Science of the Total Environment 838 (2022) 156459

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

# Maternal urinary fluoride during pregnancy and birth weight and length: Results from ELEMENT cohort study

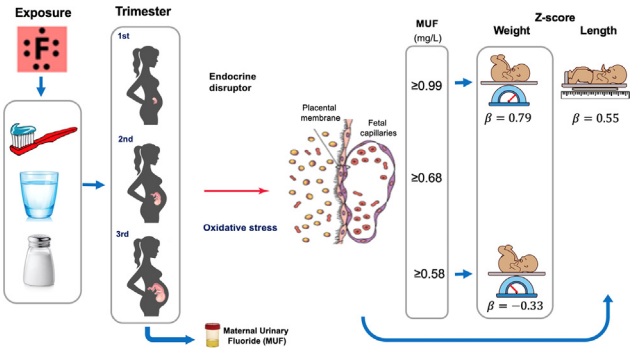
Sofía G. Ortíz-García [a], Luisa E. Torres-Sánchez [a], Teresa V. Muñoz-Rocha [a], Adriana Mercado-García [a], Karen E. Peterson [b], Howard Hu [c], Citlalli Osorio-Yáñez [d,e,*], Martha María Téllez-Rojo [a]

[a] Instituto Nacional de Salud Pública, Cuernavaca, Morelos, Mexico
[b] Department of Nutritional Sciences, University of Michigan, School of Public Health, Ann Arbor, MI, USA
[c] University of Washington, School of Public Health, Seattle, WA, USA
[d] Departamento de Medicina Genómica y Toxicología Ambiental, Instituto de investigaciones Biomédicas, Universidad Nacional Autónoma de México (UNAM), Ciudad Universitaria, Apartado Postal 70228, Ciudad de México 04510, Mexico
[e] Laboratorio de Fisiología Cardiovascular y Trasplante Renal, Unidad de Investigación UNAM-INCICH, Instituto Nacional de Cardiología Ignacio Chávez, Ciudad de Mexico, Mexico

## HIGHLIGHTS

- Salt is one of the main sources of fluoride exposure in Mexican population.
- Fluoride exposure is linked to adverse fetal and maternal outcomes.
- Maternal Fluoride (first trimester) was associated with birth weight increase.
- Maternal Fluoride (third trimester) was associated with birth weight decrease.
- Women should avoid sources of fluoride exposure during pregnancy.

## GRAPHICAL ABSTRACT




## ARTICLE INFO

Editor: Katarzyna Kordas

*Keywords:*
Fluoride
Pregnancy
Birth weight
Birth length
Early life
Salt

## ABSTRACT

Epidemiological studies assessing prenatal fluoride exposure and anthropometry at birth are scarce, inconsistent and with methodological limitations. The aim of this study was to evaluate associations between maternal urinary fluoride (MUF) at each trimester of pregnancy and birth weight and length in 536 mother-child pairs in the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) cohort study. MUF (mg/L) was measured using microdiffusion/fluoride-specific electrode from at least one trimester of pregnancy. Non-linear associations were assessed through segmented regression models (MUF and birth weight *Z*-score) and we used linear regression models for MUF and birth length Z-score. Models were adjusted for potential confounders including urinary creatinine concentrations as a covariate. Non-creatinine adjusted MUF levels at each trimester of pregnancy were 0.81, 0.86, and 0.82 mg/L, mean concentrations for first, second and third trimester, respectively. For birth weight, we identified a MUF breakpoint at 0.99, 0.68 and 0.58 mg/L, for first, second and third trimester of pregnancy, respectively. In the first trimester, an increase of 1 mg/L in MUF concentrations ≥0.99 mg/L was associated with an increase in weight *Z*-score at birth (β = 0.79; 95% CI: 0.10, 1.48; $p = 0.02$). Second trimester MUF (≥0.68 mg/L) was marginally associated with birth weight decrease (β = −0.25; 95% CI: −0.55, 0.04; $p = 0.09$) and third trimester MUF (≥0.58 mg/L) was significantly associated with birth weight decrease (β = −0.33; 95% CI: −0.63, −0.03; $p = 0.03$). We observed a linear and significant association between MUF and *Z*-score of length at birth only for the first trimester of pregnancy (β = 0.55; 95% CI:

* Corresponding author at: Unidad de Investigación UNAM-INCICH, Juan Badiano 1, Belisario Domínguez Secc 16, Tlalpan, 14080 Ciudad de México, Mexico.
*E-mail address:* citlalli.osorio@iibiomedicas.unam.mx (C. Osorio-Yáñez).

http://dx.doi.org/10.1016/j.scitotenv.2022.156459
Received 14 January 2022; Received in revised form 27 May 2022; Accepted 31 May 2022
Available online 02 June 2022

0.07, 1.04; $p < 0.02$). Prenatal fluoride exposure was associated with birthweight z-score with different susceptibility windows. Our findings reinforce the hypothesis that maternal fluoride exposure may affect birth anthropometry.

## 1. Introduction

For decades fluoride has been extensively used to prevent and delay the progression of dental caries; however, a growing body of literature highlights its association with adverse health effects even at low-level of fluoride exposure (Whelton et al., 2019; Liu et al., 2020; Malin et al., 2019; Malin et al., 2018; Wang et al., 2020). Fluoride crosses the placental barrier (Shen and Taves, 1974) and pregnancy is a window of susceptibility to the toxic effects for the offspring. Prenatal fluoride exposure has been associated with neurocognitive alterations (Bashash et al., 2018; Bashash et al., 2017; Grandjean, 2019). Also, prenatal fluoride exposure might affect fetal growth and development (Aghaei et al., 2015; Diouf et al., 2012; Gurumurthy et al., 2011) due to its potential role as endocrine disruptor (Singh et al., 2014; Susheela et al., 2005) and pro-inflammatory capacity (Barbier et al., 2010). Alterations in anthropometry at birth are predictive of neonatal and infant morbidity and mortality, as well as chronic diseases and metabolic disorders in adulthood (Das and Sysyn, 2004). Nevertheless, available literature regarding prenatal fluoride exposure and anthropometry at birth is scarce (Aghaei et al., 2015; Diouf et al., 2012; Gurumurthy et al., 2011; Goodman et al., 2021). A small cross-sectional study in India ($n = 108$) (Gurumurthy et al., 2011) and one case-control study in Senegal (Diouf et al., 2012), both with limited information on confounders, suggest that prenatal exposure to fluoride was associated with a higher risk of low birth weight (Diouf et al., 2012; Gurumurthy et al., 2011). In contrast, an ecological study conducted in Iran showed that fluoride exposure through drinking water (>1.5 mg/L, WHO drinking water limit) was not associated with lower birth weight (Aghaei et al., 2015). However, these three studies had several methodological limitations including, small sample size (~100) (Gurumurthy et al., 2011), lack of adjustment for potential confounders (Diouf et al., 2012; Gurumurthy et al., 2011), no repeated measurements of fluoride exposure during pregnancy (Aghaei et al., 2015; Diouf et al., 2012; Gurumurthy et al., 2011), and most relied on neighborhood measurements of fluoride (e.g., drinking water levels) rather than maternal urinary fluoride (MUF) (Aghaei et al., 2015; Diouf et al., 2012). MUF has been used as a proxy for prenatal fluoride exposure in epidemiological studies in women and children (Green et al., 2019; Thomas et al., 2016). Recently, a study conducted by Goodman and colleagues reported no associations between averaged MUF during pregnancy and birth weight or preterm birth in a Canadian cohort (Goodman et al., 2021). Nevertheless, none of these investigations considered windows of susceptibility to fluoride exposure during pregnancy (Aghaei et al., 2015; Diouf et al., 2012; Gurumurthy et al., 2011). The second and third trimesters of pregnancy might be a critical window to the effects of fluoride on birth anthropometry because fetal growth rate increases markedly; specifically, the major length accrual occurs in the second trimester and a large proportion of fetal weight gain occurs during the third trimester (Simmons, 2012).

In Mexico City, people are exposed to fluoride via salt (250 ± 50 mgF/kg) since 1995, dental products, diet, and to a lesser extent through natural water fluoridation (concentrations ranging from 0.26 to 1.38 mg/L) (Thomas et al., 2016; Secretaría-de-Salud, 1995; Zohoori et al., 2013; Cantoral et al., 2019; Hernández-Guerrero et al., 2005). A previous study by our group, among pregnant women from Mexico City, reported a mean creatinine adjusted MUF of 0.91 mg/L. To note, the 20% of these women had urinary fluoride concentrations six times higher than benchmark concentration levels (0.2 mg/L) proposed recently for pregnant women (Thomas et al., 2016; Grandjean et al., 2022).

To the best of our knowledge, no previous study has assessed prenatal windows of susceptibility related to fluoride exposure and birth weight and length. Therefore, we aimed to estimate the association between trimester-specific MUF during pregnancy and *Z*-score for weight and length at birth in ELEMENT cohort study.

## 2. Material and methods

### 2.1. Study participants

The mother-child pairs in this study were participants from the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) project, extensively described elsewhere (Perng et al., 2019). Of the four cohorts that comprised ELEMENT project, we did not use for our analyses data from Cohort 1 and Cohort 2B because maternal urine samples were not collected, thus there was no information on fluoride or creatinine measurements. Mothers for Cohort 2A ($n = 327$) and 3 ($n = 670$) were all recruited from the same three hospitals of the Mexican Social Security Institute (IMSS). Cohort 2A started between 1997 and 1999 and cohort 3 between 2001 and 2003. Cohort 2A was an observational study of prenatal lead exposure and neurodevelopmental outcomes in children. Cohort 3 was a randomized trial of the effect of calcium supplementation (1200 mg/day) during pregnancy on maternal blood levels (Bashash et al., 2017; Ettinger et al., 2009).

Pregnant women were eligible for this study if their gestational age at recruitment was <14 weeks of gestation and they had the intention to remain in the study area for at least 5 years. Exclusion criteria were diagnosis of high-risk pregnancy, multiple pregnancy, preeclampsia or pregnancy-induced hypertension, renal or circulatory disease. Women with a history of recurrent urinary tract infections, psychiatric disorders, seizures, gestational diabetes, daily consumption of alcoholic beverages, addiction to illegal drugs, and women with continued use of daily prescribed medications were also excluded (Ettinger et al., 2009; Tellez-Rojo et al., 2004). The study procedures were approved by the ethics committees of the National Institute of Public Health of Mexico, the University of Michigan, Indiana University, the University of Toronto, and the participating clinics. Participants received detailed information about the study procedures and expressed their agreement to participate by signing a written letter of informed consent.

### 2.2. Follow-up and collection of information

ELEMENT mothers were followed-up during pregnancy and we collected information at each trimester of pregnancy. At recruitment, we obtained information using a structured questionnaire on maternal sociodemographic characteristics (age, date of birth, total years of education, marital status), and reproductive history (gestational age and number of pregnancies). During each visit, maternal weight and height were measured by trained staff, using the same standardized protocols. Body mass index (BMI) was estimated in kg/m$^2$ for each trimester. A validated food consumption frequency questionnaire with information about 116 food items, previously used in other studies (Hernandez-Avila et al., 1998), was applied in each of the visits. Subsequently, we estimated total daily calories (kcal) and dietary calcium (mg) intake based on the daily food frequency questionnaire using nutrient composition of each food obtained from the U.S. Department of Agriculture food composition tables (US-Department-of-Agriculture, 1993-1997) and the nutrient database developed by the National Institute of Nutrition (Chávez, 1992). For those women who participated in the calcium supplementation study, total daily calcium intake also included the supplementation calcium intake corrected by the percentage of treatment adherence indicated during the last visit (1200 mg/d x % treatment adherence). Smoking history was categorized as a non-smoker (those who reported never smoking or reported <100 cigarettes in their lifetime), active smoker before pregnancy (>100 cigarettes in their lifetime before pregnancy), and active smoker during pregnancy (those who reported smoking during any of the follow-up visits) (Levy et al., 2019).

Based on the date of the last menstruation period and the visit date, we calculated the gestational age at the visit as follows: first trimester (< 13th week); second trimester (13th and 26th weeks) and third trimester (≥ 27th week). We collected information at each trimester of pregnancy and when women did not attend timely to their trimester-specific visit, we gathered information even if there were two visits in the same trimester.

### 2.3. Biological samples

From each participant, blood and urine samples were obtained at each trimester. A nonfasting spot urine sample (second-morning void) was collected in metal-free containers and kept at −80 °C until it was transported and analyzed for MUF concentrations at the Indiana University Oral Health Research Institute (Thomas et al., 2016).

For 102 women, we had two visits in the same trimester, thus, we calculated the mean of MUF, gestational age, and urinary creatinine concentrations when samples were collected.

The study visits were conducted at our research facility located at the American British Cowdray Medical Center (ABC) in Mexico City.

### 2.4. Chemical analysis urinary fluoride and creatinine

MUF concentrations were measured using an pH/ion meter with a fluoride ion-selective electrode (Thermo Scientific Orion, Cat # 13-642-265), following a method previously described (Martinez-Mier et al., 2011). Fluoride (mg/L) concentrations were obtained from electrode readings (in millivolts) calculated from a standard curve. All measuring instruments were calibrated daily, and samples were analyzed in duplicate; one blank sample was analyzed for each batch of samples. Standards obtained from the National Institute of Public Health of Quebec were used to measure analytical precision and accuracy. The recovery rate was 100% and the average coefficient of variation (CV) was less than 10% (samples with fluoride concentration > 0.2 mg/L) and 20% (samples with fluoride concentrations ≤ 0.2 mg/L). Samples with CV >20% and with enough urine volume were reanalyzed. The analytical detection limit was 0.00656 mg/L. A validation study with the Indiana University Oral Health Research Institute showed an inter-laboratory correlation of 0.92 (Thomas et al., 2016).

Urinary creatinine concentration for each sample was measured using a MicroLab AT Plus (Hamilton Co., Reno, NV, USA) and a microplate spectrophotometer (Spectra Max 340, Molecular Devices, Sunny vale, CA, USA). The urinary creatinine concentration was expressed in mg/dL.

### 2.5. Newborn information

Newborns' length and weight were measured by experienced obstetric nurses within 12 h after delivery using standardized procedures (Gonzalez-Cossio et al., 1997). Gestational age at birth was estimated using as reference the date of the beginning of the last menstrual period reported by the mother.

We calculated the *Z*-scores for birth weight and length according to newborns sex and gestational age (24–42 weeks of gestation) employing the international standards of the Intergrowth 21st Project (v1.0.6257.25111) (Villar et al., 2014). Z-scores for weight and length were used continuously as dependent variables.

### 2.6. Statistical analysis

The normal distribution of the variables was evaluated using the Shapiro-Wilk and Skewness/Kurtosis tests. Continuous variables were expressed as mean and standard deviation, and categorical variables as frequencies and percentages. We compared maternal and newborn characteristics for those included and not included in the analysis using t-Student or Chi-square tests. We used scatter plots and locally weighted regression (lowess) to visually inspect whether trimester specific MUF and anthropometry of birth (weight or height) were linearly associated. The association between MUF and length z-score was linear, thus, we applied linear regression models. Contrary, the association between MUF and weight z-score was not linear, and we statistically identified a breakpoint in the MUF and z-score relationship. Therefore, we applied segmented regression analyses (Pastor and Guallar, 1998). Briefly, segmented regression models are employed when there is a breakpoint in the exposure variable and two linear segments are identified, before and after the breakpoint (Pastor and Guallar, 1998; González-Carro, 2017; Lunt, 2006; Zhihua Liu, 2009). We statistically identified the breakpoint in the exposure variable using piecewise linear regression ('Hockey-Stick"): the -nl hockey command in Stata developed by Lunt (Pastor and Guallar, 1998; Lunt, 2006). Then we employed the breakpoints identified by hockey stick to perform segmented regression models. Two regression lines were adjusted below and above the breakpoint (one for each segment or piece of fluoride exposure).

We assessed associations between trimester specific MUF and birth weight (segmented regression) or length (linear regression) adjusting for potential confounders. We performed complete case analyses at each trimester of pregnancy (Groenwold et al., 2012).

We assessed as potential confounders variables associated with birth weight and length and/or variables that may also be potentially associated with prenatal fluoride exposure (Thomas et al., 2016; Blair et al., 2004; Howe et al., 2012). Length *Z*-score models were adjusted for maternal age, BMI at each trimester, total daily calcium intake (at each trimester), number of pregnancies (including the one of interest), smoking, maternal blood lead (at each trimester), cohort and gestational age at the time of the visit. Weight Z-score models were adjusted for all the previous variables except for smoking or number of pregnancies, because the coefficient of fluoride exposure did not change (more than 10%) when including them in the models. Level of education was not included in the final models because this variable was not associated with birth weight or length or changed the coefficient of fluoride exposure by more than 10%. We adjusted all our models for urinary creatinine as a covariate. This approach allows adjusting the analyte (MUF) for urinary dilution and the statistical significance of the other covariates in the model to be independent of the effects of creatinine concentrations (Barr et al., 2005).

Final models were selected according with criteria of goodness of fit: Akaike criteria (Portet, 2020), $R^2$ and adjusted $R^2$. Comparisons were done through F test (Alexopoulos, 2010). Analysis of residuals was conducted to evaluate whether the assumptions of the statistical models were accomplished. Five observations had residuals greater than three standard deviations and were eliminated. Once these participant records were excluded, an analysis of the plot of studentized residuals vs. leverage did not identify potential influencing observations and the assumptions of the model were met (data not shown). All statistical analyzes were performed in STATA 15 (StataCorp LP, College Station, TX, EE. UU.).

## 3. Results

Among the 782 mother-child pairs in the original cohorts, 536 were eligible after excluding newborns without information on birth weight and length ($N = 13$) and 233 women without at least one urine sample for fluoride and creatinine measurements. Among those 536 women, 276 women had one, 206 and 54 women had two and three MUF with creatinine measurements during pregnancy, respectively. Considering trimester specific MUF measurements, we had 213 women in the first, 381 in the second and 256 women in the third trimester of pregnancy. Thus, the analytical sample for this study were 536 mother-child pairs with available information for weight and length at birth, MUF, and creatinine measurements for at least one trimester of pregnancy and complete covariate data (Fig. 1).

Overall, we observed no differences in maternal or newborn characteristics comparing participants included and excluded from the study, except for cohort of origin, smoking, and energy consumption in the third trimester (Table 1). Mothers included in the study, compared to those excluded, were mainly from cohort 3 (70.5 vs 47.2%), were active smokers before pregnancy (25.4% vs 20.2%), and had a lower average total calorie intake in the third trimester (1879.9 kcal/d vs 2079.5 kcal/d). 91.8% of newborns

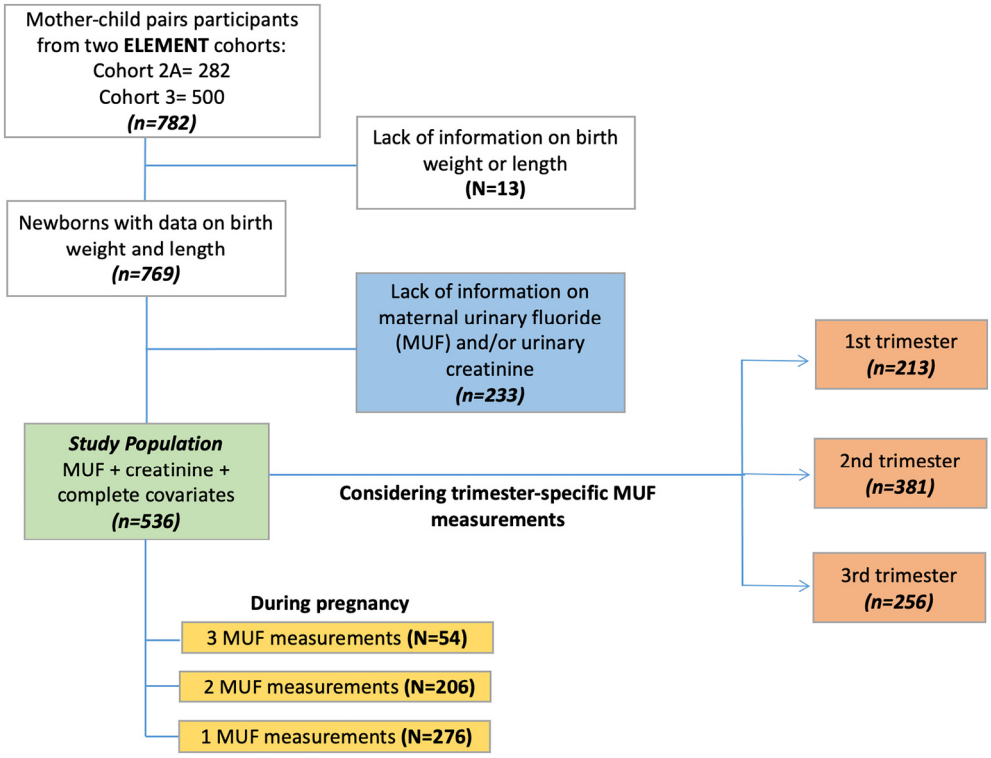



**Fig. 1.** Flowchart for the Study Population.

were products of full-term pregnancies with an average birth weight of 3.1 ± 0.4 kg. No statistical differences were observed between those included and excluded from the analysis related to birth weight or length. The frequency of low birth weight was 7.7% and 8.6%, respectively for those included and excluded (Table 1).

Mean MUF concentration was lower at the first trimester (0.81; 95% CI: 0.41–1.09 mg/L) compared to the second trimester (mean: 0.86; 95% CI: 0.46–1.11 mg/L). However, we observed no significant differences in non-creatinine adjusted MUF concentrations according to trimester of pregnancy (Table 2). Creatinine concentrations significantly decreased from the first (median: 98.1; 95% CI: 44.8–135.4 mg/dL) to the third trimester of pregnancy (median: 69.35; 95% CI: 45.60–99.05 mg/dL) ($p < 0.001$). Mean blood lead concentrations (ug/dL) ranged from 4.88 (95% CI: 2.60–5.80 μg/dL) to 5.73 (95% CI: 3.0–7.50) and we observed a marginally significant decrease across pregnancy (data not shown). Finally, 50% of women had blood Pb concentrations above the U.S. Centers for Disease Control and Prevention's (CDC) reference and the current Mexican limit of 5 μg / dL (CDC: Centers for Disease Control and Prevention, 2012; DOF: Diario Oficial de la Federación : [(accessed on April 10th, 2022).

### 3.1. Association between prenatal exposure to fluoride and birth weight Z-score

The association between urinary fluoride concentrations and birth weight Z-score depended on trimester of pregnancy and fluoride concentration (Table 3; Fig. 2). The association between MUF and birth weight was non-linear, and we observed a different breakpoint according to the trimester of pregnancy (0.99, 0.68 and 0.58 mg/L for first, second and third trimester, respectively). We observed significant associations between birth weight *Z*-score and MUF (above the breakpoint) for the first and third trimester in models adjusted for potential confounders. In the first trimester, an increase of 1 mg/L in MUF above the breakpoint (0.99 mg/L) was associated with a significant increase in birth weight *Z*-score (β = 0.79; 95% CI: 0.10, 1.48; $p = 0.02$). In the third trimester, an increase of 1 mg/L of MUF above the breakpoint (0.58 mg/L) was associated with a significant decrease in birth weight *Z*-score (β = −0.33; 95% CI: −0.63, −0.03; $p = 0.03$). For the second trimester of pregnancy, the decrease in the birth weight *Z*-score, after the breakpoint (0.68 mg/L), was marginally associated with fluoride exposure (β = −0.25; 95% CI: −0.55, 0.04; $p = 0.09$). Overall, early pregnancy MUF (above the breakpoint) was associated with an increase of birth weight; whilst late pregnancy MUF (after the breakpoint) was associated with birth weight decrease.

### 3.2. Association between prenatal fluoride exposure and length Z-score at birth

Table 3 and Fig. 3 show the associations between urinary fluoride concentrations in each trimester of pregnancy and the *Z*-score for length at birth adjusted for maternal age, BMI, total daily calcium intake, number of pregnancies, smoking, maternal blood lead concentrations, cohort, and gestational age at the time of the visit. In the first trimester of pregnancy, 1 mg/L increase in urinary fluoride was associated with a significant increase in the Z-score of length at birth (β = 0.55; 95% CI: 0.07, 1.04; $p = 0.02$). No association was observed between prenatal exposure to fluoride and the Z-score for length at second or third trimesters of pregnancy.

## 4. Discussion

Our results showed associations between prenatal fluoride exposure and birth anthropometry. Overall, early pregnancy fluoride exposure was associated with an increase of birth weight; whilst late pregnancy fluoride exposure was associated with birth weight decrease. The associations found for MUF, and birth weight depend on breakpoints, possibly thresholds, observed at each trimester of pregnancy. As far as we know, this is the first cohort study focused on associations between trimester specific MUF and birth anthropometry. Thus, comparing our results with other findings is difficult since most of previous studies are cross-sectional in nature and fluoride exposure was measured in drinking water and serum (Aghaei et al., 2015; Gurumurthy et al., 2011). However, our results linking prenatal exposure to fluoride (second and third trimester) and a decrease in birth weight at birth are in line with previous reports (Diouf et al., 2012; Gurumurthy et al., 2011). One study conducted in India reported a negative correlation ($r = -0.52$; $p < 0.0001$) between maternal serum fluoride at delivery (mean 1.21 ± 0.79 mg/L) and birth weight (Gurumurthy et al.,

**Table 1**
Characteristics of the pregnant women and newborns included and not included in the analysis.

| Characteristic | Included $n = 536$ [$\bar{X}$ ± SD or n (%)] | Excluded $n = 233$ [$\bar{X}$ ± SD or n (%)] | $p$ value[a] |
|---|---|---|---|
| Maternal | | | |
| Age (years)[b] | 26.8 ± 5.4 | 27.1 ± 4.8 | 0.51 |
| Education (years) | 10.7 ± 2.8 | 11.1 ± 3.2 | 0.14 |
| >10 years | 292 (54.5) | 137 (58.8) | 0.24 |
| Marital status | | | |
| Married | 478 (89.2) | 213 (91.4) | 0.38 |
| Single | 57 (10.6) | 20 (8.6) | |
| Missing | 1 (0.2) | – | |
| Cohort | | | |
| 2A | 158 (29.5) | 123 (52.8) | <0.001 |
| 3 placebo | 188 (35.0) | 48 (20.6) | |
| 3 supplement | 190 (35.5) | 62 (26.6) | |
| Number of pregnancies | | | |
| 1 | 185 (34.5) | 78 (33.5) | 0.88 |
| 2–3 | 308 (57.5) | 138 (59.2) | |
| ≥4 | 43 (8.0) | 17 (7.3) | |
| Smoking | | | |
| Non-smokers | 389 (72.6) | 173 (74.2) | 0.02 |
| Before pregnancy | 136 (25.4) | 47 (20.2) | |
| During pregnancy | 11 (2.0) | 12 (5.2) | |
| Missing | – | 1 (0.4) | |
| I Trimester (n) | (213) | (91) | |
| Calcium (mg/d)[c] | 1142.4 ± 563.0 | 1226.5 ± 539.8 | 0.22 |
| Energy (kcal/d) | 1920.5 ± 715.0 | 2029.3 ± 650.8 | 0.21 |
| BMI (kg/m$^2$) | 25.9 ± 3.7 | 25.5 ± 4.0 | 0.43 |
| II Trimester (n) | (381) | (208) | |
| Calcium (mg/d)[c] | 1351.1 ± 575.8 | 1336.2 ± 502.5 | 0.67 |
| Energy (kcal/d) | 1981.6 ± 648.9 | 1991.9 ± 565.0 | 0.84 |
| BMI (kg/m$^2$) | 27.1 ± 4.0 | 26.6 ± 3.9 | 0.18 |
| III Trimester (n) | (256) | (199) | |
| Calcium (mg/d)[c] | 1497.6 ± 603.6 | 1519.8 ± 575.7 | 0.80 |
| Energy (kcal/d) | 1879.9 ± 557.9 | 2079.5 ± 609.6 | <0.001 |
| BMI (kg/m$^2$) | 29.4 ± 3.8 | 29.2 ± 3.8 | 0.56 |
| Delivery | | | |
| Vaginal | 305 (56.9) | 122 (52.4) | 0.24 |
| Cesarean | 231 (43.1) | 111 (47.6) | |
| Newborn | | | |
| Sex | | | |
| Female | 277 (51.7) | 106 (45.5) | 0.11 |
| Male | 259 (48.3) | 127 (54.5) | |
| Gestational age (weeks) | 38.7 ± 1.7 | 38.4 ± 1.7 | 0.08 |
| <37 weeks (%) | 44 (8.2) | 27 (11.6) | 0.13 |
| Birth weight (kg) | 3.1 ± 0.4 | 3.0 ± 0.4 | 0.18 |
| *Z*-score[d] | 0.01 ± 0.9 | −0.02 ± 0.9 | 0.63 |
| <P10 birth weight | 49 (9.1) | 24 (10.3) | 0.61 |
| <2500 g | 41 (7.7) | 20 (8.6) | 0.65 |
| Birth length (cm) | 49.9 ± 2.6 | 49.9 ± 2.3 | 0.88 |
| Z-score[d] | 0.74 ± 1.2 | 0.76 ± 1.1 | 0.86 |

SD. Standard Deviation.
[a] Student's t for continuous variables and Chi-square for categorical variables.
[b] At the beginning of the study.
[c] Dietary calcium + (1200 mg/d x% adherence to supplement).
[d] Adjusted for gestational age and sex of the newborn.

2011). The mechanisms underlying prenatal fluoride exposure and birth weight decrease have never been explored and may include fluoride pro-oxidant capacity and inflammation (Barbier et al., 2010). Scientific literature has shown that fluoride increases reactive oxygen species (ROS) production and decreases antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, and catalase (Barbier et al., 2010). Furthermore, oxidative stress during pregnancy compromise nutrition and fetal development interfering with the normal invasion of the trophoblast, the widening of the spiral arterioles, and reducing the vascularization of the placenta (Jauniaux et al., 2006). Fetal antioxidant defenses are relative weak in early gestation and trophoblast protects against ROS damage (Ornoy, 2007; Severens-Rijvers et al., 2019). Thus, oxidative stress produced by fluoride may lead to a decrease in newborns weight. However, more epidemiological, and experimental studies are needed to confirm our findings and demonstrate the hypotheses raised here.

On the other hand, our results also showed an increase in weight and length at birth associated to MUF during the first trimester of pregnancy. To the best of our knowledge, no previous studies have linked prenatal fluoride exposure and birth weight increase. Recently, Goodman and colleagues examined the relationship between MUF (for the whole pregnancy period) and birth outcomes in a Canadian pregnancy cohort (MIREC Study) and their results showed a significant positive association between MUF and birth weight (g) in the unadjusted model (B = 78.97; 95% CI: 15.13, 142.81; $p = 0.015$); however, in covariate adjusted models the positive association was no longer significant (Goodman et al., 2021). We hypothesize that the endocrine disrupting properties of fluoride may explain the association observed in our study between first trimester fluoride exposure and the increase in the *Z*-score of weight and length at birth (Singh et al., 2014; Susheela et al., 2005). Experimental studies showed that chronic and acute fluoride exposure increases blood glucose concentrations (Chehoud et al., 2008) and epidemiologic studies have reported that fasting blood glucose concentrations greater than 6.8 mmol/L during the first trimester of pregnancy (12.9 ± 2.6 weeks of gestation) are associated with three times more risk (OR 3.1 (95% CI: 1.21, 8.0); $p = 0.02$) of having a macrosomic child (Kayemba-Kay's et al., 2013). In relation to another stage of life, a previous study from our group showed that the increase in plasma fluoride was significantly associated with higher Z-score for BMI (β = 0.20; 95% CI: 0.00, 0.40; $p = 0.05$) and trunk fat percentage (β = 0.19; 95% CI: 0.04, 0.34; $p = 0.01$) in peripubertal girls (Liu et al., 2020), suggesting a possible link between fluoride exposure and weight increase.

The results of our study should be interpreted considering its strengths and limitations. The strengths of our study include: 1) it is a prospective cohort study that ensures the temporality between the exposure and the event; 2) the ELEMENT cohorts have information on several covariates that may be confounding the association between fluoride exposure and anthropometry at birth and that were used to adjust our models; 3) we have information on MUF for the three trimesters of pregnancy; 4) the measurement of MUF had good internal quality control and high inter-laboratory reproducibility.

**Table 2**
Urinary fluoride and creatinine concentration at each trimester of pregnancy.

| Concentrations | n | $\bar{X}$ | Percentiles | | |
|---|---|---|---|---|---|
| | | | 25 | 50 | 75 |
| Urinary fluoride (mg/L) | | | | | |
| I trimester | 213 | 0.81 | 0.41 | 0.68 | 1.09 |
| II trimester | 381 | 0.86 | 0.46 | 0.77 | 1.11 |
| III trimester | 256 | 0.82 | 0.43 | 0.71 | 1.09 |
| *p* value[a] | | | | 0.30 | |
| Urinary Creatinine (mg/dL) | | | | | |
| I trimester | 213 | 99.06 | 44.80 | 98.10 | 135.4 |
| II trimester | 381 | 90.42 | 55.50 | 83.60 | 119.0 |
| III trimester | 256 | 76.39 | 45.60 | 69.35 | 99.05 |
| *p* value[a] | | | | <0.001 | |

[a] Kruskal-Wallis test for comparison between medians. Urinary fluoride was not adjusted for creatinine.

**Table 3**
Association between maternal urinary fluoride at each trimester of pregnancy and birth weight and length *Z*-score.

| | Trimester of pregnancy β (CI 95%) | | |
|---|---|---|---|
| Variables | 1st | 2nd | 3rd |
| Weight Z-score[a] | *n* = 209[d] | *n* = 378[d] | *n* = 254[d] |
| Fluoride (mg/L) | | | |
| <0.99 | −0.34 (−1.10, 0.40) | | |
| ≥0.99[b] | **0.79 (0.10, 1.48)** | | |
| <0.68 | | −0.02 (−1.03, 0.98) | |
| ≥0.68[b] | | *−0.25 (0.55, 0.04)* | |
| <0.58 | | | 0.86 (−0.45, 2.18) |
| ≥0.58[b] | | | **−0.33 (−0.63, −0.03)** |
| Length Z-score[c] | n = 209[e] | n = 378[e] | *n* = 252[e] |
| Fluoride (mg/L) | **0.55 (0.07, 1.04)** | 0.13 (−0.17, 0.44) | 0.14 (−0.18, 0.47) |

β: For linear regression models, beta represents the change in birth length z-score for each 1 mg/L of MUF. For segmented regression models, beta represents the change in birth weight z-score for each 1 mg/L of MUF below or above the breakpoint.
CI: Confidence Interval. Significant results ($p < 0.05$) are highlighted in bold and marginally significant results ($p < 0.10$) are given in italics.
[a] Independent models of segmented linear regression for each trimester adjusted for maternal age, BMI, total daily calcium intake, maternal blood lead, origin cohort, gestational age at the time of the visit and urinary creatinine concentrations.
[b] N (%) of women with concentrations equal to or above breakpoint: 62 (29.7%), 212 (56.1%), and 162 (63.7%) for the 1st, 2nd, and 3rd trimesters respectively.
[c] Independent linear regression models for each trimester adjusted for maternal age, BMI, total daily calcium intake, smoking, number of pregnancies, maternal blood lead, origin cohort, gestational age at the time of the visit and urinary creatinine concentrations.
[d] $R^2$ 1st trimester = 14.9%; 2nd trimester = 7.0% and 3rd trimester = 9.6%.
[e] $R^2$ 1st trimester = 12.4%; 2nd trimester = 4.1% y 3rd trimester = 4.9%.

Among the limitations of the study, we collected a single spot urine sample from the second void in the morning, which may not represent exposure throughout the day. However, no significant differences in MUF were observed across pregnancy, and there is evidence that fluoride concentrations are relatively stable since determinations from casual urine samples correlate adequately ($r = 0.76$, $p = 0.05$) with concentrations obtained from 24-h urine (Zohouri et al., 2006). We adjusted our models for urinary creatinine to account for urinary dilution (Barr et al., 2005). However, we cannot rule out that changes in glomerular filtration rate characteristic of pregnancy might impact urinary creatinine or fluoride concentrations (Cheung and Lafayette, 2013).

A previous study suggested that fluoride concentration in plasma is the best indicator to evaluate the impact of fluoride exposure on fetal and infant development because plasmatic fluoride moderately correlates with fluoride in amniotic fluid ($r = 0.52$; $p < 0.001$); however, when it is not available, urinary fluoride is a good indicator of fetal exposure, since it is a widely used biomarker to estimate fluoride exposure in pregnant women (Abduweli Uyghurturk et al., 2020). In our study, we used urinary fluoride because only a low percentage (<25%) of pregnant women had plasma fluoride measurements.

Other limitations include differences between maternal characteristics of the included and excluded participants. The pregnant women included in the analysis had a lower average energy consumption in the third trimester than those excluded (1879.9 ± 557.9 vs 2079.5 ± 609.6 kcal; $p < 0.001$). However, we did not observe a correlation between energy consumption and urinary fluoride concentrations; until now, there is only evidence that a low intake of calcium, aluminum and/or magnesium is associated with greater absorption of fluoride (Buzalaf and Whitford, 2011). Moreover, we could not perform a sensitivity analysis with those women with complete urinary fluoride measurements for the three trimesters of pregnancy. The sample size was very small (54 women) and did not allow us to apply a segmented regression approach. However, the possibility that our results would be a consequence of selection bias is low. Women with measurements at different time periods were practically similar in all characteristics, except for cohort of origin and gestational age at birth; both were used as covariates in our final models. Another limitation of our study

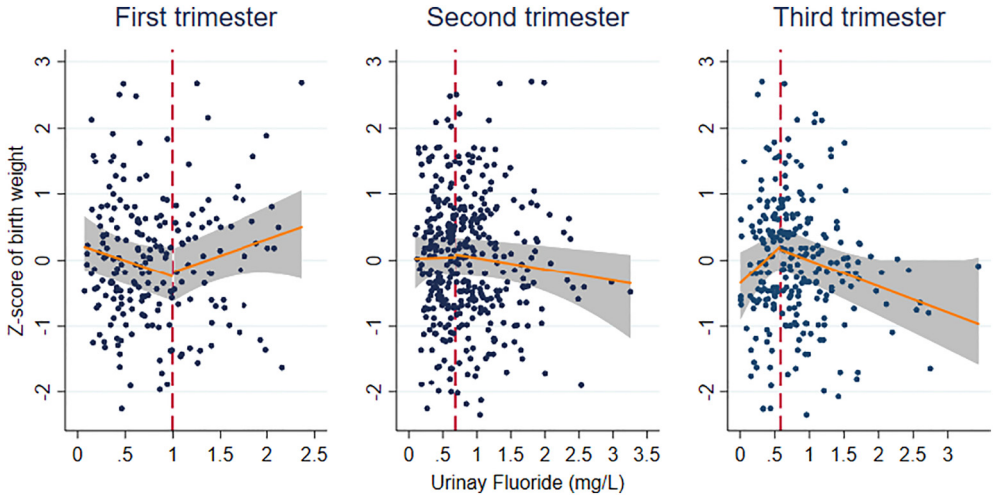



**Fig. 2.** Association between maternal urinary fluoride at each trimester and weight *Z*-score at birth. The red line represents the breakpoint in MUF; the orange line corresponds to the adjusted values of the birth weight *Z*-score and the gray area corresponds to the 95% confidence intervals. * All models were adjusted for maternal age, BMI, total daily calcium intake, maternal blood lead, origin cohort, gestational age at the time of the visit and urinary creatinine concentrations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

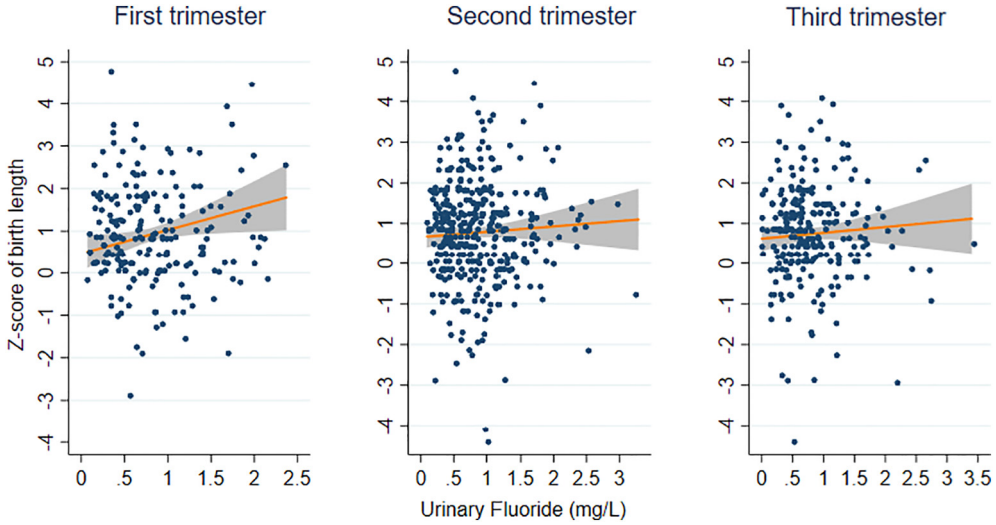



**Fig. 3.** Association between prenatal exposure to fluoride in each trimester and length Z-score at birth. The orange line corresponds to the adjusted values of the birth length Z-score and the gray area corresponds to the 95% confidence intervals. * All models were adjusted for maternal age and BMI, total daily calcium intake, smoking, number of pregnancies, maternal blood lead, origin cohort, gestational age at the time of the visit and urinary creatinine concentrations.

is its observational nature; therefore, residual confounding cannot completely rule out for unmeasured variables. In Mexico, people use traditional lead glazed ceramics to prepare serve and store food and lead in ceramics is an important source of lead exposure (Pantic et al., 2018). Although our results are adjusted for maternal blood lead concentrations; we cannot rule out that the lack of measurement of other contaminants with a potential effect on weight and height at birth may contribute to the presence of residual confounding. Finally, the generalizability of our findings is limited to pregnant women without high-risk pregnancies, who attend the clinics for prenatal care.

## 5. Conclusion

Our findings showed that prenatal fluoride exposure is associated with anthropometry at birth. The associations observed in this study depend on trimester of pregnancy, birth anthropometry parameter and MUF breakpoint at each trimester. MUF was associated with an increase in birth weight and length at first trimester and birth weight decreased at third trimester of pregnancy. Our findings reinforce the hypothesis that maternal fluoride exposure during pregnancy at the levels observed in a community with a public fluoridation program, may affect birth anthropometry. More research is needed on the consequences related to prenatal fluoride exposure, birth weight increase/decrease, and health effects later in life.

## CRediT authorship contribution statement

**Sofía G. Ortíz-García:** Conceptualization, Formal analysis, Writing – original draft. **Luisa E. Torres-Sánchez:** Conceptualization, Supervision, Writing – review & editing. **Teresa V. Muñoz-Rocha:** Formal analysis, Data curation, Supervision, Writing – review & editing. **Adriana Mercado-García:** Project administration. **Karen E. Peterson:** Writing – review & editing, Funding acquisition. **Howard Hu:** Writing – review & editing, Funding acquisition. **Citlalli Osorio-Yáñez:** Supervision, Writing – review & editing. **Martha María Téllez-Rojo:** Project administration, Supervision, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

The authors wish to acknowledge the Fluoride Program at the Indiana University Oral Health Research Institute for performing the urinary fluoride analysis. The authors also thanks mothers and children who participated in the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) study and the American British Cowdray Hospital for the use of its research facilities. This study was supported by U.S. National Institute of Health (NIH) grants R01 ES007821, R01 ES021446.

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