

Re-Examining the Fluoride Intake During Pregnancy: A Necessity or not for the Incoming Member

Katerina Patsouri

Dental surgeon, Postgraduate diploma in Restorative Dentistry in University of Athens.

Correspondence to:

Dr Katerina Patsouri, Dds, MSc, 25 Mykonou Str, 13122 Ilion, Athens.

ABSTRACT

The anticaries effect of fluoride (F) is well-known. What is not completely confirmed is the supremacy of issuing F prenatally, which is reported for the protection against the decay in the deciduous and permanent teeth of a child. Systematic fluoride intake in pregnancy is advised after the 2nd trimester of pregnancy, where via the blood circulation, it passes in the fetus. The concentration of ions in fetus' blood is lower than in the pregnant, it reaches the 25% of maternal level because of the placenta barrier. In the following literature review, research and clinical studies are investigated. The effectiveness of prenatal F intake is examined concerning the reduction of solubility of deciduous teeth and followingly the decreased rates of decay of income children and the impact in the morphology of these teeth. There is not a total agreement in clinicians in the benefit of the role of F in human pregnancy. In nowadays because of the abundance of products of oral hygiene enriched with F and of the fluoridation of drinking water in some countries, a critical thought is required regarding the necessity of prenatal intake under the control of the individual. The minimum doses during pregnancy will be mentioned.

KEYWORDS: Fluoride, Prenatal Intake, Caries Prevention, Safe Doses of Fluoride

INTRODUCTION

Systematic reviews and clinical studies were searched in Medline and Google scholar concerning the necessity of fluoride intake in pregnant women, the advantages and adverse effects in primary dentition of the fetus and the child. The research regarded professionally applied topical fluoride—including gel, foam and varnish forms—tablets or fluoridated drinking water. The goal was to offer the clinicians the newer recommendations in treating pregnant women regarding many factors such as diet, oral hygiene.

Prevention of wider population of caries has led to the reception of abundance of epidemiologic metres. Local application of fluoride, tablets during early childhood or even products of oral hygiene enriched with fluoride unions are locally applied with success.^{1,2} The fluorosis of drinking water is systematically in many countries of Europe and in countries of America, although there are researchers who dispute the necessity of this action.³⁻⁵

A point of controversy is the necessity of systematic reception of fluoride in pregnancy, in object the caries resistance of primary dentition of incoming fetus and the contingent changes of tooth morphology.⁵ This question comes up by the ascertainment that the presence of many decays in the mother is related with higher presence of decays in their children.⁶ Educating the future mother in oral hygiene, convincing her about the importance of fluoride and taking preventive measures prenatal, it is likely that there is an influence in the presence of decay

in the children and later in the adolescents.^{7,8} It is noteworthy that some researches find a connection in the presence of dental plaque in the labial surfaces of deciduous teeth with the increased presence of decays in permanent dentition.¹⁰

FLUORIDE DISTRIBUTION DURING PREGNANCY

Fluoride (F) is a element which can readily passes across the placenta from maternal to fetal blood.^{5,9,12} The significance of “placenta barrier” as a minor obstacle in the free passage of F from mother to fetus has been disputed by researchers. Although they agree with the difference in concentration of various substances, like F, in mother and fetus, this difference may be also attributed to the rapid maternal kidneys' action and to the absorption from her bones.¹ It is found that when the quantity of F in drinking water is increased then the concentration in maternal plasma, in fetus plasma and in fetal enamel of deciduous teeth is also increased. Bawden et al.(1989)⁵ have found in pigs that the increase in concentration of F in drinking water from 0 to 5 ppm and then in 20 ppm resulted in an increase in its concentration at maternal plasma 4 to 6 times. In fetus plasma it was observed a smaller increase of concentration in absolute number which was proportionally smaller too. Similar results were mentioned and in enamel.^{1,5} In general, concentration in fetus plasma is usually detected 25% less from maternal.¹⁰

The process of enamel formation can be divided into two

How to cite this article:

Patsouri K. Re-Examining the Fluoride Intake During Pregnancy: A Necessity or not for the Incoming Member. *Int J Dent Med Res* 2015;1(6):150-156.

stages: secretory and maturation.^{11,12} At the secretory stage, enamel matrix protein (amelogenin) is secreted. Proteins, water and mineral crystallites are deposited. Fluoride is detected in the extracellular fluids and it binds to the matrix proteins. It is possible to cause the hydrolysis of octacalciumphosphate (OCP) irreversibly to hydroxyapatite. In maturation stage fluoride exchanges reversibly with hydroxyl ions in the hydration shell on the apatite crystal surface. Ions of F may be dissolved between the apatite crystals, and incorporated into the lattice structure as the crystal grows.¹² Certain ions remain between the organic layers in the surface of the developing teeth.¹² The maturation of fetus enamel is observed at the 8th and 9th month of pregnancy starting from in the upper incisors. The unincorporated fluoride diffuses to the enamel surface of the deciduous dentition, creating a surface inward gradient.¹³ Teeth that receive F before their eruption have an increased concentration in crystallic structure of the enamel. Fluoroapatite is more resistant in acid attacks than hydroxyapatite which is more dissolved in acids. What is more fluoroapatite resists in caries lesions.^{4,14} The minimal concentration of F for the uptake of ions in fetal enamel is 2 mg/L or 0,7 ppm.¹⁵⁻¹⁷ Under this limit F is not detected with X-ray microanalysis in the fetal blood.¹²

FLUORIDE DISTRIBUTION POSTNATAL

Various statements have been exported from clinical trials about the way where F could provide a benefit on the prevention of caries. The most prevalents are: (a) it inhibits the demineralization and reduces the enamel solubility when incorporated into the mineral structure¹⁸⁻²⁰ (b) enhances remineralization by F released from dissolved enamel (although a greater effect of remineralization occurs from F acquired topically by saliva and dental plaque),^{20,21} (c) reduces oral bacteria causing a reduction of the rate of acid production of oral bacteria causing carious lesions,²⁰ (d) induces the re-precipitation of fluoridated hydroxyapatite phases within enamel, it reduces the net rate of transport of matter out of the enamel surface.²⁰

Some studies report a small effect on the morphology of the teeth, e.g., shallow pits and also fissures.^{20,22,23} A more recent study of Limeback et al (1999)²⁴ report that enough deficiencies are derived comparing the morphology of occlusal surfaces. Other studies used in support of the 'morphological effect' do not have an examiner blinded to the identity of the sample or use gross inter-cuspal measurements instead of precise measurements of pit and fissure morphologies in models or plaque retention in altered fissures were not examined.

Fluoride in younger ages is usually engaged systemically either by fluoridated drinking water or by tablets of fluoride dissolved in water.²⁷ The concentration of F by these means is measured and it is shown that the concentration in saliva is equal with the 2/3 of concentration in plasma.²⁵ The concentration in the saliva

is similar with the concentration in tablets, which lasts till the consumption of the pill. High rates of F are attained habitually daily by the consumption of fluoridated drinking water²⁷ but the absolute prices are smaller. The highest concentration in the saliva is achieved 40 minutes after the consumption of the tablet. After 120 minutes its concentration in saliva is so small that the anticaries action is rather insignificant. The detection in dental plaque is more positive and it is better achieved by local application.²⁸ Saliva provides a constant source of calcium and phosphate that helps inhibiting mineral loss during periods of low pH and promoting minerals when pH returns to neutral. When pH rises, saliva is secreted and its components finally form a complex of glycoprotein and calcium phosphate, named by Kleinberg-Salivary Precipitin.^{26,27} This complex is incorporated into dental plaque and it is 8–10 times more soluble than the calcium phosphate in tooth mineral which can dissolve before dissolution of tooth mineral or provide a source of ions for re-mineralization of decalcified tooth tissue.²⁸

By the local use, F is engaged by the primary teeth as well as by the alveolar bone. Ions are released during the absorption of roots of these teeth and the absorption of alveolar bone before adult teeth arise.²⁷ Moreover sustained levels of F reduce the critical pH value below which calcium and phosphate ions are solubilized from tooth enamel and dentin, thus, reducing de-mineralization and enhance re-mineralization of tooth.²⁸⁻²⁹ Hargreaves et al. (1992)¹⁷ investigated the starting date of issuing F in children in accordance with caries detected in childhood. They found that issuing 1.0 mg/day of F in children younger than 3 months, in the age of the 11-13 years they presented less decays comparatively with children that started at 6 months till the age of 3 years old.

CONTRADICTED OPINIONS CONCERNING THE BENEFIT OF PRENATAL F INTAKE

A more thorough answer as to the benefit or not of prenatal F intake can be presumed by the study of contemporary literature. There are studies that consider very important the action of F and in the contrary others which ultimately conclude that there is no statistically significant difference in pre-natal or post-natal intake, if certain conditions are dominated. The colonization of the oral bacterial implicated in causing caries defects has been studied over the years.³⁰ It is interesting to study how the presence of F can affect this colonization.

Bacterial mainly connected to the demineralisation of hard dental tissues is streptococci Mutans and various types' laktobakilus.³³ Brambilla et al. (1998)³¹ studied pregnant women who used mouthrinse with 0.05% sodium fluoride and 0.12% chlorhexidine from the sixth month of pregnancy to 24 months. They noticed that those women had less colonization of St. Mutans and their children had additionally lower colonization,

compared with the control group who received only systemic fluoride (1mg/day) in drinking water.

Differences in crystal structure of enamel after issuing F in pregnant is observed in some studies.^{18,20} The intake began from the 3rd or 6th month of pregnancy and was continued for a few months after the childbirth. Enamel in these fetuses is described with higher proportion of crystals, its crystals are 5% bigger than in those who did not receive F, the content in F and Ca is also higher and metal elements are 3% more.¹⁸ These elements induce in less decayed and filled teeth in childhood because dental tissues are more resistant in acids, It is not reported any danger by F intake in the last 6 months of pregnancy neither in mother nor in fetus. None undesirable result comes up in mother or in fetus by issuing 1 mgF/day from the 2nd trimester of pregnancy and simultaneously receiving small concentration of F in drinking water ($\leq 0,7$ ppm). DFS indicators are presented statistically smaller in children until the age of 10 with pre-natal F intake from the 2nd or 3rd trimester of pregnancy. Fluorosis is not reported in clinical examination.

Not all researches where F is given during pregnancy lead to the above results. Leverett et al. (1997)³² observed that F intake in those patients involves very small statistically improvement in oral health of child recording dmfs indicator until the age the 5.³⁵ The control group began the intake after birth, as the experimental group continued engagement of F. Drinking water did not contain fluoride. The team which received prenatal 1mgF/day, presented mild fluorosis. It is supported that F which penetrates the placenta barrier is in very low concentration compared with what exists in the blood circulation of the mother, so when it is granted in small concentrations, it cannot have any expected benefit.³⁵

The anticaries effect of F is related to the time the intake starts from the utero or after birth, as well as to the duration of intake. A research conducted by Drinkard et al. (1985)³³ to pregnant mice does not indicate that the children born have a higher proportion of F in enamel on examined molars. Mothers received F in drinking water during pregnancy and shortly after birth, where they breastfed their babies. Molars are formed after birth, so it is concluded that the F passes to the fetus blood and when its incorporation stops even by the indirect mean of breastfeeding, the newly formed teeth do not benefit from its advantages. A similar study performed in humans showed that permanent molars show fewer proximal caries lesions, when F is taken until the age of three where molar keep develop. When the incorporation is carried out only during the first year of life the proximal lesions observed are statistically more.³⁴

Of particular interest is the fact that high concentrations of F are found in the surface layers of enamel. Surface enamel abrades during life,³⁵ therefore it could not help protect teeth against caries attacks. An in vitro study of Featherstone et al. (2000)³⁶ examined whether the incorporation of F- ions in tooth structure relates with a greater resistance to acidic agents and resulted in non-

optimistic conclusions.³⁷ Examining teeth from people who used products of F concentrations up to 1000 ppm, they discovered that their teeth were more resistant to acidic solutions against those which were developed in an environment with a concentration from 20 to 100 ppm.

Incorporation of F prenatally is associated with socio-economic conditions of the population. There are cases where further supplements are not necessary. These groups comprise of people with low caries index or people who regularly use various fluoridating agents such as toothpaste or mouthrinses.³⁵ Pre or postnatal F incorporation in a systematic way F does not offer additional protection to these groups.³⁸ A research Leverett et al (1997)³² led to a similar conclusion. It was found that administration of F in women from the 4th month of pregnancy until the 3rd year of the child did not provide more protection against caries in deciduous teeth. Children lived in an environment where they received F regularly from oral hygiene products. On the contrary F incorporation is essential in areas or socioeconomic conditions with a low fluoridation.³⁹

In conclusion, the caries protection of F from the early stages -before tooth eruption- is disputed by many researchers.^{40,41} Surveys where administration starts in studing group from utero and in the control group after birth and surveys that investigate F administered from birth and in the control group it is applied locally after the 7th month conclude there is no statistically significant the incidence of caries in deciduous teeth. Very low dmfs indexes are achieved with topical application of F²¹, but the attitude of the parents, the oral hygiene habits and the diet critically influence dental caries initiation and progression.^{20,42} There is a consensus in conclusions regarding anticaries effect of F after tooth eruption. In children older than 6 years, who receive chewable tablets, decay is much less compared to those who do not receive.^{2,43} The daily amount is 1mg and the majority of children did not use oral hygiene products with fluoride often.

DANGERS FROM EARLY F⁻ INCORPORATION

Despite the benefits of F incorporation, an excess in dosage causes a greater incidence of adverse health effects. Plenty of side effects are reported in literature. These occur when the levels F in humans exceed 3.5-4 ppm in drinking water.⁴⁴ Important parameters in the occurrence of side effects are the timing of F intake and the way in which it is received, because the last one determines the amount of intake, dose, duration of administration and the concentration of other minerals or vitamins.⁴⁵

The earlier the intake begins, the more likely it is to be incorporated in the crystal structure of developing teeth.³⁶ Moreover, ingested fluoride has been correlated to delayed apoptosis of primary teeth as well as delayed teeth development.⁴⁶ A reduction in the number of osteoclasts in the alveolar bone is also referred, which are

involved in root resorption of the deciduous teeth and their alveolar bone.⁴⁰

Investigations performed in animals where they received very high concentrations of F, greater than 200 ppm F, have proved further upcoming situations such as fragility of bone and canines, exostosis, increased concentration of fluoride ions and alkaline phosphatase in the blood and urine.⁴⁸ Fluoride was given through diet soon after birth and for a long period afterwards. The clinical appearance of dental fluorosis shows up in concentrations of 190 ppm F.⁴⁸ The action of fluoride depends on components of the diet which show a synergistic effect with it.⁴⁰ F is referred to as the most reactive element in the periodic table of elements, so it reacts with many elements. Elements of nutrition, such as calcium, magnesium, boron, selenium and vitamin C limit the amount of fluoride absorbed by the human body.

People with a diet low in these nutrients who live in areas with fluoridated drinking water, show lesions caused by its absorption.⁴⁰ Defences occur in people with problems in the blood circulation and kidney, through which F is absorbed.⁴⁰ The F accumulates in bones, and when it exceeds an amount of 10-20mg/day for a period of over ten years may cause fluorosis of the bones, increasing the risk for bone fractures. Concentrations of 5mg/day for more than 6 years are also toxic, although the symptoms are milder.⁴⁰ Moreover, symptoms provoked by the toxicity of F are neurological problems, an impact in IQ index which gets lower and a higher incidence of cancer.⁴⁰ Regarding the biochemical structure of dental tissues, a high concentration of absorbed F (≥ 5 ppm in drinking water) cause adverse effects on ameloblasts in enamel construction¹⁴ or in maturation stage. Clinical characteristics as pores on the surface of enamel, hypoplasia or even complete absence of enamel are observed. Increased intake of fluoride during the maturation phase usually causes overcalcification, with the clinical picture of brown spots called fluorosis.⁴⁷ F may interact with the organic substrate preventing removal of control proteins,¹² so there is an increased proportion of stem proteins between crystals and crystals hydroxyfluorapatite.⁴⁷

Clinically, F intake at high concentrations causes fluorosis. This has the picture either of small white spots in mild form or brown or black spots or even cracks and lack of enamel in more severe forms. The dose that causes implicated is 0.04 mg/kg⁴⁰ or 0,25 mg / day when it is given before the age of 2 years long. Fluorosis occurs when the elevated fluoride levels in plasma affect the operation of ameloblasts during final maturation of enamel.⁹ The action of F may be extended to other tissues, bone, nervous-system, when this is taken systematically.⁴⁰ Levels of fluoride of 5 μ mol / L cause a severe undercalcification of enamel.⁹ The severity of the clinical picture is associated with the F intake, the age of the child, the reaction of each individual but also to other factors such as nutrition.⁴⁸

SAFE DOSES OF FLUORIDE

Toxicity of this element as well as the multitude of events that leads to irrational use has been pointed out. What is more, it is necessary to define some boundaries to obtain the safe dose of F-consumption. It is clear from the current literature that these boundaries may change depending on the area where an individual lives, the number of fluoridated products which uses and the frequency of using them.²⁰ F is found in various forms in nature like in food, drinking water and many oral hygiene products.⁴⁰

Recommendations from American organizations concerning the minimum of adequate intake of F mention 0,1-0,5mg / day for infants up to six months and 1,5-4,0 mg / day (0,7-2,0mg / liter in drinking water) to older ages and adults.^{20,40} Taking into consideration the number of sources from where someone can be exposed daily, the upper limit for children and adults is defined to 1mg/day.⁴⁰ Later surveys⁴⁹ refer to a minimum concentration of F in drinking water 0.7-1mg / liter. Conclusively, the minimum dose of adequate ingested intake is determined to 0.05 mg / kg / day for infants and children over 6 months and 3mg/day for women , including during pregnancy and 4mg/day for men. Adult's upper limit is 10mg/day.⁵⁰

The recommended safe age for beginning the supplementation is prior to the eruption of permanent dentition, at the age of 5 years, until permanent teeth eruption is completed.²⁰ The protection against caries is proved effective for the permanent dentition and if fluorosis is produced, it should not be severe at this time of fluoride incorporation into tooth structures.^{20,51-53} When F is ingested regularly through oral hygiene products or other dietary supplements no additional intake is required.²⁰

CONCLUSIONS

Dental caries is a bacterial disease. The topical application of F can have a meaningful impact in children and adults, as long as it is done in a regular base.² It is significantly important in patients with high caries risk, who do not use fluoridated oral hygiene products as well as they do not live in an area with fluoridated drinking water. Preventive systemic administration of this element in pregnant in order their children to obtain resilience in cariogenic factors, is not proved effective in all studies above. There are studies which demonstrate that ingested F in pregnancy offers no advantage when their children grow up in an environment where F exists either in drinking water or in products of oral hygiene.^{35,41}

Substantial factors in reduced dental caries indices in children are their diet, the fluoridation of drinking water, the use of products containing F and last but no least oral hygiene habits of their parents but especially those of their mother. Proper education of parturient mother in oral hygiene of herself and her children is the key for a healthy child.²¹

Researchers	Method	Results	Main points
Glenn et al(1991)¹	Group I: Pregnants from the 3 rd month received 2,2mg NaF (or 1mg F) daily and fluoridated water. Group II: Only fluoridated water in pregnant.	Group I: Children till the age of 10 showed significant reduction in caries lesions. Reduction in early birth. Reduction in the height and weight of newborns.	Numerous study group. Not observed fluorosis in children. The concentration of F in drinking water was 1ppm.
Gunay et al (1998)⁸	Group I: In pregnant 1mg F/daily. Group II: Children whose mothers were not taking F.	The postnatal F intake influence the morphology of molars causing more shallow pits and fissures.	Not studied: the width of fissures, the plaque retention. The study is not blinded.
LeGeros et al (1985)⁵⁴	In pigs. Group I: Pregnants from the 3 rd month received 2,2mg NaF. Fluoridation once per year from the age of 3. Group II: No F intake. Fluoridation once per year from the age of 3.	Group I: Higher enamel F uptake, lower C concentration. Less defects from acids. Larger crystals. Narrower intra-crystals spaces in enamel. Also use of F dentifrices.	
Kunzel et al (1985)⁵²	Group I: 0,2mm F uptake from drinking water before and after birth. II: 0,2mm F uptake before birth and 1mg F in tablets after birth. III: 1,5mm F uptake in tablets before birth and 1mg F after. IV: Only drinking water containing 1-1,5ppm F.	The before and after birth F uptake results in higher concentration of F in enamel. Better results are with tablets' consumption.	
Brambilla et al (1998)³¹	Messuring the salivary Str mutans level. Group I: In pregnant from the 6 th month a solution of 0,05% NaF and 0,12% CHX. Group II: Systemic F uptake 1mg/day.	Group I: Significant reduction in St. mutans' concentration in mothers till the 30 th month. A delay in colonization in children.	In drinking water there was 0,2 ppm F. No side effects in pregnant or children.
Gomez et al (2007)⁵³	A preventive dental program in oral hygien in pregnant and after giving birth. Group I: Mother-child following the preventive program.	Examination of children reflected a long-term reduction in the DFS score.	Only 1 st molars were examined. The preventive program continued until the children were 6 years of age. In drinking water there was 1ppm F.
Meyer et al (2010)⁵⁵	A preventive program in dental an oral health starting from pregnancy and continuing untill the age of 6 of children. Group I: Individuals following the program. Group II: Randomly selected adolescents at the same age.	The control group showed a significantly higher mean DMF-T score.	Assessed clinical parameters: clinical parameters were assessed: DMF-teeth,DMF surface, hygiene index, papilla bleeding index, Periodontal Screening Index, and Streptococcus mutans/Lactobacillus concentration in saliva. Children were examined till the age of 13-14.

REFERENCES

- Glenn FB, Glenn WD, Duncan RC: Fluoride Tablet Supplementation during Pregnancy for Caries Immunity: A Study of the Offspring Produced, *Am J Obstet Gynecol* 1982; 143: 560-5.
- Hardwick JL, Teasdale J, Bloodworth G: Caries increments over 4 years in children aged 12 at the start of water fluoridation. *Br Dent J* 1982; 53(6):217-22.
- Gedalia I, Shapira L: Effect of Prenatal and Postnatal Fluoride on the Human Deciduous Dentition. A Literature Review. *Adv Dent Res* 1989; 3:168-76.
- Fejerskov O, Larsen MJ, Richards A, Baelum V: Dental tissue effects of fluoride. *Adv Dent Res* 1994; 8:15-31.
- Bawden JW, Deaton TG, Koch GG, Crawford BP: Effect of an Acute Maternal Fluoride Dose on Fetal Plasma Fluoride Levels and Enamel Fluoride Uptake in Guinea Pigs. *J Dent Res* 1989; 68:1169-72.
- Zanata RL, Navarro MF, Pereira JC, Franco EB, Lauris JRP, Barbosa SH: Effect of caries preventive measures directed to expectant mothers on caries experience in their children. *Braz Dent J* 2003, 14(2):75-81.
- Gomez SS, Weber AA: Effectiveness of a caries preventive program in pregnant women and new mothers on their offspring. *Int J Paediatr Dent* 2001; 11(2):117-22.
- Günay H, Dmoch-Bockhorn K, Günay Y, Geurtsen W: Effect on caries experience of a long-term preventive program for mothers and children starting during pregnancy. *Clin Oral Investig* 1998; 2(3):137-42.
- Opydo-Szymaczek J, Borysewicz-Lewicka M: Variations in concentration of fluoride in blood plasma of pregnant women and their possible consequences for amelogenesis in a fetus. *HOMO - J Comp Human Biol* 2006; 57(4): 295-307.
- Parker PR, Bawden JW: Prenatal Fluoride Exposure: Measurement of Plasma Levels and Enamel Uptake in the Guinea Pig. *J Dent Res* 1986; 65:1341-5.
- Montherrat-Carret L, Perrat-Mabilon B, Barbey E, Bouloc R, Boivin G, Michelet A, Magloire H: Chemical and x-ray analysis of fluoride, phosphorus, and calcium in human foetal blood and hard tissues. *Arch Oral Biol* 1996; 41:1169-78.
- Tzamouranis AS: Istology and embryology of dental and periodontal issues. Publication Parisianou, Athens 1999. (In greek: Τζαμουράνης ΑΣ: Ιστολογία και εμβρυολογία των οδοντικών και περιοδοντικών ιστών. Εκδόσεις Παρισιάνου, Αθήνα 1999).
- Speirs RL: The Value of Prenatally Administered Fluoride. *Dent Update* 1983; 3:43-51.

14. Deutsch D, Gedalia I: Fluoride Concentration in Human Fetal Enamel. *Caries Res* 1982; 16:428-32.
15. LeGeros RZ, Glenn FB, Lee DD, Glenn WD: Some Physico-chemical Properties of Deciduous Enamel of Children with and without Pre-natal Fluoride Supplementation (PNF). *J Dent Res* 1985; 64: 465-9.
16. Gedalia I: Placental transfer of fluoride in the human fetus at low and high F intake. *J Dent Res* 1964; 43:669-71.
17. Hargreaves JA: The Level and Timing of Systemic Exposure to Fluoride with Respect to Caries Resistance. *J Dent Res* 1992; 71:1244-6.
18. Hellwig E, Lennon AM: Systemic versus Topical fluoride. *Caries Res* 2004; 38:258-62.
19. Tyler JE, Poole DFG, Stack MV, Dowell TB: Superficial fluoride levels and response to in vitro caries-like lesion induction of enamel from Bristol (UK) and Birmingham (UK) human deciduous teeth. *Arch Oral Biol* 1986; 31:201-4.
20. Ten Cate JM, Featherstone JDB: Mechanistic aspects of the interactions between fluoride and dental enamel. *Crit Rev Oral Biol Med* 1991; 2:283-96.
21. Lynch RJM, Navada R, Walia R. Low levels of fluoride in plaque and saliva and their effects on the de-mineralization and re-mineralization of enamel: role of fluoride toothpastes. *International Dental Journal* 2004;5(Suppl. 1): 304-9.
22. Simpson WJ, Castaldi CR: A study in crown morphology of newly erupted first permanent molars in Wetaskiwin Alberta (optimum fluoride) and Camrose Alberta (low fluoride). *Odontol Revy* 1969; 20:1-14.
23. Aasenden R, Peebles TC: Effects of fluoride supplementation from birth on human deciduous and permanent teeth. *Arch Oral Biol* 1974; 19:321-6.
24. Limeback H: A re-examination of the pre-eruptive and post-eruptive mechanism of the anti-caries effects of fluoride: is there any anti-caries benefit from swallowing fluoride? *Community Dent Oral Epidemiol* 1999; 27:62-71.
25. Ekstrand J, Oliveby A: Fluoride in the oral environment. *Acta Odontol Scand* 1999; 57:330-3.
26. Kleinberg I. A new saliva-based anti-caries composition. *Dentistry Today* 1999;18:98-103.
27. Cummins D: The development and validation of a new technology, based upon 1.5% arginine, an insoluble calcium compound and fluoride, for everyday use in the prevention and treatment of dental caries. *J Dent* 2013; 41:1-11. Available online at www.sciencedirect.com.
28. Lynch RJM, Navada R, Walia R: Low levels of fluoride in plaque and saliva and their effects on the de-mineralization and re-mineralization of enamel: role of fluoride toothpastes. *Int Dent J* 2004; 5(Suppl. 1): 304-9.
29. Rolla G, Ogaard B, Cruz Rde A: Topical application of fluorides on teeth. New concepts of mechanisms of interaction. *J Clin Periodont* 1993;20:105-80.
30. Davey AL, Rogers AH: Multiple types of the bacterium *Streptococcus mutans* in human mouth and their intra-family transmission. *Arch Oral Biol* 1984; 6:453-60.
31. Brambilla E, Felloni A, Gagliani A, Malerba A, Garcna-Godou F, Strohmenger L: Caries Prevention During Pregnancy: Results of a 30-month study. *JADA* 1998; 129:871-7.
32. Leverett DH, Adair SM, Vaughan BW, Proskin HM, Moss ME: Randomized clinical trial of the effect of prenatal fluoride supplements in preventing dental caries. *Caries Res* 1997; 31(3):174-9.
33. Drinkard CR, Deaton TG, Bawden JW: Enamel Fluoride in Nursing Rats with Mothers Drinking Water with High Fluoride Concentrations. *J Dent Res* 1985; 64: 877-80.
34. Groeneveld A, van Eck AAMJ, Backer Dirks O: Fluoride in caries prevention: is the effect pre- or post-eruptive? *J Dent Res* 1990; 69:751-5.
35. Weatherell JA, Deutsch D, Robinson C, Hallsworth AS: Assimilation of fluoride by enamel through the life of the tooth. *Caries Res* 1977; 11(1):85-101.
36. Featherstone JDB: The science and practice of caries prevention. *JADA* 2000; 131:887-99.
37. International Academy of Oral Medicine and Toxicology (IAOMT), submitted by Kennedy DC, 2003 as it is found in www.iaomt.org/articles/files/files196/IAOMT.pdf and shown in 15/5/2011.
38. König KG: Reasons for increasing the fluoride content of children's toothpastes. *Oralprophylaxe* 2001;23:27-31.
39. Thylstrup A, Fejerskov O, Bruun C, KANN J: Enamel Changes and Dental Caries in 7-year-old Children Given Fluoride Tablets from Shortly after Birth. *Caries Res* 1979; 13: 265-76.
40. Burt BA: The case for eliminating the use of dietary fluoride supplements for young children. *J Public Health Dent* 1999; 59:269-74.
41. Johnston DW, Grainger RM, Ryan RK: The decline of dental caries in Ontario school children. *J Can Dent Assoc* 1986; 52:411-7.
42. Granath LE, Rootzen H, Liljegren E, Holst K, Kohler L: Variations in caries prevalence related to combinations of dietary and oral hygiene habits and chewing fluoride tablets in 4-year-old children. *Caries Res* 1978; 12:83-92.
43. Petersson LG, Koch G, Rasmusson CG, Stanke H: Effect on caries of different fluoride prophylactic programs in preschool children: a two-year clinical study. *Swed Dent J* 1985; 9(3):97-104.
44. Eastoe JE, Fejerskov O: Composition of Mature Enamel Proteins from Fluorosed Teeth. In: *Tooth Enamel IV*, R.W. Fearnhead and S. Suga, Eds., Amsterdam, New York, Oxford: Elsevier Science Publishers B.V. 1984, pp. 326-30.
45. Aulerich RJ, Napolitano A C, Bursian SJ, Olson BA, Itochstein JR: Chronic Toxicity of Dietary Fluorine to Mink. *J Anim Sci* 1987; 65:1759-67. Downloaded from jas.fass.org by on February 10, 2010.
46. Limeback H: Delayed tooth eruption from water fluoridation. *J Dent Res* 1996; 75(12):1936-41.
47. Tanabe T, Aoba T, Moreno EC, Fukae M: Effect of Fluoride in the Apatite Lattice on Adsorption of Enamel Proteins onto Calcium Apatites. *J Dent Res* 1988; 67: 536-42.
48. Hiller KA, Wilfart G, Schmalz G: Developmental enamel defects in children with different fluoride supplementation: a follow-up study. *Caries Res* 1998; 32(6):405-411.
49. Hargreaves JA: Water fluoridation and fluoride supplementation: considerations for the future. *J Dent Res* 1990; 69:765-70.
50. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*. Washington, D.C.: National Academy Press; 1999, from *JADA* 2000; 131:1671.
51. Mattos-Graner RO, Zelante F, Line RCSR, Mayer MPA: Association between caries prevalence and clinical, microbiological and dietary variables in 1.0 to 2.5-year-old Brazilian children. *Caries Res* 1998; 32:319-23.

52. Kunzel W, Schaper R, Schamashula RG, Taylor CE: Effekt Pra- und Postnataler Fluoridebelastung auf den Fluoridgehalt des Milch-zahnschmelzes, Zahn-, Mund-Kieferheilkd 1985; 73:3-9.
53. Gomez SS, Emilson CG, Weber AA, Uribe S: Prolonged effect of a motherchild caries preventive program on dental caries in the permanent 1st molars in 9 to 10-year-old children. Acta Odontol Scand 2007; 65(5):271-4.
54. Legeros RZ, Tung MS: Chemical Stability of Carbonate- and Fluoride-containing Apatites. Caries Res 1983; 17:419-429.
55. Meyer K, Geurtsen W, Günay H: An early oral health care program starting during pregnancy: results of a prospective clinical long-term study. Clin Oral Investig 2010; 14(3):257-64.

Source of Support: Nil
Conflict of Interest: Nil