odd ratios for association between severe periodontitis (60% of sites with 3+ mm CAL) and PLBW were:

  7.9 (1.95 – 28.8) for all PLBW cases
  7.5 (1.52 – 41.4) for primiparous cases

* Adjusted for race, age, previous births, tobacco use, BV, Hx of bacteriuria
Offenbacher et al., *Obstetrics & Gynecology* 2006;107:29-36
December 2006 Review by Xiong et al.

- 44 studies exploring association between periodontitis and adverse pregnancy outcomes (26 case-control, 13 cohort, 5 controlled clinical trials)
- 29 suggest a positive association
- Many reports based on small samples or may not have controlled for confounders

“RESULTS: The literature search revealed 17 articles that met the inclusion criteria. Seven thousand one hundred fifty-one women participated in the studies, 1056 of whom delivered a preterm and/or low birthweight infant. The overall odds ratio was 2.83 (95% CI: 1.95-4.10, P < .0001). This pooled value needed to be interpreted cautiously because there appeared to be a clear trend for the better quality studies to be of lower association strength. CONCLUSION: These findings indicate a likely association, but it needs to be confirmed by large, well-designed, multicenter trials.”
Intervention Studies

- 18-35 year old women in Santiago, Chile
- 9-21 wks of gestation with fewer than 18 teeth and 4+ teeth with 4 mm PD and 3+ mm CAL
- Randomized to receive either SCRP + and pxB q2-3 weeks before 28 wks or no treatment
- 29 in treatment group received amoxicillin + metronidazole for severe AgP
### Intent-to-treat analysis


<table>
<thead>
<tr>
<th></th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 163</td>
<td>n = 188</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 37 weeks</td>
<td>2 (1.1%)</td>
<td>12 (6.4%)</td>
<td>0.017</td>
</tr>
<tr>
<td>&lt; 2500 g</td>
<td>1 (0.6%)</td>
<td>7 (3.7%)</td>
<td>0.083</td>
</tr>
<tr>
<td>Both</td>
<td>3 (1.6%)</td>
<td>19 (10.1%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

- 368 women between 21-25 weeks of gestation and >3 tooth sites with 3+mm CAL (UAB)
- Randomized to receive:
  1) Dental cleaning + placebo (tid)
  2) SCRP + placebo
  3) SCRP + metronidazole (250 mg tid for 1 wk)
- Randomization stratified on BMI, BV, and history of SPTB prior to 35 wks
- 723 additional women with periodontitis as controls

p = 0.12

pxs + placebo
SCR + placebo
SCR + metronidazole

< 37 weeks
< 35 weeks
Obstetrics and Periodontal Therapy Trial
The OPT Clinical Investigative Team

- **Hennepin County Medical Center**: A. DiAngelis, V. Lupo, L. Simpson, J. Anderson, K. Meyer, J. Danielson, T. Thompson
- **University of Kentucky**: M. J. Novak, J. Ferguson, D. Dawson, A. Buell, D. Mischel, P. Stein, L. Cunningham, D. Dawson
- **University of Mississippi Medical Center**: W. Buchanan, J. Bofill, S. Vance, G. Young, A. Garner, N. Wood, K. Holmes
- **University of Minnesota**: B. Michalowicz, J. Hodges, A. Deinard, P. Tschida, H. Voelker, J. Osborn, I. Olson, Y. He, Q. Cao, L. Wolff, E. Delmore
Hypothesis

• Treatment of pregnant women with periodontitis reduces the incidence of preterm delivery.
OPT Trial

• Women randomly assigned to receive scaling and root planing either prior to 21 weeks (test) or after delivery (control)
• Test subjects receive monthly polishings and oral hygiene reinforcement
• All women receive essential dental care
• Inclusion Criteria
  – At least 16 years of age
  – have at least 20 natural teeth
  – have periodontal disease, defined as: 4 or more teeth with probing depth \( \geq 4 \text{ mm} \) and clinical attachment loss \( \geq 2 \text{ mm} \), and bleeding on probing at 35 percent or more tooth sites.

• Exclusion Criteria
  – had multiple fetuses
  – required antibiotic pre-medication
  – had a medical condition that precluded elective dental treatment
  – had extensive tooth decay or were likely to have fewer than 20 teeth after initial treatment.
Obstetrical Outcomes

• Primary: Gestational age at the end of pregnancy

• Secondary: Birthweight
Consented (n=939)

Randomized (n=823)

TREATMENT GROUP (N=413)
Scaling & root planing before 21 weeks + oral hygiene instruction
- Received treatment (n=395)
- Failed treatment visits or withdrew (n=18)

CONTROL GROUP (N=410)
Scaling & root planing after delivery

Treatment Allocation

Follow-Up

Analysis

For gestational age (n=413)

For gestational age (n=410)

*Lost to follow-up, Withdrew consent, Elective abortion
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Obstetrical History</th>
<th>Control Group (N=410)</th>
<th>Treatment Group (N=413)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>119 (29.0%)</td>
<td>116 (28.1)</td>
<td>0.77</td>
</tr>
<tr>
<td>Black</td>
<td>182 (44.4)</td>
<td>190 (46.6)</td>
<td>0.64</td>
</tr>
<tr>
<td>Hispanic</td>
<td>180 (43.9)</td>
<td>170 (41.2)</td>
<td>0.43</td>
</tr>
<tr>
<td>Any pregnancy</td>
<td>305 (74.4)</td>
<td>306 (74.1)</td>
<td>0.92</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>94 (30.8)†</td>
<td>108 (35.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Induced abortion</td>
<td>67 (22.0)†</td>
<td>52 (17.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>6 (2.0)†</td>
<td>9 (2.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Live preterm birth</td>
<td>44 (16.5)*</td>
<td>33 (12.5)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

† As a fraction of women with a previous pregnancy

* As a fraction of all women with a previous live birth
## Baseline Dental Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control Group (N=410)</th>
<th>Treatment Group (N=413)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of natural teeth</td>
<td>26.8 ± 1.7</td>
<td>26.7 ± 1.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Number of qualifying teeth</td>
<td>14.4 ± 6.7</td>
<td>15.2 ± 6.8</td>
<td>0.08</td>
</tr>
<tr>
<td>% tooth sites that bled on probing</td>
<td>69.0 ± 17.1</td>
<td>69.6 ± 17.4</td>
<td>0.62</td>
</tr>
<tr>
<td>% tooth sites with probing depth ≥4 mm</td>
<td>24.8 ± 15.9</td>
<td>26.5 ± 16.6</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Cumulative Incidence of Pregnancies Ending < 37 Weeks

Logrank = 0.14  p = 0.70

Control

Treatment

Control spontaneous abortion/stillbirth

Treatment spontaneous abortion/stillbirth

Cumulative Percent Pregnancy Ended

Gestational Age In Weeks

Control: 410 410 409 408 403 398 395 393 393 399 387 385 372 353

Treatment: 413 413 413 410 406 404 401 401 400 399 397 385 378 358
Relative Hazard of the Pregnancy Ending < 37 weeks, According to Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N subjects (N events)</th>
<th>P</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst tertile %BOP at baseline</td>
<td>147 (20)</td>
<td>143 (17)</td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst 2 tertiles %BOP at baseline</td>
<td>272 (39)</td>
<td>279 (36)</td>
<td>0.59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst tertile %PD &gt;= 4mm at baseline</td>
<td>128 (12)</td>
<td>153 (16)</td>
<td>0.92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous preterm birth</td>
<td>44 (16)</td>
<td>33 (7)</td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous preterm birth, abortion, still birth</td>
<td>172 (34)</td>
<td>163 (27)</td>
<td>0.42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KY &amp; MN</td>
<td>228 (25)</td>
<td>230 (19)</td>
<td>0.32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attended 6 visits</td>
<td>236 (28)</td>
<td>200 (12)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attended &gt;=4 visits</td>
<td>377 (44)</td>
<td>358 (40)</td>
<td>0.82</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received most effective treatment</td>
<td>410 (52)</td>
<td>119 (11)</td>
<td>0.59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Birth Outcomes

<table>
<thead>
<tr>
<th>Duration of pregnancy</th>
<th>Control Group (N=405)</th>
<th>Treatment Group (N=407)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 32 wk</td>
<td>18 (4.4%)</td>
<td>10 (2.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>&lt; 35 wk</td>
<td>26 (6.4)</td>
<td>22 (5.4)</td>
<td>0.56</td>
</tr>
<tr>
<td>&lt; 37 wk</td>
<td>52 (12.8)</td>
<td>49 (12.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>Birthweight, in grams</td>
<td>3258 ± 575</td>
<td>3239 ± 586</td>
<td>0.64</td>
</tr>
<tr>
<td>&lt; 2500 g</td>
<td>43/403 (10.7%)</td>
<td>40/406 (9.9%)</td>
<td>0.73</td>
</tr>
<tr>
<td>&lt; 1500 g</td>
<td>15/403 (3.7)</td>
<td>8/406 (2.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Small for gestational age (10%)</td>
<td>48/391 (12.3)</td>
<td>51/402 (12.7)</td>
<td>0.91</td>
</tr>
</tbody>
</table>
## Birth Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control Group (N=405)</th>
<th>Treatment Group (N=407)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live births</td>
<td>391 (96.5%)</td>
<td>402 (98.8%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 32 wk</td>
<td>5 (1.3)</td>
<td>6 (1.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt; 35 wk</td>
<td>12 (3.1)</td>
<td>18 (4.5)</td>
<td>0.35</td>
</tr>
<tr>
<td>&lt; 37 wk</td>
<td>38 (9.7)</td>
<td>44 (10.9)</td>
<td>0.64</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>20 (4.9)</td>
<td>31 (7.6)</td>
<td>0.15</td>
</tr>
</tbody>
</table>
# Neonatal Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Treatment Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APGAR &lt; 7 at 1 min</td>
<td>27/383 (7.0%)</td>
<td>37/394 (9.4%)</td>
<td>0.13</td>
</tr>
<tr>
<td>APGAR &lt; 7 at 5 min</td>
<td>3/383 (0.8%)</td>
<td>4/394 (1.0%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>31/389 (8.0%)</td>
<td>45/397 (8.0%)</td>
<td>0.12</td>
</tr>
<tr>
<td>NICU stay &gt; 2 days</td>
<td>22/389 (5.7%)</td>
<td>30/397 (7.6%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Discharged Alive</td>
<td>30/31 (96.8%)</td>
<td>44/45 (97.8%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
## Periodontal Outcomes*

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Treatment Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probing depth @ sites initially 4-6 mm, in mm</td>
<td>0.38 ± 0.02</td>
<td>0.88 ± 0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Probing depth @ sites initially ≥ 7 mm, in mm</td>
<td>1.07 ± 0.14</td>
<td>1.84 ± 0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sites w/ CAL ≥ 2 mm</td>
<td>0.84 ± 0.85</td>
<td>9.72 ± 0.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% sites w/ BOP</td>
<td>2.1 ± 0.7</td>
<td>22.7 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Change from baseline. Positive number indicates an improvement.
Conclusions

In pregnant women with periodontitis:

- Non-surgical periodontal therapy delivered between 13 and 21 weeks of gestation does not significantly alter rates of preterm birth, low birthweight or fetal growth restriction
- Non-surgical periodontal therapy delivered between 13 and 21 weeks of gestation is safe and effective
Guy’s and St. Thomas Hospital

• Enrolled women at 12 weeks of gestation
• Conducted dental exams in hospital beds, evaluated two sites per tooth
• Data available for 3,452 term, 286 preterm (< 37 wks), and 112 very preterm (< 32 wks) mothers
Moore et al., *Br Dent J* (2004); 197, 251–258.
Moore et al., *Br Dent J* (2004); 197, 251–258.

- Mean PD (mm)
- Mean AL (mm)
- Median %BOP (x 10)

- Non-LBW
- LBW
- Miscarriage

$p = 0.023$
Where to go from here?

1. *Ongoing studies*
2. *Community concerns*
   • Improve dental health awareness and access to care in pregnant women with periodontitis – care to improve oral health *per se*
3. *Possible research questions*
   • Does periodontal therapy delivered prior to conception affect birth outcomes?
   • Do comprehensive approaches that address all infections/chronic inflammatory states as well as deleterious habits and lifestyles improve birth outcomes?
   • What is the effect of periodontitis on early pregnancy losses?
   • Are periodontitis and preterm birth risk features of common phenotype?