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Simple Periodontal Treatment Predict Preterm Surrogate Marker Levels

Nwhator Solomon Olusegun [1,2,*], Ogunwemimo Morolayo Tolulope[1], Dirk-Rolf Gieselmann[3], Michael Lazzara[3], Sorsa Timo[4,5]

[1]*Department of Preventive and Community Dentistry,*
Obafemi Awolowo University Teaching Hospital Complex,
Ile-Ife, Nigeria.
[2]*Department of Preventive and Community Dentistry,*
Obafemi Awolowo University,
Ile-Ife, Nigeria.
[3]*Institute for Molecular Diagnostics, 42697 Solingen, Germany*
[4]*Department of Oral and Maxillofacial Diseases, Helsinki University and University Hospital, Helsinki, Finland*
[5]*Department of Dental Medicine, Karolinska Institutet, Huddinge, Sweden*

Abstract
Objective*: To determine the effects of non-surgical periodontal therapy on salivary active metalloproteinase-8(aMMP-8) levels of pregnant women in Ile-Ife, Nigeria.*
Method: *This was an interventional study involving 128 consecutive pregnant antenatal clinic attendees using Gingival index (GI) and the Periodontal Inflamed Surface area (PISA) for gingival and periodontal assessments on or before week 15 gestational age. Patients were grouped into a test and control group based on GI and PISA scores and salivary samples collected. The test group received repeated pre-delivery scaling/polishing and/or root planing sessions with oral hygiene motivation until resolution of inflammation. The control group, however, only received oral hygiene motivation. Both groups received post-delivery scaling and polishing.*
Results: *There were significant differences in mean values of GI and PISA of both groups with the test group having a significantly higher mean score (p=0.001 and 0.046 respectively). At baseline, the test group had a significantly higher mean salivary aMMP-8 compared with the control group (p=0.000). The test group had decreased mean post-delivery salivary aMMP-8 but the control group experienced increased mean salivary aMMP-8. Linear regression showed that scaling and polishing significantly predicted salivary aMMP-8 levels (p<0.05)*
Conclusion: *while the test group experienced reduced post-delivery salivary aMMP-8, the reverse was the case in the control group. Periodontal inflammation contributed significantly increased salivary aMMP-8-- a surrogate marker for preterm birth. Early intervention in the form of scaling, polishing and/or root planing led to reduced post-delivery salivary aMMP-8 levels.*
Keywords: *aMMP-8, non-surgical intervention, periodontal diseases.*

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I. Introduction

Periodontal diseases affect the periodontium the commonest being gingivitis and periodontitis.[1, 2] Bacterial plaque remains the primary etiological factor inflammation-associated periodontal diseases but predisposing factors include calculus, faulty restorations, complications of orthodontic therapy, and self-inflicted injuries. Furthermore, some systemic or environmental modifiers include tobacco, pregnancy and diabetes mellitus among others[1,2].

A diagnosis of plaque-induced periodontal diseases usually requires detailed history and examination. Investigations may also be will be necessary including radiographic, hematological, and biochemical tests. Rarely, more complex investigations may include enzymatic and immunological assay,[3]nutritional analysis, study casts, clinical photographs, microbiology and genetic analyses[4]. More recently, an emerging investigations include sialometry and the use of salivary markers. An example of such salivary markers is the active matrixmetalloproteinase-8 (aMMP-8) also known as neutrophil collagenase. aMMP-8 is gaining prominence in the diagnosis, treatment monitoring and maintenance of periodontal health[5-7].

aMMP-8 is synthesized by polymorphonuclear neutrophils and associated with tissue destruction associated with gingivitis and periodontitis[5, 6]. Bacterial by-products like lipopolysaccharides (LPS) stimulate the cellular components of inflammation, which produce cytokines and enzymes capable of destroying host periodontal tissues."Inadvertent" host-tissue destruction akin to "by-stander damage" occurs in as inflammatory mediators attempt to get rid offending bacteria and their by-products[8, 9]. The resultant catabolic inflammatory processes ultimately destroy collagen and bone through matrix metalloproteinases (MMPs)[9-12]. It is becoming increasingly clear that periodontitis affects systemic health including pregnancy outcomes and pregnancy is one of those conditions that affect periodontal health. [13-15] The proposed pathophysiologic pathway includes through infection of the amniotic fluid and through the effect of inflammatory mediators that rise in periodontitis including TNF-alpha[16-19].

Active MMP-8 (aMMP-8) can be used to diagnose periodontal inflammation and to monitor the treatment and the maintenance of periodontal tissues. It is clear from the literature that aMMP-8 and IL-1β concentrations in the gingival crevicular fluid may correlate with periodontal disease activity and are high in patients with periodontitis compared to healthy people[20, 21]. Studies have reliably shown that raised aMMP-8 levels lead to mid-second trimester labour[22-24]. Similarly, in an Israeli study, Maymon and colleagues found aMMP-8 plays a significant role in the microbial invasion of the amniotic cavity, preterm membrane rupture and pretermlabour[25]. The workers further reported that higher aMMP-8 concentrations in the cervical fluid bathing the membrane induces membrane rupture close to the pole of the uterus[26]. Another study showed that amniotic fluid aMMP-8 of full-term mothers is significantly lower mothers of preterm babies[26]. The pathophysiology of aMMP-8 and preterm birth include aMMP-8-induced local weakness of fetal membranes as it degrades type I and II collagen in the extracellular matrix that maintains the elasticity and tension of fetal membranes. This phenomenon leads to the premature rupture of the membranes[27]. Furthermore, active/activated MMP-8 acts on cervical fibroblasts, degrades extracellular matrix collagen and relaxing the connective tissue in the cervical matrix. This induces advanced cervical maturity and expansion leading to preterm birth[27].

Treating periodontal diseases includes mechanical and chemical plaque control the former involving scaling, polishing (and root planing when indicated).[28] Root planing suffices in shallow pockets but is ineffective in deep (≥6mm) pockets which will require periodontal surgery.[28] Chemical plaque control, however, involves the use of antimicrobial solutions and may include antibiotics in certain cases[28]. The goal of chemical plaque control includes shifting the pathogenic microbiota to become compatible with periodontal health[29]. Photodynamic and non-photodynamic therapy can also combines with scaling and root planing[30] .Routine periodontal treatment usually involves scaling and polishing which have been advocated to reduce preterm birth[23,31]. However, there is little data on the effect of scaling and polishing on aMMP-8 levels, hence this study.

II. Methodology

This was an interventional study involving 128 consecutive pregnant antenatal clinic attendees. We used Gingival index (GI) and the Periodontal Inflamed Surface area (PISA) for gingival and periodontal assessments and assessed the recruited pregnant women on/before the 15th gestational week. We then grouped participants into the test (poor oral hygiene, GI > 1, PISA) $\geq$ 30mm^2). The control group comprised pregnant women with good oral hygiene, GI $\leq$ 1 and PISA £30 mm^2) and we collected salivary samples from both groups. After that, the test group received repeated pre-delivery scaling and polishing and/or root planing sessions and oral hygiene motivation (between 15th to the 28th gestational week) until resolution of inflammation. The test group received repeated pre-delivery scaling/polishing and/or root planing sessions with oral hygiene motivation until resolution of inflammation. The control group on the other hand, only received oral hygiene motivation. Both groups received post-delivery scaling and polishing after collecting post-delivery salivary samples stored at 4^{0}C. We measured aMMP-8 levels after the standard assay procedure and used Enzyme-Linked Immunosorbent Assay (ELISA) for quantitative assessment of pre and post-delivery salivary samples.

Data were analyzed with IBM SPSS Version 22, Illinois, Chicago, USA. We used descriptive statistics to characterize socio-demographic variables such as age, sex, marital status, and occupation. For categorical variables, we determined simple frequency and percentages and compared using Chi-square and used bivariate analysis such as t-test to compare between means of variables. Multivariate analysis (linear regression) after model fit was done to determine if intervention (scaling and polishing with root planning) could predict a change in aMMP-8. Date were analyzed at 95 percent CI hence statistical tests yielding p values <0.05 were considered significant.

III. Results

We recruited 128 pregnant women with a mean age (SD) of 29.63 (S3.73) years who met the inclusion criteria for the study. Sixty-one pregnant women with GI >1 and PISA >30.00mm^2 formed the test group while 67 pregnant women with GI £1 and PISA £30.00mm^2 formed the control group. The age range of both the test and the control groups was similar (19-35 years). The mean age (SD) of the test group was 29.85 (3.73) years and 29.43 (3.76) years for the control group. There was no significant difference in the mean age of the test and control groups (p=0.53).

Gingival and periodontal inflammatory parameters were assessed with GI and PISA. There were significant differences in the mean GI and PISA scores of the two groups with the test group having a significantly higher mean value compared to the control group (p=0.001 and 0.046 for GI and PISA respectively).(**Table 1)**

A significantly higher mean value for salivary aMMP-8 level was found in the test group compared to the control group (p=0.000). Interestingly, there was a decrease in the mean value of post-delivery aMMP-8 in the test group but there was an increase in the mean value of aMMP-8 among control subjects. Furthermore, the mean value of post-delivery salivary aMMP-8 of the test group was lower than the control group but not statistically significant (p=0.29). There was also a significant difference in mean pre and post-delivery aMMP-8change (p= 0.01) (**Table II**).

In the test group, there was no significant difference in mean pre and post-delivery aMMP-8 levels. However, among the control subjects had significantly higher post-delivery aMMP-8 levels (p<0.001). (**Table III**).

Linear regression analysis showed that the intervention (scaling and polishing) significantly predicted aMMP-8levels (p<0.05) (**Table IV**). The model fitting showed that 8.3% of the variation seen in the change in the aMMP-8 levels was due to the intervention judging by the value of the R^2 (0.083) which was also statistically significant (p=0.009).

IV. Discussion

The likely sources of aMMP-8 in pregnancy include a natural increase as pregnancy approaches term or from periodontal inflammation in pregnancy[32,33]. This study found that an higher levels of aMMP-8 were associated with poor oral hygiene while low aMMP-8 levels were associated with good to fair oral hygiene. Since we found significantly higher aMMP-8 in the test group than in the control group at baseline, we may safely infer that periodontal inflammation is a source of increased aMMP-8 levels in our test subjects, corroborating earlier studies[32, 34,35]. Periodontal inflammation also contributes significantly to systemic aMMP-8 through IL-1a, TNF-a and PGE_2 [25, 36]. These pro-inflammatory cytokines stimulate host cells to produce matrix metalloproteinases (MMPs), facilitate leucocyte recruitment, cytokine/chemokine processing and matrix remodeling. aMMP-8, a collagenase, and MMP-3 or stromelysin-1 are associated with periodontal diseases. MMP-3 can activate pro-MMP-1, pro-MMP-8, and pro-MMP-9 activation cascades. Several studies have shown the potential utility of aMMP-8 as a marker for periodontal treatment effectiveness and for identifying patients at the risk of progressive attachment loss [27, 36].

The test group experienced decreased mean post-intervention salivary aMMP-8 level but did not attain statistical significance. Despite not approaching statistical significance, there seems to be some clinical significance with this since aMMP-8 levels are naturally expected to increase and peak before delivery. This was noticed in the control group which experienced significant higher post-delivery salivary aMMP-8 levels from 12ng/ml to 21ng/ml. (p=0.01) It has been postulated that aMMP-8 levels increase gradually in pregnant women to a particular critical value depending on ethnicity, stress levels and other factors which stimulates labor through by degrading the extracellular matrix of the chorioamniotic membranes. This action softens the collagen in the cervix leading to rupture, a process that usually occurs at term[19]. However, critical levels of aMMP-8 could be reached earlier usually mid-second trimester if there are other sources of inflammation such as periodontal inflammation which may contribute significantly to systemic aMMP-8 levels; thus, resulting in premature labour and preterm birth[37]. The fact that post-intervention salivary aMMP-8 levels reduced in the test group despite the well-established physiological increase appears clinically significant. Based on our findings, we advocate early and regular intervention to keep the mouth free of periodontal inflammation during pregnancy. We also call for a replication of this study using more modern systems that depend on mouthrinse aMMP-8 readings which are even more sensitive that the ELISA salivary aMMP-8 methods used in this study[38].

V. Conclusion

Our findings support the postulation that periodontal inflammation contributes significantly increased aMMP-8 values in pregnancy. This is clear from the fact that a simple intervention in the form of early scaling and polishing and maintenance of periodontal health throughout pregnancy had a significant

predictive effect on the aMMP-8 levels ($p<0.05$). This reduction in post-delivery salivary aMMP-8 levels over and above the expected physiological increase appears clinical significant irrespective of statistical p-values. Since salivary aMMP-8might be a surrogate marker for preterm birth, we recommend early intervention scaling and polishing/root planing when indicated.

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Tables

Table 1: Mean Periodontal parameters by group

Periodontal Indices	Group	N	Mean	SD	t	P
GI	Test	61	1.10	0.24	3.27	0.00
	Control	65	0.94	0.32		
PISA (mm^2)	Test	61	46.41	45.98	2.01	0.04
	Control	67	29.75	47.54		

Table II: Mean pre and post-delivery aMMP-8 values and mean change in aMMP-8 by group

aMMP-8 status	Group	N	Mean	SD	t	P
aMMP-8 before delivery	Test	52	20.14	18.03	2.94	0.00
	Control	55	12.03	8.62		
aMMP-8 after delivery	Test	48	17.39	17.33	-1.07	0.29
	Control	40	21.05	14.18		
	Test	43	1.45	16.38	2.66	0.01
Mean difference in aMMP-8	Control	37	-8.54	17.14		

Table III: Paired t-test of Mean pre and post-delivery aMMP-8 value by group

Group	aMMP-8 status	Mean	N	SD	p
Test	aMMP-8 before delivery	18.60	43	17.46	0.56
	aMMP-8 after delivery	17.15	43	17.10	
Control	aMMP-8 before delivery	12.13	37	9.99	0.01
	aMMP-8 after delivery	20.67	37	14.09	

Table IV: Linear Regression between the Predictive Variable (Group) and the Outcome Variable (Mean Change in aMMP-8)

		Unstandardised Coefficients				95.0% CI for B	
Model		B	Std. Error	t	P	Lower Bound	Upper Bound
1	(Constant)	11.45	5.80	1.97	0.05	-0.10	22.99
	Group	-9.99	3.75	-2.66	0.01	-17.47	-2.52

Model fitting R squared 0.083, p =0.009