Fluoride supplements, dental caries and fluorosis

A systematic review

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Editor's note: This systematic review of the scientific literature was commissioned by the American Dental Association Council on Scientific Affairs to supply the evidence basis for the development of clinical recommendations on the use of fluoride supplements in children aged zero to 16 years. The opinions expressed in the article are solely those of the authors, not the ADA or The Journal of the American Dental Association. The Council is in the process of developing clinical recommendations on this topic. They will be based on the best available scientific evidence, including but not limited to this article. Publication of the clinical recommendations is anticipated in the summer of 2009.

The American Dental Association (ADA) endorses the daily use of fluoride supplements (as drops, tablets or lozenges) by children 16 years old or younger.[1] While the ADA and the American Academy of Pediatric Dentistry revised the supplementation schedule in 1994 in response to concerns about the increase in the prevalence of fluorosis,[2] the ADA's recommendations are inconsistent with those adopted by other dental associations or groups in other countries.[3-6] The Canadian Dental Association, for example, recommends supplements only for children who have had high caries experience and whose total intake of fluoride is below 0.05 to 0.07 milligrams of fluoride per kilogram of body weight.[4] This requirement limits the capability of health care practitioners to prescribe fluoride supplements because of the need to estimate the total intake from all sources, which is an arduous task. A group of European experts recommended in 1991 that "fluoride supplements have no application as a public health measure" and that "a dose of 0.5 mg/day fluoride should be prescribed for at-risk individuals from the age of 3 years."[5] In 2006, the Australian Research Centre for Population Oral Health's workshop

ABSTRACT

JADA CE CONTINUING EDUCATION ARTICLE 1

Background. In this review, the authors examine evidence regarding the effectiveness of fluoride supplements in preventing caries and their association with dental fluorosis.

Methods. Using tested search filters, the authors searched MEDLINE, the Cochrane Central Register of Controlled Trials, OVID Evidence-based Reviews and EMBASE. The authors agreed on the inclusion of 20 reports from 12 trials that met defined criteria. They also included five studies published since 1997 regarding the association between dental fluorosis and supplements.

Results. Eleven of the reports evaluated dosage schedules similar to that recommended by the American Dental Association. One potentially highly biased study of primary teeth of children during the first three years of life reported a 47.2 percent reduction in dental caries experience. Investigators in one trial involving 3- to 6-year-old children found a 43.0 percent difference, and another trial of children in this age group did not find a significant benefit. Researchers in several studies involving older children detected a significant reduction in caries increments in permanent teeth with the use of fluoride supplements. Fifteen of the studies had withdrawal rates of 30 percent or higher. All of the five included studies that evaluated the association between use of fluoride supplements and dental fluorosis found that use of the supplements increased the risk of mild-to-moderate fluorosis.

Conclusions. There is weak and inconsistent evidence that the use of fluoride supplements prevents dental caries in primary teeth. There is evidence that such supplements prevent caries in permanent teeth. Mild-to-moderate dental fluorosis is a significant side effect.

Clinical Implications. The current recommendations for use of fluoride supplements during the first six years of life should be re-examined.

Key Words. Fluoride; supplements; fluorosis; systematic review.
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on the use of fluorides in caries prevention concluded that "fluoride supplements in the form of drops or tablets to be chewed and/or swallowed should not be used."[6]

These differences and some additional concerns led the ADA's Council on Scientific Affairs (CSA) to commission this systematic review of the effectiveness and safety of fluoride supplements. The CSA approved the following questions for this review:

- Does the use of fluoride supplements in children aged zero to 16 years prevent dental caries?
- Does the use of fluoride supplements in children aged zero to 16 years increase the risk of dental fluorosis in the absence of other identifiable causes?

These two questions were debated at length during two conferences organized in the 1990s to review the use of fluoride in caries prevention.[7-9] The goal of this systematic review is to present and critique the evidence as well as to update the information presented at previous conferences.

Does the use of fluoride supplements in children aged zero to 16 years prevent dental caries?

METHODS AND MATERIALS

Search strategy: effectiveness of fluoride supplements. We searched four databases for relevant studies about the effectiveness of fluoride supplements: MEDLINE (January 1966-June 2006), the Cochrane Central Register of Controlled Trials (January 1941-second quarter 2006), OVID All EBM Reviews (January 1991-June 2006), and EMBASE (1974-2006). We conducted the searches using the OVID search engine and a structured search filter that was developed on the basis of the filters used by the National Institutes of Health Consensus Development Conference on Diagnosis and Management of Dental Caries Throughout Life[10] and the Cochrane Collaboration Oral Health Group's systematic review of topical fluorides.[11] The filter used in this review captured all key studies that the review team identified before beginning the search. The search filter is available from the authors upon request.

The search of the databases yielded 988 citations. We imported the titles and abstracts to ENDNOTE (Thomson-ISI Research Software, Philadelphia). Of the 988 articles, we eliminated from the database 77 that were duplicates. Of the remaining 911 reports, 826 did not meet the inclusion criteria based upon our review of the titles and abstracts. Our review of the full reports of the remaining 85 articles identified 20 reports of clinical trials (12 unique clinical trials), nine cohort studies, 22 cross-sectional studies and eight retrospective studies. Of the remaining 26 articles, seven were reviews; four were of systemic fluorides other than supplements; five did not have a control group; one included only elderly adults; two were of the fluoride distribution in enamel, dentin or saliva; two focused on the caries experience of the children but not the use of supplements; three were written in languages other than English; and two involved dental fluorosis and use of supplements but did not include data regarding dental caries. (We included one of the two studies in the fluorosis-supplement review but not the other, because it did not measure the exposure to fluoride during the first six years of life.) For the first question, we focused the review on the analysis of findings from clinical or community-based trials because these studies were more appropriate than those of other designs.

We reviewed the articles cited in the 20 reports of clinical trials (12 separate trials in total) to locate additional studies that the search filter did not identify. We reviewed the proceedings of workshops on the use of fluorides in caries prevention that were held in 1990[7] and 1994,[2] as well as papers cited in a previous review published in 1994.[12] These additional searches revealed no additional clinical trials that met the inclusion criteria used in this review.

With the aid of a research assistant, we conducted the review of titles and abstracts. When we identified differences among the reviewers during selection of studies or extraction of data, we resolved them by consensus, using the following inclusion and exclusion criteria.

ABBREVIATION KEY. ADA: American Dental Association. **APF:** Acidulated phosphate fluoride. **CSA:** Council on Scientific Affairs. **defs:** Decayed, extracted because of caries and filled surfaces of primary teeth. **deft:** Decayed, extracted because of caries, filled primary teeth. **dfs:** Decayed and filled surfaces of primary teeth. **DFS:** Decayed and filled surfaces of permanent teeth. **dmfs:** Decayed, missing and filled surfaces of primary teeth. **DMFS:** Decayed, missing and filled surfaces of permanent teeth. **F:** Fluoride. **NaF:** Sodium fluoride.

Inclusion criteria. We used the following criteria to select relevant studies for the first question:
- The study design is longitudinal and includes experimental (intervention) and control (comparison) groups.
- The intervention focused only on fluoride supplements (tablet, lozenges or drops) with or without toothbrushing at home with fluoridated dentifrice. The "control" group was not exposed to any source of systemic fluoride.
- Reports of the included studies are available in English.

Exclusion criteria. We excluded studies if they
- evaluated other systemic fluoride sources (water, salt or milk);
- used nonrandomized designs (case-control, cohort, reviews, cross-sectional).

Search strategy: dental fluorosis. We conducted the search for evidence to answer the second question using the same search terms used in a previous systematic review.[13] That previous review included cross-sectional, case-control or cohort studies that presented sufficient data for a meta-analysis of the risk of developing fluorosis in children who ingested fluoride supplements. The included studies evaluated fluorosis in children who consumed fluoride in water or from other sources during the first six years of life. For this update, we identified seven studies.[14-20] Of those, we excluded a well-designed longitudinal study conducted in Iowa[19] because the independent contribution of fluoride supplements to the risk of fluorosis could not be ascertained. We excluded another study by Morgan and colleagues[20] because relevant data regarding use of fluoride supplements were not reported.

The included studies evaluated fluorosis in children who consumed fluoride in water or from other sources during the first six years of life.

Quality assessment. As unmasked reviewers, we independently conducted the quality assessment of the included studies relevant to the first question, following the methods reported in the Cochrane Handbook of Systematic Reviews (Section 6.7).[21] Additionally, we evaluated the training and reliability of examiners and reasons for participants' withdrawals. We rated studies that met all the criteria as having low potential for bias. We rated studies that reported their randomization scheme and had withdrawal rates of 30 percent or higher as having moderate potential for bias, and studies that did not meet these criteria as having high potential for bias.

Synthesis of findings. We present only qualitative analyses of the evidence in this review because of the heterogeneity of subjects, outcomes and duration of follow-up. We have reported the means, standard deviations, risk measures and significance levels when the information was available in the original reports.

RESULTS

Fluoride supplements and dental caries. Tables 1 and 2 (page 1462) describe the characteristics of the included 20 reports of the trials.[22-41] Eleven reports of seven trials provided results of tests of dosage of fluoride supplements in children with age ranges similar to those recommended by the ADA schedule (Table 1). The findings from these studies are as follows.

Children aged 6 months to 3 years. One report provided information on the efficacy of dosage schedules similar to that recommended by the ADA.[40] In that trial, the sample included older children, and the findings could not be separated by age group. This study was conducted in Chengdu, Sichuan Province, China (a community with a water supply containing < 0.3 parts per million fluoride). Only about 17 percent of the 1,143 children aged 2 years in the schools in which fluoride supplements were provided participated in the program for 180 consecutive days. The 176 children who remained in the program formed the fluoride supplement group, and the investigators followed their cases for three years. The investigators selected a convenience sample of 148 children from the schools that did not participate in the fluoride supplementation project to serve as the control group. After three years, the 128 children who used the fluoride supplements for three years had a 47.2 percent lower mean number of decayed, missing and filled primary tooth surfaces (dmfs) compared with the children in the control group.

Children aged 3 to 6 years. A trial reported by Petersson and colleagues[37] evaluated the efficacy of twice-daily chewing of fluoride tablets (0.25 mg/day) for two years by children aged 3 years. The children who used fluoride supplements did not have significantly different mean decayed and filled primary tooth surface (dfs) increments when

TABLE 1

Studies that have evaluated fluoride (F) dosage schedules similar to that recommended by the American Dental Association (ADA).

CHILD'S AGE	ADA-RECOMMENDED DOSAGE	STUDY	DOSAGE		DURATION (YEARS)	CONCLUSIONS
			Experimental	Control		
6 Months to < 3 Years	0.25 milligram per day	Hu and colleagues, 1998[40]	0.25 mg/day for children aged 2 to < 3 years and 0.5 mg/day after the age of 3 years	No F supplements	3	Mean dmfs* increment in 2-year-old children who received F supplements was 47.2% lower in the experimental group ($P < .05$)
3 to < 6 Years	0.50 mg/day	Petersson and colleagues, 1985[37]	0.25 mg per day twice per day and a placebo dentifrice	Twice-per-day brushing with equal amounts of NaF† dentifrice containing 0.025% F	2	No significant difference was found in mean dfs‡ increment between the children who used F supplements for two years and those who did not
		Mann and colleagues, 1989[38]	4- to 5-year-olds and 6.5- to 7.5-year-olds received between 0.5 and 0.75 mg per day	No supplements given; level of F in water 0.1 to 0.3 parts per million	3	After three years, the mean deft§ increment was 43.0% lower in the experimental group ($P < .05$); no statistically significant difference was found in permanent first molars
6 to 16 Years	1.0 mg/day	DePaola and Lax, 1968[25]	Children received once daily a tablet containing 2.2 mg NaF and hexamic acid	Placebo tablet	2	Mean DFS¶ score was 20% to 23% lower in children who used tablets ($P < .05$)
		Allmark and colleagues, 1982[36]	One 2.2-mg NaF tablet per day	No tablet	6	Mean DFS score was 61% lower in experimental group ($P < .001$)
		Driscoll and colleagues, 1974[29]	1 mg APF# tablet chewed once per day	No F supplements	2.5	Reduction in DMFS** score was 6.2% ($P \approx 1.00$) in early-erupting teeth (present at baseline); for teeth erupting during study (late-erupting), reduction was 36.5%
		Driscoll and colleagues, 1977[31]			4.7	Reduction in DMFS score was 15.4% ($P < .001$) in early-erupting teeth; for teeth erupting during study, reduction was 41.9% ($P < .001$)
		Driscoll and colleagues, 1978[32]			6	Reduction in DMFS score was 22.1% ($P = .02$) in early-erupting teeth; for teeth erupting during study, reduction was 44.1% ($P < .01$)
		Driscoll and colleagues, 1979[34]			7.5	Reduction in DMFS score was 24.0% ($P = .03$) in early-erupting teeth; for teeth erupting during study, reduction was 45.9% ($P < .01$)
		Driscoll and colleagues, 1981[35]			4 years after termination	Reduction in DMFS score was 15.0% ($P = .39$) in early-erupting teeth; for teeth erupting during study, reduction was 38.6% ($P = .01$)
		Stephen and Campbell, 1978[33]	One 1-mg fluoride tablet per day	Placebo tablet	3	Reduction in DMFS increment was 70.5% ($P < .001$)

* dmfs: Decayed, missing or filled surfaces of primary teeth.
† NaF: Sodium fluoride.
‡ dfs: Decayed and filled surfaces of primary teeth.
§ deft: Decayed, extracted, filled primary teeth.
¶ DFS: Decayed and filled surfaces of permanent teeth.
\# APF: Acidulated phosphate fluoride.
** DMFS: Decayed, missing or filled surfaces of permanent teeth.

compared with the children in the control group.

The children enrolled in the retrospective study by Mann and colleagues[38] were between the ages of 4 and 5 years or 6.5 and 7.5 years at the time of the baseline examination. The children had received drops containing 0.25 mg fluoride once a day when they were aged 6 months to 3 years; 0.5 mg fluoride drops once per day between the ages of 3 and 5 years, and 0.75 mg fluoride drops once per day between the ages of 5 and 8 years. After 3 years of age, the children in the test group exhibited a 43 percent reduction in the mean decayed, extracted owing to caries and filled primary teeth (deft) increment compared with that in children in the control group ($P < .05$). This highly biased study did not find statistically significant caries reduction in permanent teeth.

Children older than 6 years. We included eight reports of four trials that evaluated the effectiveness of fluoride supplements in school-aged children according to the ADA recommendations. DePaola and Lax[25] evaluated the effectiveness of fluoride tablets used daily during the school year versus placebo tablets. The children chewed and ingested the tablets. This study was the first to provide data regarding the highly significant reduction in dental caries experience (mean decayed and filled surfaces [DFS] increment) in permanent teeth that erupted during the study. These teeth experienced a 53 percent lower mean DFS increment when compared with similar teeth in the control group ($P = .01$). Overall, the fluoride tablet program reduced the caries increment by 20 to 23 percent in two years ($P < .05$). Allmark and colleagues[36] reported a 61 percent reduction in mean DFS scores in children in the United Kingdom who ingested one 2.2-mg sodium fluoride tablet per school day for six years compared with children who did not use daily supplements ($P < .001$).

We included eight reports of four trials that evaluated the effectiveness of fluoride supplements in school-aged children.

Findings from a long-term trial in the United States in which the same children were examined at intervals 2.5, 4.7, 6.0 and 7.5 years after the start of a fluoride tablet program showed significant reductions at each follow-up period.[29,31,32,34] Chewing a fluoride tablet during school days significantly reduced caries incidence and severity. The effectiveness of the fluoride tablets increased with time and ranged from 6.2 percent after 2.5 years to 24.0 percent ($P = .03$) after 7.5 years of use in early-erupting permanent teeth. In teeth erupting during the study, the reduction ranged from 36.5 percent after 2.5 years to 45.9 percent ($P < .01$) after 7.5 years. Driscoll and colleagues[35] also found a 15.0 percent caries reduction ($P = .39$) in early-erupting permanent teeth and a 38.6 percent reduction in late-erupting permanent teeth ($P = .01$) four years after discontinuation of the program.

In Scotland, Stephen and Campbell[33] reported a significant reduction of 70.5 percent ($P < .001$) in mean decayed, missing and filled surface (DMFS) scores of first permanent molars in children who chewed and swallowed a fluoride tablet once a day during school days between the ages of 5.5 to 5.6 years and 8.5 to 8.7 years.

Additional findings. One of the first studies evaluating fluoride supplements with added vitamins was conducted in Indiana. The investigators found that children who started supplementation between birth and 3 years, following a regimen that provided higher dosage than the 1994 ADA recommendations, had a significantly lower mean number of decayed, extracted because of caries and filled (defs) surfaces of primary teeth than did children who received only vitamin supplements ($P < .001$) (Table 2).[23] This finding was confirmed by findings of another study that also was conducted in Indiana.[28] Fluoride tablets significantly reduced caries in permanent teeth after daily use for four to 5.5 years.[24,26]

The study by Leverett and colleagues[39] evaluated the use of fluoride tablets by expectant mothers starting from the fourth month of pregnancy until delivery (Table 2). After birth, the children received fluoride drops daily until they reached 3 years of age. Children in the comparison group, whose mothers did not receive fluoride supplements during pregnancy, also received fluoride drops after birth. Hence, the design allows only for comparison of prenatal fluoride use in an environment in which fluoride supplements are used starting after birth. The study concluded that prenatal fluoride supplements had no benefits.

Findings from a 1971 study (potentially highly biased, according to the criteria in Table 3) conducted in Stockholm, Sweden, revealed a reduc-

TABLE 2

Studies that have evaluated other fluoride (F) supplementation recommendations.

CHILD'S AGE AT START	STUDY	DOSAGE		DURATION (YEARS)	CONCLUSIONS
		Experimental	Control		
Prenatal	Leverett and colleagues 1997[39]	One 2.2-milligram NaF* (1 mg active F), one tablet to be taken daily from fourth month of pregnancy; after birth, F drops from birth to 2 years of age ; one 0.5-milligram tablet daily for children aged 2 to 3 years	Placebo drops and tablets	5.5 (6 months prenatal and 5 years after birth)	No statistically significant difference in caries experience between two groups (risk ratio = 0.90 [95% CI† 0.41-1.97]); prevalence of "caries-free" children 91% and 92% in control and experimental groups, respectively
Birth to 5.5 Years	Hennon and colleagues, 1966[23]	From birth to 2 years of age: NaF drops (0.5 mg) with vitamins A, C and D; 2 years and older: chewable tablets (1 mg NaF) with vitamins	Nonfluoridated vitamin supplements with same dosage	3	Reduction in defs‡ scores 69.5% lower in experimental group ($P < .001$); mean DMFS§ scores 42.6% lower in experimental group ($P > .05$ and $< .1$)
	Hennon and colleagues, 1967[24]			4	Reduction in defs scores 71.3% lower in experimental group ($P < .001$); mean DMFS 45.8% lower in experimental group ($P < .05$)
	Hennon and colleagues, 1970[26]			5.5	56.3% reduction in defs scores ($P < .001$); mean DMFS score 64.4% lower in experimental group ($P < .001$)
2 to 3 Weeks	Hamberg, 1971[27]	Vitamins plus 0.5-mg F drops	Vitamin only	6	No statistical tests or measures of variation reported; caries reduction in F group compared with control at age 3 years = 57%, 4 years = 54%, 5 years = 50% and 6 years = 49%
1 to 14 Months	Hennon and colleagues, 1977[30]	Group A: 0.5-mg NaF drops with vitamins up to 3 years of age; 1-mg F chewable tablets with vitamins after 3 years of age Group C: vitamin-fluoride combination (0.5 mg F) throughout study	Group B: vitamin tablets only	7	Difference in defs scores between Group A and C versus Group B significant ($P < .05$); reduction: Group A versus Group B = 21.6%, Group C versus Group B = 42.4%; no difference in fluorosis levels between groups
18-39 Months	Hennon and colleagues, 1972[28]	Group 2: vitamin tablet with 1 mg F Group 3: 1-mg F tablet	Group 1 (control): vitamin tablet (multivitamin with no fluoride)	2	Reduction between Groups 2 and 3 versus Group 1 was significant ($P < .001$); percent reductions: Group 1 versus Group 2 = 65.5%, Group 1 versus Group 3 = 62.6%
4.5-5 Years	Stephen and colleagues, 1990[13]	Group A: 1-mg F tablets taken daily at school, plus rinsing with 1,000 parts per million F at school every two weeks Group B: 1-mg F tablets plus placebo rinse	Group C: placebo tablets plus F rinse of 1,000 ppm F every two weeks	6	Reduction in DMFS scores significant between Groups B and C only ($P < .01$); reductions: Group B versus Group A = 36.2%, Group B versus Group C = 53.8%, Group A versus Group C = 27.6%
12 years (High Caries Experience)	Kallestal, 2005[41]	Group B: F lozenges (0.25 mg three times per day up to age 16 years and then 0.25 mg four to six times daily), chewed and ingested Group C: F varnish (applied three times per week every six months) Group D: Individual program (oral hygiene instructions, examinations and F varnish every three months)	Group A: Information on toothbrushing and advice to keep paste in mouth rather than rinse it away	5	No statistically significant differences between groups

* NaF: Sodium fluoride.
† CI: Confidence interval.
‡ defs: Decayed, extracted because of caries and filled surfaces of primary teeth.
§ DMFS: Decayed, missing or filled surfaces of permanent teeth.

tion in dental caries among children who received vitamin drops containing 0.5 mg fluoride starting at the age of 2 to 3 weeks until the age of 6 years[27] (Table 2). In 2005, investigators in another study involving 12-year-old Swedish children with high caries levels[41] found in a five-year period that the children who chewed and ingested fluoride lozenges did not have significantly different caries experience from that of children who received topical applications of fluoride varnish, or from that of children who received oral health education, or from that of children who participated in individualized oral hygiene programs.

Researchers reported in 1977 that fluoride supplementation using either 0.5-mg sodium fluoride drops until the age of 3 years followed by 1.0-mg fluoride chewable or vitamin-fluoride tablets (0.5 mg fluoride) throughout the seven years of the study[30] was effective in reducing caries in primary teeth. Researchers in a 1990 Scottish study reported that students who chewed and swallowed 1.0-mg fluoride tablets experienced reductions in caries ranging between 27.6 and 53.8 percent.[22]

Children with fluorosis had lower odds of having caries in the primary and permanent dentitions than did children who did not have fluorosis.

Quality of the included studies of the effectiveness of fluoride supplements. Seven of the 12 trials (15 reports) suffered from high rates of participant withdrawal[23,24,26-32,34-36,38,40-41] (Table 3). We rated five trials[22,25,33,37,39] as being moderately biased. The large proportions of children who withdrew from using the fluoride supplements in the included studies increased the potential for bias.

Fluoride supplements and fluorosis. On the basis of a systematic review of studies evaluating the association between the use of fluoride supplements and dental fluorosis, Ismail and Bendekar[13] reported in 1999 that the odds ratio of dental fluorosis in nonfluoridated communities was estimated to be about 2.5 among children who used fluoride supplements during the first six years of life.

In this review, we have used the same search strategy to update these findings. We identified seven additional studies, of which we included five. The additional studies[14-18] (Table 4, page 1466) confirmed the positive association between the use of fluoride supplements and dental fluorosis. (Fluorosis was measured by means of several indexes.[42-44]) The odds ratio of dental fluorosis increased by 84 percent (95 percent confidence interval [CI] of the odds ratio = 1.4-2.5) for each year of use of fluoride supplements between the ages of younger than 6 months and 7 years.[14] The study by Hiller and colleagues[15] found that use of fluoride supplements during the first two years of life increased the prevalence of fluorosis compared with children who did not use supplements. Pendrys and Katz[17] reported that the odds ratio of fluorosis was 10.3 (95 percent CI = 1.9-61.6) in children who used fluoride supplements during the first two years of life. Bottenberg and colleagues[18] found that the use of fluoride supplements and fluoridated toothpaste was associated with a slight increase in the risk of developing fluorosis. Children with fluorosis had lower odds of having caries in the primary and permanent dentitions than did children who did not have fluorosis ($P < .01$).[18]

DISCUSSION

We conducted this review to assess whether the use of fluoride supplements prevented dental caries and increased the risk of developing dental fluorosis.

Fluoride supplementation and dental caries. While we found that the quality of the research conducted to evaluate the association between the use of fluoride supplements and dental caries was low, we noted sufficient evidence to raise questions that the dental community should address. The evidence supports the effectiveness of fluoride tablets in preventing caries when used in school-aged children (primarily providing a topical effect).

During the first three years of life, however, there is only limited evidence regarding the effectiveness of fluoride supplements in preventing caries; we included only one such study in our review.[40] The investigators in that study used the recommended fluoride supplementation in subjects from younger than 6 months to younger than 3 years, and the findings showed significant reductions in caries. However, the study lost a high number of participants to withdrawal and therefore is potentially highly biased. Findings from the study by Leverett and colleagues,[39] in which expectant mothers used fluoride supplements from the fourth month of pregnancy until delivery and their children used the supplements until reaching the age of 3 years, showed no caries-preventive benefit. The researchers who

TABLE 3

Quality assessment of the included studies.

STUDY	MASKING (YES, NO)		RANDOMIZATION	ASSESSOR TRAINING	INTRA-EXAMINER AND INTER-EXAMINER RELIABILITY	WITHDRAWAL (%)*	DEGREE OF BIAS
	Examiner	Subject					
Hennon and Colleagues, 1966,[23] 1967,[24] 1970,[26] 1972,[28] 1977[30]	Yes	Yes	Random allocation to the two groups; groups were balanced in terms of age and sex; randomization procedure designed to maintain equal numbers of children in each group	One trained examiner	Not reported	61 to 81	High
Depaola and Lax, 1968[25]	Yes	Yes	Children were assigned randomly into two groups	Not reported	Not reported	19	Moderate
Hamberg, 1971[27]	Yes	Yes	Not reported	Not reported	Not reported	Not reported	High
Driscoll and Colleagues, 1974,[29] 1977,[31] 1978,[32] 1979,[34] 1981[35]	Yes	Yes	After baseline examinations, records of individuals placed into blocks according to race, sex and number of erupted permanent teeth; within each block, investigators randomly assigned individuals to one of three study groups	Two dental examiners were thoroughly familiar with classification system and were standardized in their interpretation of examination criteria	Not reported	38 to 71	High
Stephen and Campbell, 1978[33]	Yes	Yes	At baseline, investigators stratified participants by age, parental socioeconomic status and primary-tooth caries (canines and molars) experience	Not reported	One examiner did not have significantly different caries scores between first and replicate examinations ($P > .9$)	12	Moderate
Allmark and Colleagues, 1982[36]	Yes	No	Investigators equally divided schools representing areas with different social classes in London into two groups; schools in experimental and control groups were matched in size, socioeconomic status and children's age	One dental officer carried out all examinations during study period	Differences in classification were 1.2% between two examinations	67	High

* Withdrawal: Percentage of subjects who left the study.

conducted this clinical trial, which was performed in the 1990s, concluded that fluoride supplements were of limited additional benefit in an environment in which caries incidence is low and fluoridated dentifrices are used regularly at home.

Regarding children aged 3 years to younger than 6 years, there is inconsistent and weak evidence regarding the effectiveness of supplements on primary teeth and permanent teeth. However, in school-aged children, the evidence is consistent regarding the use of fluoride supplements.[22,26,30,32-37] Children who chewed and swallowed 1-mg fluoride tablets daily on school days had significantly lower caries experience than did other children who did not use fluoride supplements. It is interesting to note that fluoride tablets, when chewed and swallowed, had significant preventive benefit for teeth that erupted during the studies.[29,31-32,34-35] However, the majority of these studies were conducted at a time when fluoridated dentifrices were not used widely. The researcher who conducted one more recent study[41] that focused on schoolchildren aged 12 years with high caries experience found that the daily use of fluoride supplements for five years was not effective in reducing caries.

TABLE 3 CONTINUED

STUDY	MASKING (YES, NO)		RANDOMIZATION	ASSESSOR TRAINING	INTRA-EXAMINER AND INTER-EXAMINER RELIABILITY	WITHDRAWAL (%)*	DEGREE OF BIAS
	Examiner	Subject					
Petersson, 1985[37]	Yes	No	Children in Uddevalla, Sweden, were randomized into four groups consecutively	Two dentist examiners were trained and their technique calibrated according to examination criteria used in study	Not reported	5	Moderate
Mann and Colleagues, 1989[38]	No	No	All children (6 months-12 years of age) in six settlements in Israel were randomly allocated into two groups	One trained examiner	Not reported	30	High
Stephen and Colleagues, 1990[22]	Yes	Yes	Allocation of preventive regimens was carried out at school level; assignment to groups was carried out by Highland Health Board, which was only group that knew the children's assignments	Examiners were trained	Examiners had reliability coefficient of > 0.99	38	Moderate
Leverett and Colleagues, 1997[39]	Yes	Yes	Randomly allocated into two groups	Not reported	Not reported	32	Moderate
Hu and Colleagues, 1998[40]	No	No	Not reported	Two examiners underwent training and calibration exercises	Interexaminer κ score was 0.85	26	High
Kallestal, 2005[41]	No	No	Randomly allocated into one of four groups	Examiners were trained by dentists in diagnosis and assessment of caries	Intraexaminer κ scores ranged between 0.76 and 0.88; interexaminer κ scores ranged between 0.64 and 0.80	32	High

Fluoride supplements and fluorosis. Consistent evidence exists that use of fluoride supplements during the first years of life is associated with an increased risk of fluorosis. The use of supplements during the first three years of life increased the risk of developing fluorosis. There was evidence that the first year of life was the most important period for development of fluorosis.[19] Pendrys[16] and Pendrys and Katz[17] reached similar conclusions.

It is unfortunate that there is no method of measuring fluorosis that assesses the trade-off between esthetic acceptability and the risk of developing caries. Recently, Do and Spencer[45] found that children who had mild fluorosis had quality-of-life scores higher than those of children who had caries or more advanced fluorosis. This research should be expanded to define the societal tolerance level and perceptions of fluorosis and caries. Evidence, not our professional perceptions, should guide us to decide what is acceptable by society. Research to quantify the social impact of fluorosis is lacking in the United States. It is our opinion that the increasing prevalence of fluorosis, even in its mildest forms, in the United States[46] should not be dismissed; rather, the dental community should develop programs to reduce children's multiple exposures to fluoride products during the first three years of life. We believe that dentists should dismiss the misconception that there is a balance between caries and fluorosis, because patients can accrue the benefits of topical fluorides without developing fluorosis and without systemic intake.[47]

Quality of the studies evaluating the effectiveness of fluoride supplements. One

TABLE 4

Risk of fluorosis in users of fluoride (F) supplements: cross-sectional and case-control studies.

STUDY	METHOD/AGE OF EXPOSURE/ COUNTRY	SUBJECT GROUPS, BY EXPOSURE TO FLUORIDE SUPPLEMENTS	N	PREVALENCE (%)	ODDS RATIO* OR ATTRIBUTABLE RISK PERCENTAGE†	95% CI‡	SEVERITY OF FLUOROSIS
Wang and Colleagues, 1997[14]	Questionnaire/ Children born in 1988, exposed to toothpaste and supplements from age 6 months to < 7 years/Norway	**Group 1:** Regularly **Group 2:** Periodically **Group 3:** Seldom **Group 4:** Not at all	383	**Group 1:** 45 **Group 2:** 21 **Group 3:** 10 **Group 4:** 0	Odds ratio: 1.8 for each year of use of F supplements	1.4-2.4	Score 1 of Thylstrup-Fejerskov Index[42] was most prevalent; highest score was 3
Hiller and Colleagues, 1998[15]	Questionnaire/ children aged 8.5 to 10 years examined and given different concentrations of fluoride supplements at different ages/ Germany	**Group F1:** F 0.25 mg§/day from age zero to 2 years; 0.5 mg/day F at age 3 years and 0.75 mg/day F from ages 4 to 5 years **Group F2:** 0.25 mg F/day from age 7 months to 2 years, 0.5 mg F during age 3 years, 0.75 mg F at ages 4 and 5 years **Group F3:** 0.25 mg/day F from age zero to 2 years only **Control:** No F supplements	316	**Group F1:** 41.4 **Group F2:** 44.2 **Group F3:** 35.1 **Control:** 19.6	Odds ratios not reported; children who received fluoride supplements had significantly higher prevalence of dental fluorosis	Not reported	Scores 1 and 2 of the Modified Developmental Defects of Enamel Index[43]
Pendrys and Katz, 1998[17]	Questionnaire/ children aged 10 to 14 years in optimally fluoridated communities/ United States	**Yes:** Used supplement during first two years of life **No:** Did not use supplements during first two years of life	188	Not reported by group	Adjusted odds ratio of fluorosis: 10.83 in children who used supplements during first two years of life	1.9-61.6	Mild-to-moderate fluorosis measured using the Fluorosis Risk Index[44]
Pendrys, 2000[16]	Questionnaire/ children aged 10 to 14 years/ United States	**Group 1:** Used supplements during first year of life **Group 2:** Used supplements during ages 2 years to 8 years	**Group 1:** 250 **Group 2:** 179	Not reported by group	Attributable risk percentage: **Group 1:** 29 **Group 2:** 65	**Group 1:** –6-52 **Group 2:** 34-81	Mild-to-moderate fluorosis measured using the Fluorosis Risk Index[44]
Bottenberg and Colleagues, 2004[18]	Questionnaire/ children aged 11 years followed up after age 7 years/ Belgium	**Group 1:** Never versus ever **Group 2:** Started after 1 year of age versus before **Group 3:** Taken not in milk versus in milk **Group 4:** Administered up to 3 years of age versus longer **Group 5:** Irregular versus regular administration	3,978	Not reported by group	**Group 1:** 1.3 **Group 2:** 1.1 **Group 3:** 1.7 **Group 4:** 0.7 **Group 5:** 1.1	**Group 1:** 1.0-2.7 **Group 2:** 0.7-1.6 **Group 3:** 1.0-2.7 **Group 4:** 0.5-1.1 **Group 5:** 0.8-1.4	Lowest two scores of Thylstrup-Fejerskov Index[42]

* Odds ratio: A measure of the chance (odds) that fluorosis is present in those who use supplements relative to the chance that fluorosis is present in those who do not use supplements.
† Attributable risk percentage: The proportion of the prevalence of fluorosis in children who use supplements divided by the prevalence of fluorosis in children who do not use supplements.
‡ CI: Confidence interval.
§ mg: Milligram.

consistent finding among the majority of the studies on fluoride supplements is the subjects' low rates of compliance. The high rates at which participants withdrew from these studies overall raise a concern about the utility of advocating for this preventive regimen, which requires daily commitment from caregivers.

Like most recent dental or medical systematic reviews, our review also demonstrated that the majority of the studies were highly biased. Our major concern regarding the studies we reviewed is the high rate of subjects' withdrawal, as well as the lack of a clear definition of allocation concealment and of how the children were examined and followed up. One of our concerns about the studies that involved schoolchildren and in which the schools were randomized into different study groups is the potential bias of the examiners. Additionally, none of the investigators analyzed their data with the schools as the unit of analysis.

CONCLUSION

Fluoride supplements have been recommended for preventing caries for more than three decades. In this systematic review, we found that the evidence supporting the effectiveness of supplements in caries prevention in primary teeth is weak. In permanent teeth, the daily use of supplements prevents dental caries. The use of supplements during the first six years of life, and especially during the first three years, is associated with a significant increase in fluorosis. ■

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