Letters to the Editor

To the Editor:

Re: Treatment of Periodontal Disease and the Risk of Preterm Birth. Michalowicz BS, Hodges JS, DiAngelis AJ, et al. (*N Engl J Med* 2006;355:1885-1894).

In a recent article by Michalowicz et al.[1] published in *The New England Journal of Medicine*, the authors concluded, "Treatment of periodontitis in pregnant women . . . does not significantly alter rates of preterm birth, low birth weight, or fetal growth restriction" (abstract, page 1,885). Several authors[2,3] have commented on the validity and interpretation of these findings from a general epidemiologic perspective and discussed the importance of the study as it relates to the general field of research on treatment of periodontal disease among pregnant women. We reviewed Michalowicz et al. from a more technical perspective and have several concerns related to the statistical design and analysis aspects of the study.

For example, there was no true "negative" control group in the study (sometimes referred to as a "no-treatment concurrent control"). The control group ". . . received only a brief oral examination at monthly follow-ups but attended the same number of these visits as the treatment group" (page 1,886). Because the control group patients knew that they would be coming in for monthly follow-ups, it could be that they took better care of their teeth and gums than they would have if they were simply following their usual pattern of dental visits (e.g., semiannual or annual checkups). Thus, use of such a "positive" control group may have obscured the true treatment effect in the subsequent active versus control group statistical comparisons. Because there is no known effective dental treatment for reducing adverse pregnancy outcomes, the use of a "no-treatment" control, which is considered to be equivalent to a placebo group, would have been ethically justified.[4]

There are also several issues related to the description of the statistical analyses and the presentation of results that concern us. For example, in the abstract, it is stated that "The gestational age at the end of pregnancy was the prespecified primary outcome" (page 1,885). However, nowhere in the article is the outcome of gestational age (GA) treated as a continuous variable. It is stated that "In the time-to-event analysis, the groups did not differ significantly in gestational age at the end of pregnancy, which was censored at 37 weeks . . ." (page 1,888). However, to perform a time-to-event analysis using the log-rank test, the outcome must be dichotomous; thus, GA was converted to an outcome of preterm birth (<37 weeks GA) versus full-term birth (≥37 weeks GA). In Table 2 (page 1,891), three different cut-points are used to convert GA to a dichotomous outcome (<32, <35, and <37 weeks). It is unclear why dichotomization was used at all; statistical methods for comparing two groups in terms of a censored continuous outcome could have been applied to the data on GA, especially in light of the fact that GA was missing for only 1.1% of the study participants. (A similar argument could be made for the analysis of the data on the secondary outcome of birth weight, which was dichotomized in two different ways for the comparisons of the treated and control groups presented in Table 2.) Analyses treating GA as a censored continuous outcome would have made more complete use of the data and could have resulted in conclusions quite different from those presented in Michalowicz et al.

We also have concerns regarding the "competing-risks analysis" that was performed. No justification is given for why the authors treated the first seven birth outcomes (all of which were spontaneous abortions or stillbirths) as "hypothesis generating" and used only later such events for hypothesis testing. If all spontaneous abortions and stillbirths are included (rather than excluding the first seven events), the difference between the treated and control groups is statistically significant ($P = 0.028$ using the Fisher exact test with mid-P correction). To us, this indicates a possible protective effect of periodontal treatment in helping to prevent these adverse birth outcomes.

The authors briefly discuss the issue of non-compliance with treatment in their study (page 1,892); however, they fail to mention the results in Figure 3 for patients who attended six scheduled visits (i.e., 436 patients, which represent 53% of the 823 total subjects in the study). A subgroup analysis based only on these fully compliant subjects indicates that the treatment group was significantly better than the control in terms of preterm births ($P = 0.03$).

Finally, we have an additional concern about the power analysis and sample-size calculation for the study. No citation is given for the method used by the authors to determine the required sample size. Most commonly, the calculation of the sample size required for a time-to-event analysis like the one performed in this study is based on the clinically significant hazard ratio that one wishes to detect in the proposed study (the hazard ratio being the primary determinant of the

power of the log-rank test). This calculation could have indicated a very different value for the required sample size than the one that was eventually used in the study.

In conclusion, although the study by Michalowicz et al. is an interesting examination of an extremely important public health issue, we feel that it provides, at best, inconclusive evidence regarding the effectiveness of the treatment of periodontal disease in preventing adverse pregnancy outcomes.

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