Role of Oral Hygiene in the Management of Gingivitis and Implications for Patients that are Pregnant

Microbial Etiology of gingivitis - a plaque induced inflammation of the gingiva. Progressive periodontal diseases are a significant burden to oral health worldwide.[1] In addition to tooth loss, chronic periodontal diseases are increasingly suggested as significant factors in development and/or progression of a variety of systemic conditions including cardiovascular disease, rheumatoid arthritis, Alzheimer's disease and pre-term births.[2-5] Periodontal disease initially presents as gingivitis, a plaque induced inflammation of the marginal and attached gingiva.[6] The clinical symptoms of gingivitis include redness, edema, and bleeding at the gingival margin. Demonstration that periodontal diseases are of microbial origin was proven by landmark experimental gingivitis (EG) studies in the 1960s, which demonstrated that the suspension of oral hygiene resulted in rapid dental plaque formation.[7-9] Left undisturbed, maturation of the dental plaque over time inevitably produced gingival inflammation, albeit with variable onset and progression. The microbial composition of dental plaque during the development of gingivitis was associated with proliferation of Gram negative bacteria when assayed by culturing techniques.[10-12] Pathogens associated with gingivitis display unique metabolic activities (production of hydrogen sulfides and short chain carboxylic acids[13]) and express lipopolysaccharides (LPS's) or endotoxins in their cell walls.[14-15] The LPS from Gram negative bacteria, and the lipoteichoic acid produced by some Gram positive pathogens can be considered to be a major factor in the pathogenesis of progressive periodontal diseases.[16]

Gingivitis is a risk factor for a more advanced form of periodontal disease, periodontitis. Gingivitis precedes the development of progressive periodontal disease. The clinical symptoms of gingivitis include redness, edema, and bleeding at the gingival margin. Gingival bleeding, an objective measure of inflammation has been positively correlated to histologic changes in the gingiva, which include a greater percentage of cell-rich collagen-poor connective tissue consistent with an inflammatory infiltrate, as compared to non-bleeding sites.[17] The clinical significance of gingival bleeding should not be underestimated, as chronic inflammation of the gingiva and periodontium has been shown to be a significant risk factor for both periodontal attachment loss and recession. Sites with persistent gingival bleeding over multiple periodic examinations have been shown to have higher odds for progressive attachment loss compared to non-bleeding sites.[18] Over a 26-year observation period in a population of well-maintained, well-educated men who practiced regular oral hygiene, sites that bled consistently throughout the course of the study had approximately 70% more attachment loss than sites that were consistently noninflamed, yielding an odds ratio of 3.22 for inflamed sites (bleeding) converting to attachment loss.[18] These persistent bleeding sites can exist even if patients are considered generally healthy. In addition, the absence of persistent gingival bleeding on probing has also been shown to have a high negative predictive value of 98.1% for disease progression, as measured by ≥2 mm attachment loss, in a periodontal maintenance population over a 2.5-year observation period.[19] The established relationship between persistent gingival bleeding and attachment loss is the mechanistic basis for gingival inflammation as a risk factor for tooth mortality. Importantly, teeth surrounded by persistent inflamed gingival tissue (presence of bleeding) had a 46-fold higher risk of being lost over a 26-year observation period, compared to teeth surrounded by inflammation-free gingival tissues (absence of bleeding).[20]

Pregnant women are at increased risk of gingivitis. The presence of an exaggerated gingivitis response in pregnant women was described in the scientific literature as early as 1877.[21] In previous studies, gingival

inflammation has a reported range of prevalence of 30 – 100% in pregnant women.[22,23] The Centers for Disease Control (CDC) has reported that 60 - 75% of pregnant women have gingivitis, an early sign of periodontal disease.[24] Ringsdorf et al. (1962) reported that 72% of pregnant women experienced gingivitis.[25] Loe & Silness (1963) and Hilming et al. (1950) both found that 100% of pregnant women examined experienced gingivitis during pregnancy.[22,26] The increased gingival inflammation associated with pregnancy is initiated by dental plaque and exacerbated by an increase in endogenous steroid hormones.[27,28] A strong correlation exists between increasing severity of gingivitis and increasing levels of estrogen, progesterone, and relaxin between the 2nd to 8th months of pregnancy.[29] Subsequent studies have confirmed a positive correlation between progesterone levels in the circulation and increasing severity of gingivitis, which is predicated on progesterone increasing the permeability of blood capillaries in the gingiva making the tissue more sensitive to bacteria and it's toxins.[30,31] Importantly, plaque control is an important aspect in the development and prevention of pregnancy gingivitis, as removal of plaque through prophylaxis and oral hygiene reduced gingivitis by approximately 50%.[29]

Pregnant women with periodontitis are at increased risk for compromised pregnancy outcomes. Periodontal disease in pregnant women has been reported to be associated with a number of conditions including preterm birth, low birth weight babies, and pregnancy hypertension (preeclampsia). Pregnant women with pre-existing periodontitis are at increased risk for experiencing preterm birth. The 2018 systematic review and meta-analyses, by Daalderop et al., evaluated 17 studies in 6,741 patients and reported that periodontitis increases the risk of preterm birth with a relative risk of ratio of 1.6 (95% CI:1.3-2.0).[32] Manrique-Corredor et al. in 2019 published a systematic review and meta-analyses evaluating 20 studies in 10,215 patients and reported that periodontitis increases the risk of preterm birth with a relative risk of ratio of 2.01 (95% CI:1.71-2.36).[33] These pair of meta-analyses are consistent with a 2011 systematic review and meta-analyses, by Chambrone et al., that evaluated 7 studies in 9,491 patients and reported that periodontitis increases the risk of preterm birth with a relative risk of ratio of 1.7 (95% CI:1.03-2.81).[34] Pregnant women with pre-existing periodontitis are at increased risk for having low birth weight babies. Daalderop et al., evaluated 10 studies in 5,693 patients and reported that periodontitis increases the risk of low birth weight with a relative risk of ratio of 1.7 (95% CI:1.4-3.4).[32] Chambrone et al., evaluated 4 studies in 6,050 patients and reported that periodontitis increases the risk of low birth birth with a relative risk of ratio of 2.11 (95% CI:1.05-4.23).[34] Furthermore, pregnant women with pre-existing periodontitis are at increased risk for experiencing the combination of preterm birth and low birth weight babies. Daalderop et al., evaluated 4 studies in 2,263 patients and reported that periodontitis increases the risk of preterm birth with low birth weight with a relative risk of ratio of 3.4 (95% CI:1.3-8.4).[32] Chambrone et al., that evaluated 5 studies in 2,839 patients and reported that periodontitis increases the risk of preterm birth with low birth weight with a relative risk of ratio of 3.57 (95% CI:1.87-6.84).[34] Lastly, pregnant women with pre-existing periodontitis are at increased risk for developing preeclampsia (pregnancy hypertension). Daalderop et al., evaluated 15 studies in 5,111 patients and reported that periodontitis increases the risk of preeclampsia with an odds ratio of 2.2 (95% CI:1.5-3.4).[32] Wei et al. in 2013 published a systematic review and meta-analyses evaluating 15 studies in 1089 patients and reported that periodontitis increases the risk of preeclampsia with an odds ratio of 2.79 (95% CI:2.01-3.01).[35] These pair of meta-analyses are consistent with a 2008 systematic review and meta-analyses, by Conde-Aguelo et al., that evaluated 6 studies in 639 patients and reported that periodontitis increases the risk of preeclampsia with an odds ratio of 2.37 (95% CI:1.36-4.14) in a random effects model and 1.74 (95% CL:1.43-2.18) in a fixed effects model.[36]

Periodontal therapy in the form of subgingival scaling and root planing improves pregnancy outcome endpoints. Over the last 25 years, dozens of randomized controlled clinical trials (RCT) and systematic reviews with meta-analyses have been published examining the effects of periodontal therapy (scaling & root planing) on pregnancy outcomes. The results of this body of research has been varied with some studies supporting the ability of periodontal therapy to provide benefits to pregnancy outcomes, while others have failed to support a benefit. In general, the majority of RCTs have failed to support a benefit for periodontal therapy. However, the most contemporary systematic reviews with meta-analyses do provide a level of support for the benefits of periodontal therapy on pregnancy outcomes. Iheozor-Ejifor et al., 2017;

reported that periodontal therapy reduced the occurrence of preterm birth with a Relative Risk Ratio = 0.87 (95% CI:0.70-1.10), p>0.05 in 11 studies in 5,671 patients and that periodontal therapy reduced the occurrence of low birth rate with a Relative Risk Ratio = 0.67 (95% CI:0.48-0.95), p<0.05 in 7 studies in 3,470 patients.[37] This research supports a statistically significant benefit for periodontal therapy reducing the occurrence of low birth weight babies and a directional but nonsignificant benefit for reducing the occurrence of preterm birth. Da Silva et al., 2017; reported that periodontal therapy reduced the risk of preterm birth with a Relative Risk Ratio = 0.54 (95% CI:0.38-0.77), p<0.05 in 4 studies in 349 patients and that periodontal therapy reduced the risk of low birth rate with a Relative Risk Ratio = 0.78 (95% CI:0.50-1.21), p>0.05 in 4 studies in 349 patients.[38] This research supports a statistically significant benefit for periodontal therapy reducing the occurrence of preterm birth and a directional but nonsignificant benefit for reducing the occurrence of low birth weight babies. These results tend to support those of a meta-analyses from 2011. George et al., 2011; reported that periodontal therapy reduced the occurrence of preterm birth with a Relative Risk Ratio = 0.65 (95% CI:0.45-0.93), p<0.05 in 10 studies in 5,645 patients and that periodontal therapy reduced the occurrence of low birth rate with a Relative Risk Ratio = 0.53 (95% CI:0.31-0.92), p<0.05 in 10 studies in 5,645 patients.[39] Collectively, these 3 meta-analyses provide evidence that periodontal therapy can impact pregnancy outcomes.

Use of antimicrobial mouthrinse improves pregnancy outcome endpoints. There is evidence that antimicrobial mouthrinses in pregnant women with periodontitis provide a level of protection relative to pregnancy outcomes. Boutin et al., 2013; published a systematic review with meta-analysis based on 5 clinical studies that reported daily use of chlorhexidine mouthrinse was associated with a reduction in preterm birth with a relative risk = 0.69 (95% CI:0.50-0.95).[40] Jeffcoat et al., 2011; published a randomized controlled clinical trial reporting that cetypyridinium chloride (CPC) mouthinse reduces the risk of preterm birth in a high risk population of 77 pregnant women with periodontitis relative to 155 healthy pregnant women controls with a relative risk = 0.26 (95% CI:0.096-0.70).[41] Jiang et al. 2016; published a randomized controlled clinical trial reporting that cetypyridinium chloride (CPC) mouthrinse reduces the risk of premature rupture of membranes in a population of 232 pregnant women with periodontitis relative to 234 healthy pregnant women controls with aa odds ratio = 0.23 (95% CI:0.07-0.84).[42] However, this study did not observe any other differences between treatment groups for other pregnancy outcomes. Finally, P&G sponsored the multicenter randomized controlled OH MOM clinical study at University of Alabama Birmingham and University of Pennsylvania that examined the ability of an oral care regimen (SnF2 toothpaste, OR power toothbrush, CPC mouthrine, floss, and patient education) to reduce the occurrence of adverse pregnancy outcomes (endpoints were gestational age, birth weight, and prematurity) in 613 pregnant women relative to the control group (manual toothbrush, NaF Tootpaste). The oral care regimen resulted in an increase in gestational age of ~2.0 days relative to the control (mean regimen = ~39.13 wks vs mean control = ~38.85 wks, p=0.040). This difference is statistically significant, but the clinical relevance of the difference has not been established. A directional increase in premature birth was observed in the control group (10.3%) relative to the regimen group (7.0%), but was not statistically significant (p=0.106) Collectively, these data support that antimicrobial mouthrinses that have been shown to reduce gingival inflammation may reduce the risk of compromised pregnancy outcomes.

SnF2 dentifrice is an effective antimicrobial in plaque and gingivitis control. The management of gingivitis can be attained through repeated mechanical removal of microbial dental plaque from the teeth and/or suppression of bacterial plaque biofilm growth and metabolism. The mechanical control of plaque is accomplished with daily oral hygiene including thorough tooth brushing and flossing. The suppression of plaque growth and metabolism can be achieved through the application of topical antimicrobials added to toothpastes or mouthrinses. Antimicrobials with proven efficacy for the control of plaque associated gingivitis include chlorhexidine, cetypyridinium chloride, mixtures of essential oils, triclosan and stannous fluoride, among others.[43,44] The use of stannous fluoride for the treatment and prevention of plaque and gingivitis began in the 1980's with the application of topical gels, however today its use includes multiple commercial dentifrices sold and distributed around the world.[45-47] Clinical studies have demonstrated significant efficacy of stannous fluoride for the reductions in the amount of supragingival plaque and plaque associated gingivitis – these having been the subject of systematic reviews of randomized clinical studies.[48-50] A recent meta-analysis revealed that during Crest Pro Health (CPH) stannous fluoride dentifrice use 3 out of 4 participants using CPH

transitioned to gingival health[49] as defined by guidelines for the 2017 World Workshop of Periodontology.[48] The results of this meta-analyses representing 18 studies in 2,890 patients support that stannous fluoride dentifrices reduce gingival bleeding sites by 51% relative to sodium fluoride control dentifrices in studies of up to 3 months duration.[49]

Stannous fluoride has both, bactericidal and bacteriostatic effect on plaque bacteria. Recently, it has been demonstrated that SnF2 dentifrice can penetrate into subgingival crevicular fluid during brushing and stannous is retained in subgingival plaque.[51] This SnF2 has been shown to decrease biofilm virulence via attaching to lipopolysaccharide (LPS) and lipoteicoic acid (LTA) molecular patterns on bacterial surfaces interfering with pathogen stimulation of toll receptors[52,53] the latter of which are associated with the initialization of the inflammatory processes involved in periodontal disease.[54-59] Samples of plaque from subgingival areas in subjects brushing with stannous fluoride dentifrice have been shown to exhibit decreased virulence ex vivo.[60,61] In addition, stannous fluoride formulations have been shown to reduce bacterial metabolic products including short chain fatty acids propionic and butyric acid which are derived from bacterial metabolism in deeper parts of plaque biofilms in anaerobic environments.[62] Collectively, research demonstrates significant efficacy for stannous fluoride for the treatment and prevention of gingivitis and has established plaque control including quantity and toxicity as mechanisms for clinical efficacy.

OR (OSCILLATION-ROTATION) POWER TOOTHBRUSHES ARE EFFECTIVE IN PLAQUE AND GINGIVITIS CONTROL.
Toothbrushes are designed to physically break apart plaque biofilm and facilitate removal. A recent meta-analysis revealed that use of OR power toothbrushes resulted in 2 out of 3 patients transitioning to gingival health[63] as defined by guidelines for the 2017 World Workshop of Periodontology.[48] Patients using OR power toothbrushes (381/587 = 65%) were three times more likely to transition to generally healthy than patients using a manual toothbrush (32/160 = 20%).[63] The results of this meta-analyses representing 16 studies in 2,145 patients support that OR power toothbrushes reduce gingival bleeding sites by 50% relative to ordinary manual toothbrushes in studies of up to 3 months duration.[63] These benefits in controlling plaque build-up, to both resolve existing gingival inflammation and prevent future gingival inflammation appear to have periodontal benefits with respect to reducing pocket depth (PD) and attachment loss progression. Pitchika et al., 2019; published a 11-year cohort study and reported that patients using power toothbrushes (PTB) had 22% less mean PD progression relative to manual toothbrush users (MTB) over a period of 11 years, with MTB = 0.41 mm vs. PTB = 0.32.[64] Similar, results were observed with respect to clinical attachment level (CAL), where PTB users had statistically significantly less CAL progressive loss compared to MTB.[64]

ROLE OF ORAL HYGIENE PRODUCTS IN PLAQUE AND GINGIVITIS CONTROL IN PATIENTS THAT ARE PREGNANT.
Pregnant women with periodontal disease are at higher risk for compromised pregnancy outcomes including preterm birth, delivery of low birth rate babies, and development of preeclampsia. These compromised pregnancy outcomes are putatively influenced by the impact of local chronic periodontal inflammation leading to an increase in systemic inflammatory mediators in the vascular system. The patient and dental professional must work together to stop this cycle before it begins by being attentive to daily oral hygiene: brushing and flossing, getting regular oral health checkups, and properly treating periodontal disease early on. Oral hygiene in pregnant women can be improved by increased education on the requirements for elevated oral hygiene and also the selection and application of selective oral products applied to their personal hygiene. The primary causative factor for gingivitis in pregnant women, toxic plaque can likely be ameliorated by improved hygiene including the selection and use of antimicrobial products with proven efficacy in the prevention of plaque and gingivitis. The use of stannous fluoride dentifrice and OR power tootbrushes as part of oral hygiene may represent a useful tool for pregnant women in maintaining their oral health.

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