Primary Tooth Fluorosis and Amoxicillin Use During Infancy

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Abstract

Objective: *It has been speculated that amoxicillin use could be associated with enamel defects, but there have been few studies of this possible relationship. This study assessed the association between amoxicillin use during the first year of life and primary tooth fluorosis.* ***Methods:*** *Subjects (n=490) were recruited at birth and followed prospectively with a series of questionnaires to gather information on fluoride intake and amoxicillin use. Primary tooth fluorosis was assessed by calibrated examiners at approximately 5 years of age.* ***Results:*** *Amoxicillin use for 6 weeks to 3 months and 3 months to 6 months significantly increased the risk for fluorosis of primary second molars in bivariate analyses. However, after controlling for fluoride intake, the adjusted risks of fluorosis were not significant for amoxicillin use. No other antibiotics were significantly associated with fluorosis in the bivariate analyses. In multivariate analyses with logistic regressions, only fluoride intake was statistically significantly related to fluorosis.* ***Conclusion:*** *Fluoride exposure was the sole predictor of primary tooth fluorosis in a multivariate model. However, bivariate results suggest that amoxicillin could play a contributing role in the development of primary tooth fluorosis, especially for children exposed to lower levels of fluoride. An investigation of the relationship between amoxicillin intake and fluorosis of permanent teeth is warranted. [J Public Health Dent 2004;64(1):38-44]*

Key Words: dental defects, dental fluorosis, antibiotics, amoxicillin, infancy.

Dental fluorosis is a well-known developmental enamel defect due to excessive fluoride ingestion during enamel formation, generally from chronic, long-term exposure to elevated levels of fluoride. The prevalence of permanent tooth fluorosis has increased during the past few decades in many developed countries, in both fluoridated and nonfluoridated areas (1-3). Although much less has been reported regarding primary tooth fluorosis, it is likely that primary tooth fluorosis prevalence has increased or is increasing (4-6). Over the past 40+ years, the number of different sources of ingested fluoride has increased and includes intentional sources such as foods, beverages, and dietary supplements, and unintentional sources of fluoride such as ingestion from fluoride dentifrices, mouthrinses, and other topical fluoride products (7).

Ameloblasts are sensitive to insults in the environment of developing enamel. It is not certain if the reaction of the ameloblasts to excessive fluoride is specific or different from the reaction to other forms of insult (8). It is likely that many factors such as malnutrition and childhood infections can act individually or in combination to produce fluorosis-like defects (9,10). Although it is important and necessary to continue to investigate the various fluoride exposures, other factors that also could be linked to the increase in prevalence and severity of fluorosis or fluorosis-like enamel defects should be studied in the etiology of dental fluorosis. Therefore, caution is warranted in concluding that the increased prevalence of enamel fluorosis is due solely to the increased use of fluoride.

Antibiotics have been found to influence the development of teeth, with tetracyclines as a well-known example. Tetracyclines use during early childhood can result in clinically evident tooth discoloration. During the past several decades, many antibiotics, including amoxicillin, have been introduced and are commonly prescribed to treat childhood infections (11,12). However, little is known regarding the effects, if any, of these newer antibiotics on tooth development.

A significant shift in prescription patterns toward more expensive and broader spectrum antibiotics has been observed in pediatric patients (13). Among these changes, the most notable was a significant increase in the use of amoxicillin, which has been associated mainly with the treatment of otitis media (12-15). Concerns have been raised about whether amoxicillin use during enamel formation contributes to the increase in the prevalence and/or severity of fluorosis or directly results in fluorosis-like enamel defects (16,17). However, a recent investigation of 85 children in Missouri did not find a significant association, although amoxicillin use and demarcated opacities were positively related) (Simoes E, Perkins MD, Phillips P, Beltrán-Aguilar ED, Barker L, Espinoza L, et al. Development defects of enamel and early exposure to antibiotics in schoolchildren—Missouri, 2002, personal communication). An Iceland study found an association between repeated episodes of ear infections and hypoplastic and demarcated opacities, but not diffuse opacities (18).

Enamel mineralization is a complex process, and basically involves removal of enamel matrix and deposit of mineral crystals. There is significant interaction between matrix proteins and mineral deposition and growth.

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Any insult occurring during the continuous formative stages of enamel development could result in enamel defects. Since the investigation of possible association between amoxicillin use and enamel defects is only in a exploratory stage, the mechanism by which amoxicillin could possibly affect enamel mineralization is unclear. Amoxicillin could have a different mechanism of action on mineralization compared with tetracyclines or fluoride, which affect enamel mineralization by binding to hydroxyapatite. One possible mechanism for amoxicillin's effect could be a delay in the removal of matrix proteins.

The purpose of this paper is to report on the association between primary tooth fluorosis and longitudinal patterns of amoxicillin use during the first year of life in the cohort followed from birth in the "Iowa Fluoride Study."

Methods

Subjects were part of the Iowa Fluoride Study (IFS) cohort (20), which was recruited from eight Iowa hospital postpartum wards from March 1992 to February 1995 (14-15,19), using Institutional Review Board-approved informed consent procedures. This cohort has been followed prospectively since birth to investigate longitudinal fluoride exposures, biological and behavioral factors, and children's dental health. Demographic data at the time of recruitment included sex, race, family income, mother's and father's education level, and mother's and father's age, weeks of gestation, birth weight and height. Relevant to this report, questionnaires were sent to the mothers when the children reached the ages of 6 weeks, and 3, 6, 9, and 12 months concerning fluoride intakes from various sources, antibiotic use, children's illnesses, and breast-feeding patterns during the first year. Six hundred and ninety-eight children had dental examinations of the primary teeth for fluorosis and caries at about 5 years of life, at which time a health history was obtained including systemic developmental disorders.

Data collection on fluoride intake from water, foods and beverages, dietary fluoride supplements, and fluoride dentifrice has been described in detail previously (20). Regarding antibiotic use, parents were asked to report the occurrence of selected illnesses for which antibiotics were prescribed during the previous reporting period (14,15). A list of illnesses was provided, including "ear infections" (otitis media), "pneumonia/bronchitis/RSV," "strep throat/throat infection/pharyngitis," "bladder/kidney/urinary infections," "skin infections/rash/thrush," "colds and coughs/fever/sinusitis/influenza," "pink eye/eye infection," "other," and "don't know." The "other" option asked parents to provide explanations for selecting that choice. Also, parents were asked to identify specific antibiotics that were prescribed and given to the child by selecting from a list of antibiotic drugs commonly used: amoxicillin, penicillin, sulfa, erythromycin, cephalosporins, Pediazole®, Augmentin™, Nystatin®, and any other that was not on the list. Parents also reported whether antibiotic drugs were administered orally (swallowed by mouth) or topically (applied on skin or mouth), the number of episodes of illnesses for which antibiotics were used, and the numbers of days of combined antibiotic use during a reporting period selected from: 1–7 days, 8–14 days, 15–21 days, 21–28 days, and 29–60 days. The antibiotic information was reported only by the parents without validation by physician interview or chart review.

Four hundred and ninety subjects had complete data on antibiotic use during the first year of life, and 208 subjects had missing data for one or more reporting intervals because questionnaires were not returned or parents did not answer the questions on antibiotic use. No statistically significant differences were found between children with complete antibiotic data and those with incomplete antibiotic data with regard to demographic characteristics, fluorosis prevalence, and amoxicillin use. Therefore, 490 subjects with complete antibiotic data were used in analyses to avoid the problem of missing data. Using midpoints of the duration intervals, combined days of amoxicillin use were calculated. If amoxicillin and other systemic antibiotics were both used, the midpoints of each range were split evenly among different types of antibiotics.

As described previously (6), children were examined for primary tooth fluorosis at about 5 years old by two trained and calibrated examiners using a modified Tooth Surface Index of Fluorosis (TSIF) (21). A mouth mirror and exam light were used, but teeth were not dried. Fluorosis was differentiated from nonfluorosis opacities based on differences in shape, demarcation, color, and detection ability of the lesions through Russell's criteria (22). Fluorosis also was distinguished from enamel demineralization ("white spot" lesions) based on color, texture, demarcation, and relationship to the gingival margin (23). A case of fluorosis was specifically defined as having two or more primary second molars with fluorosis. Those with fluorosis on only one primary molar were excluded, and all other subjects were defined as controls. Lastly, inter-examiner reliability was assessed by duplicate examinations of approximately 10 percent of subjects with 91 percent agreement at the subject level (kappa=0.57).

Descriptive analyses were conducted for baseline demographic characteristics, distribution of primary tooth fluorosis, and patterns of amoxicillin use. Chi-square tests were used to assess the associations between fluorosis and amoxicillin use for each reporting interval and cumulatively to 6 months and to 12 months. Odds ratios and 95 percent confidence intervals were calculated. The estimated daily total fluoride intake for the first year was categorized into three levels: <.037 mg per kg bw per day, 0.037–0.074 mg per kg bw per day, and >0.074 mg per kg bw per day. These cut-points of 0.037 and 0.074 mg per kg separated the sample into three equal segments. Thus, the estimated daily fluoride intake of <0.037 mg per kg bw was considered as low fluoride intake, 0.037–0.074 mg per kg bw as moderate, and >0.074 mg per kg bw as high. The association between the three levels of estimated daily fluoride intake and fluorosis was assessed using chi-square tests. Three components of fluoride intake were examined individually for the association with fluorosis using chi-square tests. They were fluoride concentration in drinking water (three categories: <0.5 ppm, 0.5–1.2 ppm, >1.2ppm), use of fluoride supplements (yes/no), and use of fluoride toothpaste (yes/no). Fluoride concentration in public tap water, private well water, and bottled water was weighted according to individual usage volume of each type.

The associations between fluoride intake and amoxicillin use were assessed by Kruskal-Wallis tests. With three levels of fluoride intakes as categorized above, the effect of amoxicillin use on fluorosis was further assessed controlling for fluoride intake using the Mantel-Haenszel stratified method. Breslow-Day tests assessed the homogeneity of the odds ratios of amoxicillin use across three levels of daily fluoride intake. Cochran-Mantel-Haenszel tests were used to examine the significance of adjusted overall odds ratios for amoxicillin use after controlling for level of fluoride intake. Using simple logistic regression, use of other antibiotics (including cephalosporins, penicillins, sulfas, erythromycins, and Pediazole®), and other variables, including sex (female/male), family income at baseline (<$20,000,$ 20,000–$39,999, $40,000 or more), mother's age at birth of child (years), mother's educational level at baseline (up to high school, some college, college graduate or more), birth weight (<2.5 kg or ≥2.5 kg), illness during the first year (yes/no), developmental disorders (yes/no), gestational age (weeks) and breast-feeding (<6 months or ≥6 months) also were assessed for individual association with fluorosis. Variables with *P*-values <.25 in bivariate analyses were selected for multivariable logistic regression, and the main effect of individual variables and interactions between them were assessed.

Finally, amoxicillin use was categorized into mutually exclusive groups: never use during the first year (n=128), use only during birth to 6 weeks (n=4), use only during 6 weeks to 3 months (n=13), use only during 3–6 months (n=35), use only during 6–9 months (n=49), use only during 9–12 months (n=61), and use during multiple time periods (n=197). Chi-square tests were used to assess the associations between these mutually exclusive groups and primary tooth fluorosis. The significance level was set at α=0.05, with data analyzed using SAS for Windows™ Version 8 (SAS Institute Inc., Cary, NC).

Results

Table 1 summarizes selected characteristics of the 490 subjects. About half were female (51.4%) and 41.4 percent of children were first children. The vast majority of this cohort was normally developed and healthy. The mean gestational age was 39.5 weeks. Only 3.0 percent of children were born with low birth weight (<2.5 kg) and 2.7 percent were born with systemic developmental disorders such as mental retardation or hearing defects. Duration of breast-feeding of six months or more was reported by 31.6 percent, 20.9 percent reported 6–12 months, and 10.7 percent reported more than 12 months. Almost half of mothers and fathers were college graduates and 88.6 percent had family income of $20,000 or more at baseline.

Among the 490 subjects, 53 (10.8%) had fluorosis on two or more primary second molars and were considered as cases in the analyses (6). Three subjects had fluorosis on only one primary second molar and were excluded in the analyses, so 434 subjects who had no fluorosis on primary second molars served as the control group. The mean numbers of teeth and surfaces with fluorosis were 0.44 and 0.65, respectively, for the entire sample. Primary second molars were most commonly affected, accounting for 81.8 percent of all teeth affected. Among the second molars, buccal surfaces were most commonly affected, accounting for nearly 78.2 percent of surfaces affected. On the buccal surfaces of the second molars, gingival thirds were most frequently affected, accounting for 64.2 percent of all buccal surfaces with fluorosis. Almost all fluorosis (97.4%) was mild (TSIF score=1).

Amoxicillin use was common during the first year of life in this cohort. The prevalence of amoxicillin use increased with age, with 7.8 percent, 13.6 percent, 32.2 percent, 38.2 percent, and 41.3 percent at birth–6 weeks, 6 weeks–3 months, 3–6 months, 6–9 months, and 9–12 months, respectively. Cumulatively to 6 months, 41.9 percent reported amoxicillin use, while 73.7 percent reported amoxicillin use by age 12 months. Among those who used amoxicillin, the majority of subjects reported 1–20 days of amoxicillin use during each reporting interval. The estimated mean numbers of days of amoxicillin use were 12.9, 9.8, 11.1, 12.6, and 12.4 days during birth–6 weeks, 6 weeks–3 months, 3–6 months, 6–9 months, and 9–12 months, respectively. Cumulatively to 6 months, the estimated mean number of days of amoxicillin use was 13.8 days, with 29.4 cumulative days at age 12 months.

TABLE 1
Selected Characteristics of Sample (n=490)

Characteristic	
Child's sex	
Female	51.4%
Male	48.6%
First child (yes)	41.4%
Gestational age (weeks)	
Mean	39.5±1.91
Range	27.0–50.0
Birth weight (kg)	
<2.5	3.0%
≥2.5	97.0%
Mean	3.5±0.52
Range	1.1–5.2
Birth height (cm)	
Mean	51.5±2.72
Range	35.6–59.1
Breast-feeding	
<6 months	68.4%
≥6 months	31.6%
Systemic developmental disorders	
No	97.3%
Yes	2.7%
Mother's age (years)*	
Mean	29.8±5.10
Range	17.0–45.0
Father's age (years)*	
Mean	32.1±5.72
Range	18.0–60.0
Mother's education*	
Up to high school	18.2%
Some college	34.7%
College grad. or more	47.1%
Father's education*	
Up to high school	28.1%
Some college	28.4%
College grad. or more	43.3%
Family income	
<$20,000	11.4%
$20,000–$39,999	37.0%
$40,000 or more	51.6%
Average daily fluoride intake (mg/kg bw)	
<0.037	33.6%
0.037–0.074	33.4%
>0.074	33.0%

*Mother' age, father's age, mother's education level, father's education level, and family income were collected at time of recruitment.

Table 2 shows the bivariate associations between primary tooth fluorosis

TABLE 2
Prevalence of Primary Tooth Fluorosis* by Amoxicillin Use and Significance (n=487)

Age	No Amoxicillin	Any Amoxicillin	Odds Ratio	95% CI	P-value
Birth to 6 weeks	10.91% (49/449)	10.50% (4/38)	0.96	0.32, 2.82	.952
>6 weeks to 3 months	9.74% (41/421)	18.18% (12/66)	2.06	1.02, 4.16	.040†
>3 months to 6 months	8.79% (29/330)	15.29% (24/157)	1.87	1.05, 3.34	.031†
>6 months to 9 months	10.30% (31/301)	11.83% (22/186)	1.17	0.65, 2.08	.598
>9 months to 12 months	10.14% (29/286)	11.94% (24/201)	1.20	0.67, 2.13	.529
Cumulatively to 6 months	8.48% (24/283)	14.22% (29/204)	1.78	1.01, 3.17	.046
Cumulatively to 12 months	7.03% (9/128)	12.26% (44/359)	1.85	0.87, 3.89	.103

*Primary tooth fluorosis was defined as fluorosis on two or more primary second molars.
†Statistically significant at α=0.05, based on chi-square tests.

TABLE 3
Summary of Mantel-Haenszel Stratified Analyses for Association Between Amoxicillin Use and Primary Tooth Fluorosis after Controlling for Fluoride Intake

	Odds Ratios (95% CI) for Amoxicillin Users Relative to Nonusers Stratified by Fluoride Intake Levels (n=452)*			P-value of Breslow-Day Test for Homogeneity of Odds Ratios	Mantel-Haenszel Odds Ratio Adjusted for Daily F Intake (95% CI)	P-value of Cochran-Mantel-Haenszel Test for MH Odds Ratio
Age	<0.037 mg/kg bw per Day (n=152)	0.037–0.074 mg/kg bw per Day (n=151)	>0.074 mg/kg bw per Day (n=149)			
Birth to 6 weeks	NA†	NA†	1.21 (0.31, 4.62)			
>6 weeks to 3 months	1.89 (0.21, 17.30)	2.14 (0.53, 8.54)	1.37 (0.50, 3.83)	0.874	1.62 (0.75, 3.51)	0.219
>3 months to 6 months	1.59 (0.28, 9.03)	0.86 (0.25, 2.94)	2.35 (1.01, 5.45)	0.409	1.67 (0.89, 3.15)	0.107
>6 months to 9 months	4.37 (0.77, 24.59)	1.46 (0.47, 4.60)	0.78 (0.34, 1.80)	0.169	1.19 (0.64, 2.19)	0.582
>9 months to 12 months	1.35 (0.26, 6.93)	2.11 (0.67, 6.65)	0.83 (0.36, 1.92)	0.426	1.17 (0.63, 2.17)	0.612
Cumulatively to 6 months	1.92 (0.37, 9.86)	0.58 (0.17, 1.97)	2.14 (0.90, 5.12)	0.203	1.43 (0.77, 2.68)	0.260
Cumulatively to 12 months	1.76 (0.20, 15.54)	1.36 (0.36, 5.20)	1.98 (0.64, 6.16)	0.916	1.71 (0.77, 3.83)	0.187

*Three subjects with fluorosis on only one primary second molar and 35 subjects with missing values for daily fluoride intake were excluded from analysis.
†The odds ratio was not available because no subjects had fluorosis.

and amoxicillin use. Amoxicillin users generally had higher prevalence of fluorosis than nonamoxicillin users. For example, for 3–6 months, the odds ratio (OR) was 1.87, with 95 percent confidence interval (CI) 1.05–3.34. Amoxicillin use during 6 weeks–3 months (OR=2.06, P=.040) and 3–6 months (OR=1.87, P=.031) resulted in statistically significant increased risk for fluorosis on primary second molars. Cumulatively for the first year of life, the association was still evident (OR=1.85), but not significant (P=.103). The risk for fluorosis was also significantly related to the duration of amoxicillin use during 3–6 months, with P=.047.

A strong, significant association was found between estimated daily fluoride intake and fluorosis on primary second molars (P<.0001) during the first year of life, with P-values for individual components of fluoride intake from drinking water, dietary supplement, and dentifrice being .0001, .310, and .359, respectively. Children with higher levels of daily F intake generally had greater duration of amoxicillin use. This trend was generally consistent throughout the first year of life and Kruskal-Wallis tests showed a significant association for the first 6 months (P=.001). Using Mantel-Haenszel stratified analyses, the effect of amoxicillin use on primary tooth fluorosis was assessed after controlling for fluoride intake (Table 3). Daily fluoride intakes were cate-

gorized into three levels: low (<0.037 mg/kg bw per day), moderate (0.037–0.074 mg/kg bw per day), and high (>0.074 mg/kg bw per day). For low levels of daily fluoride intake, results suggest a consistent, increased risk for fluorosis with amoxicillin use, but not statistically significant. However, for moderate or high levels of daily fluoride intake, this elevated risk based on point estimates was not found. The Breslow-Day tests consistently showed homogeneity of the odds ratios for amoxicillin use across three levels of daily fluoride intake for each reporting time interval, indicating that odds ratios were consistent across fluoride intake levels throughout the first year. The overall Mantel-Haenszel odds ratios for amoxicillin use after adjustment for daily fluoride intake were 0.65, 1.62, 1.67, 1.19, 1.17, 1.43, and 1.71, respectively, for birth–6 weeks, 6 weeks–3 months, 3–6 months, 6–9 months, 9–12 months, cumulatively to 6 months and 12 months. Cochran-Mantel-Haenszel tests showed none of these time periods statistically significant.

Other antibiotics, including cephalosporins, penicillins, sulfas, erythromycins, and Pediazole®, were not found to be significantly associated with primary tooth fluorosis. Other factors collected in the Iowa Fluoride Study also were assessed for individual association with primary tooth fluorosis. Variables and *P*-values were sex (0.481), family income at baseline (0.959), mother's age at birth of child (0.270), mother's educational level at baseline (0.462), birth weight (0.260), illness during the first year (0.592), developmental disorders (0.743), body mass index at 12 months (0.792), gestational age (0.897), and breast-feeding (0.225).

Variables with individual *P*-values <.25 in bivariate analyses were selected for inclusion in a multivariable logistic regression model. These variables were amoxicillin use from 6 weeks–3 months (yes/no), amoxicillin use from 3–6 months (yes/no), mean annual daily fluoride intake (<0.037 mg/kg bw, 0.037–0.074 mg/kg bw, >0.074 mg/kg bw), and breast-feeding duration (<6 months or ≥6 months). All four predictive variables were categorical. For amoxicillin use, nonuser group was the reference group. For fluoride intake, the group of low daily fluoride intake (<.037 mg/kg bw) was the reference group. For breast-feeding, the group of ≥6 months breast-feeding was the reference group. Table 4 presents an assessment of the full model with these four variables. Only estimated daily fluoride intake was found to be statistically significant (*P*=.002 for the joint effect, 2 degrees of freedom) when other variables were included in the model. The best single-variable model based on statistical significance is the model with mean daily fluoride intake as the only significant factor (*P*<.0001). However, the best two-variable model includes the mean daily fluoride intake (*P*=.0002) and amoxicillin use at 3–6 months (*P*=.108), with the interaction effect not significant (*P*=.675).

TABLE 4
Assessment of Full Model with Four Predictor Variables (*N*=452)*

	Risk Group	Odds Ratio (95% CI)	Wald Chi-square	*P*-value
Amoxicillin use from 6 weeks to 3 months	Yes	1.43 (0.64, 3.18)	0.77	.379
Amoxicillin use from 3–6 months	Yes	1.58 (0.83, 2.99)	1.93	.164
Breast-feeding during first year	<6 months	1.26 (0.60, 2.71)	0.38	.540
Average daily fluoride intake (mg/kg bw)	0.037–0.074	2.26 (0.82, 6.23)	2.49	.115
	>0.074	5.52 (2.07, 14.73)	11.66	.0006

*Three subjects with fluorosis on only one primary second molar and 35 subjects missing data on daily fluoride intake were excluded from analysis.
Note: No significant two-way interactions were found.

Amoxicillin use during multiple time periods was statistically significantly associated with primary tooth fluorosis (bivariate chi-square *P*=.035). However, after controlling for fluoride intake and breast-feeding status, it was no longer significant (*P*=.097). Chi-square tests for the associations between sole use of amoxicillin during specific time periods and primary tooth fluorosis were statistically unstable due to limited sample size and case numbers.

Discussion

The primary purpose of this analysis was to explore possible relationships between amoxicillin use and enamel defects. Findings from this study show an increased, bivariate risk for fluorosis with amoxicillin use during the first year of life. For individual time intervals, amoxicillin use from 6 weeks–3 months and 3–6 months significantly increased the risk of fluorosis on primary second molars, suggesting that amoxicillin use might interfere with enamel formation of primary teeth largely during the first 6 months.

When controlling for fluoride intake, however, none of the adjusted risks were statistically significant, although amoxicillin use still generally was positively associated with fluorosis. It is interesting to note that, when fluoride intake was low (<0.037 mg/kg bw per day), a consistent, elevated, but nonsignificant risk of fluorosis was found. However, this consistency was not true for higher levels of daily fluoride intake in amoxicillin users. These results could indicate that the effects of amoxicillin use on enamel development were more detectable when fluoride intake was low. However, the adjusted risks from amoxicillin use were not significant even at a low level of daily fluoride intake. This nonsignificance could be partly due to the small sample size of fluorosis cases, which reduced the statistical power to detect true differences.

Ingested fluoride is the only documented etiologic factor for enamel fluorosis (24). This study confirmed that fluoride is the main etiologic factor for fluorosis, since it is the only significant factor when controlling for other risk factors in the logistic regression analyses. When fluoride intake was included in the multivariable re-

gression model, no other risk factors were significant, including amoxicillin use, due to the overwhelming effect of fluoride intake. There was no significant interaction between fluoride and amoxicillin use, so the effects of fluoride and amoxicillin on enamel formation are largely independent of each other. While the approach of categorization of amoxicillin use currently employed in the multiple logistic model used a reference group that included all subjects who did not take amoxicillin during that specific time period, another approach would be to use the mutually exclusive exposure categories, such as never used, used only from 6 weeks to 3 months, etc. This approach would remove the possible cumulative effect of amoxicillin use. However, because few children had only one period of amoxicillin use (4 used amoxicillin for only from birth to 6 weeks, 13 for only from 6 weeks to 3 months, and 35 for only from 3 to 6 months), it is problematic due to limited power to assess each time period of use with mutually exclusive groups. We did conduct such analyses and found generally similar patterns of fluorosis prevalence in these mutually exclusive groups (OR=3.97, P=.048 for 6 weeks to 3 months; OR=1.20, P=.79 for 3–6 months); however, since the power to detect differences was very limited, we did not pursue multivariable analyses in this manner.

Timing is important in the assessment of risk factors for developmental disorders, such as enamel defects, because the defects occur only when there are sufficient insults during certain time periods of development. It is generally accepted that the early maturation stage is the most critical stage of enamel formation related to dental fluorosis (25,26). When assessing the effects of amoxicillin use on enamel development, it is important to note the pattern of amoxicillin use. Amoxicillin use is generally episodic, which is quite different from the pattern of fluoride intake, which can be considered continuous, but somewhat variable, after birth due to various sources. Therefore, it should be recognized that the chance for amoxicillin to interfere with developing enamel, if any, probably is less than that for fluoride ion due to the nature of the pattern of amoxicillin use. Thus, because of fluoride's much larger effect, it is not surprising that amoxicillin use was only associated with fluorosis in bivariate and not in multivariable analysis. Nevertheless, amoxicillin use was consistently associated with increased risk for fluorosis and, given a larger sample size, could conceivably be a significant factor for primary tooth fluorosis. The posttest power analysis indicated that, after adjustment for covariates in the multiple logistic regression model, the estimated power associated with the observed effect size for amoxicillin use from 1.5–3 months was 14 percent, and it was 29 percent for amoxicillin use from 3–6 months. These power levels are quite low compared to a generally desired power of 80 percent.

While this study utilized a fairly large sample, with the low primary fluorosis prevalence, a larger sample would be necessary to allow for more power to detect significant relationships. In addition, the study had others limitations. The cohort was a convenience sample. Children were from families with relatively high socioeconomic status. This makes the generalizability of the study results to other populations difficult. In addition, there is the possibility of measurement error because there could be faulty recall of antibiotic use and fluoride intake on which parents were asked to report during the previous 3–4 months at each questionnaire time period. Both fluoride intake data and antibiotic data were obtained through self-administered questionnaires by parents without direct verification. Meanwhile, antibiotic use information was not verified by review of local pharmacies' or patients' physicians' records. The numbers of days of amoxicillin use were estimated by using midpoints for each range listed in the questionnaires. When amoxicillin use was combined with other antibiotics during a specific reporting time period, parents reported the total days of antibiotic use and no specific days were reported for amoxicillin use separately. We divided the total days evenly among all antibiotics used, and obviously this was somewhat arbitrary and did not represent the real situation when children had taken them.

Despite some limitations, the study was unique and allowed for more meaningful analyses of the amoxicillin-fluorosis relationship because of its longitudinal design, the cohort followed since birth. Both fluoride intake data and antibiotic data were collected periodically at 6-week or 3-month intervals. These period-specific data are unique compared to many previous studies, most of which were retrospective and cross-sectional. There are very few longitudinal studies on either fluoride intake or antibiotic use. The period-specific data on amoxicillin use allow assessment of the importance of each individual time period.

Compared with the primary tooth fluorosis, permanent tooth fluorosis generally is more prevalent and more severe. Also, the duration of enamel development of permanent dentition is much longer than for the primary dentition. For example, for the esthetically important anterior teeth, the risk period could be from birth to six years of life, and is primarily the first 36–48 months (28,29). Thus, the possible effects of amoxicillin use could be more easily detected.

In conclusion, fluoride intake is confirmed to be most strongly predictive of primary tooth fluorosis. However, this study also suggests that amoxicillin use might be a contributing factor. The data do not implicate any other class of antibiotic. Studies on the permanent dentition in this cohort are warranted.

Reference

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