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Periodontal therapy and preterm birth

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I would like to start my presentation with acknowledging Dr Steven Offenbacher and Dr Jim Beck [University of North Carolina (UNC)]. They were responsible for conduct and data management/analysis of the research I will present today. My talk will briefly review the overall significance of the preterm birth problem. I will summarize the risk factors for preterm births. Then, I will discuss in more detail the design of our study and its results. I will wrap up my presentation with a few conclusions.

Let me share a few interesting numbers on preterm birth that were published by the US National Center for Health Statistics (1). By definition 'preterm' means birth was given before the end of the 37th week of gestation. Preterm babies are on the rise in the US! Since 1990, preterm births have increased by approximately 18%. In 2004, about one in eight of all registered births were preterm. The highest rate of preterm births, about one in six, was reported for African-Americans. In contrast, the lowest rate, one in 10, was observed in Asian or Pacific Islanders. The US Surgeon General has released a report (2) on objectives for population health in the year 2010. One of the designated goals is lowering the prevalence of preterm births to a population-wide average of 7.6%. For comparison, I reviewed the respective numbers for countries in the European Union. On average, the reported frequency has been slightly below 10%.

Preterm births can have a significant impact on society as they are accompanied by substantial mortality (3). They account for about two-thirds of all infant deaths. The chance of survival decreases dramatically among babies born before week 32, and is only about 20% for babies born in week 25. However it is great to know that infants born at or after 37 weeks of gestation have an almost perfect chance of survival.

Preterm birth has substantial economic impact (S. Offenbacher, personal communication): the average cost for neonatal intensive care for a preterm baby is about $56 000. In the USA, total cost of neonatal intensive care amounted to approximately $17 billion in the year 2000. Note, the dollar amount did not include physician fees, professional fees, or long-term neonatal or child care. Neurological disorders are a very frequent consequence of preterm birth, especially impairment of vision and hearing. Unfortunately, these conditions persist lifelong and therefore generate costs lifelong.

What are the known risk factors for preterm birth? Number one among all factors is genetic predisposition. Evidence from twin studies (4, 5) suggests a genetic predisposition with heritability between 20% and 40%. For example, about 30% of all women whose first child was born preterm, will have a preterm birth when they have a second child. Interestingly enough, if the second child was conceived with a different partner, the risk of preterm birth will be reduced by about one-third. Besides genetic factors, maternal age is important too. Mothers younger than 18 years and mothers older than 35 years share an increased risk for preterm births. Underweight and overweight before pregnancy are also considered risk factors as are short stature, African-American origin or low socio-economic status. Last but not least, infection, stress and obesity can contribute to the risk of preterm birth.

I will now discuss an interventional study on preterm birth that Philips Oral Healthcare conducted in collaboration with a team at the UNC (Offenbacher S, Lin DM, Strass R et al, unpublished data). A recent review paper (7) summarized the results of 25 studies on the relationship between periodontal disease and preterm birth. Although, a majority of the mostly cross-sectional studies confirmed the original findings, several studies disagreed with the proposed link. To better understand the proposed association between oral and systemic health, it is therefore important that more evidence is generated. Especially interventional studies are needed because they allow testing a causal relationship. The Philips/UNC study, executed in pregnant women with mild to moderate periodontal disease, was designed to investigate the effects of improved periodontal health on premature birth. The rationale for executing the study was that infectious processes, independent of their location in the body, can contribute to premature birth. Almost 10 years ago, a pioneering publication (6) suggested an association between periodontal disease and preterm birth.

The study was designed to have two arms and was single blinded, which means that the clinical examiner was not aware of the subject's treatment assignment. One arm (intervention) provided non-surgical periodontal therapy [scaling and rootplaning (S&RP)] during the second trimester, and oral hygiene was maintained using a Sonicare power toothbrush and instructions for home use. Subjects who were randomized to the second arm (delayed treatment) received a polish at baseline during the second trimester and a manual toothbrush for home use. They received S&RP and the Sonicare after delivery.

The inclusion criteria required that participants had to be pregnant for *<22* weeks at the time of S&RP or supragingival polish, had to be willing to provide consent, be randomized, and complete treatment protocols. With regard to periodontal parameters; two or more sites measuring ≥5 mm in probing depths were required with at least one site also exhibiting attachment loss of ≥2 mm. Subjects had to be at least 18 years old, have 20 or more natural teeth, and they had to have a history of preterm low birth weight delivery. The latter was the biggest obstacle among the inclusion criteria, ultimately leading to a very slow enrolment.

It is well known that multiple birth babies, e.g. twins, triplets or quadruplets, have a lower birth weight. Therefore, women with multiple births were excluded. Subjects were also excluded when they presented with a positive history of HIV infection, AIDS, diabetes, contra indication to periodontal probing and use of phen-fen for weight loss. In addition, women who were prescribed chronic intake of anti-inflammatory drugs were excluded, as well as subjects on medication that can lead to gingival enlargement. Specific dental exclusion criteria were five or more teeth that required extraction, rampant decay or any other condition that could expose subjects to an unacceptable risk. Finally, subjects were also excluded if they were using Peridex, Periguard, Chlorhexidine or any other mouth rinse with known anti-plaque or anti-inflammatory effects, or if they were undergoing periodontal treatment at the time of the study.

Clinical diagnostic procedures executed at baseline and after giving birth included gingival index, plaque index and probing pocket depths using a manual probe – six sites per tooth were probed – recession was also measured using a manual probe, again at six sites per tooth. Attachment levels were calculated from probing pocket depths and recession measurements. Bleeding on probing was assessed following probing. Various biomarkers [prostaglandin (PG) E_2, $PGF_{2\alpha}$, interleukin (IL)-1β, IL-6] were studied in crevicular fluid that was sampled in all quadrants from the two most posterior teeth, for a total of 16 samples per subject. Serum samples were collected from peripheral blood. Serum biomarkers included soluble (s) intercellular adhesion molecule-1,

s glycoprotein 130 (a subunit for signal transduction), IL-6 soluble receptor (IL-6sR), $PGF_{2\alpha}$ and C-reactive protein. Finally, subgingival plaque samples were collected and a number of well-known representatives of the oral microflora were investigated using checkerboard DNA–DNA hybridization (8) analysis.

Data management and statistical analysis were carried out at UNC. In any statistical calculation the individual was used as the statistical unit. Statistical significance was set at $P = 0.05$. Initially the study was powered at 80%, resulting in an estimated sample size of 160 subjects. However, as the study encountered insurmountable recruitment problems, this goal was abandoned. Overall, 692 pregnant women were screened, 109 were randomized. Seventy-four women completed the study, 40 women were examined postpartum in the intervention group and 34 women in the control group.

In a clinical trial, randomization provides confidence that no systematic bias exists with respect to a group's collective attributes. This was the case for almost all variables that were investigated, for example, maternal age, prepregnancy weight, race, smoking history, insurance coverage and education. No differences were found between the two groups for history of preterm delivery, gravida, weight gain, gestational diabetes, preeclampsia and bacterial infections of the vagina. However, a difference was discovered among dental measurements. In fact, at baseline the intervention group had greater mean probing depths than the delayed treatment group. The extent of pockets ≥4 mm was similar between groups, but there was a significant difference in the extent of pockets ≥5 mm.

Let me now present some of the results. The odds ratio for preterm birth was the primary outcomes variable for this study. It was estimated using logistic regression models including a number of potential cofactors. Two factors turned out to be statistically significant, one was baseline frequency of pockets with probing depths ≥5 mm. The other factor was intervention. The resulting odds ratio for intervention of 0.26 converts into a three to four times lower risk of having a preterm baby if the mother received the intervention provided in our study.

Not surprisingly, significantly smaller probing depths were found in the intervention group than in the delayed treatment group. In the intervention group, a statistically significant decrease of probing depth was observed during the study. In contrast, probing depth increased significantly in the delayed treatment group. Similar results were obtained for frequencies of pockets ≥4 mm and ≥5 mm in probing depth.

Differences were also found among variables of subgingival plaque microbiota. We arranged bacteria into clusters as proposed by Socransky (9) and observed a statistically significant decrease of the orange cluster (*Prevotella intermedia*, *Prevotella nigrescens*, *Campylobacter rectus*, *Fusobacterium nucleatum*) in subjects allocated to the intervention group. In contrast, no statistically significant difference between treatment arms was found for species of the red cluster.

The intervention also affected inflammatory biomarkers in crevicular fluid and maternal serum. In crevicular fluid, a difference between the treatment arms was found for IL-1β, and in the delayed treatment group, IL-6 increased as compared with baseline. In serum, lower IL-6sR concentrations were measured in the intervention group than in the delayed treatment group. Combining all IL-6 related serum parameters into an 'IL-6 axis' cluster, statistically significantly lower mean scores were found for the intervention group.

The data gathered in this study, combined with data obtained from the published literature (10), permitted us to formulate a simple intervention model that could be useful to formulate new hypotheses about the systemic link. As a starting point, the model assumes that S&RP plus maintenance of oral hygiene will reduce the degree of periodontal infection. As a consequence, locally produced IL-1β levels will decrease, too. In turn, the change in IL-1β level can affect the expression of tumour necrosis factor-α, which regulates nuclear factor κB to trim down the production of IL-6, matrix metalloproteinases (MMP)-6 and MMP-1. Alternatively, the intervention can also affect IL-6 directly. Eventually, the combined effects on IL-6 and the metalloproteinases can translate into a reduced inflammatory challenge, locally and possibly systemically.

In summary, in a population of pregnant women at risk for preterm births, S&RP in addition to regular homecare using a Sonicare, was associated with a significant decrease in the rate of preterm delivery. The intervention reduced the overall bacterial load, especially among bacteria associated with the orange clusters, resulting in lower local IL-1β levels, serum levels of the IL-6 axis cluster, and improved clinical parameters of periodontal inflammation. Further, the effect of pregnancy as a periodontal inflammatory stressor was demonstrated by increased gingival inflammation and pocketing in the delayed treatment arm. We believe this study was the first one to show pregnancy induced changes in crevicular fluid concentrations of IL-1β and IL-6. And, last but not least, the study provided evidence that S&RP (in addition to Sonicare for maintenance of oral hygiene) is a safe measure if it is provided during the second trimester of pregnancy.

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