HHS Public Access
Author manuscript
Environ Adv. Author manuscript; available in PMC 2023 January 13.

Published in final edited form as:
Environ Adv. 2022 April ; 7: . doi:10.1016/j.envadv.2021.100135.

Maternal fluoride exposure, fertility and birth outcomes: The MIREC cohort

Carly Goodman[a,1], **Meaghan Hall**[a,1], **Rivka Green**[a], **Richard Hornung**[b], **Esperanza Angeles Martinez-Mier**[c], **Bruce Lanphear**[d], **Christine Till**[a,*]

[a]Department of Psychology, Faculty of Health, York University, 4700 Keele St, Toronto, Ontario M3J 1P3, Canada

[b]Pediatrics and Environmental Health, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[c]School of Dentistry, Indiana University, Indianapolis, IND, USA

[d]Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia, Canada

Abstract

Objective: Fluoride exposure >1.5 mg/L from water has been associated with adverse pregnancy and birth outcomes. Little is known, however, about the effect of fluoride at levels consistent with water fluoridation (i.e., 0.7 mg/L) on pregnancy and birth outcomes. We examined the relationship between maternal fluoride exposure, fertility, and birth outcomes in a Canadian pregnancy cohort living in areas where municipal drinking water fluoride concentrations ranged from 0.04 to 0.87 mg/L.

Methods: Using data from the Maternal-Infant Research on Environmental Chemicals (MIREC) study, we estimated fluoride exposure during pregnancy using three different metrics: (1) maternal urinary fluoride concentrations standardized for specific gravity (MUF_{SG}) and averaged across all three trimesters (N = 1566), (2) water fluoride concentration (N = 1370), and (3) fluoride intake based on self-reported consumption of water, coffee, and tea, adjusted for body weight (N = 1192). Data on fertility, birth weight, gestational age, preterm birth, and small-for-gestational age (SGA) were assessed. We used multiple linear regression to examine associations between fluoride exposure, birth weight and gestational age, and logistic regression to examine associations with fertility, preterm birth, and SGA, adjusted for relevant covariates.

---

*Corresponding author. ctill@yorku.ca (C. Till).
1Indicates co-first authors.

CRediT authorship contribution statement
Carly Goodman: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Meaghan Hall:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Rivka Green:** Conceptualization, Writing – review & editing. **Richard Hornung:** Validation, Writing – review & editing. **Esperanza Angeles Martinez-Mier:** Resources, Writing – review & editing. **Bruce Lanphear:** Conceptualization, Writing – review & editing, Funding acquisition. **Christine Till:** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest
No conflicts of interest to disclose.

Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.envadv.2021.100135.

Results: Median (IQR) MUF_{SG} was 0.50 (0.33–0.76) mg/L, median water fluoride was 0.52 (0.17–0.64) mg/L, and median fluoride intake was 0.008 (0.003–0.013) mg/kg/day. MUF_{SG}, water fluoride concentrations, and fluoride intake were not significantly associated with fertility, birth weight, gestational age, preterm birth, or SGA. Fetal sex did not modify any of the associations.

Conclusion: Fluoride exposure during pregnancy was not associated with fertility or birth outcomes in this Canadian cohort.

Keywords

Fluoride; Pregnancy; Birth outcomes; Fertility; Drinking water

Introduction

Exposure to toxic chemicals during gestation has been associated with adverse birth outcomes, including preterm birth (< 37 weeks gestation), low birth weight (LBW; < 2500 g), and decreased fetal growth, also termed small-for-gestational age (SGA; Berkowitz et al., 2006; Lam et al., 2014; Latini et al., 2003; National Toxicology Program, 2012; Stieb et al., 2012; U.S. Environmental Protection Agency, 2013). Complications related to these adverse birth outcomes are a leading cause of infant mortality (Ely and Driscoll, 2020; Statistics Canada, 2021). Infants born preterm or LBW are at increased risk of various developmental and health related issues, including acute respiratory and immunologic problems, as well as long-term motor, cognitive, behavioural, and social-emotional deficits (Bélanger et al., 2018; Bhutta et al., 2002; Hall et al., 2008; Lemons et al., 2001; U.S. Environmental Protection Agency, 2013). Exposure to toxic chemicals prior to conception has also been associated with reduced fertility (Buck Louis, 2014; Chevrier et al., 2013; Cole et al., 2005; Fei et al., 2009; Whitworth et al., 2012).

Fluoridated water contributes the largest source of fluoride exposure in adolescents and adults (U.S. Environmental Protection Agency, 2010). Fluoride can occur naturally in some freshwater or be added to public water supplies at a level of 0.7 mg/L for protection against dental caries. In some parts of the world, naturally occurring fluoride levels can far exceed the recommended upper limit of 1.5 mg/L (World Health Organization, 2004).

High levels of fluoride exposure in pregnant women living in Africa and India have been associated with greater risk of miscarriage and stillbirth (Goyal et al., 2020), as well as preterm and LBW infants (Diouf et al., 2012; Sastry et al., 2011). These observed associations may be explained, in part, by the increased risk of anemia that has been linked to high-level fluoride exposure (Goyal et al., 2020; Susheela et al., 2016, 2010). High water fluoride concentrations have also been associated with reductions in annual fertility rate in ecological studies (Freni, 1994; Yousefi et al., 2017). In experimental studies, long-term exposure to sodium fluoride (NaF) in mice and rats has been linked to reductions in fertility, number of viable fetuses, concentration of reproductive hormones, total number of follicles, and sperm quality (Chaithra et al., 2020; Darmani et al., 2001; Elbetieha et al., 2000; Gupta et al., 2007; Pushpalatha et al., 2005; Yin et al., 2015; Zhou et al., 2013b).

Recent epidemiological studies conducted in communities with fluoridation have associated fluoride exposure in pregnancy with increased risk of neurotoxicity in the offspring (Green et al., 2019; Bashash et al., 2017); however, little is known about the effect of exposure to these concentrations of fluoride on fertility or birth outcomes. Some studies have suggested that lower-level fluoride exposure (~0.7 mg/L) for pregnant women may protect against the adverse effects of maternal periodontal disease on birth outcomes. Specifically, an experimental study conducted in mice subjected to intrauterine inflammation during gestation (a sequela of maternal periodontal disease; Jia et al., 2019) reported that exposure to low levels of fluoride was associated with reduced prevalence of preterm birth. An ecologic study (Zhang et al., 2019) showed that dental cleaning, and dental cleaning in tandem with community water fluoridation (CWF) were associated with reduced prevalence of preterm birth; yet there was no association with CWF alone. While an increased risk of adverse birth outcomes has been observed among women with oral health diseases other than caries (i.e., periodontal disease; Xiong et al., 2007), no associations have been identified between dental caries in pregnancy and birth outcomes, including preterm birth (Wagle et al. 2018).

Considering the ubiquity of fluoride exposure and the large social, health, and economic burdens of infertility and preterm birth (Behrman and Butler, 2007), we examined the relationship between maternal fluoride exposure and fertility as well as birth outcomes, including birth weight, gestational age, preterm birth, and SGA. We measured fluoride concentrations in urine and tap water, and fluoride intake was estimated through beverage consumption in a large sample of pregnant women living in 10 cities across Canada, seven of which have CWF. Given that this is the first cohort study to examine the relationship between fluoride exposure, fertility and birth outcomes among pregnant women living in communities with and without CWF, we do not propose specific hypotheses.

Methods

Study population

Between 2008 and 2011, the Maternal-Infant Research on Environmental Chemicals (MIREC) study recruited 2001 pregnant women from 10 cities across Canada. Women were recruited if they could communicate in English or French, were 18 years of age or older, and were within the first 14 weeks of gestation. Women were excluded if there were known fetal abnormalities, medical complications, or illicit drug use during pregnancy. For the fertility outcome sample, women were excluded if their male partner reported infertility. For the birth outcomes sample, women were excluded if they did not have singleton, live births and one mother-infant pair was excluded due to an extremely small birth weight (~1110 g). Additional details are provided by Arbuckle et al. (2013).

Of the 2001 women recruited, 1983 had available questionnaire data; 1566 of these women had three urinary fluoride measures of which fertility and birth outcomes with complete covariates were available for 1382 (88.3%) and 1350 (86.2%), respectively; 1370 women had water fluoride concentration of which fertility and birth outcomes with complete covariates were available for 1208 (88.2%) and 1082 (79.0%), respectively; and 1192 women had fluoride intake measured of which fertility and birth outcomes with complete covariates were available for 1061 (89.0%) and 1045 (87.7%), respectively (see Fig. 1 for our population flow chart and Supplemental Fig. 1 for complete covariates).

Participants completed a questionnaire during the first and third trimester of pregnancy. Sociodemographic (e.g., maternal age, level of education, income, ethnicity, and marital status) and behavioural information (e.g., beverage consumption and smoking) were collected. Pre-pregnancy body mass index (BMI) was determined by dividing self-reported weight (kg) by measured height squared (m2).

The MIREC study received ethics approval from all recruitment sites and this study received ethics approval from Health Canada and York University. All women in MIREC provided written informed consent.

Measures

Maternal urinary fluoride (MUF) concentration

We collected urine spot samples at each trimester of pregnancy (see Till et al., 2018). Urine was collected in Nalgene containers and then aliquoted into smaller cryovials. Samples were stored and shipped at appropriate temperatures. To strengthen reliability, women were only included in the analysis if they had all three spot samples. Urine samples were analyzed for fluoride at the Indiana University School of Dentistry using a modification of the hexamethyldisiloxane (Sigma Chemical Co., USA) microdiffusion method with ion-selective electrode (Martínez-Mier et al., 2011). The limit of detection for urinary analyses was 0.02 mg/L; precision and validity of the analyses used are reported in Martínez-Mier et al. (2011).

To account for variability in urinary dilution, each trimester MUF value (mg/L) was standardized for specific gravity (SG), prior to calculating the average MUF concentration, using the following formula (Till et al., 2018):

$$MUF_{SG} = MUF_i \times (SG_M - 1)/(SG_i - 1)$$

Where MUF_{SG} is the SG-standardized fluoride concentration (mg/L), MUF_i is the observed fluoride concentration (mg/L), SG_i is the SG of the individual urine sample, and SG_M is the median SG for the cohort.

After standardizing for SG, one average MUF concentration was excluded because the adjusted value exceeded the highest concentration standard (5 mg/L) and there was less certainty of it being a representative exposure value.

Water fluoride

Water fluoride concentration was determined for women who reported drinking tap water during pregnancy, by matching participants' postal codes to municipal water treatment plants. Water treatment plants measured fluoride levels daily if fluoride was added to public drinking water, and weekly or monthly if fluoride was not added to public water (Till et al., 2018). To estimate water fluoride concentration for each woman, we calculated geometric means across pregnancy.

Maternal fluoride intake

Information on women's body weight and consumption of tap water, tea, and coffee in their first and third trimesters were collected through the self-report questionnaire. We estimated maternal fluoride intake (mg/kg/day) adjusted for body weight in trimester one and three separately by multiplying water fluoride concentration (mg/L) by total volume (L) consumed of water, tea, and coffee; we then added the additional fluoride content that would be expected from each cup of black tea or green tea consumed. We used 0.326 mg as an estimate of fluoride intake in a 200-mL cup of black tea and 0.260 mg as an estimate of fluoride intake in a 200-mL cup of green tea (Krishnankutty et al., 2021). The final estimate of maternal fluoride intake (mg/kg/day) was derived by taking the average of the two estimates for trimesters one and three. Overall, maternal fluoride intake was calculated using the following formula:

$$\frac{\frac{(WaterF_{T1} * TotalCups_{T!}) + BlackTeaF_{T1} + GreenTeaF_{T1}}{BW_{T1}} + \frac{(WaterF_{T3} * TotalCups_{T3}) + BlackTeaF_{T3} + GreenTeaF_{T3}}{BW_{T3}}}{2}$$

Where WaterF is the amount of fluoride in a 200mL cup based on each women's individual water fluoride concentration, TotalCups is the total volume of water, coffee, and tea consumed, BlackTeaF is the fluoride intake in a 200-mL cup of black tea, GreenTeaF is the fluoride intake in a 200-mL cup of green tea, and BW is maternal body weight in kilograms. The subscript T1 represents trimester 1 data, and the subscript T3 represents trimester 3 data.

Outcome measures

In the MIREC cohort, fertility was assessed through answers to the following question: "How many months did it take you to get pregnant with this pregnancy?" Infertility was defined as a time to conception of 12 months or longer. This measure is consistent with the World Health Organization's definition of infertility as "a failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse" (Zegers-Hochschild et al., 2009). Birth weight was extracted from medical charts at delivery and was measured in grams. SGA was assessed using sex-specific, Canadian-based reference charts assessing birth weight for gestational age (Kramer et al., 2001). Infants were categorized as SGA if their birth weight was less than the 10th percentile for gestational age (Kramer et al., 2001). Gestational age was determined based on last menstrual period (LMP) or ultrasound established dates. LMP was used unless LMP and ultrasound established dates differed by more than seven days; in which case ultrasound dates were used (Kieler et al., 1993). Preterm birth was defined as a gestational age at delivery of less than 37 weeks.

Statistical analyses

We used linear regression models to estimate the associations between our three measures of fluoride exposure (MUF_{SG}, water fluoride, and fluoride intake) and birth weight and gestational age. We used logistic regression models to estimate the associations between our three measures of fluoride exposure (MUF_{SG}, water fluoride, and fluoride intake) and increased odds of dichotomous outcomes: infertility, SGA, and preterm birth. In supplementary analyses, chi-square tests for categorical covariates and t-tests for continuous covariates were used to test for sampling differences. Given that MUF_{SG} is the gold standard for measuring fluoride exposure, we specifically tested for differences between the sample with MUF_{SG} and outcome data and the original group of women included in the MIREC cohort.

Potential covariates were identified *a priori* based on biologically plausible and reported associations with fluoride, fertility, gestational age, and birth weight (Buzalaf et al., 2015; Buzalaf and Whitford, 2011; Cogswell and Yip, 1995; Kelly-Weeder and Cox, 2006; Stephen and Chandra, 2006; Till et al., 2018) and were conceptualized in directed acyclic graphs (DAGs; see Supplemental Fig. 1). Based on the relationships outlined within our DAGs, a covariate was retained in a model if its *P* value was less than .20 and its inclusion changed the regression coefficient associated with fluoride exposure measures by more than 10%.

For our analysis of fertility, the covariates considered included pre-pregnancy BMI, ethnicity (white, other), maternal age, income (less than $100,000, $100,000 or more), level of education (bachelor’s degree or higher, trade school diploma or lower), exposure to secondhand smoke (yes, no), smoking in first trimester (yes, no), and city of residence.

For our analyses of birth outcomes, the covariates considered included pre-pregnancy BMI, infant sex, ethnicity (white, other), parity (zero, one, two or more), marital status (in a relationship, single), maternal age, income (less than $100,000, $100,000 or more), level of education (bachelor’s degree or higher, trade school diploma or lower), alcohol intake during pregnancy (yes, no), exposure to secondhand smoke (yes, no), smoking in first trimester (yes, no), and city of residence.

Models estimating odds of SGA and preterm birth were adjusted for the same set of covariates as those used in the analyses of birth weight and gestational age. Given findings that males may be more sensitive to prenatal fluoride exposure (Green et al., 2020), we also examined sex-specific associations in all birth outcome models by testing the interaction between child sex and each fluoride measure; however, no interactions were observed (i.e., all p values > .20).

Regression diagnostics confirmed that there were no issues with collinearity in any of the models (variance inflation factor <4 for all covariates). Plots of residuals against fitted values did not suggest any assumption violations. Sensitivity analyses run without influential observations, as measured by studentized residuals, leverages, Cook’s distance and DFITS, provided no substantial differences. Including quadratic effects of MUF_{SG}, water fluoride, or fluoride intake did not significantly improve the regression models.

Analyses were conducted using STATA version 16.1 (STATA corporation). The *P* value level of significance was .05, and all tests were 2-tailed. All coefficients are reported for every

1 mg/L increase in MUF_{SG} and water fluoride concentration, and for every 0.01 mg/kg increase in fluoride intake per day.

Results

Demographic characteristics of the subsamples with data on $MUF_{SG,}$ water fluoride, and fluoride intake and fertility and birth outcomes can be found in Tables 1 and 2, respectively. The 1382 women with data on MUF_{SG}, fertility and complete covariates did not significantly differ from the original sample of 1983 women on most of the demographic characteristics except for the percentage of smokers in trimester 1 (Supplemental Table 1). Similarly, the 1350 mother-child dyads with MUF_{SG}, singleton, live births and complete covariate data did not differ significantly from the original sample of 1828 women with singleton, live births on many of the demographic characteristics except for the mean gestational age and percentage of women with a graduate school education (Supplemental Table 2).

Approximately 12% of the women took 12 months or longer to become pregnant. Infants had a mean birth weight of 3478 g (SD = 471.8; range: 1765–5070) and a mean gestational age of 39.47 weeks (SD = 1.41; range: 33.30–42.40). Approximately 5% of women delivered infants who were preterm or SGA. Among fetal growth outcomes, birth weight and gestational age were moderately correlated (r = .46).

Fluoride measurements

In both our fertility and birth outcomes samples, the median MUF_{SG} concentration was 0.50 mg/L (range: 0.05–3.33; IQR: 0.33–0.76 mg/L). Similarly, the median water fluoride concentration was 0.52 mg/L (range: 0.04–0.87; IQR: 0.17–0.64 mg/L), and the median estimated fluoride intake was 0.008 mg per kg of body weight per day (range: 0.000–0.043; IQR 0.003–0.013 mg/kg/day). MUF_{SG} was moderately correlated with both water fluoride concentration (r = .35; $p < .001$) and fluoride intake (r = .47; $p < .001$); likewise, water fluoride concentration was highly correlated with fluoride intake (r = .68; $p < .001$).

Fluoride exposure and birth weight and gestational age

There was a significant positive association between MUF_{SG} and birth weight in the unadjusted model (B = 78.97; 95% CI: 15.13, 142.81; $p = .015$); however, in covariate-adjusted models, no significant associations were observed between MUF_{SG} and birth weight or gestational age (see Fig. 2 and Table 2). Similarly, no significant associations were detected between water fluoride concentration or fluoride intake and birth weight or gestational age in either unadjusted or covariate-adjusted models (see Fig. 2 and Table 2).

Fluoride exposure and preterm birth, SGA, and infertility

No significant associations were observed between MUF_{SG}, water fluoride concentration, or fluoride intake and the risk of preterm birth, SGA, or infertility in either the unadjusted or covariate-adjusted models (Table 2).

Discussion

To our knowledge, this is the first cohort study to examine the relationship between maternal fluoride exposure and both fertility and birth outcomes in women living in regions with and without water fluoridation. The majority of women in MIREC were exposed to water fluoride levels lower than 0.7 mg/L. Fluoride measured in women's urine and in tap water, as well as maternal fluoride intake estimated via consumption of water, tea, and coffee, was not significantly associated with fertility, birth weight, gestational age, preterm birth, or SGA. Non-significant findings were coupled with small effect sizes, despite reporting coefficients for every 1 unit increase in fluoride exposure (i.e., 1 mg/L), which represents a higher level of exposure for this group of women.

We did not find evidence of an association between fluoride exposure in pregnancy and risk of female infertility. In contrast, one ecological study based in the U.S. reported that counties with higher levels of fluoride in drinking water had lower total fertility rates among women aged 10 to 49 years (Freni, 1994). Another ecological study based in Iran found that women aged 10 to 49 years living in areas with high water fluoride levels (~10 mg/L) were less fertile and had higher rates of both infertility and abortion without known etiology when compared to women exposed to relatively lower levels of fluoride (~1.5 mg/L; Yousefi et al., 2017). Experimental studies have also demonstrated that NaF toxicity decreases the rate of successful pregnancy, inhibits the synthesis and secretion of reproductive hormones, and causes structural damage to the ovaries and uterus (Al-shammari, 2019; Al-Hiyasat et al., 2000; Darmani et al., 2001; Thakare & Dhurvey, 2012; Zhou et al., 2013a, 2013b). It is possible that fluoride exposure levels in the current sample were too low to impact fertility in females; however, more research is warranted on this topic given that lower levels of fluoride exposure may interact with specific genes to impact reproductive hormones (Zhou et al., 2016). Measures of women's reproductive hormone levels may be a more reliable estimate of female fertility and may also be more sensitive to detecting an effect than a retrospective self-report about the amount of time it took to get pregnant (Cooney et al., 2009).

Future studies may also want to consider the effects of fluoride exposure on the male reproductive system as a potential contributor to fluoride-induced infertility. In experimental studies, significant reductions in the number of mature Leydig and Sertoli cells, weight of testes, serum concentration of testosterone, and sperm count, motility, density, and viability have been observed among NaF-treated mice and rats (Chaithra et al., 2020; Elbetieha et al., 2000; Gupta et al., 2007; Pushpalatha et al., 2005). Importantly, direct associations have been established between these histological alterations and infertility, even when those males were mated with untreated, healthy females (Chaithra et al., 2020; Elbetieha et al., 2000).

To date, few studies have examined the association between fluoride exposure and birth outcomes, especially among women living in areas with levels of fluoride consistent with water fluoridation. Of these, some have found increased risk of adverse birth outcomes in areas where fluoride levels in drinking water are high (> 1.5 mg/L; Diouf et al., 2012; Goyal et al., 2020; Sastry et al., 2011; Susheela et al., 2010), whereas others have found that fluoride exposure may offer protection against adverse birth outcomes

(Aghaei et al., 2015; Jia et al., 2019; Zhang et al., 2019). Inconsistency in results from the present study and those from pre-existing studies may be attributed to differences in characteristics of the study populations, methodology, quality of the exposure matrix, and levels of fluoride exposure. Specifically, some studies reporting that high-level fluoride is associated with birth outcomes have relied on correlational analyses, failed to control for relevant confounders (Aghaei et al., 2015; Sastry et al., 2011), and, therefore, are subject to confounding bias (Skelly et al., 2012). Past studies examining fluoride and birth outcomes have evaluated fluoride exposure using measures of dental fluorosis (Diouf et al., 2012), drinking water fluoride concentration (Aghaei et al., 2015; Zhang et al., 2019), whether an individual gets dental cleaning (potentially exposing them to fluoride by fluori-dated prophylaxis pastes; Zhang et al., 2019), and serum fluoride concentration (Sastry et al., 2011).

Strengths and limitations

Strengths of this study include the use of a large pregnancy cohort with robust measures of fluoride exposure. Fluoride exposure was assessed using three different methods that resulted in a better individualized assessment of exposure levels, and included a fluoride biomarker (urinary fluoride), water fluoride concentration, and an estimate of fluoride intake from beverage consumption. Measuring fluoride in urine and from tea consumption (used to estimate fluoride intake) allowed us to assess additional sources of fluoride beyond that from drinking water. Moreover, our statistical analyses controlled for a wide array of potential confounding factors.

Our study also has some limitations. Compared to the general Canadian population, women in the MIREC cohort tend to be older, predominantly Caucasian, have higher household incomes and education levels, and are more likely to be married/common law and less likely to smoke (Arbuckle et al., 2013). Many of these sociodemographic factors have been shown to be protective against low birth weight and preterm birth (Hidalgo-Lopezosa et al., 2019). Indeed, the prevalence of preterm birth and SGA among our sample was only 5%, which is lower than the national average of around 8% (Public Health Agency of Canada, 2013). Future studies are needed to determine if the obtained results are generalizable to other, more diverse populations. An additional limitation is that we used spot urine samples without control for behaviours that could contribute to acute changes in fluoride concentration, such as consumption of fluoride-free bottled water prior to urine collection. Effects of this limitation were minimized by averaging urine fluoride across all three trimesters of pregnancy and adjusting for urinary dilution. Finally, we used urine samples collected in pregnancy and water fluoride concentrations matched in time to the pregnancy period as a proxy for preconception fluoride exposure. While some studies report consistent fluoride metabolism among nonpregnant and pregnant women (Maheshwari et al., 1983, 1981), others have reported lower urinary excretion of fluoride in pregnant women compared to nonpregnant women, that is likely due to increased fetal uptake (Gedalia et al., 1959; Opydo-Szymaczek & Borysewicz-Lewicka, 2005). Considering these inconsistencies, future studies should aim to obtain urine samples prior to conception when examining the association between fluoride exposure and fertility outcomes.

Conclusion

In this large Canadian pregnancy and birth cohort, fluoride exposure during pregnancy was not significantly associated with fertility or birth outcomes after controlling for important covariates. Given the ubiquity of fluoride exposure among pregnant women, prospective cohort studies in other populations are warranted to validate the current findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Nicole Lupien, BA, Stéphanie Bastien, BA, and Romy-Leigh McMaster, BA (Centre de Recherche, CHU Sainte-Justine), and the MIREC Study Coordinating Staff for their administrative support, the MIREC study group of investigators and site investigators, as well as the MIREC Biobank; Dr. Jillian Ashely-Martin and Dr. Tye Arbuckle for their review of our manuscript as the Knowledge Translation representatives for the MIREC study; Christine Buckley, MSc, Frank Lippert, PhD, and Prithvi Chandrappa, MSc (Indiana University School of Dentistry), for their analysis of urinary fluoride and specific gravity at the Indiana University School of Dentistry. We also thank staff affiliated with community water treatment plants who helped to provide water fluoride data for this study. No compensation was received from a funding sponsor for these contributions.

Funding

This study was supported by the National Institute of Environmental Health Science (grant numbers R21ES027044, 2016–2019; R01ES030365, 2019–2024). The Maternal-Infant Research on Environmental Chemicals Study was supported by the Chemicals Management Plan at Health Canada, the Ontario Ministry of the Environment, and the Canadian Institute for Health Research (grant MOP-81285, 2006).

References

Aghaei M, Derakhshani R, Raoof M, Dehghani M, Mahvi AH, 2015. Effect of fluoride in drinking water on birth height and weight: an ecological study in Kerman Province, Zarand county, Iran. Fluoride 48 (2), 160–168. https://www.fluorideresearch.org/482/files/FJ2015_v48_n2_p160-168_sfs.pdf.

Al-Hiyasat AS, Elbetieha AM, Darmani H, 2000. Reproductive toxic effects of ingestion of sodium fluoride in female rats. Fluoride 33 (2), 79–84. https://www.fluorideresearch.org/332/files/FJ2000_v33_n2_p79-84.pdf.

Al-shammari ZM, 2019. Hormonal changes in sodium fluoride exposed female rats and its amelioration by Urticadioca leaf extract. Indian J. Public Health Res. Dev 10 (11), 4979–4984. 10.5958/0976-5506.2019.03939.1.

Arbuckle TE, Fraser WD, Fisher M, Davis K, Liang CL, Lupien N, Bastien S, Velez MP, Von Dadelszen P, Hemmings DG, Wang J, Helewa M, Taback S, Sermer M, Foster W, Ross G, Fredette P, Smith G, Walker M, Ouellet E, 2013. Cohort profile: the maternal-infant research on environmental chemicals research platform. Paediatr. Perinat. Epidemiol 27 (4), 415–425. 10.1111/ppe.12061. [PubMed: 23772943]

Bashash M, Thomas D, Hu H, Martínez-Mier EA, Sanchez BN, Basu N, Peterson KE, Ettinger AS, Wright R, Zhang Z, Liu Y, Schnaas L, Mercado-García A, Téllez-Rojo MM, Hernández-Avila M, 2017. Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6–12 years of age in Mexico. Environ. Health Perspect 125 (9), 097017 10.1289/ehp655. [PubMed: 28937959]

Behrman RE, Butler AS, 2007. Preterm birth: Causes, consequences, and prevention. The National Academies Press. https://www.ncbi.nlm.nih.gov/books/NBK11362/pdf/Bookshelf_NBK11362.pdf.

Bélanger R, Mayer-Crittenden C, Minor-Corriveau M, Robillard M, 2018. Gross motor outcomes of children born prematurely in northern Ontario followed by a neonatal follow-up programme. Physiother. Canada 70 (3), 233–239, 10.3138%2Fptc.2017-13.

Berkowitz Z, Price-Green P, Bove FJ, Kaye WE, 2006. Lead exposure and birth outcomes in five communities in Shoshone County, Idaho. Int. J. Hyg. Environ. Health 209 (2), 123–132. 10.1016/j.ijheh.2005.11.001. [PubMed: 16376613]

Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJS, 2002. Cognitive and behavioural outcomes of school-aged children who were born preterm. JAMA 288 (6), 728–737. 10.1001/jama.288.6.728. [PubMed: 12169077]

Louis B, M G, 2014. Persistent environmental pollutants and couple fecundity: an overview. Reproduction 147 (4), R97–R104. 10.1530/REP-13-0472. [PubMed: 24310101]

Buzalaf CP, Leite ADL, Buzalaf MAR, 2015. Fluoride metabolism. In V. R. Preedy Fluoride: Chemistry, Analysis, Function and Effects. Royal Society of Chemistry, pp. 54–72. 10.1039/9781782628507-00054.

Buzalaf MAR, Whitford GM, 2011. Fluoride intake, metabolism and toxicity. In Buzalaf MAR (Ed.). In: Fluoride and The Oral Environment, 22. Karger, pp. 20–36. 10.1159/isbn.978-3-8055-9659-6.

Chaithra B, Sarjan HN, Shivabasavaiah, 2020. Sodium fluoride and fluoride contaminated ground water induced altered reproductive performances in male rats. Biol. Trace Elem. Res 195 (2), 544–550. 10.1007/s12011-019-01882-5. [PubMed: 31463763]

Chevrier C, Warembourg C, Gaudreau E, Monfort C, Le Blanc A, Gauldner L, Cordier S, 2013. Organochlorine pesticides, polychlorinated biphenyls, seafood consumption, and time-to-pregnancy. Epidemiology 24 (2), 251–260. 10.1097/EDE.0b013e31827f53ec. [PubMed: 23348067]

Cogswell ME, Yip R, 1995. The influence of fetal and maternal factors on the distribution of birthweight. Semin. Perinatol 19 (3), 222–240. 10.1016/s0146-0005(05)80028-x. [PubMed: 7570074]

Cole DC, Wainman B, Sanin LH, Weber J-P, Muggah H, Ibrahim S, 2005. Environmental contaminant levels and fecundability among non-smoking couples. Reprod. Toxicol 22 (1), 13–19. 10.1016/j.reprotox.2005.12.001.

Cooney MA, Buck Louis GM, Sundaram R, McGuiness BM, Lynch CD, 2009. Validity of self-reported time to pregnancy. Epidemiology 20 (1), 56–59. 10.1097/ede.0b013e31818ef47e. [PubMed: 19057382]

Darmani H, Al-Hiyasat AS, Elbetieha AM, 2001. Effects of sodium fluoride in drinking water on fertility in female mice. Fluoride 34 (4), 242–249. https://www.fluorideresearch.org/344/files/FJ2001_v34_n4_p242-249.pdf.

Diouf M, Cisse D, Lo CMM, Ly M, Faye D, Ndiaye O, 2012. Pregnant women living in areas of endemic fluorosis in Senegal and low birthweight newborns: Case-control study. Revue d'Epidemiologie et de Sante Publique 60 (2), 103–108. 10.1016/j.respe.2011.09.009.

Elbetieha A, Darmani H, Al-Hiyasat AS, 2000. Fertility effects of sodium fluoride in male mice. Fluoride 33 (3), 128–134. https://www.fluorideresearch.org/333/files/FJ2000_v33_n3_p128-134.pdf.

Ely DM, Driscoll AK, 2020. Infant mortality in the United States, 2018: data from the period linked birth/infant death file. Natl. Vital Stat. Rep 69 (7), 1–18.

Fei C, McLaughlin JK, Lipworth L, Olsen J, 2009. Maternal levels of perfluorinated chemicals and subfecundity. Hum. Reprod 24 (5), 1200–1205. 10.1093/humrep/den490. [PubMed: 19176540]

Freni SC, 1994. Exposure to high fluoride concentrations in drinking water is associated with decreased birth rates. J. Toxicol. Environ. Health 42 (1), 109–121. 10.1080/15287399409531866. [PubMed: 8169995]

Gedalia J, Brzezinski A, Bercovici B, 1959. Urinary fluorine levels in women during pregnancy and after delivery. J. Dent. Res 38 (3), 548–551. 10.1177/00220345590380031701. [PubMed: 13654605]

Goyal LD, Bakshi DK, Arora JK, Manchanda A, Singh P, 2020. Assessment of fluoride levels during pregnancy and its association with early adverse pregnancy outcomes. J. Fam. Med. Prim. Care 9 (6), 2693–2698. 10.4103/jfmpc.jfmpc_213_20.

Green R, Rubenstein J, Popoli R, Capulong R, Till C, 2020. Sex-specific neurotoxic effects of early-life exposure to fluoride: a review of the epidemiologic and animal literature. Curr. Epidemiol. Rep 7, 263–273. 10.1007/s40471-020-00246-1. [PubMed: 33816056]

Green R, Lanphear B, Hornung R, Flora D, Martínez-Mier EA, Neufield R, Ayotte P, Muckle G, Till C, 2019. Association between maternal fluoride exposure during pregnancy and IQ scores in offspring in Canada. JAMA Pediatr. 173 (10), 940–948. 10.1001/jamapediatrics.2019.1729. [PubMed: 31424532]

Gupta RS, Khan TI, Agrawal D, Kachhawa JBS, 2007. The toxic effects of sodium fluoride on the reproductive system of male rats. Toxicol. Ind. Health 23 (9), 507–513. 10.1177/0748233708089041. [PubMed: 18681235]

Hall RW, Huitt TW, Thapa R, Williams DK, Anand KJS, Garcia-Rill E, 2008. Long-term deficits of preterm birth: evidence for arousal and attentional distrubances. Clin. Neurophysiol 119 (6), 1281–1291. 10.1016/j.clinph.2007.12.021. [PubMed: 18372212]

Hidalgo-Lopezosa P, Jiménez-Ruz A, Carmona-Torres JM, Hidalgo-Maestre M, Rodríguez-Borrego MA, López-Soto PJ, 2019. Sociodemographic factors associated with preterm birth and low birth weight: a cross-sectional study. Womend Birth 32 (6), e538–e543. 10.1016/j.wombi.2019.03.014.

Jia B, Zong L, Lee JY, Lei J, Zhu Y, Xie H, Clemens JL, Feller MC, Na Q, Dong J, McLane MW, Jones-Beatty K, Burd I, 2019. Maternal supplementation of low dose fluoride alleviates adverse perinatal outcomes following exposure to intrauterine inflammation. Sci. Rep 9 (1), 2575. 10.1038/s41598-018-38241-8. [PubMed: 30796233]

Kelly-Weeder S, Cox CL, 2006. The impact of lifestyle risk factors on female infertility. Women Health 44 (4), 1–23. 10.1300/j013v44n04_01.

Kieler H, Axelsson O, Nilsson S, Waldenström U, 1993. Comparison of ultrasonic measurement of biparietal diameter and last menstrual period as a predictor of day of delivery in women with regular 28 day-cycles. Acta Obstet. Gynecol. Scand 72 (5), 347–349. 10.3109/00016349309021110. [PubMed: 8392263]

Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, Blondel B, Bŕeart G, 2001. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics 108 (2), E35. 10.1542/peds.108.2.e35. [PubMed: 11483845]

Krishnankutty N, Jensen TS, Kjaer J, Jørgensen JS, Nielsen F, Grandjean P, 2021. Public-health risks from tea drinking: Fluoride exposure. Scand. J. Public Health 8, 1–7. 10.1177/1403494821990284.

Lam J, Koustas E, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA, Woodruff TJ, 2014. The Navigation Guide – evidence-based medicine meets environmental health: integration of animal and human evidence for PFOA effects on fetal growth. Environ. Health Perspect 122 (10), 1040–1051. 10.1289/ehp.1307923. [PubMed: 24968389]

Latini G, De Felice C, Presta G, Del Vecchio A, Paris I, Ruggieri F, Mazzeo P, 2003. In utero exposure to di-(2-ethylhexyl) phthalate and duration of human pregnancy. Environ. Health Perspect 111 (14), 1783–1785. 10.1289/ehp.6202. [PubMed: 14594632]

Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ, Verter J, Temprosa M, Wright LL, Ehrenkranz RA, Fanaroff AA, Stark A, Carlo W, Tyson JE, Donovan EF, Shankaran S, Stevenson DK, 2001. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. Pediatrics 107 (1), E1. 10.1542/peds.107.1.e1. [PubMed: 11134465]

Maheshwari UR, King JC, Brunetti AJ, Hodge HC, Newbrun E, Margen S, 1981. Fluoride balances in pregnant and nonpregnant women. J. Occup. Med 23 (7), 465–468. 10.1097/00043764-198107000-00012. [PubMed: 7252609]

Maheshwari UR, King JC, Leybin L, Newbrun E, Hodge HC, 1983. Fluoride balances during early and late pregnancy. J. Occup. Med 25 (8), 587–590. [PubMed: 6886867]

Martínez-Mier EA, Curry JA, Heilman JR, Katz BP, Levy SM, Li Y, Maguire A, Margineda J, O'Mullane D, Phantumvanit P, Soto-Rojas AE, Stookey GK, Villa A, Wefel JS, Whelton H, Whitford GM, Zero DT, Zhang W, Zohouri V, 2011. Development of gold standard ion-selective electrode-based methods for fluoride analysis. Caries Res. 45 (1), 3–12. 10.1159/000321657. [PubMed: 21160184]

National Toxicology Program, 2012. NTP Monograph on Health Effects of Low-Level Lead. https://ntp.niehs.nih.gov/ntp/ohat/lead/final/monographhealtheffectslowlevellead_newissn_508.pdf.

Opydo-Szymaczek J, Borysewicz-Lewicka M, 2005. Urinary fluoride levels for assessment of fluoride exposure of pregnant women in Poznan, Poland. Fluoride 38 (4), 312–317. https://

www.researchgate.net/profile/Justyna-Opydo-Szymaczek/publication/265318084_Urinary_fluoride_levels_for_assessment_of_fluorifl_exposure_of_pregnant_women_in_Poznan_Poland/links/5e0b12c44585159aa4a70b12/Urinary-fluoride-levels-for-assessment-of-fluoride-exposure-of-pregnant-women-in-Poznan-Poland.pdf.

Public Health Agency of Canada. http://publications.gc.ca/collections/collection_2014/aspc-phac/HP7-1-2013-eng.pdf.

Pushpalatha T, Srinivas M, Reddy S, 2005. Exposure to high fluoride concentration in drinking water will affect spermatogenesis and steroidogenesis in male albino rats. BioMetals 18 (3), 207–212. 10.1007/s10534-005-0336-2. [PubMed: 15984565]

Sastry MG, Mohanty S, Varma Bhongir A, Mishra A, Rao P, 2011. Association of higher maternal serum fluoride with adverse fetal outcomes. Int. J. Med. Public Health 1 (2), 13–17. 10.5530/ijmedph.2.2011.4.

Skelly AC, Dettori JR, Brodt ED, 2012. Assessing bias: the importance of considering confounding. Evid. Based Spine Care J 3 (1), 9–12. 10.1055/s-0031-1298595.

Stephen EH, Chandra A, 2006. Declining estimates of infertility in the United States: 1982–2002. Fertil. Steril 86 (3), 516–523. 10.1016/j.fertnstert.2006.02.129. [PubMed: 16952500]

Stieb DM, Chen L, Eshoul M, Judek S, 2012. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. Environ. Res 117, 100–111. 10.1016/j.envres.2012.05.007. [PubMed: 22726801]

Susheela AK, Mondal NK, Gupta R, Ganesh K, Brahmankar S, Bhasin S, Gupta G, 2010. Effective interventional approach to control anaemia in pregnant women. Curr. Sci 98 (10), 1320–1330. https://www.jstor.org/stable/24107510.

Susheela AK, Gupta R, Mondal NK, 2016. Anaemia in adolescent girls: An intervention of diet editing and counselling. Natl. Med.l J. India 29 (4), 200–204. https://www.nmji.in/temp/NatlMedJIndia294200-532958_144815.pdf.

Thakare MT, Dhurvey VT, 2012. Histopathological changes in the Uterus of Rats after an administration of sodium fluoride. Int. J. Sci. Res 3 (6), 431–433. 10.15373/22778179/june2014/146.

Till C, Green R, Grundy JG, Hornung R, Neufeld R, Martínez-Mier EA, Ayotte P, Muckle G, Lanphear B, 2018. Community water fluoridation and urinary fluoride concentrations in a national sample of pregnant women in Canada. Environ. Health Perspect 126 (10), 107001 10.1289/ehp3546. [PubMed: 30392399]

Wagle M, D'Antonio F, Reierth E, Basnet P, Trovik TA, Orsini G, Manzoli L, Acharya G, 2018. Dental caries and preterm birth: a systematic review and meta-analysis. BMJ Open 8 (3), e018556, 10.1136%2Fbmjopen-2017-018556.

Whitworth KW, Haug LS, Baird DD, Becher G, Hoppin JA, Skjaerven R, Thomsen C, Eggesbo M, Travlos G, Wilson R, Longnecker MP, 2012. Perfluorinated compounds and subfecundity in pregnant women. Epidemiology 23 (2), 257–263. 10.1097/EDE.0b013e31823b5031. [PubMed: 22081060]

World Health Organization, 2004. Guidelines for drinking-water quality Vol. 1. https://www.who.int/water_sanitation_health/dwq/GDWQ2004web.pdf.

Xiong X, Buekens P, Vastardis S, Yu SM, 2007. Periodontal disease and pregnancy outcomes: state-of-the-science. Obstetr. Gynecol. Surv 62 (9), 605–615. 10.1097/01.ogx.0000279292.63435.40.

Yin S, Song C, Wu H, Chen X, Zhang Y, 2015. Adverse effects of high concentrations of fluoride on characteristics of the ovary and mature oocyte of mouse. PLoS ONE 10 (6), e0129594. 10.1371/journal.pone.0129594. [PubMed: 26053026]

Yousefi M, Mohammadi AA, Yaseri M, Mahvi AH, 2017. Epidemiology of drinking water fluoride and its contribution to fertility, infertility, and abortion: An ecological study in west Azaerbaijan province, Poldasht county, Iran. Fluoride 50 (3), 343–353. http://www.fluorideresearch.org/503/files/FJ2017_v50_n3_p343-353_sfs.pdf.

Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, Vanderpoel S, 2009. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. Fertil. Steril 92 (5), 1520–1524. 10.1016/j.fertnstert.2009.09.009. [PubMed: 19828144]

Zhang X, Lu E, Stone SL, Diop H, 2019. Dental Cleaning, Community Water Fluoridation and Preterm Birth, Massachusetts: 2009–2016. Matern. Child Health J 23 (4), 451–458. 10.1007/s10995-018-2659-y. [PubMed: 30542985]

Zhou G, Ren L, Hou J, Cui L, Ding Z, Cheng X, Zhu J, Cui R, Ba Y, 2016. Endemic fluorosis in Henan province, China: ERα gene polymorphisms and reproductive hormones among women. Asia Pac. J. Clin. Nutr 24 (4), 911–919. 10.6133/apjcn.062016.01.

Zhou Y, Qiu Y, He J, Chen X, Ding Y, Wang Y, Liu X, 2013a. The toxicity mechanism of sodium fluoride on fertility in female rats. Food Chem. Toxicol 62, 566–572. 10.1016/j.fct.2013.09.023. [PubMed: 24071475]

Zhou Y, Zhang H, He J, Chen X, Ding Y, Wang Y, Liu X, 2013b. Effects of sodium fluoride on reproductive function in female rats. Food Chem. Toxicol 56, 297–303. 10.1016/j.fct.2013.02.026. [PubMed: 23459146]

Statistics Canada (2021). Table 13-10-0395-01 Leading causes of death, infants. doi: 10.25318/1310039501-eng.

U.S. Environmental Protection Agency. (2013). America's children and the environment. 240-R-13-001. https://permanent.fdlp.gov/gpo63641/ace3_2013.pdf.

U.S. Environmental Protection Agency. (2010). Fluoride: exposure and relative source contribution analysis. 820-R-10-015. https://www.epa.gov/sites/production/files/2019-03/documents/fluoride-exposure-relative-report.pdf.

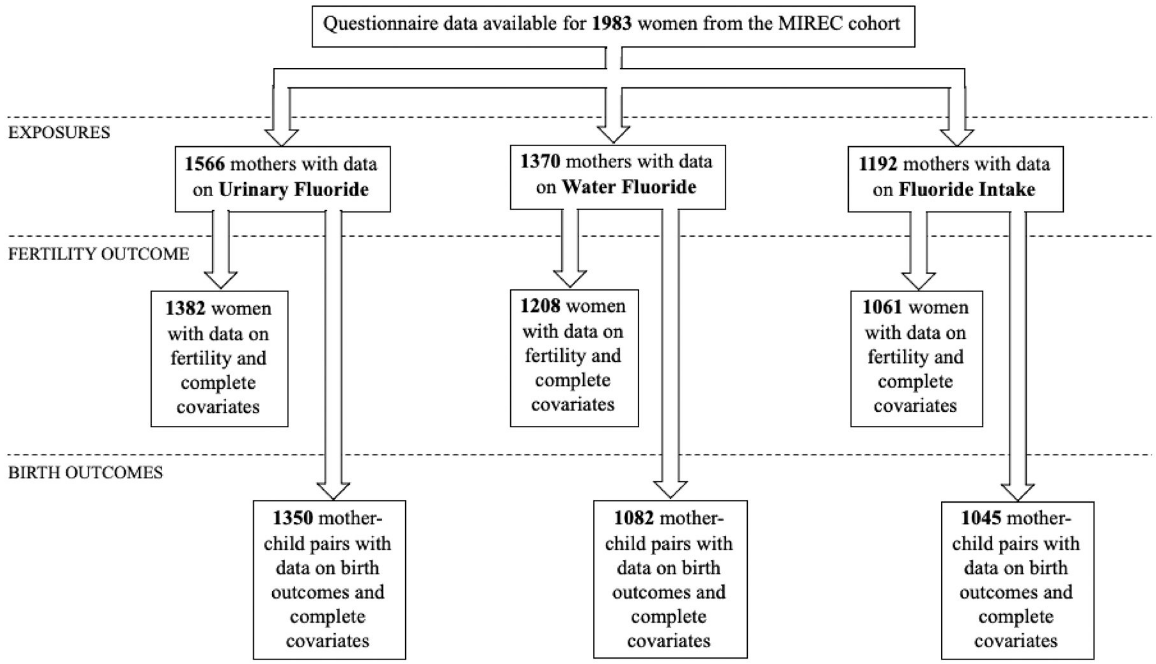

Fig. 1.

Population flow chart. Eligible participants recruited from the Maternal-Infant Research on Environmental Chemicals (MIREC) study.

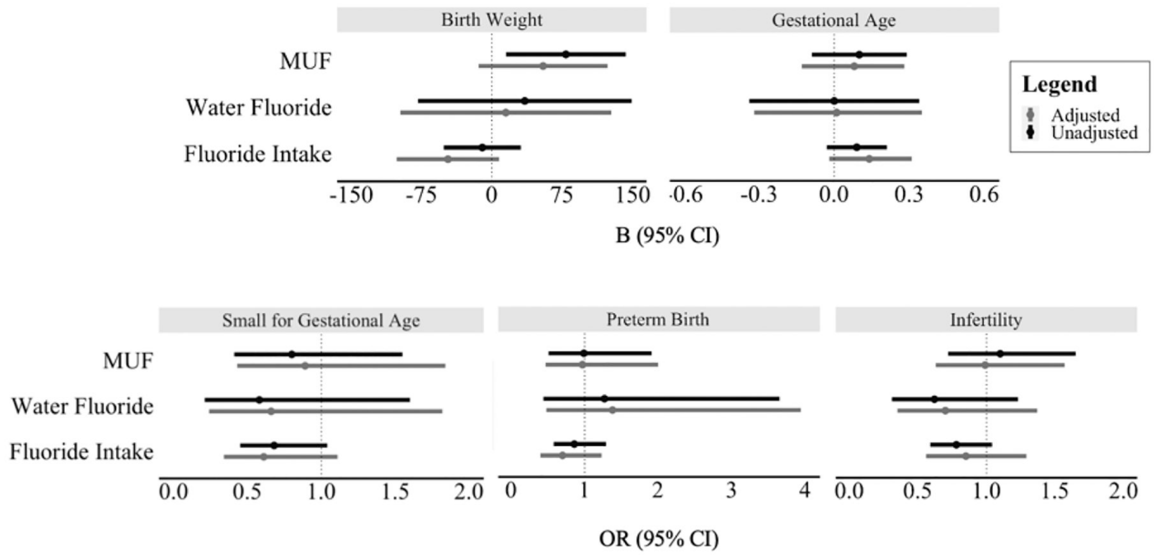

Fig. 2.

Unadjusted and adjusted effect estimates of association between fluoride exposure variables and birth weight, gestational age, small for gestational age, preterm birth, and infertility. Abbreviations: MUF = maternal urinary fluoride, adjusted for specific gravity.

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Demographic characteristics of the subsamples with data on fertility, complete covariates and MUF_{SG} (N = 1382), water fluoride (N = 1208), or fluoride intake (N = 1061). Continuous variables are reported as mean (± SD), +9s n (%).

	Exposure Predictor for Fertility Sample:		
Characteristics	**MUF_{SG} (N = 1382)**	**Water Fluoride (N = 1208)**	**Fluoride Intake (N = 1061)**
Outcomes			
Infertility			
Yes	159 (11.51)	141 (11.67)	124 (11.69)
No	1223 (88.49)	1067 (88.33)	937 (88.31)
Time to conception (months)	5.18 (±10.47)	5.07 (±9.88)	5.11 (±9.97)
Covariates			
Ethnicity			
White	1202 (86.98)	1016 (84.11)	893 (84.17)
Other	180 (13.02)	192 (15.89)	168 (15.83)
Maternal age (yr)	32.41 (±4.85)	32.62 (±5.07)	32.58 (±5.05)
Pre-pregnancy BMI (kg/m^2)	24.80 (±5.38)	24.56 (±5.22)	24.53 (±5.19)
Household income (CAD)			
<100 000	807 (58.39)	689 (57.04)	609 (57.40)
≥100 000	575 (41.61)	519 (42.96)	452 (42.60)
Level of Education			
College degree or less	478 (34.59)	386 (31.95)	333 (31.39)
Graduate school	904 (65.41)	822 (68.05)	728 (68.61)
Smoked in trimester 1			
Yes	58 (4.20)	53 (4.39)	43 (4.05)
No	1324 (95.80)	1155 (95.61)	1018 (95.95)
Second hand smoke in trimester 1			
Yes	74 (5.35)	63 (5.22)	57 (5.37)
No	1308 (94.65)	1145 (94.78)	1004 (94.63)

Abbreviations: MUF_{SG} = maternal urinary fluoride standardized for specific gravity; BMI = body mass index.

Table 2

Demographic characteristics of the subsamples with data on singleton, live births, complete covariates and MUF_{SG} (N = 1350), water fluoride (N = 1082), or fluoride intake (N = 1045). Continuous variables are reported as mean (± SD), and categorical variables are reported as n (%).

Characteristics	Exposure Predictor for Birth Outcomes Sample: MUF_{SG} (N = 1350)	Water Fluoride (N = 1082)	Fluoride Intake (N = 1045)
Outcomes			
Birth weight (g)	3479 (±468.2)[a]	3473 (±480.4)[b]	3468 (±480.3)[c]
Gestational age (wks)	39.48 (±1.39)	39.48 (±1.43)	39.48 (±1.44)
Small-for-gestational age			
Yes	70 (5.20)	62 (5.75)	62 (5.96)
No	1275 (94.8)	1016 (94.25)	979 (94.04)
Preterm birth			
<37	61 (4.52)	58 (5.36)	56 (5.36)
≥37	1289 (95.48)	1024 (94.64)	989 (94.64)
Covariates			
Infant sex			
Boy	706 (52.30)	579 (53.51)	559 (53.49)
Girl	644 (47.70)	503 (46.49)	486 (46.51)
Ethnicity			
White	1174 (86.96)	915 (84.57)	880 (84.21)
Other	176 (13.04)	167 (15.43)	165 (15.79)
Maternal age (yr)	32.39 (±4.86)	32.56 (±5.01)	32.54 (±5.04)
Pre-pregnancy BMI (kg/m^2)	24.84 (±5.43)	24.64 (±5.27)	24.58 (±5.19)
Parity			
0	612 (45.33)	509 (47.04)	498 (47.66)
1	537 (39.78)	420 (38.82)	406 (38.85)
2+	201 (14.89)	153 (14.14)	141 (13.49)
Marital status			
Married or common-law	1297 (96.07)	1031 (95.29)	994 (95.12)
Single	53 (3.93)	51 (4.71)	51 (4.88)
Household income (CAD)	791 (58.59)	626 (57.86)	602 (57.61)
<100 000	559 (41.41)	456 (42.14)	443 (42.39)
≥100 000			
Level of Education			
College degree or less	471 (34.89)	342 (31.61)	331 (31.67)
Graduate school	879 (65.11)	740 (68.39)	714 (68.33)
Drinks alcohol			
Yes	250 (18.52)	206 (19.04)	199 (19.04)
No	1100 (81.48)	876 (80.96)	846 (80.96)
Smoked in trimester 1	57 (4.22)	44 (4.07)	43 (4.11)
Yes	1293 (95.78)	1038 (95.93)	1002 (95.89)

Characteristics	Exposure Predictor for Birth Outcomes Sample: MUF$_{SG}$ (N = 1350)	Water Fluoride (N = 1082)	Fluoride Intake (N = 1045)
No			
Second hand smoke in trimester 1			
Yes	72 (5.33)	59 (5.45)	57 (5.45)
No	1278 (94.67)	1023 (94.55)	988 (94.55)

Abbreviations: MUF$_{SG}$ = maternal urinary fluoride standardized for specific gravity; BMI = body mass index.

[a] N = 1345.

[b] N = 1078.

[c] N = 1041.