

Assessment of fluoride levels during pregnancy and its association with early adverse pregnancy outcomes

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ABSTRACT

Background and Aim: There is sparse data available on human subjects regarding the affect of excessive fluoride exposures on pregnancy. The aim of this study was to examine the association between elevated urinary fluoride levels during early pregnancy and maternal anemia and adverse fetal outcome. **Patients and Methods:** We enrolled 600 pregnant patients with gestational age less than 20 weeks and with a high urinary fluoride levels(>1 mg/L). We also documented the fluoride levels in the tap water and ground water samples collected from the areas where these women resided during pregnancy. These patients were also evaluated for hemoglobin levels and detailed fetal examination by ultrasound. Data was assessed by SPSS version 16.0 software and $P < 0.05$ was considered to be significant. **Results:** Urinary fluoride averaged 2.65 mg/L and ranged from 1.0 to 4.3 mg/L while all the water samples revealed fluoride levels greater than WHO prescribed the limit of 1.5 mg/L. A total of 402 patients (67%) were found to be anemic with hemoglobin levels ranging from 6.2 to 11.9 g/dl (9.28 ± 1.29). Eighty one patients (13.5%) had adverse fetal outcomes that comprised abortions, congenital abnormalities, and intrauterine deaths (IUDs). There was a negative correlation between urinary fluoride and hemoglobin levels ($P = 0.031$, $r = -0.59$) and females with elevated urinary fluoride levels were found to have a strong association with the pregnancy complications, i.e., anemia, miscarriage, abortion, and still birth ($\chi^2 = 9.23$, $P < 0.05$). **Conclusions:** Excess fluoride exposures can have deleterious effects on the expecting mother and fetus and is associated with adverse pregnancy outcomes.

Keywords: Complications, fetus, fluoride, fluorosis, pregnancy

Introduction

Fluoride is one of the vital elements affecting human health as its deficiency leads to faulty enamel formation and the excess causes dental, skeletal, and extra skeletal fluorosis. Therefore, it is important

to keep the fluoride ingestion at an optimum level.^[1] Fluorosis is one of the important public health issues in many parts of the developing world. In India many areas are fluoride endemic and around 25 million people are currently affected by fluorosis. Like many other countries, India is also located in the topographical fluoride belt where owing to high fluoride amount in rocks or soil, the leakage of fluoride happens, causing surplus fluoride level in groundwater.^[1-3] Drinking water is usually the chief source of fluoride.^[4]

In many developing countries fluoride quantity in drinking water is much more than the safe prescribed limits. The maximum

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appropriate limit for fluoride levels in drinking water has been fixed as 1.0 mg/L by the Bureau of Indian Standards (BIS), and allowable limit in the lack of another source has been set as 1.5 mg/L.^[5] Too much fluoride in drinking water causes fluorosis that is seen in endemic proportions in many parts of the world. Nearly 20 states of India have been recognized as endemic for fluorosis and around 66 million people living in these areas are at the danger of fluoride contamination. Fluoride intake through groundwater is the major cause of fluorosis and has become one of the most critical issues affecting human health.^[1-3]

Reports on trans placental fluoride passage suggest that fluoride is transmitted through placenta to the fetus while the benefit of fluoride intake during human pregnancy is still debatable.^[6] Not much is known about excess fluoride exposure during pregnancy and its affect on pregnancy outcome. The state of Punjab is one of the fluorosis endemic zones in India. Faridkot, with its semi-arid weather and dependence on ground water for drinking, makes it vulnerable to be one of the fluorosis endemic districts of Punjab.^[7] The present study was conducted among pregnant women from lower socioeconomic strata from Faridkot district of the state of Punjab (India) in order to know the urinary fluoride levels and its association with hemoglobin levels and adverse fetal outcomes during early periods of gestation. This study further aims to improve our knowledge regarding excess fluoride exposure during pregnancy.

Patients and Methods

Study design

In the period of years 2015 to 2017, we recruited 600 women from prenatal clinics of our tertiary care teaching hospital with the following inclusion criteria: Ability to communicate in the local language, above 18 years of age, gestational age less than 20 weeks, and those who provided written informed consent. Following were the exclusion criteria: Mental illnesses, addiction to alcohol or illegal drugs, high-risk pregnancies, Pre-eclampsia, renal disease, hypertension, gestational diabetes, abnormal biochemical indicators, and those who were more than 20 weeks pregnant or there was a known fetal abnormality in the previous off springs. The sample size was calculated as 396 based on the prevalence of fluorosis (4.1%) as per study done by Plaka K, *et al.*^[8] at 95% confidence interval and precision (d) as the half of prevalence and assuming 10% attrition. This study was approved by the Institutional Ethical Committee vide letter no. BFUHS/IEC/15/170 dated 17th October 2015. The information regarding socio-economic profile and source of water for intake, cooking, and other day-to-day purposes, type of foodstuffs eaten and the usage of fluoride-containing commodities were documented. Following parameters were estimated and documented in the patients: Gestational age, hemoglobin levels, and fluoride amount in urine.

Estimation of fluoride and hemoglobin levels

The free ionic form of fluoride was calculated in urine samples by employing an ion-selective electrode-based assay (Thermo-Scientific

Orion 4 star) and those patients with level above 1.0 mg/l were included in the study. These patients were divided into three groups based on the urinary fluoride levels ranging between: 1–1.9, 2–2.9, and ≥ 3 mg/L. Hemoglobin assessment was done by cyanomethemoglobin method. Based on the hemoglobin levels, patients were divided into 4 groups as per the Indian Council of Medical Research categories of anemia in pregnancy^[9] i.e. mild (10–10.9), moderate (7.0–10.0), severe (<7), very severe (<4).

These patients were further evaluated for the following factors: Diet survey for assessment of the source of fluoride in food consumed as well as use of fluoridated toothpaste, mouth rinses, cosmetics etc., Water samples used by these patients for cooking and drinking purpose were collected and the fluoride levels were assessed using fluoride ion specific electrode. The data of fluoride, hemoglobin levels, and ultrasound findings were documented. Patients with high fluoride level - >1 mg/l) were recommended nutritional intervention and were counseled to use alternate safe water source with low fluoride level. Further, evidence-based material such as posters/banners/brochures portraying the reasons and prevention of fluorosis were printed in the local language. Awareness workshops for the information of pregnant and other patients on fluorosis and its prevention were organized in the affected villages.

Assessment of fetal parameters and pregnancy complications by ultrasound

Gestational age was assessed by fetal biometry on an ultrasound scan using a Philips Affinity 70 machine (PhilipsHealthcare, Best, The Netherlands). Crown-rump length (CRL) was used to assess the gestational age before 14 weeks and after 14 weeks, the measurements comprised biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL). HC and AC were obtained using the ellipse measurement instrument, by positioning the calipers on the outer edges of the circumference. Fetal heart rate was calculated by M-mode ultrasound and was documented. Any congenital abnormality and the status of placenta and amniotic fluid was also documented. Ultrasound examination was done during 1st trimester of pregnancy and was repeated in 2nd trimester of pregnancy at around 18 weeks of pregnancy to look for any congenital abnormalities.

Data evaluation

The data was sorted out in Microsoft Excel and the results were statistically evaluated by the Student's *t*-test, Pearson's correlation coefficient, and chi square test wherever indicated. Results were assessed by SSPS version 16.0 for windows (SSPS Inc., Chicago, IL, USA). A probability value (*P* value) of < 0.05 was considered as significant.

Results

Sociodemographic profile of patients

All the patients ($n = 600$) in the present study were the residents of Faridkot district of Punjab, India out of which

420 patients (70%) belonged to rural areas [Table 1]. These patients used tap water or ground water for drinking and household purposes. Most of the patients were either illiterate (21%) or had schooling till primary level (45%) and belonged to lower or upper lower socio-economic class as per socio-economic status scale.^[9]

Fluoride levels

Ground and tap water samples were collected and the fluoride levels in the water samples were 2.35 ± 0.39 mg/l (range 2.1–3.3 mg/l) and 2.4 ± 0.25 mg/l (range 1.9–2.8 mg/l), respectively. All (100%) the ground water and tap samples showed fluoride concentration more than the WHO prescribed limit of 1.5 mg/L. No significant difference in fluoride levels was seen in water and urinary samples collected from rural or urban areas and from tap or ground water ($P > 0.05$). Urinary Fluoride levels averaged 2.65 mg/L and ranged from 1.0 to 4.3 mg/L. Based on the urinary fluoride levels, these patients were divided into three groups Group 1 (1–1.9 mg/l; n = 155), Group 2 (2–2.9 mg/l; n = 199) and Group 3 (≥ 3 mg/l; n = 246) [Table 1].

Table 1: Showing socio-demographic profiles, urinary fluoride concentrations and hemoglobin levels of pregnant patients

	Total Pregnant Patients (600 women) n (%)
Age (years)	
18-23	174 (29)
24-29	299 (49.9)
30-35	107 (17.8)
36-41	20 (3.3)
Urinary Fluoride Concentration (mg/l)	
Group 1 (1-1.9)	155 (25.8)
Group 2 (2-2.9)	199 (33.2)
Group 3 (≥ 3)	246 (41)
Hemoglobin levels (g/dl)	
Category 1 (10.0-10.9)	90 (22.4)
Category 2 (7.0-10.0)	285 (70.8)
Category 3 (<7.0)	27 (6.8)
Category 4 (<4.0)	0
Socio-economic class ¹	
Lower	399 (66.5)
Upper Lower	201 (33.5)
Lower Middle	0
Upper Middle	0
Upper Class	0

¹ Revised Kuppuswamy's socioeconomic status scale^[10]

Hemoglobin (Hb) levels

Overall hemoglobin levels in the patients ranged from 6.2–11.9 g/dl (mean; SD 9.28 ± 1.29). A total of 402 patients (67%) were anemic based on the ICMR criteria of anemia during pregnancy. Based on the hemoglobin (Hb) levels, the patients were divided into four groups as per above criteria [Table 1]. Majority of the anemic patients (70.8%) had moderately low Hb levels and hence belonged to 2nd group.

Elevated urinary fluoride levels, maternal anemia, and adverse fetal outcomes

Nearly 80% of the patients in group 3 of the urinary fluoride concentration were anemic, while 63% and 36% were anemic in group 2 and group 1, respectively and this difference between the groups was statistically significant ($P < 0.05$). There was a negative correlation between urinary fluoride and hemoglobin levels and this inverse relation was statistically significant ($P = 0.031$, $r = -0.59$).

A total of 81 patients (13.5%) had adverse fetal outcomes that included abortions, congenital abnormalities, and intrauterine deaths (IUD). Out of these 81 patients, 34 (42%) had obvious congenital abnormalities that were detected on ultrasound done at the 18 weeks of gestation. Of these 34 patients, ultrasound detected 30 patients with neural tube defects and 4 patients with cardiac abnormalities. Rest of the 47 patients (58%) had either abortions (n = 35; 74%) or IUD's (n = 12; 26%) that were confirmed on ultrasound examination [Figure 1]. Nearly 16% of the patients in group 3 of the urinary fluoride concentration, 13% patients of group 2, and 10% of group 3 had adverse fetal outcomes, though this difference between groups was not statistically significant ($P > 0.05$) [Table 2; Figure 2]. Females with elevated urinary fluoride levels were found to have a strong association with the pregnancy complications i.e. anemia, miscarriage, abortion, still birth, and congenital anomalies ($\chi^2 = 9.23$, $P < 0.05$).

Discussion

Fluoride in drinking water is accepted for both useful and harmful effects on health. Fluorosis is prevalent in many developing Asian and African countries in the form of "linked disorders" as fluoride being a reactive ion and an oxidizing agent acts as an enzyme inhibitor, hormone disruptor, and neurotoxin.^[11-15] Because of more than 90% bioavailability, the consumption of excess of fluoride through drinking water is one of the main causes of

Table 2: Showing data of different fluoride concentration groups and adverse pregnancy outcomes

	Urinary Fluoride Levels (mg/l)			Total
	Group 1 (n=155)	Group 2 (n=199)	Group 3 (n=246)	
No Adverse Outcome (n)				
Pregnancy complications				
Anemia in patients (n)	84	48	7	117
fetal miscarriage, abortion or congenital abnormalities (n)	56	125	199	402
	15	26	40	81

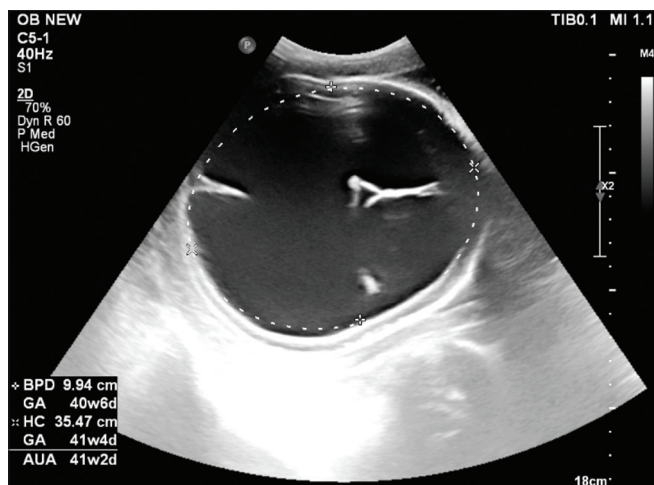


Figure 1: Ultrasound image from a patient with neural tube defect showing gross hydrocephalous with thinning of the parenchyma

fluorosis.^[16,17] We examined a group of 600 pregnant women of reproductive age group from lower socioeconomic strata who were regularly exposed to fluoride by means of drinking water with the aim of detecting the early adverse pregnancy outcomes comprising abortions, IUDs, and congenital abnormalities. This study was done in Faridkot district of Punjab, India and on the examination of groundwater and tap water, it was detected that the mean value of the water fluoride content was 2.4 mg/L that is more than the permissible limits. As per the WHO guidelines the maximum allowable limit of fluoride in drinking water is 1.5 mg/L, whereas according to the BIS the safer limit is around 1 mg/L.^[5] Hence, it may be concluded that the exposure to fluoride from drinking water is of considerable concern in this region.

Other factors such as diet, excessive tea consumption, other concomitant nutritional deficiencies, and, the usage of fluoridated tooth paste have also an effect on the occurrence and severity of fluorosis.^[18] The patients enrolled in our study mainly depended on locally grown vegetarian food for their day-to-day supplies and had a history of regular intake of tea and usage of Fluoridated toothpastes. In the present study, 402 patients (67%) were anemic based on the ICMR criteria of anemia during pregnancy. Further, there was a negative correlation between urinary fluoride and hemoglobin levels. Vitamin B12 is one of the important elements of hemoglobin and is manufactured by probiotic bacteria in the gut that are diminished by excessive fluoride leading to anemia. The excess consumption of fluoride also leads to non absorption of nutrients due to the damage of intestinal microvilli.^[19] Hillman *et al.* documented that levels of serum folic acid and vitamin B12 in body were reduced by fluoride overdose leading to anemia in cattle.^[20] Another study from India documented that anemia in school children was owing to consuming drinking water with high fluoride level and there was an inverse relationship between urinary fluoride and hemoglobin levels.^[21]

Although plasma fluoride level is a contemporary biomarker for intake of fluoride, still urine has been counted as the very

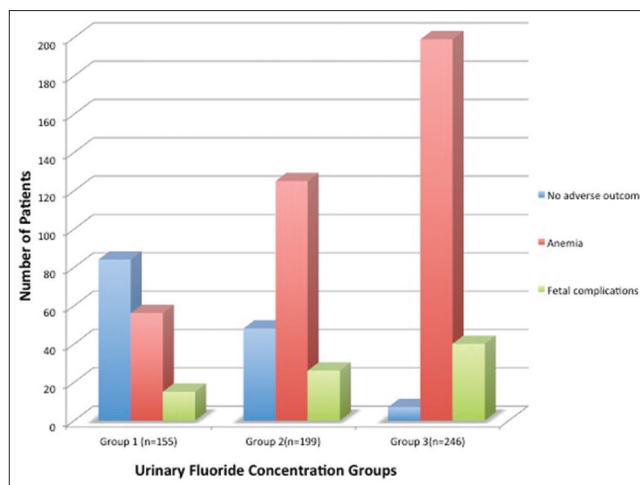


Figure 2: Bar diagram showing different fluoride levels groups and the pregnancy complications

valuable biomarker for fluoride intake since it is commonly used, comparatively simple to collect, and non invasive.^[22,23] Possible harm to the developing embryo and fetus in the backdrop of high maternal intake of fluoride has been a source of concern, with only very few studies evaluating this risk in humans. In the present study we found that females with elevated urinary fluoride levels have more chances of pregnancy complications such as anemia and adverse fetal outcomes. Fluoride crosses the placenta and it has been documented that the mean umbilical cord blood levels of fluoride are around 60% of maternal serum levels.^[24] Unfavorable perinatal outcomes such as pre term and small-for-gestational-age infants and the increased incidence of perinatal mortality have been found in the offspring of the anemic mothers. Evidence from some of the human studies suggests that excessive fluoride influences neural development in utero and can lead to neurological malformations.^[16,24-29] In a paper published by AK Susheela *et al.*^[30] it was found that the intake of fluoride free water and food decreased the incidence of preterm deliveries by 4 times and low birth weight babies by 2 times. This paper also documented that iron and folate supplementations to the pregnant women decreased the possibility of low birth weight only if these supplements are accompanied by nutritional food and less fluoride intake.

Family physicians are the essential contributors of care for females of the reproductive-age group that incorporates healthcare before, during, and after pregnancy. Primary care physicians are uniquely poised to guide patients regarding excessive fluoride exposures during pregnancy; by designing and conducting awareness programmes, by discussing harmful effects of fluorosis including adverse pregnancy outcomes and by contributing towards its management by focusing on timely treatment, healthy diets, and safe drinking water. Further, family physicians can synchronize the healthcare of such pregnant patients among different specialties, which can ultimately lead to better health outcomes.

The drawback of this study was that mainly drinking water was examined for fluoride content and patients were followed only till 20 weeks of gestation. The amount of fluoride intake due to food and drinks such as tea was not determined. We feel that further studies are needed in order to recognize more factors related with adverse pregnancy outcomes due to water contaminants and the findings of the present study ought to be corroborated in other study populations. Hence, multicentric studies with a larger sample size and with a regular monitoring of 24-hour urine samples along with plasma samples may lead to the better understanding of the deleterious effects of excessive fluoride exposures during pregnancy. Nevertheless, our study has highlighted this important public health issue and is likely to set a benchmark for other studies on this subject so that this issue can be explored in depth. Based on the findings of this research the authors would like to make following recommendations:

- All the pregnant patients residing in fluoride endemic areas should be screened for anemia and high urinary fluoride levels, as the later test is simple, non invasive and inexpensive.
- Ultrasound examination is recommended at prescribed intervals for patients with high urinary fluoride levels to look for any congenital anomalies and other adverse fetal outcomes. Therefore, family physicians have an important role to play in minimizing the complications by conducting an early screening of this disease and hence ensuring timely treatment.
- Further, efforts must be made to address the low level of health literacy about fluorosis as well as the prevalent dietary habits and behaviors that lead to excessive fluoride exposures.

Conclusions

The study confirms the presence of excess fluoride levels in the underground and tap water of Faridkot district of north India. Excess fluoride intake during early pregnancy may lead to increased prevalence and severity of maternal anemia as well as adverse fetal outcomes in the form of miscarriages, abortions, intra-uterine deaths, and congenital malformations. Further, multicentric studies with large study populations are required in order to better establish the relationship of the excess fluoride exposures with adverse pregnancy outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

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Conflicts of interest

There are no conflicts of interest.

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