Maternal Periodontitis Treatment and Child Neurodevelopment at 24 to 28 Months of Age

WHAT'S KNOWN ON THIS SUBJECT: Some maternal infections increase the risk of impaired infant neurodevelopment. Periodontitis is a bacterial infection that leads to more frequent bacteremia and increased serum inflammatory biomarker levels. No studies have determined whether maternal periodontitis treatment is associated with child neurodevelopment.

WHAT THIS STUDY ADDS: We compared cognitive, motor, and language development between children of mothers who were or were not treated for periodontitis during pregnancy. Neither receipt of treatment nor change in periodontitis status during pregnancy was associated with these outcomes in children.

abstract

BACKGROUND: Some maternal infections are associated with impaired infant cognitive and motor performance. Periodontitis results in frequent bacteremia and elevated serum inflammatory mediators.

OBJECTIVE: The purpose of this study was to determine if periodontitis treatment in pregnant women affects infant cognitive, motor, or language development.

METHODS: Children born to women who had participated in a previous trial were assessed between 24 and 28 months of age by using the Bayley Scales of Infant and Toddler Development (Third Edition) and the Preschool Language Scale (Fourth Edition). Information about the pregnancy, neonatal period, and home environment was obtained through chart abstractions, laboratory test results, and questionnaires. We compared infants born to women treated for periodontitis before 21 weeks' gestation (treatment group) or after delivery (controls). In unadjusted and adjusted analyses, associations between change in maternal periodontal condition during pregnancy and neurodevelopment scores were tested by using Student's *t* tests and linear regression.

RESULTS: A total of 411 of 791 eligible mother/caregiver-child pairs participated. Thirty-seven participating children (9.0%) were born at <37 weeks' gestation. Infants in the treatment and control groups did not differ significantly for adjusted mean cognitive (90.7 vs 91.4), motor (96.8 vs 97.2), or language (92.2 vs 92.1) scores (all $P > .5$). Results were similar in adjusted analyses. Children of women who experienced greater improvements in periodontal health had significantly higher motor and cognitive scores ($P = .01$ and $.02$, respectively), although the effect was small (~ 1 -point increase for each SD increase in the periodontal measure).

CONCLUSION: Nonsurgical periodontitis treatment in pregnant women was not associated with cognitive, motor, or language development in these study children. *Pediatrics* 2011;127:e1212–e1220

AUTHORS: Bryan S. Michalowicz, DDS, MS,^a James S. Hodges, PhD,^b Richard C. Lussky, MD,^c Henrietta Bada, MD,^d Twila Rawson, PhD,^e L. Susan Buttross, MD,^e Claudia Chiriboga, MD, MPH,^f Anthony J. DiAngelis, DMD, MPH,^g M. John Novak, BDS, LDS, PhD,^h William Buchanan, DDS, MMdSc,ⁱ Dennis A. Mitchell, DMD,^j and Panos N. Papapanou, DDS, PhD^k

^aDepartment of Developmental and Surgical Sciences, School of Dentistry and ^bDivision of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota; Departments of ^cPediatrics and ^dDentistry, Hennepin County Medical Center, Minneapolis, Minnesota; ^eDepartment of Pediatrics, College of Medicine, and ^fCenter for Oral Health Research, College of Dentistry, University of Kentucky, Lexington, Kentucky; ^gDepartment of Pediatrics, School of Medicine, and ^hDepartment of Periodontics, School of Dentistry, University of Mississippi Medical Center, Jackson, Mississippi; ⁱDepartment of Pediatric Neurology, College of Physicians and Surgeons and Harlem Hospital Center, New York, New York; and ^jDepartment of Periodontics and Preventive Sciences, College of Dental Medicine, Columbia University, New York, New York

KEY WORDS

child neurodevelopment, periodontitis, pregnancy, treatment

All authors critically reviewed the draft manuscript and approved the submitted version. Dr Michalowicz procured funding for the project and the parent trial, helped analyze and interpret the findings, and wrote the manuscript; Dr Hodges performed the power calculations, analyzed the data, and helped interpret the results; Drs Chiriboga, Lussky, Bada, Rawson, and Buttross selected the questionnaire items and tests used to assess children and mother/caregivers; Drs Lussky, Bada, Buttross, and Rawson helped guide the analyses and interpret the neurodevelopment outcomes and results; Drs DiAngelis, Novak, Buchanan, Mitchell, and Papapanou helped collect the oral health information and supervised study staff; and Drs Michalowicz, Hodges, DiAngelis, Novak, Buchanan, Mitchell, and Papapanou helped design the parent clinical trial.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-3129

doi:10.1542/peds.2010-3129

Accepted for publication Jan 31, 2011

Address correspondence to Bryan S. Michalowicz, DDS, MS, Department of Developmental and Surgical Sciences, School of Dentistry, University of Minnesota, 17-116 Moos Tower, 515 Delaware St SE, Minneapolis, MN 55455. E-mail: micha002@umn.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2011 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

Funded by the National Institutes of Health (NIH).

Maternal infections may adversely affect neurodevelopment in fetuses and later performance in infants. Chorioamnionitis accounts for an estimated 12% of all spastic cerebral palsy in term infants and 28% of cerebral palsy in preterm infants.¹ Untreated urinary tract, kidney, and bladder infections, sepsis, fever $>38^{\circ}\text{C}$ during labor, and HIV (transmitted in utero) have been associated with impaired infant mental and motor ability or with unexplained cerebral palsy.^{2–5}

Maternal infection or inflammation may damage developing fetal brains by several mechanisms.^{6,7} Hypoxic-ischemic brain damage may result from the action of pro-inflammatory cytokines, including tumor necrosis factor- α , interleukin-1, and interleukin-6, which can damage oligodendrocyte progenitors and induce cystic periventricular leukomalacia. Pro-inflammatory cytokines may originate either from the maternal uterus and placenta or stimulated fetal microglia and astrocytes.

Periodontitis is a chronic, bacteria-induced infection of structures supporting the teeth. Gingival bleeding and poor oral hygiene are associated with more frequent and severe bacteremia after routine events such as eating or toothbrushing.^{8,9} Thus, oral bacteria may gain access to the placenta and fetus through the vasculature by means of gingival inflammation.¹⁰ Periodontitis is also associated with elevated systemic cytokine levels,^{11–13} which in animals have been shown to directly affect neuronal development.⁷

The purpose of the present study was to explore associations between maternal periodontitis treatment and cognitive, motor, and language development in infants. We hypothesized that treating periodontitis during pregnancy would improve neurodevelopment in these infants.

METHODS

Parent Trial

We recruited women who participated in the Obstetrics and Periodontal Therapy trial (ClinicalTrials.gov identifier NCT00066131) and their children born during the trial.¹⁴ This study was a randomized controlled trial to test whether periodontal therapy reduced the severity or frequency of premature birth in women with periodontitis. Briefly, women were recruited from obstetrics clinics at 4 sites (Kentucky, Minnesota, Mississippi, and New York). After baseline assessments between 13 and 16 $\frac{1}{2}$ weeks' gestation, women were randomly assigned to receive scaling and root planing and oral hygiene instruction either before 21 weeks' gestation or after delivery. Women were seen monthly for tooth polishing and oral hygiene instruction (treatment group) or brief examinations (controls). All women were evaluated and offered treatment before 21 weeks for abscessed, extensively decayed, or fractured teeth.

Women in both groups received periodontal examinations at baseline and at 21 to 24 and 29 to 32 weeks' gestation. Calibrated, blinded examiners evaluated the severity and extent of periodontitis using standard clinical measures.*

*Probing depth is the depth, in millimeters, of the cuff of gum around the teeth. Clinical attachment loss is the amount of tooth root, measured in millimeters vertically along the root, which has been denuded of its supporting structures. Gingival bleeding on probing is the presence (yes or no) of any blood around the gum cuff within 30 seconds after probing. Periodontally healthy teeth generally have no clinical attachment loss, probing depths <4 mm, and no bleeding after probing. All 3 measures are commonly used to diagnose and monitor periodontal status in clinical and research settings. In the parent study, these measures were scored at 6 sites on all teeth excluding third molars. Probing depth changes were summarized as the change, from baseline, in percentage of tooth sites with probing depths ≥ 4 mm. Clinical attachment loss changes were summarized as the change in percentage of tooth sites with changes

The study was approved by institutional review boards at participating centers. Adults provided written consent. As compensation, mothers/caregivers received a \$50 gift certificate to a retail store and infants an age-appropriate toy worth \$10 to \$15.

Infant Assessments

A battery of tests was conducted when infants were aged 24 to 28 months by trained, experienced child psychologists, occupational therapists, speech pathologists, and physical therapists. Cognitive and motor development was assessed by using the Bayley Scales of Infant and Toddler Development (Third Edition), which is a norm-referenced instrument providing scaled scores, composite scores, percentile ranks, and growth scores for cognitive and motor functions. Scaled fine and gross motor scores are combined to form the motor scale composite score. Composite scores have a mean of 100 and an SD of 15. A score of ≤ 70 indicates developmental delay.

The Preschool Language Scale (Fourth Edition) was used to assess language development at the same study visit. This instrument is a standardized scale with auditory comprehension and expressive communication components. The comprehensive (summed) score has a standardized mean of 100 and an SD of 15. The Spanish version was used when necessary. Language was not assessed at the New York site because of the numerous languages and dialects spoken by that site's participants. Translators were available for non-English speakers during cognitive and motor assessments at all sites. Testing, conducted in the mother/caregiver's presence, did not exceed 2 hours. Breaks were provided as needed depending on the child's state.

≥ 2 mm. Change in bleeding on probing was summarized as the change in percentage of tooth sites that bled after probing.

Examiner Training and Calibration

Before study enrollment, examiners were trained by Harcourt Assessment, publisher of the Bayley Scales of Infant and Toddler Development (Third Edition) and the Preschool Language Scale (Fourth Edition). Examiners also participated in a 2-day training/calibration exercise, during which nonstudy children were scored by 1 examiner while others observed and scored from behind a 2-way mirror. Examiners discussed and resolved systematic scoring differences.

Medical History and Growth

Questionnaires and medical record reviews identified chronic or recurrent illnesses that could affect neurodevelopment. History of seizures, trauma, ventilator use, or steroid use during hospitalizations was assessed by using medical record review. Serum lead and hematocrit levels were assayed at each site (not by a central laboratory). Infants were included in the study even if their mothers refused the blood draw. Fronto-occipital head circumference was measured and percentile rank determined using population norms.¹⁵

Mothers' demographic and obstetrical data, collected between 13 weeks' gestation and delivery, were available from the parent trial, including 1- and 5-minute infant Apgar scores and head circumference at birth.

Family History

The child's mother/primary caregiver was interviewed regarding history of child care, parent education, and health-related behaviors in the household. The home environment and caregiver-child interactions were assessed using the infant/toddler version of the Home Observation for Measurement of the Environment inventory.¹⁶ Assessment was done at the clinical sites, which is comparable to

TABLE 1 Variable Blocks Used in Adjusted Analyses

Block No./Descriptor	Variables Within Block
1/pregnancy	Periodontal treatment group assignment Self-reported drug and/or alcohol addiction during pregnancy Maternal race (black vs nonblack) Public assistance status Cigarette smoking
2/neonatal period	Gestational age at delivery Small for gestational age (≤ 10 th percentile) 5-min Apgar score Head circumference at birth (≤ 10 th percentile) Intraventricular hemorrhage, respiratory distress syndrome requiring ventilator support, or steroid use during the first hospitalization (yes or no for any)
3/early environment	Head circumference at 26 mo Serum lead level at 26 mo Blood hematocrit at 26 mo Educational level of primary caregiver ^a Educational level of biological father ^a No. of biological parents in household HOME inventory

HOME indicates Home Observation for Measurement of Environment.

^a Education: ≤ 9 , 10 to 12, or > 12 years (some college, college graduate, or graduate school).

in-home assessment.¹⁷ This inventory is used to assess emotional and verbal responsiveness of the mother/primary caregiver, avoidance of restriction and punishment, organization of the physical and temporal environment, provision of appropriate play material, maternal involvement with the child, and variety in daily stimulation.

Statistical Analyses

A priori, we estimated that 400 caregiver-infant pairs (200 per treatment group) would give 80% power to detect a 4.2-point difference between groups in motor and cognitive scores. Thus, our final sample had good power to detect small between-group differences.

Three approaches were used to analyze the association between neurodevelopment scores and maternal periodontal treatment. The simplest analyses were multiple linear regressions with a neurodevelopment score as the dependent variable and periodontal treatment group assignment, clinical site, and their interaction as independent variables. A weighted version of this analysis weighted each included child by the

inverse of its probability of participating in the study (estimated by logistic regression of participation on maternal and child characteristics). Because the unweighted and weighted results were similar, weighted analyses were omitted.

Finally, we compared the groups by adjusting for 3 "blocks" of variables. Blocks 1 to 3 contained, respectively, maternal characteristics at randomization into the parent study, characteristics of the child at or just after birth, and characteristics of the child and his or her home environment at 24 to 28 months of age (Table 1). These blocks made the analyses more manageable given the many adjusters and the primary interest in comparing periodontal treatment and control groups. Adjusted analyses were not weighted for differential study participation because weighting had little effect on unadjusted analyses.

We tested associations between neurodevelopment scores and the mother's change in periodontal status during pregnancy using data from the 378 mother-infant pairs with infant neurodevelopment scores and complete ma-

ternal periodontal data (from the parent trial). Change in periodontal status (baseline to 29–32 weeks' gestation) was characterized using 3 clinical measures.*

Multiple linear regression was used to test associations between neurodevelopment scores and changes in periodontal measures, with dependent variable a neurodevelopment score and the independent variables study group, clinic, and change in periodontal status entered as a continuous measure. Associations between neurodevelopment scores and changes in periodontal status were expressed as the average change in neurodevelopment score associated with a 15 percentage point difference in the changes in periodontal status (ie, the approximate SD of the change in each periodontitis measure within the treatment and control groups.) Additional analyses included interactions between periodontitis measures and either clinic or group. Some interactions had *P* values barely below the conventional significance threshold (*P* = .05). None would remain significant after accounting for multiple comparisons by any rule and all were small in magnitude; these analyses were therefore omitted.

RESULTS

Sample Population

Figure 1 summarizes the disposition of participants from the parent trial through the follow-up study. Approximately half (411 of 789 [52%]) of eligible women participated. Most nonparticipants could not be located (*n* = 139) or declined participation (*n* = 106). Recruitment ranged from 69.5% at the Minnesota site to 32.3% at the New York site. We excluded from all analyses 5 infants with congenital anomalies or conditions associated with motor or cognitive impairment (eg, hydrocephaly, unspecified neuro-

FIGURE 1

Disposition of study participants throughout the parent clinical trial and the present study. OPT, obstetrics and periodontal therapy.

muscular disorder, hypoglycemia/polycythemia, ventriculomegaly).

Approximately two-fifths of the mothers were black, and nearly half were Hispanic (Table 2). Few women reported using cigarettes or alcohol during pregnancy. Public assistance programs paid for significantly more control than treatment group deliveries (*P* = .01). The groups did not differ significantly in other characteristics considered except periodontal measures, which improved, as expected, during pregnancy more in the treatment group than in the control group.

Table 3 lists selected delivery and neonatal outcomes. The groups did not differ significantly on these measures. Of the 37 preterm infants in the follow-up study, only 1 was born at <32 weeks' gestation. One mother but no infants

were HIV-positive at delivery. No infant had a 5-minute Apgar score <4 or a history of grade 3 or 4 intraventricular hemorrhage. Four infants required ventilator support and 3 were administered steroids during their first hospitalization.

Table 4 lists characteristics of the child, caregiver, and home environment at 24 to 28 months of child age. The groups did not differ significantly for any measure. Approximately 25% of mothers/primary caregivers reported using alcohol regularly; few reported using marijuana or illicit drugs. Groups did not differ in terms of either parent's education (*P* > .60). Nine children had lead levels ≥ 10 $\mu\text{g}/\text{dL}$, and 190 had hematocrit levels at <36%.

Combining treatment and control groups, mean cognitive, motor, and

TABLE 2 Characteristics of Women in the Control and Treatment Groups During Pregnancy

	Control Group (N = 200)	Treatment Group (N = 205)	P ^a
Age, mean (SD), y ^b	26.2 (5.6)	26.8 (5.8)	.27
Black race, n (%)	70 (35.0)	80 (39.0)	.40
Hispanic, n (%)	95 (47.5)	97 (47.3)	.97
Smoked during pregnancy, n (%) ^c	15 (7.6)	20 (10.0)	.40
Used alcohol during pregnancy, n (%)	3 (1.5)	4 (2.0)	.72
Chorioamnionitis, n (%) ^d	4 (2.0)	5 (2.5)	.76
Delivery paid by public program, n (%)	153 (76.5)	134 (65.4)	.01
Education ^b			
<8 y	43	44	.84
8–12 y	114	112	
>12 y	43	49	
Change in periodontal measures ^e			
Sites with probing depth > 4 mm, mean (SD), %	−0.82 (10.05)	−13.60 (13.71)	<.001
Sites with CAL > 2 mm, mean (SD), %	0.28 (16.05)	−11.69 (18.36)	<.001
Sites with BOP, mean (SD), %	−1.71 (13.15)	−23.64 (17.99)	<.001

CAL indicates clinical attachment loss; BOP, bleeding on probing.

^a From χ^2 test except for age (Student's *t* test).

^b At 13 to 16½ weeks' gestation.

^c Total number equals 198 in the control group, 201 in treatment group.

^d Total number equals 197 in the control group, 201 in the treatment group.

^e Change from baseline to 29 to 32 weeks' gestation (or to 21–24 weeks' if missing 29- to 32-week data).

TABLE 3 Neonatal Characteristics of Infants Born to Women in the Control and Treatment Groups

	Control Group	Treatment Group	P ^a
Born at <37 wk gestation, n/N (%)	18/200 (9.0)	19/205 (9.3)	.61
Birth weight < 2500 g, n/N (%)	12/200 (6.0)	15/205 (7.3)	.57
SGA, <10th percentile, n/N (%)	24/200 (12.0)	24/205 (11.7)	.93
5-min Apgar score < 7, n/N (%)	4/198 (2.0)	5/203 (2.5)	.84
Head circumference at birth, mean (SD), cm	34.0 (1.5)	33.9 (1.7)	.37
Head circumference < 10th percentile, n/N (%) ^b	6/189 (3.2)	9/189 (4.8)	.43
NICU stay ≥ 2 d, n/N (%)	9/198 (4.5)	13/203 (6.4)	.65
Blood culture positive for sepsis, n/N (%)	7/190 (3.7)	9/197 (4.6)	.66

SGA indicates small for gestational age.

^a From χ^2 test except for head circumference at birth (Student's *t* test).

^b For preterm infants, calculations were based on data from Riddle et al.²⁸

TABLE 4 Selected Infant, Primary Caregiver, and Environmental Characteristics in Control and Treatment Groups Assessed at 24 to 28 Months of Age

Characteristic	Control Group	Treatment Group	P ^a
Infant			
Head circumference, mean (SD), cm	48.7 (1.7)	48.9 (1.8)	.25 ^b
Head circumference < 10th percentile, n (%) ^c	13/194 (6.7)	8/195 (4.1)	.26
Serum lead, mean (SD), µg/dL	3.40 (3.10)	2.86 (1.30)	.17 ^b
Hematocrit, mean (SD), %	35.15 (2.21)	35.50 (2.50)	.19 ^b
No. of parents in household, n1/n2 (%) ^a	58/141 (29.1)	60/143 (29.6)	.93
HOME inventory, mean (SD)	27.12 (3.29)	26.77 (3.57)	.31 ^b
Primary caregiver			
Language, n (%)			
English	90 (45.0)	85 (41.5)	.61
Spanish	101 (50.5)	107 (52.2)	
Other	9 (4.5)	13 (6.3)	
Cigarette smoking, n/N (%)	19/200 (9.5)	31/205 (15.1)	.09
Alcohol use, n/N (%)	51/200 (25.5)	52/204 (25.4)	.99
Marijuana use, n/N (%)	5/200 (2.5)	5/205 (2.4)	.61
Illicit drug use, n/N (%)	3/200 (1.5)	0/205 (0)	.13

HOME indicates Home Observation for Measurement of Environment; n1/n2, the number of one- and two-parent households, respectively; %1, the percentage of one-parent households.

^a From χ^2 test except as noted.

^b From Student's *t* test except serum lead, which used a Student's *t* test on log10-transformed serum lead value.

^c From Centers for Disease Control and Prevention data, computed separately for boys and girls.

language scores were less than the population norm of 100 (Table 5). The fraction of infants with scores of ≥ 2 SDs below the norm (ie, ≤ 70) ranged from 1.0% for motor performance to 6.7% for language development.

Associations Between Periodontal Treatment Group and Neurodevelopment Outcomes

Mean cognitive, motor, and language scores did not differ significantly between treatment and control groups in unadjusted analyses (Table 6; all, $P > 0.5$). For all outcomes, scores differed significantly among clinical sites (Table 7; $P < .001$) the differences varied by outcome. The site-by-treatment group interaction was not significant for any score (all $P > 0.2$; data not shown); that is, the relationship between treatment group and neurodevelopment scores did not differ significantly between sites.

Cognitive, motor, and language scores also did not differ significantly between treatment groups in adjusted analyses ($P = .10, .31$, and $.72$, respectively). Table 8 lists variables significantly associated with the outcomes. Again, cognitive and motor scores differed significantly among sites ($P < .001$). Maternal alcohol use was associated with cognitive scores in block 1 and blocks 1 + 2 adjusted analyses but did not remain significant when block 3 was included. Gestational age at delivery and 5-minute Apgar scores were associated with some but not all outcomes. Other measures, including serum lead levels, hematocrit, biological father's education, number of biological parents in the household, and public assistance status, were not associated with any outcome ($P > .1$). Importantly, adjusting for variable blocks did not alter the nonsignificant association between treatment group and any neurodevelopment outcome.

TABLE 5 Overall Summaries of Infants' Standardized Cognitive, Motor, and Language Scores at 24 to 28 Months of Infant Age

	Cognitive	Motor	Language (PLS-4)
<i>n</i>	405	405	342
Mean (SD)	92.4 (9.6)	97.7 (10.3)	93.1 (15.0)
Median	90	97	93
Minimum, maximum	65, 130	61, 127	55, 144
Score ≤ 70 , <i>n</i> (%)	13 (3.2)	4 (1.0)	23 (6.7)

PLS-4 indicates the Preschool Language Scale (Fourth Edition).

TABLE 6 Adjusted Average Neurodevelopment Scores According to Study Group

	Control Group, Mean (SE)	Treatment Group, Mean (SE)
Cognitive score	91.4 (0.7)	90.8 (0.7)
Motor score	97.2 (0.8)	96.8 (0.8)
Language score	92.1 (1.2)	92.3 (1.2)

The SEs are pooled. *N* = 200 for control group and 205 for treatment for cognitive and motor scores. *N* = 171 for each group for language scores; language development was not assessed at the New York site.

Associations Between Change in Maternal Periodontitis and Neurodevelopment Outcomes

Cognitive score was significantly but weakly associated with change in clinical attachment loss ($P = .02$) (Table

9). Comparing mothers who differed by 15 percentage points in improvement (ie, in the percentage of sites with clinical attachment loss ≥ 2 mm), children of mothers with greater improvement scored on average 1 point higher on the cognitive test. No association was found with probing depth or bleeding on probing.

Motor score was also associated with change in clinical attachment loss ($P = .01$) (Table 9). Again, the association was weak and clinically insignificant. Comparing mothers who differed by 15 percentage points in periodontal improvement, infants of mothers with greater periodontal improvement

scored on average 1.2 points higher. No association was found with probing depth or bleeding on probing.

Finally, language score was not significantly associated with changes in periodontal measures (Table 9). All estimates were negative; that is, improvement in each of the periodontal measures was associated with nonsignificant improvements in language scores.

Comparing Neurodevelopment Study Participants and Nonparticipants

Nonparticipants were younger (1.1 year on average; $P = .006$) and more likely to be black (37.6% of participants, 49.5% of nonparticipants; $P = .008$) and to have smoked cigarettes while pregnant (9.2% vs 14.6%; $P = .03$). Randomized group assignment in the parent trial was not associated with participation in the follow-up study (51.5% vs 51.2% for treatment and control groups, respectively).

On average and compared with participants, nonparticipants delivered earlier (271.6 vs 274.2 days' gestation; $P = .02$) and had lighter infants (3204 vs 3289 g; $P = .04$). Only 1 of 9 eligible infants born earlier than 32 weeks' gestation participated in the follow-up study. Fractions of infants small for gestational age at birth and mean Apgar scores did not differ significantly between participants and nonparticipants.

DISCUSSION

Periodontitis treatment in pregnant women during the second trimester did not significantly affect cognitive, motor, and language development in their children at 24 to 28 months of age. Changes in clinical periodontitis measures during pregnancy also were not consistently associated with these outcomes. Although change in clinical attachment loss was associated with cognitive and motor scores ($P = .02$

TABLE 7 Adjusted Average Neurodevelopment Scores According to Clinical Center

	Kentucky, Mean (SE)	Minnesota, Mean (SE)	Mississippi, Mean (SE)	New York, Mean (SE)
Cognitive score	91.6 (0.9)	96.1 (0.7)	88.7 (1.0)	87.9 (1.3)
Motor score	94.5 (1.0)	99.5 (0.8)	99.5 (1.1)	94.6 (1.4)
Language score	93.2 (1.5)	96.6 (1.2)	86.9 (1.6)	—

The SEs are pooled. *N* = 200 for control group and 205 for treatment for cognitive and motor scores. *N* = 171 for each group for language scores; language development was not assessed at the New York site.

TABLE 8 Adjusted Analyses: Explanatory Variables That Were Significant ($P < .05$ From Multiple Linear Regression) for Cognitive, Motor, and Language Scores

Block ^a	Cognitive	Motor	Language
1	Clinic Alcohol use ^b	Clinic	Mother's race (black vs nonblack)
1 + 2	Clinic Alcohol use ^b	Clinic GA at delivery 5-min Apgar score	Clinic
1 + 2 + 3	Clinic	Clinic GA at delivery 5-min Apgar score HC ≤ 10 th percentile Primary caregiver education	HC ≤ 10 th percentile HOME inventory

GA indicates gestational age; HC, head circumference at 26 months.

^a See Table 1 for the list of variables in each block.

n = 398 for block 1 analyses, 369 for block 1 + 2 analyses, and 286 for block 1 + 2 + 3 analyses for cognitive and motor scores.

^b Alcohol use was assessed at 13 to 16% weeks' gestation and scored as yes or no.

TABLE 9 Estimated Change in Infant Neurodevelopment Outcomes Associated With Change in Maternal Periodontitis Status During Pregnancy

Outcome	Periodontitis Measure	Estimate ^a	SE	P
Cognitive	Change in PD	0.01	0.62	.98
	Change in CAL	−0.97	0.42	.02
	Change in BOP	0.58	0.47	.22
Motor	Change in PD	−0.61	0.69	.38
	Change in CAL	−1.16	0.47	.01
	Change in BOP	−0.12	0.53	.82
Language	Change in PD	−1.28	1.04	.22
	Change in CAL	−1.04	0.70	.14
	Change in BOP	−1.35	0.84	.11

PD indicates probing depth; CAL, clinical attachment loss; BOP, bleeding on probing.

^a Estimate is the change in the development score (outcome) as a function of a 15-percentage point improvement (decrease) in the periodontitis measure. Negative numbers indicate that a greater improvement in the periodontitis measure was associated with a higher development score.

and .01, respectively, uncorrected for multiple comparisons), we deem these effect sizes to be of little or no clinical significance.

To our knowledge, this is the first study to explore associations between maternal periodontitis treatment and child development. Emerging evidence suggests that periodontitis and periodontitis-associated bacteria are associated with impaired cognition and memory and incident dementia in adults and the elderly.^{18–21} Moreover, rodent studies suggest that nonuterine infections elicit systemic inflammatory responses that affect development or activities of neuronal cells in the fetal brain^{22,23} and that anti-inflammatory drugs can reverse lipopolysaccharide-induced inhibition of neurogenesis.²⁴ Despite the plausibility of such a link, we found no consistent evidence that treatment of bacterial-induced oral inflammation in pregnant women affects motor, language, or cognitive functions in children.

All women in the parent trial had periodontitis, which may explain why mean Bayley scores were lower than national norms. Because we did not study pregnant women without periodontitis, we could not establish whether disease per se was associated with neurodevelopment. The design of the parent trial only enabled us to explore

associations with periodontitis treatment and changes in periodontitis status that occurred after 21 weeks of gestation. However, treatment was associated with significant improvements in the mothers' periodontal condition, suggesting that reduced exposure to maternal disease and disease-related microorganisms in midpregnancy do not improve outcomes in children.

At the start of the parent trial, most women had generalized early-to-moderate periodontitis. Because any systemic effect of periodontitis may be more pronounced in severe disease, our findings may have differed had we enrolled only women with advanced periodontitis. However, the prevalence of advanced disease in this age group is low (~1%),²⁵ so even if a treatment effect exists in this subgroup, the public health implications of identifying and treating affected women would be limited.

The study treatment consisted of mechanical therapy (scaling and root planing and monthly tooth polishings). In rare instances, women who were refractory to this treatment were given systemic antibiotics. Sustained-release, locally delivered antibiotics were not used because all such products in the United States are tetracycline derivatives, which are relatively contraindicated during pregnancy be-

cause of concerns about embryotoxicity, retarded fetal skeletal development and discoloration of primary teeth. Our results again may have differed had we provided periodontal treatment earlier in gestation (even before conception), repeatedly, or more aggressively (ie, included the routine use of systemic antibiotics or periodontal surgery). Nonetheless, associations that were statistically significant were weak. A 1 SD relative improvement in attachment loss was associated with an ~1-point improvement in motor and cognitive scores, suggesting that even large clinical improvements in the mother yielded only nominal improvements in motor and cognitive scores in the infants.

A limitation of this study is that only about half of eligible women from the parent trial participated. The parent trial recruited from underserved and relatively transient populations. Of women eligible for the current study, 109 (13.8%) declined to participate or withdrew consent (Fig 1), and even more women simply could not be located. The numbers of treatment and control group women were similar, indicating that the timing of periodontitis treatment was not associated with later study participation. Although the proportion of preterm and low birth weight infants was similar in the 2 groups, mothers of very preterm or very low birth weight infants were less likely to participate than mothers of term or normal birth weight infants. We considered this differential loss to follow-up in weighted analyses, but the low number of very preterm or very low birth weight infants limits our findings to groups at relatively low risk for developmental delay. The relationship between child neurodevelopment and change in maternal status or receipt of treatment during pregnancy may differ in cohorts of only preterm or very preterm infants. As with any study, our

findings should be interpreted in terms of characteristics of the women—who were predominantly from minority and lower income groups—and of the range of cognitive, motor, and language scores in these children.

We collected extensive information regarding the child but did not test for associations between individual characteristics and neurodevelopment outcomes. Instead, we grouped covariates into blocks on the basis of when they would be expected to affect neurodevelopment: during pregnancy, in the neonatal period, or before 24 to 28 months of age. We also ignored statistical interactions in the adjusted analyses and instead focused on estimating the effect on development scores

of periodontal treatment group or change in periodontitis measures. As noted, the few interactions that were statistically significant were barely so and either described small effects or were noninterpretable.

CONCLUSIONS

Although we found no consistent evidence suggesting that periodontitis treatment in pregnant women improves neurodevelopment outcomes in children, we have previously shown that treatment is safe and improves both clinical and microbiologic measures of disease.^{14,26,27} These efforts, as well as others, to reduce the oral microbial load in expectant mothers may reduce the frequency of later mother-to-infant transmissions of oral patho-

gens and ameliorate the persistently high oral disease burdens in some child populations.

ACKNOWLEDGMENTS

This research was supported by grant U01 DE014338 from the National Institute of Dental and Craniofacial Research, National Institutes of Health.

We thank the study participants and the study personnel including L. Long-Simpson, S. Hieb-Stewart, and M. Huschle (Hennepin County Medical Center); D. Fogle, R. Caldwell, M. Reynolds, and J. Sutherland (University of Kentucky); S. Vance (University of Mississippi Medical Center); D. Starr (Columbia University); and H. Voelker and I. Olson (University of Minnesota).

REFERENCES

- Schendel DE, Schuchat A, Thorsen P. Public health issues related to infection in pregnancy and cerebral palsy. *Ment Retard Dev Disabil Res Rev*. 2002;8(1):39–45
- McDermott S, Callaghan W, Szejnbka L, Mann H, Daguise V. Urinary tract infections during pregnancy and mental retardation and developmental delay. *Obstet Gynecol*. 2000;96(1):113–119
- Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birth weight. *JAMA*. 1997;278(3):207–211
- Smith R, Malee K, Charurat M, et al. Timing of perinatal human immunodeficiency virus type 1 infection and rate of neurodevelopment. The Women and Infant Transmission Study Group. *Pediatr Infect Dis J*. 2000;19(9):862–871
- Chase C, Ware J, Hittelman J, et al. Early cognitive and motor development among infants born to women infected with human immunodeficiency virus. Women and Infants Transmission Study Group. *Pediatrics*. 2000;106(2). Available at: www.pediatrics.org/cgi/content/full/106/2/e25
- Huleihel M, Golan H, Hallak M. Intrauterine infection/inflammation during pregnancy and offspring brain damages: possible mechanisms involved. *Reprod Biol Endocrinol*. 2004;2:17
- Jonakait GM. The effects of maternal inflammation on neuronal development: possible mechanisms. *Int J Dev Neurosci*. 2007;25(7):415–425
- Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. *Circulation*. 2008;117(24):3118–3125
- Lockhart PB, Brennan MT, Thornhill M, et al. Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. *J Am Dent Assoc*. 2009;140(10):1238–1244
- Han YW, Fardini Y, Chen C, et al. Term stillbirth caused by oral *Fusobacterium nucleatum*. *Obstet Gynecol*. 2010;115(2 pt 2):442–445
- Nibali L, D'Aiuto F, Griffiths G, Patel K, Suvan J, Tonetti MS. Severe periodontitis is associated with systemic inflammation and a dysmetabolic status: a case-control study. *J Clin Periodontol*. 2007;34(11):931–937
- McFarlane CG, Meikle MC. Interleukin-2, interleukin-2 receptor and interleukin-4 levels are elevated in the sera of patients with periodontal disease. *J Periodontol Res*. 1991;26(5):402–408
- Duarte PM, da Rocha M, Sampaio E, et al. Serum levels of cytokines in subjects with generalized chronic and aggressive periodontitis before and after non-surgical periodontal therapy: a pilot study. *J Periodontol*. 2010;81(7):1056–1063
- Michalowicz BS, Hodges JS, DiAngelis AJ, et al. Treatment of periodontal disease and the risk of preterm birth. *N Engl J Med*. 2006;355(18):1885–1894
- Centers for Disease Control and Prevention. Epi Info version 3.5.1. Available at: www.cdc.gov/epiinfo. Accessed October 1, 2008
- Bradley RH, Caldwell BM. Home observation for measurement of the environment: a validation study of screening efficiency. *Am J Ment Defic*. 1977;81(5):417–420
- Gottfried AW. *Home Environment and Early Cognitive Development: Longitudinal Research*. Orlando, FL: Academic Press; 1984:383
- Yu YH, Kuo HK. Association between cognitive function and periodontal disease in older adults. *J Am Geriatr Soc*. 2008;56(9):1693–1697
- Noble JM, Borrell LN, Papapanou PN, Elkind MS, Scarmeas N, Wright CB. Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES-III. *J Neurol Neurosurg Psychiatry*. 2009;80(11):1206–1211
- Kim JM, Stewart R, Prince M, et al. Dental health, nutritional status and recent-onset dementia in a Korean community population. *Int J Geriatr Psychiatry*. 2007;22(9):850–855
- Stein PS, Desrosiers M, Donegan SJ, Yepes JF, Kryscio RJ. Tooth loss, dementia and neuropathology in the Nun study. *J Am Dent Assoc*. 2007;138(10):1314–1322; quiz 1381–1382
- Cai Z, Pan ZL, Pang Y, Evans OB, Rhodes PG. Cytokine induction in fetal rat brains and brain injury in neonatal rats after maternal lipopolysaccharide administration. *Pediatr Res*. 2000;47(1):64–72
- Golan HM, Lev V, Hallak M, Sorokin Y, Huleihel M. Specific neurodevelopmental damage in mice offspring following maternal inflammation during pregnancy. *Neuropharmacology*. 2005;48(6):903–917

24. Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. *Science*. 2003;302(5651):1760–1765
25. Demmer RT, Papapanou PN. Epidemiologic patterns of chronic and aggressive periodontitis. *Periodontol 2000*. 2010;53:28–44
26. Michalowicz BS, DiAngelis AJ, Novak MJ, et al. Examining the safety of dental treatment in pregnant women. *J Am Dent Assoc*. 2008;139(6):685–695
27. Novak MJ, Novak KF, Hodges JS, et al. Periodontal bacterial profiles in pregnant women: response to treatment and associations with birth outcomes in the obstetrics and periodontal therapy (OPT) study. *J Periodontol*. 2008;79(10):1870–1879
28. Riddle WR, DonLevy SC, Lafleur BJ, Rosenbloom ST, Shenai JP. Equations describing percentiles for birth weight, head circumference, and length of preterm infants. *J Perinatol*. 2006;26(9):556–561