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THE IMPORTANCE OF TIMING IN FLUORIDE-INDUCED DEVELOPMENTAL NEUROTOXICITY

ABSTRACT: Exposure to the fluoride ion can, in sufficient dose, induce neurotoxicity at any age, in both adults and children, but for fluoride-induced neurotoxicity to occur, in response to exposure to low doses of fluoride in the developing brain, the timing of the exposure is of importance. The evidence to date indicates that the developing brain is most sensitive to fluoride-induced neurotoxicity during the intrauterine period. Exposure to a low dose of fluoride later in childhood, at ages approximately 6–13 years, may or may not be associated with a reduction in IQ or school performance. Whether or not fluoride exposure in later childhood is associated with developmental neurotoxicity may reflect the degree to which later childhood exposure parallels intrauterine exposure. In stable societies with a single source of fluoride, such as the water supply, and no fluoride pollution from burning coal or other industrial sources, e.g., the villages of Wamiao and Xinhuai in rural China studied by Xiang et al., a higher correlation may be present between intrauterine and later childhood exposure than in societies where multiple fluoride sources are present such as industrial sources, foods high in fluoride, fluoridated salt, and fluoridated toothpaste, e.g., Mexico City studied by Bashash et al. and Thomas et al. The findings of two recent studies, in 2019, by Soto-Barreras et al. and Green et al. are consistent with this interpretation of the data.

Keywords: Childhood fluoride exposure; Fluoride-induced neurotoxicity; IQ, Maternal fluoride exposure.

Exposure to the fluoride ion (F) can, in sufficient dose, induce neurotoxicity at any age, in both adults and children,[1] but for fluoride-induced neurotoxicity to occur, in response to exposure to low doses of fluoride in the developing brain, the timing of the exposure is of importance. The evidence to date indicates that the developing brain is most sensitive to fluoride-induced neurotoxicity during the intrauterine period. Exposure to a low dose of fluoride later in childhood, at ages approximately 6–13 years, may[2-10] or may not[11,12] be associated with a reduction in IQ or school performance. Whether or not fluoride exposure in later childhood is associated with developmental neurotoxicity may reflect the degree to which later childhood exposure parallels intrauterine exposure. In stable societies with a single source of fluoride, such as the water supply, and no fluoride pollution from burning coal or other industrial sources, e.g., the villages of Wamiao and Xinhuai in rural China studied by Xiang et al.,[2] a higher correlation may be present between intrauterine and later childhood exposure than in societies where multiple fluoride sources are present such as industrial sources, foods high in fluoride, fluoridated salt, and fluoridated toothpaste, e.g., Mexico City studied by Bashash et al.[11] and Thomas et al.[12] The findings of two recent studies, in 2019, by Soto-Barreras et al.[13] and Green et al.[14] are consistent with this interpretation of the data.

The aim of the study by Soto-Barreras et al.[13] was to evaluate the impact of fluoride exposure on the prevalence of dental caries and the intellectual ability of children. In a cross-sectional study, 161 children in Chihuahua, Mexico, from 9 to 10 years of age were evaluated. The concentrations of fluoride in drinking water and urine were analyzed individually. The oral health status regarding dental caries and dental fluorosis was assessed. The intellectual ability of children was evaluated through the Raven's Colored Progressive Matrices. In addition, variables such as diet, oral hygiene, body mass index, and socioeconomic status were included. The results showed that there was a negative relationship between the DMFT index and the level of dental fluorosis. In the logistic regression analysis, a water fluoride exposure above 1.0 mg/L showed less risk of dental caries (OR = 0.41; p = 0.025). Parental education level lower than high school raised significantly the risk of dental caries (OR = 2.81; p = 0.036). No relationship was found between intellectual ability and fluoride exposure variables such as, dental fluorosis, levels of fluoride in drinking water and urine, and exposure dose. The authors concluded that the results suggest that exposure to fluoride reduces the prevalence of dental caries, but no association was found to the intelligence of children.

The aim of the study by Green et al.[14] was to examine the association between fluoride exposure during pregnancy and IQ scores in a prospective birth cohort. The prospective, multicenter birth cohort study used information from the Maternal-Infant Research on Environmental Chemicals cohort. Children were born between 2008 and 2012; 41% lived in communities supplied with fluoridated municipal water. The study sample included 601 mother-child pairs recruited from 6 major cities in Canada; children were between ages 3 and 4 years at testing. Data were analyzed between March 2017 and January 2019. Data on the maternal urinary fluoride (MUFSG), adjusted for specific gravity and averaged across 3 trimesters, were available for 512 pregnant women. In addition, information on the self-reported maternal daily fluoride intake from water and beverage consumption was available for 400 pregnant women. The children's IQ was assessed at ages 3 to 4 years using the Wechsler Primary and Preschool Scale of Intelligence-III. Multiple linear regression analyses were used to examine covariate-adjusted associations between each fluoride exposure measure and the IQ score. Of 512 mother-child pairs, the mean (SD) age for enrollment for mothers was 32.3 (5.1) years, 463 (90%) were white, and 264 children (52%) were female. Data on MUFSG concentrations, IQ scores, and complete covariates were available for 512 mother-child pairs; data on maternal fluoride intake and children's IQ were available for 400 of 601 mother-child pairs.Women living in areas with fluoridated tap water (n = 141) compared with nonfluoridated water (n = 228) had significantly higher mean (SD) MUFSG concentrations (0.69 [0.42] mg/L vs 0.40 [0.27] mg/L; P = 0.001; to convert to millimoles per liter, multiply by 0.05263) and fluoride intake levels (0.93 [0.43] vs 0.30 [0.26] mg of fluoride per day; P = 0.001). Children had mean (SD) Full Scale IQ scores of 107.16 (13.26), range 52–143, with girls showing significantly higher mean (SD) scores than boys: 109.56 (11.96) vs 104.61 (14.09); P = 0.001. There was a significant interaction (P = 0.02) between child sex and MUFSG (6.89; 95% CI, 0.96–12.82) indicating a differential association between boys and girls. A 1-mg/L increase in MUFSG was associated with a 4.49-point lower IQ score (95% CI, –8.38 to –0.60) in boys, but there was no statistically significant association with IQ scores in girls (B = 2.40; 95% CI, –2.53 to 7.33). A 1-mg higher daily intake of fluoride among pregnant women was associated with a 3.66 lower IQ score (95% CI, –7.16 to –0.14) in boys and girls. The authors concluded that maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years and that these findings indicate the possible need to reduce fluoride intake during pregnancy.

Thus, Soto-Barreras et al.[13] found no relationship between IQ and fluoride exposure at ages 9–10 years in children in Chihuahua, Mexico, while Green et al.[14]

found a relationship between IQ and intrauterine fluoride exposure during pregnancy. Rather than these two studies being seen to have conflicting results on the effect of fluoride on IQ, both results are consistent with the model that it is intrauterine exposure that is important for the occurrence of fluoride-induced developmental neurotoxicity rather than exposure later in childhood at ages of approximately 6–13 years.

In the same manner, earlier large ecological studies of New Zealand children in 1998 by Spittle et al.[15] and in 2014 by Broadbent et al.[16] can been seen to be consistent with this model.

Spittle et al.[15] studied a birth cohort of 1,265 born in Christchurch in 1977. Cognitive ability was assessed at ages 8 and 9 years using the Wechsler Intelligence Scale for Children (WISC-R) and the children were grouped according to their exposure, to age 7 years, to fluoridated water in Waimairi County, Christchurch, New Zealand, with 1 ppm of fluoride, or to non-fluoridated water in the rest of Christchurch, with <0.1 ppm of fluoride. No relationship was found between fluoride and IQ and there was no trend for the IQ to decline with increasing exposure to fluoridated water. Those who lived the longest (7 years) in the area with fluoridated water had the highest mean IQ scores, although the difference was not statistically significant.

Broadbent et al.[15] aimed to clarify the relationship between community water fluoridation (CWF) and IQ. They conducted a prospective study of a general population sample of 1,037 born in Dunedin, New Zealand, between April 1, 1972, and March 30, 1973 (95.4% retention of cohort after 38 years of prospective follow-up). Residence in a CWF area, use of fluoride dentifrice, and intake of 0.5-milligram fluoride tablets were assessed in early life (prior to age 5 years) and the IQ was repeatedly assessed between ages 7 to 13 years and at age 38 years. They found no significant differences in IQ because of fluoride exposure. These findings held after adjusting for potential confounding variables, including sex, socioeconomic status, breastfeeding, and birth weight (as well as educational attainment for adult IQ outcomes). They concluded that their findings did not support the assertion that fluoride in the context of CWF programs is neurotoxic and that associations between very high fluoride exposure and low IQ reported in previous studies may have been affected by confounding, particularly by urban or rural status.

Both the Spittle et al.[15] and the Broadbent et al.[16] studies were ecological in design and did not measure the intrauterine exposure of the subjects to fluoride. The lack of a significant relationship between IQ and fluoride exposure in childhood, prior to ages 7 and 5 years, respectively, is consistent with the findings of Bashash et al.[11] and Thomas et al.[12] who did not find a relationship between IQ and fluoride exposure at ages 6–12 years although prenatal intrauterine fluoride exposure was significantly associated with impaired cognitive outcomes in children at ages 1, 2, 3, 4, and 6–12 years. However, the Broadbent et al. study has also been critiqued on the grounds that the estimated difference in the exposure to fluoride, of less than 0.2 mg /day, between the CWF group and the non-CWF group (intakes of 1.36 and 1.19 mg/day, respectively) was so small that it was unlikely to lead to a detectable difference in IQ.[17]

That intrauterine exposure to fluoride can cause IQ loss is also supported by the study by Valdez Jiménez et al.[18] They evaluated the association between *in utero* exposure to fluoride and Mental and Psychomotor Development (MDI and PDI) evaluated through the Bayley Scale of Infant Development II (BSDI-II) in infants. The sample included 65 mother-infant pairs. Environmental exposure to fluoride was quantified in tap and bottled water samples and fluoride in maternal urine was the biological exposure indicator. The samples were collected during the 1st, 2nd, and 3rd trimesters of pregnancy. The mean values of fluoride in tap water for the 1st, 2nd, and 3rd trimester were 2.6±1.1, 3.1±1.1, and 3.7±1.0 mg/L, respectively, with 80% of the samples exceeding the reference value of 1.5 mg/L (NOM-127-SSA1-1994). The mean values for the maternal urinary fluoride were 1.9±1.0, 2.0±1.1, and 2.7±1.1 mg/L for the 1st, 2nd and 3rd trimesters, respectively. The percentages of infants with MDI and PDI scores of less than 85 points were 38.5% and 20.9%, respectively. After adjusting for potential confounding factors (gestational age, age of child, marginalization index, and type of water consumed), the MDI showed an inverse association with the maternal urinary fluoride levels for the first (b= –19.05, p=0.04) and second (b= –19.34, p=0.01) trimesters. The data suggested that cognitive alterations in children born to mothers exposed to fluoride could start in the early prenatal stages of life.[18] Fluoride toxicity can result in pre-term delivery(<34 weeks gestational age)[19] which is a risk factor for impaired IQ[20] but, as gestational age was allowed for as a confounding factor by Valdez Jiménez et al., their study supports the first and second trimesters of pregnancy as an *in utero* period when the embryo or foetus is at risk of fluoride-induced neurotoxicity.

In addition, studies of the brains of aborted foetuses of mothers with dental fluorosis or both dental and skeletal fluorosis show that *in utero* fluoride exposure can produce neurologic damage.[21-23]

Thus the current data on fluoride-induced developmental neurotoxicity give a coherent picture with intrauterine exposure to low doses of fluoride being associated with impaired cognitive functioning. Fluoride, the ion of fluorine, is not an essential trace element in humans or necessary for the development of healthy teeth and bones.[24] It is likely that there is no threshold for fluoride neurotoxicity in drinking water, and the only assuredly safe level is zero.[25,26] The currently recommended level of 0.7 mg F/L for community water systems[25] and the provision of fluoridated salt are no longer appropriate for preventing dental caries because they will result in pregnant women and children having a F intake above the estimated safe daily intakes of approximately 0.04 mg F/day (0.0006 mg F/kg bw/day for a 70 kg woman) and 0.15 mg F/day (0.003 mg F/kg bw/day for a 45 kg child, the 90th percentile children's body mass at 8–13 yr), respectively.[25] The oral reference value for longer-term (up to 10% of an average life span) exposure (RfV_{LO}) can be calculated to be approximately 0.0006 mg/kg bw/day (0.04÷70=0.00057).

Preventing fluoride-induced IQ loss in children by lowering the dietary fluoride intake to the estimated safe level for pregnant women and children may not be easily achievable but a start could be made by relatively simple measures such as avoiding fluoridated water, fluoride-rich foods, and fluoridated dental products.[27]

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