



# **Oral and General Health - Exploring the Connection**

*Research Review June 2010*

**Associations between Periodontal Disease and Adverse Pregnancy**

**Outcomes**

**PROFESSIONAL VERSION**

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**ORAL AND SYSTEMIC HEALTH CONNECTIONS**  
*Quarterly Research Review June 2010*  
**Associations between Periodontal Disease**  
**and Adverse Pregnancy Outcomes**

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### **Executive Summary**

Over half a million babies are born too early or too small in the United States each year. This is one in eight or 12.8%, an average of 1,800 immature infants born each day. These children are more likely to die within their first year of life. The survivors often require extended medical care and various educational and social support throughout their lives with subsequent loss of productivity. Thus, prematurity is a major public health concern that takes its toll on the individuals, their families and their social network, as well as society as a whole.

Periodontal diseases are some of the most common chronic, infections in humans. Due to hormonal changes, the majority of pregnant women develop “pregnancy gingivitis”. Ten to 90 percent of the world’s adults have chronic periodontitis, with severe periodontitis in five to 15 percent. Anaerobic bacteria colonize the depth of the pockets surrounding the teeth, leading to irreversible damage of the tissues supporting the teeth in chronic periodontitis. The vascular permeability of inflamed periodontal tissues is increased, facilitating diffusion of bacteria and their byproducts into the host tissues and the blood stream, where they can locate anywhere in the mother and unborn child. This dissemination of the bacteria and other products is thought to contribute to a systemic inflammatory burden.

Adverse pregnancy outcomes are undesirable events occurring during pregnancy and childbirth in mother or child, such as preterm birth, low birth weight, gestational diabetes, and preeclampsia. Known risk factors are: history of preterm birth; alcohol, tobacco, and illicit drugs; low educational level; very young (<18) or old (>37) maternal age; lack of prenatal care; poor nutritional status; obesity, diabetes, and infections/inflammation. Periodontal pathogens and their antibodies have been detected in amniotic fluid, placenta, and umbilical cord, having crossed the placental barrier. They contribute to the systemic burden of infection/inflammation that is believed to be a major mechanism causing adverse pregnancy outcomes.

It has not been unequivocally shown that periodontal diseases cause adverse pregnancy outcomes, although associations exist in several subpopulations around the world, based on reports from case-control and cohort observational studies, and some clinical trials. No evidence from large, multi-center randomized clinical trials exists that periodontal treatment decreases the occurrence of adverse pregnancy outcomes. However, research has demonstrated that non-surgical periodontal treatment is effective in reducing levels of periodontal disease in pregnancy. Furthermore, it is established that provision of such treatment is safe for both the mother and the child.

## Conclusion

Unambiguous evidence that treating periodontal infection decreases the risk for adverse pregnancy outcomes is lacking. However, because it is known that 1) infection with its inflammatory response is a risk factor for adverse pregnancy outcomes, 2) periodontal diseases are infections, and 3) it is safe to provide preventive and therapeutic, non-surgical periodontal treatment during pregnancy, health caregivers should make every effort to contribute to the prevention and treatment of periodontal diseases both before and during pregnancy.

## **I. Introduction**

Over 4,300,000 babies are delivered each year in the United States<sup>1,2</sup>. Almost one in eight, or 12.7 percent, is born prematurely, or *preterm*, defined as before completion of the 37<sup>th</sup> gestational week<sup>1,3</sup>. On average, 1,800 immature infants are born each day, totaling over half a million a year. Many newborns are small: 8.2 percent of all US births in 2007 weighed less than 2,500g or 5.5 pounds<sup>1</sup>. Despite advances in modern medicine, the rate of prematurity has steadily increased for several decades in many countries in the world. In the United States, the percentage of all births classified as late preterm (34-36 weeks) has increased 20% between 1990 and 2006<sup>3</sup>, so every day more than 900 late preterm babies are born, adding up to 333,461 in the year 2006<sup>3</sup>. Newborns, who are delivered either too early, too small for their gestational age, or both, most often represent a large burden on the parents, the families, the communities, and the country. These infants are typically not fully matured and therefore will often require costly medical care in hospital neonatal (intensive care) units. Prematurity is the main cause of neonatal death. Low birth weight babies are about twenty times more likely to die before their one-year birthday, and the individuals who survive frequently suffer not only from neonatal conditions that are resolved in infancy or early childhood, but also from permanent cognitive and physical disabilities. Therefore, they would require special medical, educational, and support services throughout their lives. Consequently, prematurity represents an immense public health problem.

Adverse pregnancy outcomes are multi-factorial. Several risk factors are known to be associated with adverse pregnancy outcomes, such as history of preterm birth; abuse of alcohol, tobacco, and illicit drugs; low educational level; very young (<20) or old (>40) maternal age; lack of prenatal care; poor nutritional status; obesity; diabetes; and infections and the host's inflammatory responses. Infection – with its subsequent inflammatory response – is a known risk factor for preterm births and low birth weight, and periodontal diseases are inflammatory in nature. It is important to emphasize that the non-specific, general inflammatory mediators induced by periodontal diseases are the same ones that play an important role in the initiation of labor. Thus, it is logically reasonable as well as biologically

plausible to hypothesize that periodontal infection contributes to adverse pregnancy outcomes in the form of early delivery.

Consequently, an increasing number of publications and ongoing studies address the question: “Is maternal periodontal disease a risk factor for adverse pregnancy events or pregnancy outcomes?” and subsequently: “Can periodontal treatment decrease the rate of adverse pregnancy events or pregnancy outcomes?”

The goal of this report is to present the most recent evidence of associations between periodontal disease and adverse pregnancy outcomes. In 1996, Offenbacher and colleagues were the first to report data that suggested periodontal diseases could represent a previously unrecognized and clinically significant risk factor for preterm low birth weight in humans<sup>4</sup>. Thus, the body of evidence for such association has developed only during the last 14 years. The report will focus primarily on reports published the last three years.

### ***Organization of this Report***

The remainder of the report is organized as follows: Section II presents a methodological overview of the report’s preparation, first defining periodontitis and adverse pregnancy outcomes, then briefly describing the general strategy for selecting articles for review and the framework used to consider the level of evidence in rating reports. Next, the report describes evidence linking periodontal disease and adverse pregnancy outcomes from several perspectives: a) observational epidemiologic studies evaluating pregnancy outcomes assessed in meta-analyses, followed by individual reports of cohort, case control, and cross-sectional studies (Section III); b) intervention studies of the role of periodontal therapy in preventing adverse pregnancy outcomes assessed in meta-analyses and systematic reviews, followed by individual original research reports (Section IV); c) intervention studies providing information on the safety of provision of routine periodontal care during pregnancy (Section V); d) observational and intervention studies exploring mechanisms involving inflammation and periodontal pathogens (Section VI); followed by the conclusion (Section VII) and a bibliography of the citations referred to in the text (Section VIII).

Section IX is the Appendix: Appendix 1 details the literature search process, and Appendix 2 displays the levels of hierarchy of evidence used to rate the evidence. In Appendix 3, Tables 3A (intervention studies), 3B (etiologic observational studies), and 3C (intervention and etiologic studies on mechanisms) provide a comprehensive overview of the body of evidence published between January 1st, 2007, and December 31, 2009, displaying the full reference citation for each

report, the study design, and position in the hierarchy of evidence. Appendix 4 displays an example of a form currently in use by prenatal caregivers in New York State for referring pregnant patients for oral health consultation.

Throughout this report, the adjusted odds (risk) ratios are cited if available, as opposed to crude odds (risk) ratios. Only statistically significant findings are reported, unless otherwise noted.

## II. Methods

### **II.A. Definitions**

#### **1. Periodontal diseases**

Periodontitis is a bacteria-induced, localized, chronic inflammatory disease that destroys connective tissue and bone supporting the teeth. Periodontal disease is one of the most common chronic infectious conditions in humans with a prevalence of ten to 90 percent, depending on the population and subgroup studied and the case definition for periodontal disease used<sup>5,9-11,17</sup>. An estimated five to 15% of any population in the world has severe periodontitis<sup>11a</sup>, although mild to moderate periodontitis affects a majority of adults<sup>6</sup>. Periodontal diseases are more prevalent in groups that exhibit such risk factors as being male, older age, genetics, lower socio-economic status (income, education, and occupation taken together), cigarette smoking, diabetes, and compromised immune response. Because several of these demographic and behavioral factors also are risk factors for adverse pregnancy outcomes, it is important to control for them in any analysis attempting to assess the effect of periodontal infection on pregnancy outcomes. For instance, adverse pregnancy outcomes are more prevalent in the very young (<20 years) and older (>40 years)<sup>11b</sup>, so any effect of periodontal infection on pregnancy outcomes needs to be controlled for age. Due to hormonal changes, pregnant women are prone to develop gingivitis, presenting as inflamed and swollen gingival tissues. This reversible, gingival condition is so common it is called “pregnancy gingivitis”. The vascular permeability of the gingival tissues is increased, facilitating the diffusion of bacteria, their endotoxins and other byproducts. Pregnancy is not a risk factor for chronic periodontitis<sup>11a</sup>. However, the composition of subgingival plaque changes during pregnancy, so the ratio of Gram-negative bacterial species to aerobic species increases during the second trimester. This change occurs regardless of whether the outcome is a full-term, normal weight infant or not.

#### **2. Adverse Pregnancy Outcomes**

A multitude of maternal, placental, and fetal factors and conditions are required in order for a pregnancy to terminate at a normal gestational age in a normally developed infant with normal weight. When a pregnancy ends with a different, sometimes tragic result, the term adverse

pregnancy outcomes is used. Adverse pregnancy outcomes encompass events such as preterm birth, very preterm birth, low birth weight, small for gestational age, intrauterine growth restriction, and fetal death (spontaneous abortion/pregnancy loss or miscarriage and stillbirth).

The maternal pregnancy related conditions gestational diabetes and preeclampsia are also referred to as adverse pregnancy outcomes, regardless of whether the fetus is affected. The review by Wimmer and Philstrom<sup>12</sup> provides a listing of universally accepted definitions of adverse pregnancy outcomes along with their source references. Preterm birth (PTB) refers to a delivery occurring before completion of gestational week 37, and low birth weight (LBW) is less than 2,500g or 5.5 pounds. Very low birth weight (VLBW) is a term used for infants born at less than 1,500g or just under three pounds. Intrauterine growth restriction (IUGR) indicates the fetus has developed less than optimally during gestation. IUGR is closely associated with small for gestational age (SGA) that describes a newborn weighing less than either the 5<sup>th</sup> or the 10<sup>th</sup> percentile of the peers. Very preterm birth (VPTB) usually refers to births before week 32, but some authors use the limit before week 35. Preeclampsia is a dangerous hypertensive disorder associated with pregnancy<sup>13</sup>. The condition affects both the mother and the child. Its etiology remains elusive. Preeclampsia usually starts after the 20<sup>th</sup> gestational week and is diagnosed when a pregnant woman develops high blood pressure (two separate readings taken at least 4 hours apart of 140/90 or more) *and* 300 mg of protein in a 24-hour urine sample (proteinuria). Severe preeclampsia involves blood pressure over 160/110 and edema. Preeclampsia may, but rarely does, progress to eclampsia, a condition characterized by the appearance of seizures that are potentially fatal. The fetal syndrome encompasses fetal growth restriction, reduced amniotic fluid, and abnormal oxygenation<sup>14</sup>. For many years, gestational diabetes (GDM) or “pregnancy diabetes” has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy<sup>15</sup>, where glucose intolerance refers to excessive elevation of blood sugar levels after ingestion of carbohydrates. However, an international consensus group recently recommended that high risk women found to have diabetes at their initial prenatal visit receive a diagnosis of overt, not gestational, diabetes<sup>15</sup>. This recommendation is included in the American Diabetes Association’s position statement on diagnosis and classification of diabetes mellitus as of January 2010.

## **II.B. Strategy for Selecting and Rating Reports**

With information expert assistance, a search of reports on original studies was conducted. Meta-analyses and systematic reviews were also included. A description of the search strategy and process of selecting publications for this report is included in the Appendix, along with a description of the hierarchy of the levels of evidence used. Further, a listing of all original reports published

from 2007 through 2009 is displayed in the Appendix with their levels of evidence as assigned by the authors of this report.

### **III. Observational Epidemiological Studies (Cohort, Case-control, and Cross-Sectional Studies)**

#### **Linking Periodontal Disease and Adverse Pregnancy Outcomes to Address the Question: “*Should Periodontitis Be Considered an Independent Risk Factor (Risk Indicator for Cross-Sectional Studies) for Adverse Pregnancy Outcomes?*”**

##### **III.A. Preterm Birth and Low Birth Weight**

Several reviews of various adverse pregnancy outcomes and of varying quality have been published. Thirteen reviews were published since 2006: six were published in 2007, five in 2008, and two in 2009. Some authors have deemed the observational studies too heterogeneous to perform meta-analysis<sup>12, 16-17</sup> and have therefore published narrative reviews only.

##### **III.A1. Meta-analyses and Systematic Reviews of Observational Epidemiological (Cohort, Case-Control & Cross-Sectional) Studies**

###### ***a. Meta-Analyses***

A meta-analysis of data from five observational studies<sup>18</sup>, including two case-control studies and three prospective cohort studies concluded that periodontal disease was strongly associated with PTB, LBW, and PTB/LBW. Another meta-analysis of 17 studies (4 cohort, 11 case-control, 2 cross-sectional) with 7,151 pooled subjects delivering 1,056 PTB and/or LBW infants (14.8%) estimated the odds for PTB/LBW were 2.8 times greater in women with periodontal disease than those without periodontal disease<sup>19</sup>. However, the studies in the second meta-analysis were generally assigned low quality scores, 30%-82%, so the authors warn the result needs to be interpreted cautiously as there was a trend for the better quality studies to show lower strength of the association.

###### ***b. Systematic Reviews***

Three of the four systematic reviews published between 2003 and 2007<sup>17, 20, 21</sup> concluded that periodontal disease may be associated with undesirable pregnancy results, but the fourth stated it was not possible to reach a firm conclusion due to the heterogeneity of the studies<sup>16</sup>. The authors of the fourth review stated that although 26 of the 36 studies reviewed reported finding associations between periodontal disease and adverse pregnancy outcomes, there was clearly heterogeneity among the studies, both regarding assessment of the disease and the types of outcomes. For instance, they noted that 13 different definitions of periodontal disease were used in the 26 studies.

### **III.A2. Individual Observational Epidemiological Studies (Cohort, Case-control, and Cross-sectional Studies)**

#### ***a. Cohort Studies***

Five cohort studies were published from 2007 through 2009. Four demonstrated statistically significant associations between periodontal disease and adverse pregnancy outcomes of preterm and low birth weight infants<sup>22-25</sup>. These 4 studies were conducted in Argentina<sup>24</sup>, Fiji Islands<sup>25</sup>, Malaysia<sup>23</sup>, and the US (Massachusetts)<sup>22</sup>. Findings were reported on 108, 670, 472, and 1,635 women, respectively. The study in the US was remarkable, as it was conducted in middle-class women with a racial distribution mirroring the actual composition of the total United States population, whereas the other studies were conducted among minorities and populations with lower socio-economic status (SES). The US study assessed periodontal disease by self-report (without clinical verification) during the second trimester; 3.8% of the participants reported having periodontal disease. Eleven percent of all the participants delivered preterm or small for gestational age babies with two-fold greater odds of such deliveries for women having periodontal disease. The Argentine study included lower SES and younger women, as 41.6% were under 20 years of age. Still, 23.9% had periodontitis and 54% gingivitis. Among the Fijians, over half of the women delivering preterm babies had periodontitis versus 13% among full term mothers. In Malaysia, the odds of delivering a low birth weight baby were almost four-fold higher for women with periodontal disease. The fifth cohort study was conducted in Pakistan, where perinatal mortality rates are more than ten times greater than that in the United States<sup>26</sup>. Ninety-one percent of the study participants had not received any dental care the previous year and 87% had periodontal disease with poor oral hygiene<sup>27</sup>. Preterm birth and low birth weight were not related to periodontal status in that study.

#### ***b. Case-Control Studies***

Eight case-control studies showed mixed results: Five of the eight studies reported statistically significant associations between periodontal disease and preterm /low birth weight infants. The case-control studies that reported associations were conducted in Brazil<sup>31</sup>, India<sup>32</sup>, Jordan<sup>33</sup>, Turkey<sup>34</sup>, and Vietnam<sup>35</sup> and included 124, 300, 586, 48, and 390 subjects, respectively. Studies reporting no associations occurred in Brazil<sup>36</sup>, Italy<sup>37</sup>, and Thailand<sup>38</sup> and included 915, 220, and 934 pregnant women. These eight studies represent a variety of different populations in several parts of the world with each study using a different periodontal disease case definition. No evident pattern of association with periodontal disease in this set of studies allows any definitive conclusion to be drawn regarding periodontal disease as a risk factor for adverse pregnancy outcomes.

### ***c. Cross-Sectional Studies.***

Among the six cross-sectional studies published since 2006, two were conducted in Brazil<sup>39, 40</sup>, and one each in Finland<sup>41</sup>, Iran<sup>42</sup>, South Africa<sup>43</sup>, and Turkey<sup>44</sup>. Two of these studies are not considered further in this report<sup>40, 43</sup>. Three reports found statistically significant associations between periodontal disease and the adverse pregnancy outcomes preterm birth<sup>39, 42, 44</sup>, low birth weight<sup>39, 44</sup>, and intrauterine growth restriction<sup>39</sup>. The Finnish study concluded the oral health parameters were no different in women delivering preterm and full term infants<sup>41</sup>. In Finland, 5.9% of all births are preterm (less than half the rate in the US), as is the case in the rest of Europe with five to seven percent preterm deliveries<sup>41</sup>.

It is not possible to draw consistent conclusions about periodontal disease as a risk indicator for adverse pregnancy outcomes in this set of cross-sectional studies. The results of this set of studies suggest a possible relationship between periodontal disease and adverse pregnancy outcomes in socially and economically vulnerable subgroups and in countries that lack universal, comprehensive health care.

#### **III.A.1.a. Fetal Death**

The ultimate degree of preterm birth and low birth weight is fetal death, namely spontaneous abortion, pregnancy loss, or miscarriage plus stillbirth. Few studies have reported findings on fetal death and periodontal infection and will therefore be mentioned together in this section instead of under each study design category. A comprehensive review – citing 207 references – of medical disorders and infections during pregnancy resulting in stillbirths estimated two-thirds of the world's 3.2 million stillbirths occur antenatally, i.e. prior to labor, and are often overlooked in policies and programs<sup>28</sup>. Three periodontal *cohort studies*, conducted in the UK<sup>29</sup>, Pakistan<sup>27</sup>, and India<sup>30</sup>, were included in the review. All three cohort studies reported significant associations between periodontal infection and the risk of fetal death.

A *case-control study* in which 53 cases of idiopathic fetal or neonatal deaths were matched with 111 term deliveries concluded that maternal periodontal disease may contribute to perinatal mortality, especially that caused by extreme prematurity<sup>96</sup>. Women with perinatal loss were more than twice as likely to have periodontal disease, and women experiencing perinatal loss due to extreme prematurity were more than four times more likely to have periodontal disease, compared to women with full-term, live-born infants.

A *cross-sectional study* in Finland examined oral health care patterns as they related to a history of miscarriage<sup>41</sup>. Having had a dental examination within the last twelve months was considered receiving preventive care. Women who had no dental examination but did have restorations placed were categorized as receiving urgency-based treatment. Those with urgency-based oral health care pattern were more than two and a half times more likely to have had a miscarriage as those who received preventive care. Preventive care demonstrated a marginally significant inverse relation with having experienced a miscarriage.

### **III.B. Preeclampsia**

Preeclampsia affects both the mother and the fetus in 5-10% of all pregnancies<sup>14</sup>. It is a major cause for maternal and perinatal mortality and morbidity worldwide, particularly in developing countries. Preeclampsia is the most common factor associated with maternal mortality in the developed world, responsible for 15-20%<sup>14</sup> of maternal deaths. In the United States, 5-7 percent – or about 250,000 – of the pregnancies are affected by preeclampsia annually. Preeclampsia is believed to be responsible for 15% of premature deliveries and 17.6% of maternal deaths<sup>45</sup> in the US.

#### **III.B1. Meta-analyses and Systematic Reviews of Observational Epidemiological (Cohort, Case-Control & Cross-Sectional) Studies**

A systematic review and meta-analysis of 49 studies investigating maternal infection and risk of preeclampsia included nine studies on periodontal infection, namely two cohort and seven case-control studies<sup>46</sup>. Seven of the nine studies reported a significant association. After combining the results of all nine studies, risk of preeclampsia in women with periodontal disease was significantly increased with a pooled odds ratio of 1.6, meaning the risk for preeclampsia in pregnant women with periodontal disease was 1.6 times greater than in women without periodontal disease. However, the authors state that most of the studies they reviewed did not control for important confounders. Controlling for confounders (or characteristics associated with both periodontal disease and adverse pregnancy outcomes) could enhance or diminish the associations estimated in their meta-analyses.

#### **III.B2. Individual Observational Epidemiological (Cohort, Case-control, and Cross-sectional) Studies**

The first report of an association between periodontal disease and preeclampsia appeared in 2003<sup>47</sup>. Women with moderate to severe periodontal disease had 2.4 times greater risk of having preeclampsia than periodontally healthy women. In addition, those whose periodontal disease progressed were more likely to get preeclampsia. Similar results were later confirmed by the same group research group with an increased risk estimated to be 3.5 times greater for women with

periodontal disease<sup>48</sup>. The incidence of preeclampsia in that study was 4% (31/ 775). Also, a case-control study in Brazil<sup>49</sup> reported periodontally diseased women to be 1.5 to 2 times more likely to have preeclampsia, and the odds increased with the severity of periodontal disease. A cross-sectional study in Turkey also found that periodontal disease is associated with severe preeclampsia<sup>50</sup>. A study from Holland reported a significant association between a recent history of early-onset preeclampsia and severe periodontal disease. In that study, 82% of women with periodontal disease vs. 37% of periodontally healthy individuals exhibited preeclampsia. This study estimated the odds to be eight-fold greater for women with periodontal disease having preeclampsia.<sup>51</sup> Preeclampsia was found to not be associated with periodontal disease in a large prospective cohort study in which about 6% of the participants developed preeclampsia<sup>52</sup>. Another investigative group<sup>53</sup> applied six different periodontal case definitions in their analysis of data from a case-control study and found no evidence of an association between periodontal disease and preeclampsia.

### **III.C. Gestational Diabetes (GDM)**

Pregnancy complications associated with GDM include pregnancy-induced hypertension, preeclampsia, preterm birth, and increased need for Cesarean section because of difficulties in delivering the large baby that develops in many women with diabetes<sup>54</sup>. Furthermore, 50-70% of women with GDM develop type 2 diabetes within ten years after pregnancy<sup>54</sup>. In the United States, GDM is diagnosed in about seven percent of pregnant women – over 300,000 annually type – with Native Americans (5.8-14.3%), Asian/Pacific Islanders (3.9-7.4%), and Hispanics (3.5-7.5%) more often affected than African Americans (1.7-3.9%) and non-Hispanic Whites (2.2-3.6%)<sup>55</sup>.

#### **III.C1. Meta-analyses and Systematic Reviews of Observational Epidemiological Studies (Cohort, Case-Control & Cross-Sectional Studies)**

No meta-analyses or systematic reviews were published on associations between gestational diabetes and periodontal disease.

#### **III.C2. Individual Observational Epidemiological (Cohort, Case-control, and Cross-sectional Studies)**

Reports on two case-control studies were published the last three years. One case-control study supported the hypothesis of an association between periodontal disease and GDM. The study included 53 women with GDM and 106 matched healthy pregnant women<sup>56</sup>. The severity of periodontal disease was measured in quartiles of probing depth and clinical attachment loss. The proportions with periodontal disease were 77.4% in GDM vs. 57.4% in healthy women. Women with periodontal disease were 2.6 times more likely to have GDM than women without periodontal

disease. When comparing the odds ratios of having GDM between women in the highest to the lowest quartiles of PD and CAL, the odds ratios were 3.8 and 4.5, respectively.

In the second case-control study, presence of clinical periodontal disease failed to be associated with a statistically significant greater risk for GDM where the prevalence of periodontal disease was 50% in those with GDM vs. 37.3% in the healthy group who did not have GDM<sup>55</sup>. However, this same study reported significantly higher vaginal levels of the periodontal pathogen, *Tannerella forsythia*, in women with GDM than in those without GDM.

#### **IV. Intervention Studies (Randomized Clinical Trials and Clinical Treatment Studies) Linking Periodontal Disease and Adverse Pregnancy Outcome to Address the Question: “*Could Treating Periodontitis Reduce the Risk for Adverse Pregnancy Outcomes?*”**

##### **IV.A. Preterm Birth and Low Birth Weight**

##### **IV.A1. Meta-analyses and Systematic Reviews of Intervention Studies (Randomized Clinical Trials and Clinical Treatment Studies)**

###### ***a. Meta-Analyses***

A recent meta-analysis<sup>57</sup> assessed seven randomized clinical trials reporting results published between 2002 and 2007. The studies were conducted in Chile<sup>59, 60</sup>, India<sup>30</sup>, Iran<sup>61</sup>, and the US<sup>58, 62, 63</sup> and encompassed a cumulated 2,575 subjects. A cumulative total of 136 (9.7%) PTBs were observed in the treatment groups versus 165 (14.7%) in the control groups. In five studies, the rate of PTBs was higher in the non-treated (or control) arm, while in two<sup>58, 60</sup>, similar rates were observed in the both the treatment and control arms. The authors concluded that scaling and root planing resulted in significantly lower PTB and LBW; the risks for either PTB or LBW were approximately half in women receiving periodontal treatment than in the control group who did not receive periodontal treatment. The authors of this meta-analysis are aware they analyzed published study results, not individual, subject-level data, and were therefore not able to apply uniform periodontal disease case definitions to the data. The authors of this meta-analysis found moderate heterogeneity among the studies. For example, one of the reviewed studies reported on maternal gingivitis only, the rest on mild to moderate periodontitis. This meta-analysis also concluded that women with less periodontal disease at baseline and without a history of preterm deliveries seemed to benefit most.

Another meta-analysis<sup>17</sup> evaluated five clinical trials published by the end of 2006 – two non-randomized<sup>60, 64</sup> and three RCTs<sup>58, 61, 62</sup>. The authors of this meta-analysis concluded prophylaxis and non-surgical periodontal treatment may reduce the risk of PTLBW by approximately 50%, but did not significantly reduce the risk of either PTB or LBW, when assessed separately. One RCT included

only 30 subjects<sup>61</sup>. The two other RCTs failed to show significant effects of periodontal treatment on PTB, LBW, and IUGR<sup>58</sup> and PTB<sup>62</sup>, the latter using adjunctive metronidazole. It can be debated whether randomized and non-randomized intervention studies should be included in the same meta-analysis, as their designs are different and the potential for bias is greater in non-RCTs. While the results of this meta-analysis support a beneficial effect for periodontal treatment in reducing the risk of adverse pregnancy outcomes, this meta-analysis still does not provide definitive evidence.

### ***Other Reviews***

A comprehensive narrative review (169 citations) published in 2009<sup>12</sup> included five clinical trials that reported statistically significant beneficial effects of periodontal treatment on the adverse pregnancy outcomes PTLBW, PTB, and LBW<sup>30, 59-61, 65</sup> and two that did not<sup>58,62</sup>. Based on their critical review of existing RCTs, the reviewers concluded there was no consistent evidence that treating periodontal disease is likely to have any effect on adverse pregnancy outcomes. The authors purport that of the seven reviewed trials with findings published until 2007, only one RCT<sup>58</sup> met the generally accepted standards for clinical trials.

The reviewers point out the importance of the RCT by Michalowicz et al.<sup>58</sup> providing sound, scientific data that show, for the first time, that provision to pregnant women of non-surgical periodontal treatment is safe for the mother as well as the fetus and that it is effective in reducing signs of maternal periodontal disease. “In view of reluctance of many dentists to care for women during pregnancy, this may well be the most important conclusion of this entire review”, Wimmer and Philstrom state at the end of their conclusion.

## **IV.A2. Individual Intervention Studies (Randomized Clinical Trials (RCT) and Other Treatment Studies)**

### ***Large Randomized Clinical Trials (RCT)***

Practically all reviews and reports of observational and small interventional individual studies have called for large, multi-center RCTs as necessary to determine whether periodontal treatment can reduce the risk of adverse pregnancy outcomes. Findings from three large, multi-center RCTs conducted in the US<sup>58, 66</sup> and one in Australia<sup>67</sup> have been reported. The American studies were called 1) Obstetrics and Periodontal Therapy (OPT)<sup>58</sup> and 2) Maternal Oral Therapy to Reduce Obstetric Risks (MOTOR)<sup>66</sup>, respectively, and the Australian is referred to as the 3) SMILE Study<sup>67</sup>. None of these studies included use of antibiotic medication, neither topical nor systemic, as no such drugs currently are approved by the Federal Drug Administration for use during pregnancy.

1) The Obstetrics and Periodontal Therapy (OPT) study<sup>58</sup> is a well-designed, randomized, blinded and controlled trial of the effects of non-surgical periodontal treatment during pregnancy on gestational age at birth and on birth weight. Pregnant participants who were at least 16 years old and had at least 20 teeth were recruited in the four states of Minnesota, Kentucky, Mississippi, and New York (Harlem). 45% were African Americans. All 812 participants enrolled had periodontal disease and had completed less than 17 weeks of their pregnancy at the time of enrollment. Periodontitis was diagnosed in the case where an individual had at least four teeth with at least 4 millimeters probing depth and at least 2 millimeters clinical attachment loss as well as bleeding on probing (BOP) at 35 percent or more of all sites probed. This study is the only large study that includes the wisdom teeth. Participants were randomly assigned to test and control groups. The test group received initial scaling and root planing (SRP) with oral hygiene instruction (OHI) during up to four visits, followed by monthly periodontal examinations with tooth polishing and OHI. The control (delayed treatment) group had an initial periodontal examination only, followed by monthly, brief periodontal examinations. Both groups received site-specific rescue therapy (SSRT), if necessary, defined as sites with 3mm or more clinical attachment loss (CAL). Postpartum, the control group received the same treatment as the test group did initially. The incidence of delivering preterm was about the same in the two groups: 12.0% in the test and 12.8% in the control groups. No statistically significant effects of periodontal treatment were observed on the adverse pregnancy outcomes preterm birth, low birth weight, nor small for gestational age. Importantly, though, the study demonstrated for the first time that non-surgical periodontal treatment is effective in reducing periodontal disease during pregnancy<sup>58</sup>.

2) The Maternal Oral Therapy to Reduce Obstetric Risks (MOTOR)<sup>66</sup> was a randomized, treatment-masked, controlled clinical trial designed to test the effect of maternal periodontal disease treatment on the incidence of preterm birth, i.e. delivery prior to completing the 37<sup>th</sup> week of gestation. The study was conducted at four sites, namely two in North Carolina and one each in Alabama and Texas with 37% being African American. A total of 1,806 women who were at least 18 years of age and had periodontal disease were randomly assigned to either the test group or the control (delayed treatment) group. A periodontal case required at least 3 sites with 3mm or more CAL. BOP was not included in the case definition. The test group received SRP and OHI at up to four visits in the beginning of the study, with the control group only receiving initial periodontal examinations. After delivery, the control group received the same treatment as the test group. No follow-up visits, periodontal examinations, nor SSRT were conducted during the study prior to delivery. The incidence of preterm birth prior to the completion of the 37<sup>th</sup> gestational week was not significantly different in the two arms of the study with 13.1% versus 11.5%, respectively. Non-surgical

periodontal treatment was not shown to have any effect on incidence of preterm birth (neither < 37 weeks, < 35 weeks, nor < 32 weeks) nor on birth weight (preterm or full-term)<sup>66</sup>.

3) The Australian Smile Study<sup>67</sup> was carried out at seven sites in the city of Perth, where 1,078 pregnant subjects with periodontal disease were enrolled and randomly assigned to one of two study groups, test and control (delayed treatment). The periodontal case definition required at least 12 sites with probing depth (PD) of 4mm or more. PD was used in order to measure current, not cumulated past, disease, and neither BOP nor CAL was used for diagnosing periodontal disease. The test group received initially SRP, OHI, and motivation, and had restorations with overhang that could irritate the soft tissues revised. If needed, the test group was re-treated one month later. The control group was examined only in the beginning of the study and received the treatment postpartum. Rates of preterm delivery (<37 weeks) were similar in the two groups: 9.7% versus 9.3% in the test versus control groups. No significant associations were reported between periodontal treatment and preterm birth nor birth weight/growth restriction. However, maternal periodontal status improved significantly after the non-surgical treatment<sup>67</sup>, so the study demonstrated that non-surgical periodontal treatment is effective when provided during pregnancy.

#### ***Small Randomized Controlled Trials (RCT)***

Three reports on smaller RCTs conducted in Hungary<sup>68, 69</sup> and India<sup>30</sup> were also published the last three years. The two Hungarian reports (by the same group of authors) both study 83 women with threatening preterm labor hospitalized at the same maternity ward. These two reports differ slightly, so it is unclear whether the reports concern the same study. In these reports, women who did not receive prenatal periodontal treatment were 3.4 to 4.5 times more likely to deliver infants who were preterm, low birth weight, or both. In the Indian study of 200 women, those without periodontal treatment were more likely to deliver preterm and low birth weight infants<sup>30</sup>. Prevalence of PTB was 53.5% in the treatment group and 76.4% in the control group. Corresponding figures for LBW were 26.3% vs. 53.9% with average birth weights at 2,565g vs. 2,459g, both statistically significant differences. 76% of the LBW was due to PTB. These rates for LBW were higher than the estimated 40% in the Indian population.

#### ***Non-RCT Treatment Studies***

A non-randomized treatment study of 450 women conducted in Brazil found a statistically significant difference between preterm delivery rates in periodontally healthy (4.1%), periodontally diseased with antenatal periodontal treatment (7.5%), and without such treatment (79 %) <sup>70</sup>.

#### **IV.B. Preeclampsia**

All three large randomized, clinical trials, OPT, MOTOR, and the Smile Study found no significant associations between non-surgical periodontal treatment and preeclampsia<sup>58, 66, 67</sup>. In the treatment vs. control groups in these studies, the rates of preeclampsia were 7.6% vs. 4.9% (treatment group non-significantly higher)<sup>58</sup>, 3.4% vs. 4.1%<sup>67</sup>, and 7.6% vs. 8.4%<sup>66</sup>.

#### **IV.C. Gestational Diabetes (GDM)**

No treatment studies investigating the role of periodontal therapy in risk of adverse pregnancy outcomes in women with GDM were published in 2007 through 2009.

### **V. Intervention Studies (Randomized Clinical Trials) Providing Information to Address the Question:**

#### ***“Is It Safe to Provide Dental Treatment to Pregnant Patients?”***

1) The large Obstetrics and Periodontal Therapy study (OPT) was the first to demonstrate in a large RCT that the provision of non-surgical periodontal treatment during pregnancy is safe for both mother and child<sup>58</sup>. The safety of dental treatment in pregnant patients has been further described<sup>93</sup>, based on provision of essential dental treatment with anesthesia as needed before 21 weeks of gestation, in addition to the periodontal treatment just described during the OPT study. Essential dental treatment (EDT) was defined as treatment of 1) odontogenic abscesses, 2) decayed teeth that were judged likely to become symptomatic during the course of the study if left untreated, and 3) fractured or decayed teeth that were judged as adversely affecting the health of adjacent soft tissues. EDT was needed for 483 (58.7%) of the women, and almost three quarters of the treatment offered was provided. Study participants were closely monitored by obstetric nurses and study obstetricians throughout the trial. The conclusion of the study findings was that EDT in pregnant women at 13 to 21 weeks gestation was not associated with an increased risk of experiencing serious medical adverse events or adverse pregnancy outcomes. The clinical implications are important and have already proved far-reaching: This study provided, for the first time, evidence that essential dental treatment and use of topical and local anesthetics provided during 13 to 21 weeks gestation is safe for the mother as well as for the child<sup>93</sup>.

2) The large Smile Study in Australia confirmed that provision of non-surgical periodontal treatment during pregnancy is effective in reducing periodontal disease and is not hazardous for mother and fetus<sup>67</sup>.

3) A randomized, delayed-treatment controlled pilot clinical trial involving 67 pregnant subjects concluded that treatment was safe, improved periodontal health, and prevented periodontal disease progression<sup>65</sup>.

## VI. Observational and Intervention Studies Elucidating Mechanisms Linking Periodontal Disease and Adverse Pregnancy Outcomes

In order to explore mechanisms underlying any associations between adverse pregnancy outcomes and periodontal disease and its treatment, observational and intervention studies have investigated the roles of inflammation and periodontal pathogens. It is hypothesized that inflammation is the major underlying factor, and studies have addressed various aspects of inflammation, such as the acute inflammatory marker C-reactive protein (CRP)<sup>48,71-76</sup>, and other inflammatory biomarkers such as TNF-alpha, IL-1beta, IL-6, PGE<sub>2</sub>, IL-10, and 8-isoPGF<sub>2alpha</sub><sup>50,55,77-81</sup>. Taken together, the evidence supports both maternal and fetal inflammatory responses to periodontal pathogens contributing to adverse pregnancy outcomes.

It has been reported that up to half of all cases of preterm labor involve bacterial infections, and this is true for up to 80 percent of preterm deliveries before the 30<sup>th</sup> gestational week<sup>82</sup>. Periodontal pathogens and antibodies to them have been found not only in supra- and subgingival plaque, gingivo-crevicular fluid, and periodontal tissues, but also dispersed systemically in maternal serum and plasma, vagina, placenta, amniotic fluid, and umbilical chord<sup>82-91</sup>. It is hypothesized that if lipopolysaccharides (i.e. endotoxins) from periodontopathogens gain access to the placenta, they could stimulate IL-1 $\beta$  and PGE<sub>2</sub> production in chorioamniotic and trophoblastic cells, leading to preterm labor<sup>91a</sup>. Some examples of recent reports supporting the dissemination of periodontal pathogens and the maternal and fetal immuno-inflammatory response to these pathogens contributing to adverse pregnancy outcomes follow.

One small cross-sectional study demonstrated the presence of *Porphyromonas gingivalis* antigens in five cell types in the placental tissues<sup>82</sup>. The findings suggest that *P. gingivalis* may commonly colonize placental tissue, leading to an inflammatory response and thereby contributing to preterm delivery. Another cross-sectional study demonstrated the simultaneous presence of the *Porphyromonas gingivalis* in the periodontal pockets and in the amniotic fluid in women pregnant with threatening preterm labor<sup>84</sup>. A cross-sectional study comparing the levels of six periodontopathic bacteria in the placenta of women with preeclampsia and in healthy pregnant women found statistically higher bacterial counts of all six bacterial species in the placenta of women with preeclampsia<sup>89</sup>. A cohort study found women with fetal exposure to oral pathogens have increased plasma levels of sFlt-1, an antiangiogenic factor that induces endothelial dysfunction and is increased in the placenta and plasma of women with preeclampsia.<sup>90</sup> In another report from the same cohort study<sup>91</sup>, live preterm births were associated with decreased serum levels of IgG

antibody to periodontal pathogens in women with periodontitis when assessed during the second trimester.

Evidence of such broad dispersal supports the hypothesized distal adverse effects of periodontal bacteria, their antibodies and byproducts as they disseminate throughout the mother's body and cross the placental barrier to the developing fetus. When taking into account the maternal systematic inflammatory responses elicited by periopathogens as well as their potentially direct immunoinflammatory effect on the developing fetus, current evidence continues to support the biologic plausibility that periodontal disease could adversely affect birth outcomes. This effect may be limited to certain sub-populations.

## **VII. Conclusion**

Associations between periodontal disease and risk of adverse pregnancy outcomes are relatively consistent in most smaller observational studies. However, at this time, evidence from large-scale randomized clinical trials does not support recommending routine periodontal care as an effective strategy to prevent adverse pregnancy outcomes. Yet, evidence is mounting regarding inflammatory mechanisms involved in the relationship between periodontal infection and adverse health outcomes. Relationships between oral health and adverse pregnancy outcomes through inflammatory pathways are biologically plausible and supported by some empirical evidence.

Only an estimated quarter to one-half of pregnant women in the United States will likely visit a dentist in a year<sup>92</sup>, even though it has been demonstrated that provision of routine periodontal care, including non-surgical periodontal treatment, is effective in improving maternal oral health. Furthermore, such periodontal treatment has been shown to be safe for both mother and child. Therefore, it seems prudent for all caregivers to attempt to ensure pregnant women have their oral health status evaluated and receive non-surgical periodontal treatment as needed.

## VIII. Bibliography: References Cited in the Text in this Report\*

*\*Please, also see Appendix 3: Classification of All Original Research Reports Related to Oral Health and Adverse Pregnancy Outcomes Published From January 1, 2007, through December 31, 2009*

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## **IX. APPENDIX**

- Appendix 1. Literature Search Process and MEDLINE Search Strategy
- Appendix 2. Level of Evidence Provided by Various Types of Studies
- Appendix 3. Classification of Original Research Reports Related to Oral Health and Adverse Pregnancy Outcomes from January 1, 2007, through December 31, 2009
- Appendix 4. Consultation Form from the New York State Department for Prenatal Care Givers to Refer Pregnant Patients to Receive Oral Health Care and for the Dentist to Provide Feedback

## **APPENDIX 1**

### **Literature Search Process and MEDLINE Search Strategy**

The literature search strategy team consisted of two content expert investigators and a medical librarian expert in systematic review search methodologies. Initially, the former identified a set of sentinel articles based on their knowledge of the literature. This formed the basis of the initial search strategy, suggesting relevant Medical Subject Headings (MeSH) and text words or phrases for the search. This initial search strategy was reviewed and revised in an iterative process that was validated by testing the search results for inclusion of twelve sentinel articles that the content experts on beforehand had decided should be included in a good search. The process culminated in the MEDLINE search strategy displayed in the following. The main search was conducted on December 10, 2009, and supplemented later.

MeSH terms selected included terms relevant to periodontology in various aspects of the profession and its practice, as well as anatomical terms and disease terms specific to that anatomical area. In addition, common diagnosis and oral health assessment tools and terms were included. Following the development of the filter to gather periodontics literature, a broad search on pregnancy and its outcomes was added into the search strategy. Limits were applied for Humans and English Language results, but no time span due to a priori knowledge of relevant reports stemming back only about two decades. The search was run several times and each time adjusted according to the display of irrelevant citations.

The two content expert authors perused the final search results consisting of 618 (648 minus 30 duplicate) citations resulting from the MEDLINE search relating to periodontitis and pregnancy outcomes to the present. Each selected citations to further pursue, based only on the title of the publication in order to avoid any publication bias introduced by knowledge of the names of the journals and authors. After further review of the abstracts, a subset was selected for reading of the full text. Additional citations came from hand-search of relevant journal lists of contents, from references cited in relevant reports, and from the authors' weekly automated searches of by National Center for Biotechnology Information (NCBI) until and including January 27, 2010. A total of 199 articles resulted from combining the selected publications and agreeing on further pursuit, including acquiring the full-text articles. The most illustrative and recent publications were selected for this report, along with articles that provide a historical perspective of the area of research. During the process of writing this report, additional citations were added in the form of original research reports, reviews, guidelines, and online citations.

The following final MEDLINE database search strategy provided 648 citations, of which 30 turned out to be duplicates:

#### **MEDLINE Database Search Strategy**

- 1 Pregnancy/ (629738)
- 2 Reproduction/ (34623)
- 3 Pregnancy, High-Risk/ (3769)
- 4 Pregnancy in Adolescence/ (6027)
- 5 exp Pregnancy Outcome/ (31564)
- 6 exp Infant, Newborn/ (443557)
- 7 exp Pregnancy Complications/ (297490)
- 8 exp Birth Weight/ (30126)
- 9 Fetal Weight/ (845)
- 10 (preterm or "pre-term" or "PT/LBW" or PLBW).mp. (32994)
- 11 ((spontaneous adj abortion\$1) or (miscarry or miscarri\$4) or stillbirth\$1 or (pregnancy adj4 loss)).mp. (20412)
- 12 (low-birthweight or (low adj3 ("birth weight" or birthweight))

- or (growth adj3 restriction)).mp. (30327)
- 13 (pre-eclampsia\$1 or preeclampsia\$1 or eclampsia\$1 or pregnan:  
or eph or "hypertension-edema-proteinuria" or hypertension or  
edema or proteinuria) adj (toxemia\$1 or gestosis))).mp. (27273)
- 14 (pregnan: or prenatal or antenatal or neonatal or antepartum or postpartum or "post-partum" or  
primiparous or primipara or primiparity or primigravida or childbearing).mp. (813774)
- 15 or/1-9 (996822)
- 16 or/10-14 (835286)
- 17 or/15-16 (1113851)
- 18 exp Periodontal Diseases/ (61209)
- 19 exp Periodontics/ (18514)
- 20 exp Periodontitis/ (19238)
- 21 exp Periodontium/ (30802)
- 22 periodont:.mp. (58359)
- 23 gingiv:.mp. (40463)
- 24 (gum\$1 adj3 disease\$1).mp. (114)
- 25 exp Gingival Crevicular Fluid/ (2118)
- 26 Fibromatosis, Gingival/ (301)
- 27 exp Gingival Hemorrhage/ (1932)
- 28 CPITN.mp. (491)
- 29 exp Dental Fistula/ (563)
- 30 exp Gingival Neoplasms/ (1717)
- 31 exp Dental Health Surveys/ (16906)
- 32 ((periodontal or plaque or dental or "oral health" or schei)adj3 index).mp. (8377)
- 33 exp Oral Health/ (8018)
- 34 exp Mouth, Edentulous/ (8382)
- 35 edentu:.mp. (10967)
- 36 or/18-35 (118659)
- 37 17 and 36 (2294)
- 38 exp Child/ (1349524)
- 39 exp Adult/ (4672454)
- 40 exp Adolescent/ (1369403)
- 41 38 not (39 or 40) (579102)
- 42 37 not 41 (2110)
- 43 limit 42 to animals (236)
- 44 limit 42 to humans (1893)
- 45 43 not 44 (129)
- 46 42 not 45 (1981)
- 47 limit 46 to english language (1491)
- 48 exp Epidemiologic Methods/ (3342632)
- 49 (ep or sn).fs. (1135334)
- 50 Meta-Analysis.pt. (24622)
- 51 exp clinical trial/ (619173)
- 52 or/48-51 (3911832)
- 53 47 and 52 (648)
- 54 ("19701034" or "17306654" or "17079762" or "16913241" or  
"16460334" or "16277587" or "11887460" or "11480640" or "11330932" or "8910829" or  
"15974837").ui. (12)
- 55 53 or 54 (**648**)

## APPENDIX 2

### **Level of Evidence Provided by Various Types of Studies**

The variation in the strength of evidence due to different study designs has led to the development of several schemes providing a hierarchy of evidence to rank studies according to the way in which their design contributes to the strength of evidence provided. The hierarchy is a way to reflect the potential of each type of study design to answer a particular type of question, based on the probability that its design has minimized the impact of bias on the results. The hierarchy in the following table is an ordering of the strength of the evidence each properly designed study type can yield<sup>94</sup>.

**Table APP2.1. Evidence Hierarchy Adapted from the Australian Government’s National Health and Medical Research Council’s Designation of ‘Levels of Evidence’ According to Type of Research Question<sup>94</sup>.**

*Please see explanatory notes below this table*

<b>Level</b>	<b>Intervention<sup>a</sup></b>	<b>Etiology<sup>b</sup></b>
I <sup>c</sup>	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A prospective cohort study
III-1	A pseudo-randomized controlled trial (e.g. alternate allocation)	All or none <sup>d</sup>
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> <li>▪ Non-randomized, experimental trial<sup>e</sup></li> <li>▪ Cohort study</li> <li>▪ Case-control study</li> <li>▪ Interrupted time series with a control group</li> </ul>	A retrospective cohort study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> <li>▪ Historical control study</li> <li>▪ Two or more single arm study<sup>f</sup></li> <li>▪ Interrupted time series without a parallel control group</li> </ul>	A case-control study
IV	Case series with either post-test or pre-test/post-test outcomes	A cross-sectional study or case series

Explanatory notes:

- a) Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence*<sup>95</sup>.
- b) If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the ‘Intervention’ hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the ‘Etiology’ hierarchy of evidence should be utilized.
- c) A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision

of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

- d) All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series, which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.
- e) This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C with statistical adjustment for B).
- f) Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C but where there is no statistical adjustment for B).

### APPENDIX 3

#### **Classification of Original Research Reports Related to Oral Health and Adverse Pregnancy Outcomes Published From 2007 through October 2009**

*This table's three parts are presented to provide the reader with a comprehensive overview of the body of evidence published since in 2007 to 2009. The hierarchy of evidence used is according to the Australian Government's National Health and Medical Research Council's designation of levels of evidence<sup>94,95</sup>.*

**Table APP3.A. Intervention Studies Published 2007 to 2009: Study Design and Evidence Level**

<b>3A. Intervention Studies</b>	<b>Study Design</b>	<b>Evidence Level</b>
Polyzos NP, Polyzos IP, Mauri D, Tzioras S, Tsappi M, Cortinovis I, et al. Effect of periodontal disease treatment during pregnancy on preterm birth incidence: a metaanalysis of randomized trials. <i>American Journal of Obstetrics &amp; Gynecology</i> 2009;200(3):225-32.	Meta-Analysis RCTs	Intervention I
Xiong X, Buekens P, Vastardis S, Yu SM. Periodontal disease and pregnancy outcomes: state-of-the-science. <i>Obstetrical &amp; Gynecological Survey</i> 2007;62(9):605-15.	Meta-Analysis RCT+Non-RCT	Intervention I + Etiology I
Michalowicz BS, Hodges JS, Novak MJ, Buchanan W, DiAngelis AJ, Papapanou PN, et al. Change in periodontitis during pregnancy and the risk of pre-term birth and low birthweight. <i>Journal of Clinical Periodontology</i> 2009;36(4):308-14.	RCT	Intervention II
Newnham JP, Newnham IA, Ball CM, Wright M, Pennell CE, Swain J, et al. Treatment of periodontal disease during pregnancy: a randomized controlled trial. <i>Obstet Gynecol</i> 2009;114(6):1239-48.	RCT	Intervention II
Novak T, Radnai M, Gorzo I, Urban E, Orvos H, Eller J, et al. Prevention of preterm delivery with periodontal treatment. <i>Fetal Diagnosis &amp; Therapy</i> 2009;25(2):230-3.	RCT	Intervention II
Offenbacher S, Beck JD, Jared HL, Mauriello SM, Mendoza LC, Couper DJ, et al. Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial [See Comments]. <i>Obstetrics &amp; Gynecology</i> 2009;114(3):551-9.	RCT	Intervention II
Radnai M, Pal A, Novak T, Urban E, Eller J, Gorzo I. Benefits of periodontal therapy when preterm birth threatens. <i>Journal of Dental Research</i> 2009;88(3):280-4.	RCT	Intervention II
Tarannum F, Faizuddin M. Effect of periodontal therapy on pregnancy outcome in women affected by periodontitis.[see comment]. <i>Journal of Periodontology</i> 2007;78(11):2095-103.	RCT	Intervention II
Conde-Agudelo A, Villar J, Lindheimer M. Maternal infection and risk of preeclampsia: systematic review and metaanalysis.[see comment]. <i>American Journal of Obstetrics &amp; Gynecology</i> 2008;198(1):7-22.	Meta-Analysis Non-RCT	Etiology I
Gazolla CM, Ribeiro A, Moyses MR, Oliveira LAM, Pereira LJ, Sallum AW. Evaluation of the incidence of preterm low birth weight in patients undergoing periodontal therapy. <i>Journal of Periodontology</i> 2007;78(5):842-8.	Non-RCT treatment study	Intervention III-2

**Table APP3.B. Etiologic Observational Studies Published 2007 to 2009: Study Design and Evidence Level**

<b>3B. Etiologic Observational Studies</b>	<b>Study Design</b>	<b>Evidence Level</b>
Mobeen N, Jehan I, Banday N, Moore J, McClure EM, Pasha O, et al. Periodontal disease and adverse birth outcomes: a study from Pakistan. <i>American Journal of Obstetrics &amp; Gynecology</i> 2008;198(5):514.e1-8.	Cohort*	Etiology II
Pitiphat W, Joshipura KJ, Gillman MW, Williams PL, Douglass CW, Rich-Edwards JW. Maternal periodontitis and adverse pregnancy outcomes. <i>Community Dentistry &amp; Oral Epidemiology</i> 2008;36(1):3-11.	Cohort	Etiology II
Saddki N, Bachok Na, Hussain NHN, Zainudin SLA, Sosroseno W. The association between maternal periodontitis and low birth weight infants among Malay women. <i>Community Dentistry &amp; Oral Epidemiology</i> 2008;36(4):296-304.	Cohort	Etiology II
Sanchez AR, Bagniewski S, Weaver AL, Vallejos N. Correlations between maternal periodontal conditions and preterm low birth weight infants. <i>Journal of the International Academy of Periodontology</i> 2007;9(2):34-41.	Cohort	Etiology II
Sharma R, Maimanuku LR, Morse Z, Pack AR. Preterm low birth weights associated with periodontal disease in the Fiji Islands. <i>International Dental Journal</i> 2007;57(4):257-60.	Cohort	Etiology II
Srinivas SK, Sammel MD, Stamilio DM, Clothier B, Jeffcoat MK, Parry S, et al. Periodontal disease and adverse pregnancy outcomes: is there an association? <i>American Journal of Obstetrics &amp; Gynecology</i> 2009;200(5):497.e1-8.	Cohort	Etiology II
Bassani DG, Olinto MTA, Kreiger N. Periodontal disease and perinatal outcomes: a case-control study. <i>Journal of Clinical Periodontology</i> 2007;34(1):31-9.	Case-control	Etiology III-3
Caruso F, Natri L, Arienzo M, Signoriello G, Picardi C, Mazza C, et al. Association between threatened pre-term labour and periodontal disease: does a relationship exist? A matched case-control study. <i>Minerva Stomatologica</i> 2007;56(9):415-26.	Case-control	Etiology III-3
Khader Y, Al-shishani L, Obeidat B, Khassawneh M, Burgan S, Amarin ZO, et al. Maternal periodontal status and preterm low birth weight delivery: a case-control study. <i>Archives of Gynecology &amp; Obstetrics</i> 2009;279(2):165-9.	Case-control	Etiology III-3
Kushtagi P, Kaur G, Kukkamalla MA, Thomas B. Periodontal infection in women with low birth weight neonates. <i>International Journal of Gynaecology &amp; Obstetrics</i> 2008;101(3):296-8.	Case-control	Etiology III-3
Le HTT, Jareinpituk S, Kaewkungwal J, Pitiphat W. Increased risk of preterm birth among non- smoking, non- alcohol drinking women with maternal periodontitis. <i>Southeast Asian Journal of Tropical Medicine &amp; Public Health</i> 2007;38(3):586-93.	Case-control	Etiology III-3
Lohsoonthorn V, Kungsadalpipob K, Chanchareonsook P, Limpongsanurak S, Vanichjakvong O, Sutdhibhisal S, et al. Is maternal periodontal disease a risk factor for preterm delivery? <i>American Journal of Epidemiology</i> 2009;169(6):731-9.	Case-control	Etiology III-3
Marakoglu I, Gursoy UK, Marakoglu K, Cakmak H, Ataoglu T. Periodontitis as a risk factor for preterm low birth weight. <i>Yonsei Medical Journal</i> 2008;49(2):200-3.	Case-control	Etiology III-3

Santos-Pereira SA, Giraldo PC, Saba-Chujfi E, Amaral RLG, Morais SS, Fachini AM, et al. Chronic periodontitis and pre-term labour in Brazilian pregnant women: an association to be analysed. <i>Journal of Clinical Periodontology</i> 2007;34(3):208-13.	Case-control	Etiology III-3
Shub A, Wong C, Jennings B, Swain JR, Newnham JP. Maternal periodontal disease and perinatal mortality. <i>Australian &amp; New Zealand Journal of Obstetrics &amp; Gynaecology</i> 2009;49(2):130-6.	Case-control	Etiology III-3
Xiong X, Elkind-Hirsch KE, Vastardis S, Delarosa RL, Pridjian G, Buekens P. Periodontal disease is associated with gestational diabetes mellitus: a case-control study. <i>Journal of Periodontology</i> 2009;80(11):1742-9.	Case-control	Etiology III-3
Agueda A, Ramon JM, Manau C, Guerrero A, Echeverria JJ. Periodontal disease as a risk factor for adverse pregnancy outcomes: a prospective cohort study.[see comment]. <i>Journal of Clinical Periodontology</i> 2008;35(1):16-22.	Cross-sectional	Etiology IV
Africa CWJ, Bayingana C, Yasin-Harnekar S. The use of Perioscan as a potential screening test for mothers at risk for delivery of pre-term and low birth-weight infants. <i>Journal of the International Academy of Periodontology</i> 2009;11(2):193-9.	Cross-sectional	Etiology IV
Heimonen A, Rintamaki H, Furuholm J, Janket S-J, Kaaja R, Meurman JH. Postpartum oral health parameters in women with preterm birth. <i>Acta Odontologica Scandinavica</i> 2008;66(6):334-41.	Cross-sectional	Etiology IV
Siqueira FM, Cota LOM, Costa JE, Haddad JPA, Lana AMQ, Costa FO. Intrauterine growth restriction, low birth weight, and preterm birth: adverse pregnancy outcomes and their association with maternal periodontitis.[see comment]. <i>Journal of Periodontology</i> 2007;78(12):2266-76.	Cross-sectional	Etiology IV
Toygar HU, Seydaoglu G, Kurklu S, Guzeldemir E, Arpak N. Periodontal health and adverse pregnancy outcome in 3,576 Turkish women. <i>Journal of Periodontology</i> 2007;78(11):2081-94.	Cross-sectional	Etiology IV
Vettore MV, Leal Md, Leao AT, da Silva AMM, Lamarca GA, Sheiham A. The relationship between periodontitis and preterm low birthweight. <i>Journal of Dental Research</i> 2008;87(1):73-8.	Cross-sectional	Etiology IV
Vettore MV, Leao AT, Leal MdC, Feres M, Sheiham A. The relationship between periodontal disease and preterm low birthweight: clinical and microbiological results. <i>Journal of Periodontal Research</i> 2008;43(6):615-26.	Cross-sectional	Etiology IV
Zadeh-Modarres S, Amooian B, Bayat-Movahed S, Mohamadi M. Periodontal health in mothers of preterm and term infants. <i>Taiwanese Journal of Obstetrics &amp; Gynecology</i> 2007;46(2):157-61.	Cross-sectional	Etiology IV

\*"Cohort" refers to Prospective Cohort.

**Table APP3.C. Intervention and Observational Studies Regarding Mechanisms Involved in Association between Periodontal Disease and Adverse Pregnancy Outcomes; Reports Published 2007-2009: Study Design and Evidence Level**

<b>3C. Intervention and Observational Studies Regarding Mechanisms Involved in Association between Periodontal Disease and Adverse Pregnancy Outcomes</b>	<b>Study Design</b>	<b>Evidence Level</b>
Ebersole JL, Novak MJ, Michalowicz BS, Hodges JS, Steffen MJ, Ferguson JE, et al. Systemic immune responses in pregnancy and periodontitis: relationship to pregnancy outcomes in the Obstetrics and Periodontal Therapy (OPT) study. <i>Journal of Periodontology</i> 2009;80(6):953-60.	RCT	Intervention II
Michalowicz BS, Novak MJ, Hodges JS, DiAngelis A, Buchanan W, Papananou PN, et al. Serum inflammatory mediators in pregnancy: changes after periodontal treatment and association with pregnancy outcomes. <i>Journal of Periodontology</i> 2009;80(11):1731-41.	RCT	Intervention II
Novak MJ, Novak KF, Hodges JS, Kirakodu S, Govindaswami M, Diangelis A, et al. Periodontal bacterial profiles in pregnant women: response to treatment and associations with birth outcomes in the obstetrics and periodontal therapy (OPT) study. <i>Journal of Periodontology</i> 2008;79(10):1870-9.	RCT	Intervention II
Offenbacher S, Lin D, Strauss R, McKaig R, Irving J, Barros SP, et al. Effects of periodontal therapy during pregnancy on periodontal status, biologic parameters, and pregnancy outcomes: a pilot study. <i>Journal of Periodontology</i> 2006;77(12):2011-24.	RCT	Intervention II
Akalın FA, Baltacıoğlu E, Alver A, Karabulut E. Total antioxidant capacity and superoxide dismutase activity levels in serum and gingival crevicular fluid in pregnant women with chronic periodontitis. <i>Journal of Periodontology</i> 2009;80(3):457-67.	Cohort*	Etiology II
Dashash M, Nugent J, Baker P, Tansinda D, Blinkhorn F. Interleukin-6 -174 genotype, periodontal disease and adverse pregnancy outcomes: a pilot study. <i>Journal of Clinical Immunology</i> 2008;28(3):237-43.	Cohort	Etiology II
Horton AL, Boggess KA, Moss KL, Beck J, Offenbacher S. Maternal periodontal disease and soluble fms-like tyrosine kinase-1 expression. <i>Journal of Periodontology</i> 2009;80(9):1506-10.	Cohort	Etiology II
Horton AL, Boggess KA, Moss KL, Jared HL, Beck J, Offenbacher S. Periodontal disease early in pregnancy is associated with maternal systemic inflammation among African American women.[see comment]. <i>Journal of Periodontology</i> 2008;79(7):1127-32.	Cohort	Etiology II
Horton AL, Boggess KA, Moss KL, Beck J, Offenbacher S. Periodontal Disease, Oxidative Stress, and Risk for Preeclampsia. <i>Journal of Periodontology</i> (Ahead of Print). Available at: <a href="http://www.joponline.org.proxy.lib.umich.edu/toc/jop/0/0">http://www.joponline.org.proxy.lib.umich.edu/toc/jop/0/0</a> . Accessed 01/29/2010.	Cohort	Etiology II
Ruma M, Boggess K, Moss K, Jared H, Murtha A, Beck J, et al. Maternal periodontal disease, systemic inflammation, and risk for preeclampsia. <i>American Journal of Obstetrics &amp; Gynecology</i> 2008;198(4):389.e1-5.	Cohort	Etiology II

Dasanayake AP, Chhun N, Tanner ACR, Craig RG, Lee MJ, Moore AF, et al. Periodontal pathogens and gestational diabetes mellitus. <i>Journal of Dental Research</i> 2008;87(4):328-33.	Case-control	Etiology III-3
Durand R, Gunselman EL, Hodges JS, Diangelis AJ, Michalowicz BS. A pilot study of the association between cariogenic oral bacteria and preterm birth. <i>Oral Diseases</i> 2009;15(6):400-6.	Case-control	Etiology III-3
Herrera JA, Parra B, Herrera E, Botero JE, Arce RM, Contreras A, et al. Periodontal disease severity is related to high levels of C-reactive protein in pre-eclampsia. <i>Journal of Hypertension</i> 2007;25(7):1459-64.	Case-control	Etiology III-3
Kunnen A, Blaauw J, van Doormaal JJ, van Pampus MG, van der Schans CP, Aarnoudse JG, et al. Women with a recent history of early-onset pre-eclampsia have a worse periodontal condition. <i>Journal of Clinical Periodontology</i> 2007;34(3):202-7.	Case-control	Etiology III-3
Lin D, Moss K, Beck JD, Hefti A, Offenbacher S. Persistently high levels of periodontal pathogens associated with preterm pregnancy outcome. <i>Journal of Periodontology</i> 2007;78(5):833-41.	Case-control	Etiology III-3
Lohsoonthorn V, Kungsadalpipob K, Chanchareonsook P, Limpongsanurak S, Vanichjakvong O, Sutdhibhisal S, et al. Maternal periodontal disease and risk of preeclampsia: a case-control study. <i>American Journal of Hypertension</i> 2009;22(4):457-63.	Case-control	Etiology III-3
Siqueira FM, Cota LOM, Costa JE, Haddad JPA, Lana AMQ, Costa FO. Maternal periodontitis as a potential risk variable for preeclampsia: a case-control study. <i>Journal of Periodontology</i> 2008;79(2):207-15.	Case-control	Etiology III-3
Barak S, Oettinger-Barak O, Machtei EE, Sprecher H, Ohel G. Evidence of periopathogenic microorganisms in placentas of women with preeclampsia. <i>Journal of Periodontology</i> 2007;78(4):670-6.	Cross-sectional	Etiology IV
Canakci V, Canakci CF, Yildirim A, Ingec M, Eltas A, Erturk A. Periodontal disease increases the risk of severe pre-eclampsia among pregnant women.[erratum appears in <i>J Clin Periodontol.</i> 2007 Dec;34(12):1097]. <i>Journal of Clinical Periodontology</i> 2007;34(8):639-45.	Cross-sectional	Etiology IV
Heimonen A, Janket S-J, Kaaja R, Ackerson LK, Muthukrishnan P, Meurman JH. Oral inflammatory burden and preterm birth. <i>Journal of Periodontology</i> 2009;80(6):884-91.	Cross-sectional	Etiology IV
Katz J, Chegini N, Shiverick KT, Lamont RJ. Localization of <i>P. gingivalis</i> in preterm delivery placenta. <i>J Dent Res</i> 2009;88(6):575-8.	Cross-sectional	Etiology IV
Leon R, Silva N, Ovalle A, Chaparro A, Ahumada A, Gajardo M, et al. Detection of <i>Porphyromonas gingivalis</i> in the amniotic fluid in pregnant women with a diagnosis of threatened premature labor. <i>Journal of Periodontology</i> 2007;78(7):1249-55.	Cross-sectional	Etiology IV
Sasahara J, Kikuchi A, Takakuwa K, Sugita N, Abiko Y, Yoshie H, et al. Antibody responses to <i>Porphyromonas gingivalis</i> outer membrane protein in the first trimester. <i>Australian &amp; New Zealand Journal of Obstetrics &amp; Gynaecology</i> 2009;49(2):137-41.	Cross-sectional	Etiology IV
Stonek F, Hafner E, Metzenbauer M, Katharina S, Stumpflen I, Schneeberger C, et al. Absence of an association of tumor necrosis factor (TNF)-alpha G308A, interleukin-6 (IL-6) G174C and interleukin-10 (IL-10) G1082A polymorphism in women with pre-	Cross-sectional	Etiology IV

eclampsia. Journal of Reproductive Immunology 2008;77(1):85-90.		
Vettore MV, Leao AT, Leal MdC, Feres M, Sheiham A. The relationship between periodontal disease and preterm low birthweight: clinical and microbiological results. Journal of Periodontal Research 2008;43(6):615-26.	Cross-sectional	Etiology IV

\*"Cohort" refers to Prospective Cohort.

**APPENDIX 4:**

**Consultation Form from the New York State Department for Prenatal Care Givers to Refer Pregnant Patients to Receive Oral Health Care and for the Dentist to Provide Feedback\***

\* The form in Word format is downloadable online and can be modified as desired:

[http://www.nyhealth.gov/prevention/dental/oral\\_health\\_care\\_pregnancy\\_early\\_od.htm](http://www.nyhealth.gov/prevention/dental/oral_health_care_pregnancy_early_od.htm)

**Consultation Form for Pregnant Women to Receive Oral Health Care**

Referred to: \_\_\_\_\_ Date: \_\_\_\_\_

Patient Name: (Last) \_\_\_\_\_ (First) \_\_\_\_\_

DOB: \_\_\_\_\_ Estimated delivery date: \_\_\_\_\_ Week of gestation today: \_\_\_\_\_

**KNOWN ALLERGIES:** \_\_\_\_\_

**PRECAUTIONS:**  NONE  SPECIFY (If any):  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

This patient may have routine dental evaluation and care, including but not limited to:

- Oral health examination
- Dental x-ray with abdominal and neck lead shield
- Dental prophylaxis
- Local anesthetic with epinephrine
- Scaling and root planing
- Root canal
- Extraction
- Restorations (amalgam or composite) filling cavities

Patient may have: (Check all that apply)

- Acetaminophen with codeine for pain control
- Alternative pain control medication: (Specify) \_\_\_\_\_
- Penicillin
- Amoxicillin
- Clindamycin
- Cephalosporins
- Erythromycin (Not estolate form)

Prenatal Care Provider: \_\_\_\_\_ Phone: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

**DO NOT HESITATE TO CALL FOR QUESTIONS**

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**DENTIST'S REPORT  
(for the Prenatal Care Provider)**

Diagnosis: \_\_\_\_\_  
\_\_\_\_\_

Treatment Plan: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

NAME: \_\_\_\_\_ Date: \_\_\_\_\_ Phone: \_\_\_\_\_

Signature of Dentist: \_\_\_\_\_