Letters to EBD

Periodontal treatment did not prevent complications of pregnancy. *Evidence-based Dentistry* 2010; **11:** 18–19

Dear Sir,

I am strongly inclined to the view that that the commentary accompanying the above summary highlights the limitations of high levels of specialisation. I believe that the summary in question and the arguments below exemplify the need for the *Evidence-based Dentistry* and the *British Dental Journal* to consider engaging collaborative specialist reviewers for multidisciplinary studies and summaries.

In the summary in question, Dr Niederman argues that scaling and root planing may be an inappropriate treatment modality for studying the relationship between preterm or low birthweight and periodontal disease on the grounds that, "Almost all the trials refuting the original Offenbacher hypothesis (including Offenbacher's 2009 study) used scaling and root planing to treat the periodontal infection. Interestingly, there is little or no evidence that this therapy significantly reduces or alters the periodontal microbial infection". He then draws attention to the proven effectiveness of systemic antibiotics (specifically combined short-term metronidazole and amoxicillin) to produce long-term reductions in periodontal bacterial infection and secure improved periodontal health, apparently citing one paper in support?

The author concludes, "I would be inclined to treat the periodontal disease with scaling and root planing and with metronidazole plus amoxicillin — and hope that the curses didn't return." In the abstract of the relevant paper, however, the relevant authors state that the, "mean total DNA probe counts and counts of the majority of the 40 test species were significantly reduced over time in both groups, with no significant differences detected at any time point between groups. At 12 months many of the species were still present at significantly lowered levels compared with their baseline counts in both groups."[2] This appears to call into question the chemotherapeutic approach advocated in the *EBD* summary. Furthermore, the issue of the use of metronidazole during pregnancy does not appear to have been considered in the commentary? This use of metronidazole for the management of periodontal disease during pregnancy may be questioned on a number of grounds including:

- *British National Formulary* (www.bnf.org/bnf/index.htm): "manufacturer advises avoidance of high-dose regimens"
- Flagyl (metronidazole) tablets: "Flagyl is contraindicated d uring the first trimester of pregnancy" and, "because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed" (www.pfizer.com/files/products/uspi_flagyl.pdf)
- Shennan *et al.*:[3] "Metronidazole does not reduce early preterm birth in high risk pregnant women selected by history and a positive vaginal fFN [foetal fibronectin] test. Preterm delivery may be increased by metronidazole therapy."

Based upon my understanding of the article, whereas the depth of knowledge articulated ostensibly suggests an erudite and robust summary, it appears deficient on account of its lack of depth and failure to consider the issue in its entirety, as opposed to the periodontal implications alone.

Paul V McCrory
Stockport

1. Offenbacher S, Beck JD, Jared HL, et al. Effects of periodontal therapy on rate of preterm delivery: a randomised controlled trial. *Obstet Gynecol* 2009; **114:** 551–559.
2. López NJ, Socransky SS, Da Silva I, Japlit MR, Haffajee AD. Effects of metronidazole plus amoxicillin as the only therapy on the microbiological and clinical parameters of untreated chronic periodontitis. *J Clin Periodontol* 2006; **33:** 648–660.
3. Shennan A, Crawshaw S, Briley A, et al. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET Study. *Br J Obstet Gynaecol* 2006; **113:** 65–74.

Richard Niederman responds:

Dear Sir,

Mr McCrory raises important and interesting issues, all of which I disagree with conceptually and specifically. First, conceptually, severe periodontal disease is a significant oral infection that can be systemically disseminated. I am unaware, but am ready to be found wrong, of significant medical infections that are successfully reduced or eliminated solely with mechanical therapy. Thus, my bias is that mechanical therapy is an overused and misused approach to care. More specifically:

1. Although my summary cited only one article on the use of metronidazole and amoxicillin, a search of Medline for amoxicillin AND metronidazole AND periodontal diseases identified 43 human clinical trials, and two systematic reviews with meta-analysis. Both systematic reviews indicated the superiority of periodontal care with adjunctive metronidazole plus amoxicillin.[1,2]
2. The reduction in bacteria following scaling and root planing or surgery may be statistically significant (eg, 10-fold reduction). To be clinically significant in reducing periodontal disease and increasing attachment levels, a sustained microbial reduction of 100-fold or more plus a change in the constituents of the microflora from disease- to health-related are both required. This is not seen with mechanical therapy, but is found with metronidazole plus amoxicillin.
3. The dose of metronidazole plus amoxicillin found to be effective for treating periodontal disease is 250–500 mg three to four times per day for 7–10 days. This is not a high dose.
4. Drug administration during pregnancy is always of concern. The questions are two, namely which trimester, and what is "unnecessary". The risk of preterm/low birthweight is a third-trimester

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issue, so would more reasonably be considered in the third not first trimester administration. The issue of "unnecessary" revolves around the relative risk of preterm/ low birthweight. If metronidazole plus amoxicillin therapy in women who have significant periodontal disease significantly reduces preterm/low birthweight, then there was a significant benefit.

5. The fact that metronidazole administered for a urogenital problem does not reduce preterm/low birthweight is irrelevant in treating periodontal infections. First, and most obviously, the infections are different. Secondly, periodontal infections and their sequellae are reduced by metronidazole plus amoxicillin, but not by metronidazole alone .
6. Finally, the citation of metronidazole use to treat urogenital problems (item 5) contradicts the previous argument against its use (item 4).

In short, I stand behind the hypothesis that the use of a metronidazole plus amoxicillin combination during the third trimester for women who have significant periodontal disease will decrease the incidence of preterm/low birthweight, if periodontal disease is in fact a cause of preterm low birthweight. The fact here is that we will not know until the clinical trials are executed.

1. Haffajee AD, Socransky SS, Gunsolley JC. Systemic anti-infective periodontal therapy. A systematic review. *Ann Periodontol* 2003; **8:** 115–181.
2. Herrera D, Sanz M, Jepsen S, Needleman I, Roldán S. A systematic review on the effect of systemic antimicrobials as an adjunct to scaling and root planing in periodontitis patients. *J Clin Periodontol* 2002; **29 (suppl. 3):** S136–S159.

Periodontal treatment could improve glycaemic control in diabetic patients. *Evidence-based Dentistry* 2009; **10:** 20–21

Dear Sir,

In his commentary on the study by Darré *et al.*[1] Dr Garcia reports that its authors noted that one[2] out of the nine clinical trials that they deemed eligible for inclusion in the meta-analysis, upon sensitivity analysis, significantly deviated from the calculated overall treatment effect and that, without this study, the overall standardised mean difference (SMD) decreased to a nonsignificant value. As one of the co-authors of the study in question (Stewart *et aI.*),[2] I suggest that the difference in robustness of results between my study and the others arises from the fact that we extracted numerous nonrestorable teeth in addition to providing periodontal treatment.

Specifically, we removed teeth that had either excessive alveolar bone loss secondary to advanced periodontal disease (teeth which were often mobile and likely not to be readily debrided by the patient) or peri-apical infections (teeth with an osteolytic process at their apex arising from dental caries infecting the dental pulp and rendering them nonvital). Both of these conditions are known to cause significant local and systemic inflammatory reactions that may impair glycaemic control and were, therefore, best managed by extraction.

In my experience, it is very unusual to have random populations of patients with generalised advanced periodontal disease that do not need extraction of some teeth. Thus, I can only assume that our patients may have had a greater burden of chronic infection/ inflammation than those in the other studies and that our patients, therefore, required extractions in addition to nonsurgical periodontal therapy, ultimately resulting in the more profound treatment effect that we demonstrated.

Furthermore, I wrote a Letter to the Editor[3] of the journal in which Darré's paper appeared and advised the authors that our results probably arose because we provided other anti-infective/ anti-inflammatory dental services in addition to periodontal treatment (namely, exodontias). I also suggested to the authors that they re-review the other eight studies and determine the severity of dental disease that was present in their diabetic patient populations and determine whether all the required dental treatment, including the extraction of nonrestorable teeth, was in fact, rendered. In response, Darré *et al.* reviewed all of the studies and noted[4] that the two studies[2,5] that reported performing extractions of nonrestorable teeth were also the two that obtained the greatest treatment effect. I also reviewed the paper by Kiran *et al*[5] and discovered that, in addition to exodontia, these researchers also provided endodontic therapy.

Dr Garcia notes that our project did not make use of randomised controlled trials (RCT), but fails to mention that Darré *et al.* also recognised this issue and justified the inclusion of our study in the meta-analysis because patients in the treatment and control groups were contemporaneous and from the same population, and because comparison made at baseline of HbA1c levels found no statistically significant difference between the two groups.

Lastly, Dr Garcia heralds a forthcoming large-scale, multicentre, definitive RCT which will evaluate the effects of periodontal scaling and root planing in subjects who have type 2 diabetes and untreated, moderate to advanced chronic periodontitis. This construct appears less than realistic given that some patients who have difficult-to-control diabetes also have concomitant oral infections/ inflammation requiring a number of other treatment modalities including antibiotics, periodontal surgery, endodontics and exodontia. I am unfamiliar with the exact nature of the aforementioned National Institutes for Health (NIH) research protocol so I am perplexed as to how this issue should be addressed?

Arthur H Friedlander

Veterans Affairs Greater Los Angeles Healthcare System, Hospital Dental Service, University of California–Los Angeles Medical Center, Los Angeles, California, USA

1. Darré L, Vergnes IN, Gourdy P, Sixou M. Efficacy of periodontal treatment on glycaemic control in diabetic patients: a meta-analysis of interventional studies. *Diabetes Metab* 2008; **34:** 497–506.
2. Stewart JE, Wagner KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycemic control in patients with type 2 diabetes mellitus. *J Clin Periodontol* 2001; **28:** 306–310.
3. Friedlander AH. Exodontia may improve glycemic control in diabetic patients with periodontitis. *Diabetes Metab* 2010; **36:** 88.
4. Vergnes IN. Letter to the Editor: "Efficacy o f periodontal treatment on glycaemic control in diabetic patients. A meta-analysis of interventional studies." *Diabetes Metab* 2010; **36:** 89–90.
5. Kiran M, Arpak N, Unsal E, Erdogan MF. The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. *J Clin Periodontol* 2005; **32:** 266–272.

Raul Garcia responds:

Dear Sir,

Dr Friedlander's letter raises several important points. First, he appropriately notes the relevant distinction between periodontal treatment and exodontia. He states that clinicians in the study by Stewart *et al.*,[1] "extracted numerous teeth in addition to providing periodontal treatment." He appears, however, to ascribe some importance to possible beneficial effects of the exodontia, as the

extracted teeth had, "either excessive alveolar bone loss … or peri-apical infections." That study's use of multiple interventions (ie, periodontal treatment and exodontia) raises the important question as to whether any improvements in HbA1c levels were the result of the periodontal treatment rendered (ie, "full mouth scaling, sub-gingival curettage, and root planing performed under local anesthesia"), or the result of the extractions, or some combination thereof.

Second, despite the absence of randomisation of study subjects, Friedlander argues for the relevance of the study's results, noting that Darre *et al*.[2] presented several reasons to justify its inclusion in their meta-analysis. It should be noted that Darre *et al*. acknowledged that "retaining this non-randomised study in the present meta-analysis was a matter of debate."[2] The nature of the debate may in part have resulted from the fact that, as Stewart and colleagues[1] themselves reported, "nothing was known regarding the dental status of the control group" and that "the dental status of the control group was not investigated." Darre and co-authors[2] also assessed the quality of the eight studies they included in their meta-analysis, using standard criteria.[3,4] The highest quality study "was a randomised, controlled, single-blind intention-to-treat study, in which the number of subjects was calculated a priori." In contrast, Darre *et al*.[2] ranked the Stewart *et al*. study[1] lowest in quality among those included in their meta-analysis.

In his closing paragraph, Friedlander raises a key question regarding the inclusion and exclusion criteria that may be most appropriate to use for subject selection in an RCT to test whether a periodontal intervention improves glycaemic control. The Diabetes and Periodontal Therapy Trial (DPTT; www.clinicaltrials.gov/ct2/show/NCT00997178), funded by the US NIH, aims to "determine if non-surgical periodontal therapy (scaling and root planing and supportive periodontal therapy) is efficacious compared to delayed therapy in reducing elevated glycosylated haemoglobin (HbA1c) at 6 months post-randomisation in subjects with type 2 diabetes and untreated, moderate to advanced chronic periodontitis." The DPTT inclusion criteria define moderate to severe chronic periodontitis as, "loss of clinical attachment and probing depth of >5 mm at two sites in the mouth in two or more quadrants." Importantly, one of the trial's exclusion criteria is any requirement for "essential dental care (eg, treatment for grossly decayed teeth, broken teeth, dental abscesses, peri-apical infections, other dental infections)." The DPTT is currently enrolling subjects and expects to complete primary outcome data collection by June 2013. Thus, until a significant beneficial effect has been reported from a high-quality multicentre RCT, it remains prudent for clinicians to continue to recommend periodontal treatment for diabetics for the primary purpose of improving their patients' periodontal health. Whether such treatment can also improve their diabetic health status remains an open question.

1. Stewart JE, Wagner KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycemic control in patients with type 2 diabetes mellitus. *J Clin Periodontal* 2001; **28:** 306–310.
2. Darré L, Vergnes IN, Gourdy P, Sixou M. Efficacy of periodontal treatment on glycaemic control in diabetic patients: a meta-analysis of interventional studies. *Diabetes Metab* 2008; **34:** 497–506.
3. Begg C, Cho M, Eastwood S, *et al*. Improving the quality of reporting of randomised controlled trials. The CONSORT statement. *J Am Med Assoc* 1996; **276:** 637–639.
4. Verhagen AP, de Vet HC, de Bie RA, *et al*. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998; **51:** 1235–1241.

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