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# 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

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### KEY WORDS

child neurodevelopment, periodontitis, pregnancy, treatment

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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.<sup>1</sup> 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.<sup>2–5</sup>

Maternal infection or inflammation may damage developing fetal brains by several mechanisms.<sup>6,7</sup> Hypoxic-ischemic brain damage may result from the action of pro-inflammatory cytokines, including tumor necrosis factor- $\alpha$ , 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.<sup>8,9</sup> Thus, oral bacteria may gain access to the placenta and fetus through the vasculature by means of gingival inflammation.<sup>10</sup> Periodontitis is also associated with elevated systemic cytokine levels,<sup>11–13</sup> which in animals have been shown to directly affect neuronal development.<sup>7</sup> 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.<sup>14</sup> 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  $\geq 4$  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  $\leq 70$  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.

$\geq 2$  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. Frontal-occipital head circumference was measured and percentile rank determined using population norms.<sup>15</sup>

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.<sup>16</sup> 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 ( $\leq 10$ th percentile) 5-min Apgar score Head circumference at birth ( $\leq 10$ 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 <sup>a</sup> Educational level of biological father <sup>a</sup> No. of biological parents in household HOME inventory

HOME indicates Home Observation for Measurement of Environment.

<sup>a</sup> Education:  $\leq 9$ , 10 to 12, or  $> 12$  years (some college, college graduate, or graduate school).

in-home assessment.<sup>17</sup> 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-

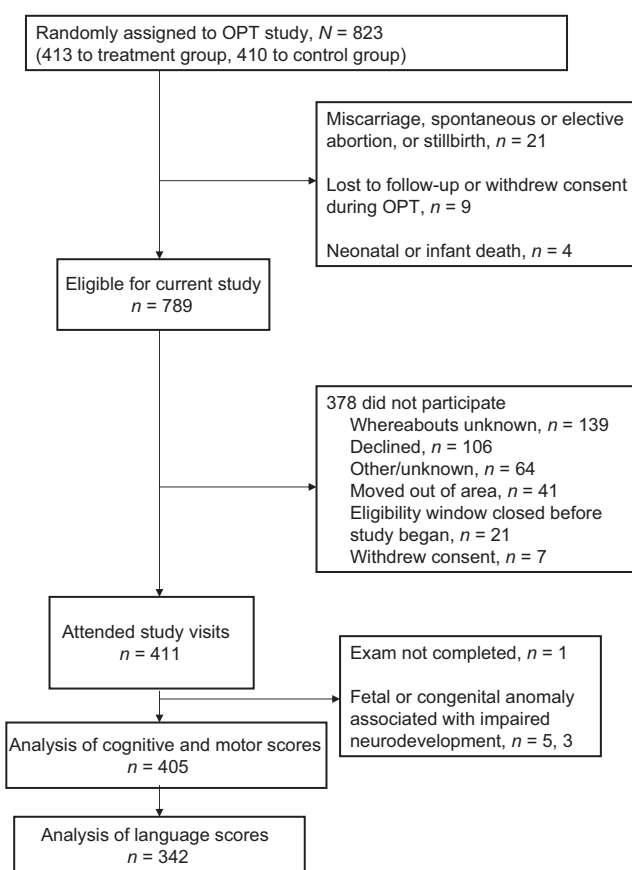
ternal periodontal data (from the parent trial). Change in periodontal status (baseline to 29–32 weeks' gestation) was characterized using 3 clinical measures.\*

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  $\geq 10$   $\mu\text{g}/\text{dL}$ , 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 <sup>a</sup>
Age, mean (SD), y <sup>b</sup>	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 (%) <sup>c</sup>	15 (7.6)	20 (10.0)	.40
Used alcohol during pregnancy, n (%)	3 (1.5)	4 (2.0)	.72
Chorioamnionitis, n (%) <sup>d</sup>	4 (2.0)	5 (2.5)	.76
Delivery paid by public program, n (%)	153 (76.5)	134 (65.4)	.01
Education <sup>b</sup>			
< 8 y	43	44	.84
8–12 y	114	112	
> 12 y	43	49	
Change in periodontal measures <sup>e</sup>			
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.

<sup>a</sup> From  $\chi^2$  test except for age (Student's *t* test).

<sup>b</sup> At 13 to 16 $\frac{1}{2}$  weeks' gestation.

<sup>c</sup> Total number equals 198 in the control group, 201 in treatment group.

<sup>d</sup> Total number equals 197 in the control group, 201 in the treatment group.

<sup>e</sup> 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 <sup>a</sup>
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 (%) <sup>b</sup>	6/189 (3.2)	9/189 (4.8)	.43
NICU stay $\geq$ 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.

<sup>a</sup> From  $\chi^2$  test except for head circumference at birth (Student's *t* test).

<sup>b</sup> For preterm infants, calculations were based on data from Riddle et al.<sup>28</sup>

**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 <sup>a</sup>
<b>Infant</b>			
Head circumference, mean (SD), cm	48.7 (1.7)	48.9 (1.8)	.25 <sup>b</sup>
Head circumference < 10th percentile, n (%) <sup>c</sup>	13/194 (6.7)	8/195 (4.1)	.26
Serum lead, mean (SD), $\mu\text{g}/\text{dL}$	3.40 (3.10)	2.86 (1.30)	.17 <sup>b</sup>
Hematocrit, mean (SD), %	35.15 (2.21)	35.50 (2.50)	.19 <sup>b</sup>
No. of parents in household, n1/n2 (%) <sup>a</sup>	58/141 (29.1)	60/143 (29.6)	.93
HOME inventory, mean (SD)	27.12 (3.29)	26.77 (3.57)	.31 <sup>b</sup>
<b>Primary caregiver</b>			
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; %, the percentage of one-parent households.

<sup>a</sup> From  $\chi^2$  test except as noted.

<sup>b</sup> From Student's *t* test except serum lead, which used a Student's *t* test on log<sub>10</sub>-transformed serum lead value.

<sup>c</sup> 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  $\geq 2$  SDs below the norm (ie,  $\leq 70$ ) 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 ( $P = .10, .31, \text{ and } .72$ , 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 $\leq 70$ , <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  $\geq 2$  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 <sup>a</sup>	Cognitive	Motor	Language
1	Clinic Alcohol use <sup>b</sup>	Clinic	Mother's race (black vs nonblack)
1 + 2	Clinic Alcohol use <sup>b</sup>	Clinic GA at delivery 5-min Apgar score	Clinic
1 + 2 + 3	Clinic	Clinic GA at delivery 5-min Apgar score HC $\leq 10$ th percentile Primary caregiver education	HC $\leq 10$ th percentile HOME inventory

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

<sup>a</sup> 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.

<sup>b</sup> 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 <sup>a</sup>	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.

<sup>a</sup> 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.<sup>18–21</sup> Moreover, rodent studies suggest that nonuterine infections elicit systemic inflammatory responses that affect development or activities of neuronal cells in the fetal brain<sup>22,23</sup> and that anti-inflammatory drugs can reverse lipopolysaccharide-induced inhibition of neurogenesis.<sup>24</sup> 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%),<sup>25</sup> 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.<sup>14,26,27</sup> 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.

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