

EPIDEMIOLOGY OF DRINKING WATER FLUORIDE AND ITS CONTRIBUTION TO FERTILITY, INFERTILITY, AND ABORTION: AN ECOLOGICAL STUDY IN WEST AZERBAIJAN PROVINCE, POLDASHT COUNTY, IRAN

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ABSTRACT: Research, including animal studies, shows that the fluoride ion (F) adversely impacts the reproductive system in mammals. However, the gene-environment interaction mechanisms involved in this association remain unclear. The objective of the present study was to measure the F level in two regions of Poldasht county, Iran, with low and high drinking water F levels (means 1.90 and 8.10 mg/L, respectively) and to examine, in females living in the areas, the relationship between the drinking water F and (i) fertility, (ii) infertility without known etiological factors, and (iii) abortion without known etiological factors. Comparing the women in the low and high F areas, the respective rates were: (i) fertility: 105/1993, 5.3%; 70/1224, 0.5%; (ii) infertility without known etiological factors: 17/1993, 0.9%; 24/1224, 2.0%; and (iii) abortion without known etiological factors: 6/105, 5.7%; 11/70, 10.0%. We found that there were no statistically significant differences in the reproductive parameters between the low and high F regions when the women were considered by 5-year age groups, but, when the data were pooled and all the age groups were considered together in a group with ages 10–49 yr, those in the low F group were more fertile ($p < 0.05$) and had lower rates of (i) infertility without known etiological factors ($p < 0.001$) and (ii) abortion without known etiological factors ($p < 0.001$).

Keywords: Abortion; Drinking water; Fertility; Fluoride; Infertility; Iran; Poldasht.

INTRODUCTION

The fluoride ion (F) at high concentrations in drinking water has a negative effect on human life and a guideline value for the upper limit of F in drinking water of 1.5 mg/L was set by the WHO in 1984 and reaffirmed in 1993.¹ However, in setting national standards or local guidelines for F, or in evaluating the possible health consequences of exposure to F, it was noted that it was essential to consider the total intake in the population of interest from both water and other sources such as food and air.¹ Where the intakes were likely to approach or be greater than 6 mg/day, a guideline concentration for the upper limit of F in drinking water of >1.5 mg/L was seen to be appropriate.¹

A dental fluorosis prevalence of 12–33% has been reported with drinking water concentrations of 0.9–1.2 mg/L and a high F intake may cause serious toxic effects in consumers such as anemia in pregnancy, low birth weight babies, neurological problems and lowered IQ, chronic cognitive impairment and dementia, disturbed thyroid hormone metabolism, and infertility problems.^{2–11} The adverse effects of F on human health may be treatable, or permanent and irreversible.¹² The World

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Health Organization defines the term infertility as a failure to achieve a successful pregnancy after 12 months or more of appropriate, timed, unprotected sexual intercourse. About 10% to 15% of all couples are unable to conceive a child after 1 year of trying to become pregnant.¹³ Many factors such as environmental and lifestyle factors can affect human fertility.^{14–16} Freni reported in 1994 that a high content of F in drinking water could lead to a decrease in the rate of reproduction.¹⁷ A variety of clinical studies have found a correlation between the long-term uptake of drinking water with a high concentration F and impaired reproduction. Research has shown that high F exposure is associated with decreased estrogen and testosterone levels. In addition, the adverse results found include interference with spermatogenesis, a decline in sperm motility, and a decrease in the sperm count and other reproductive functions.^{17–22}

Infertility is one of the most fundamental problems in the world, and is a growing global public health issue. In the Republic of Iran, 2 in 10 couples (20%) will experience difficulty in conceiving. Comparable societies report rates between 8% and 20%.^{23–24} The annual incidence of infertility is estimated at 200 couples per 1000 total general population. In Iran's population of 70 million, 3 million couples are grappling with infertility.²⁵ Infertility is a complex disorder and can be caused by multiple factors including physical, chemical, biological, behavioral, social, and economic. The environmental factors that may affect reproductive health include exposure, during critical periods of human development, to risk factors such as contamination of drinking water with lead, arsenic, chromium, and F.^{26–28} The effects of F on fertility and infertility, in both women and men, is a matter of concern in the scientific community. The role of F on reproductive health system is complex and the mechanisms involved are uncertain. Although many studies have been carried out world-wide on F and fertility, few have been epidemiological studies on the correlation between human F exposure and the prevalence of fertility, infertility, and abortion.

Thus, the objectives of the present study were to examine the relationship between the prevalence of fertility, infertility, and abortion in females who were exposed to high and low levels of F in drinking water in West Azerbaijan Province, Poldasht County, Iran.

MATERIAL AND METHODS

Study areas: Poldasht County is located in West Azerbaijan Province in north western Iran with UTM coordinates: zone/sector 39S, 446625–513055 m E, and 4344280–4402863 m N. The Poldasht meteorological station showed that in the long-term, the average rainfall was equal to 131.5 mm.²⁹ The County has a border in the west and north with Turkey. Two study areas (five villages) were selected in Poldasht County with almost the same socioeconomic status and dietary habits but different natural concentrations of F in their drinking water. Two villages had a high level of F (Sarisoo and Konikor) and three villages had a low level of F (Daiankendi, Eshgabad, and Moradloo).

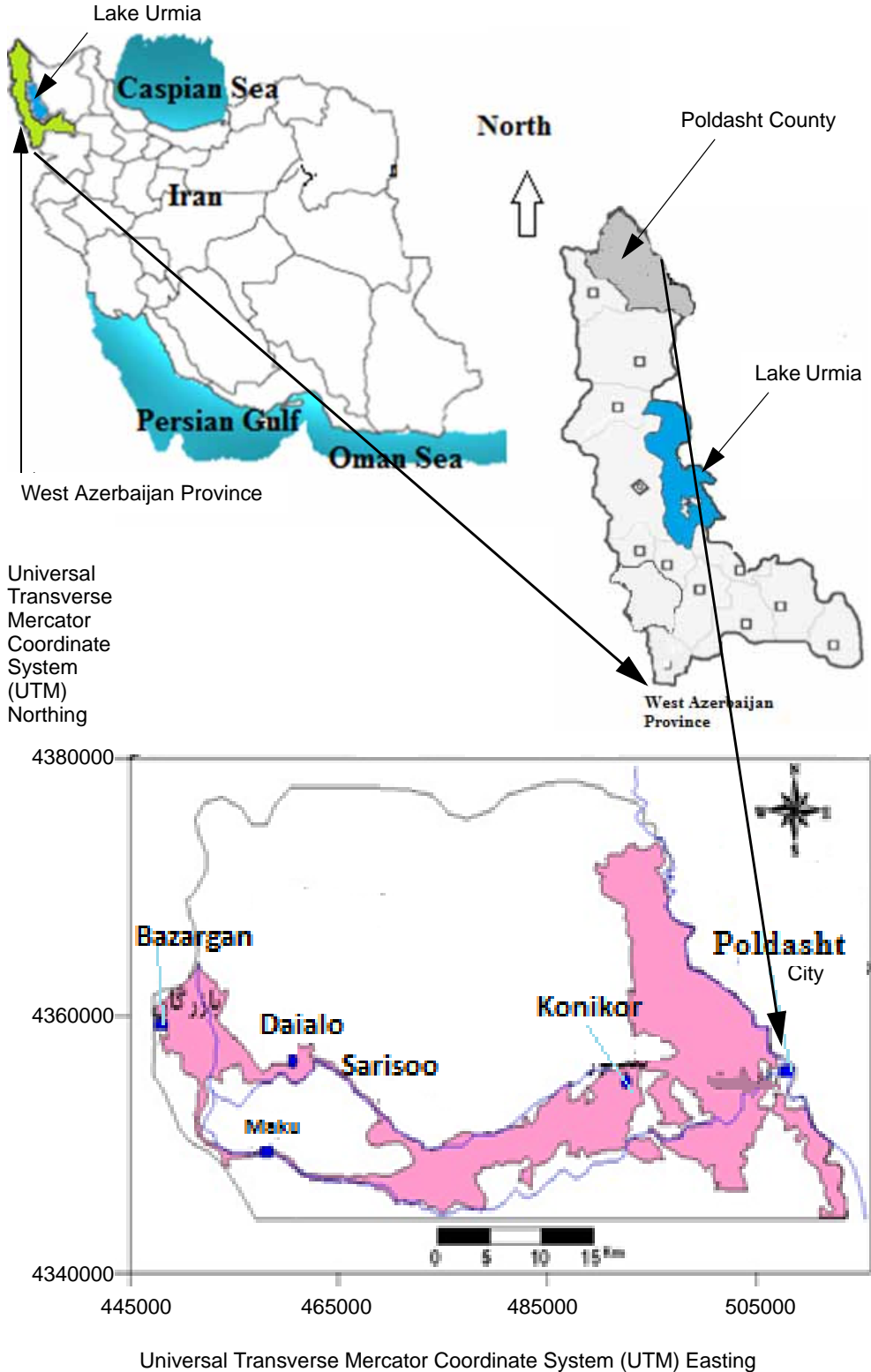


Figure 1. Location of study sites.

Determination of the water fluoride concentration: Five drinking water wells in the area were selected. A total of 20 samples were collected over three consecutive years in 2013, 2014, and 2015. The water samples were collected from the ground water wells in sterile plastic 2 L containers and then transported to the Laboratory for Water and Sewage Poldasht. The F concentration in the water samples was determined using the SPADNS method according to the standard method.³⁰

Data gathering for fertility: The data on the prevalence of fertility, infertility, and abortion, were derived from the health records of the areas being investigated. Based on the health records, 2098 women in the high F area (Sarisoo and Konikor) and 1294 people in the low F area (Daiankendi, Eshgabad, and Moradloo) were identified. Many women were excluded from the study because of the presence of known causes of infertility such as diabetes mellitus, obesity, smoking, and consumption of alcohol.

Statistical analysis: To present the data we used the mean standard deviation, frequency, and percent. To compare the groups regarding the rate and prevalence of the outcomes, we used Poisson regression and logistic regression analysis within a GEE method to consider the possible correlation of area with time. All statistical analyses were performed with the SPSS (IBM SPSS Statistics for Windows. Version 24.0. released 2016. Armonk, NY: IBM Corp; 2016.) p-values less than 0.05 were considered to be statistically significant.

RESULTS

All the subjects in the study were residents of Poldasht County, an endemic fluorosis area. In the rural areas studied, the range of F concentrations in the drinking water was 1.46–10.3 mg/L. Eighty-five % of the samples showed a F level higher than the WHO recommended upper limit of 1.5 mg/L and 15% of the water samples were below this in the acceptable range of <1.5 ppm (Table1).

Table 1. Drinking water fluoride (F) concentration (mg/L) in 2013–2015 in the rural areas studied of Poldasht County, Iran

Drinking water F parameter	Drinking water F concentration (mg/L)	
	Low F villages (Daiankendi, Eshgabad, Moradloo)	High F villages (Sarisoo, Monikor)
Mean	1.90	8.10
Standard deviation	0.37	1.44
Median	1.76	8.28
Minimum	1.46	6.00
Maximum	2.81	10.30

The results showed that the mean F concentration in the groundwater resources in the five villages studied was higher than the maximum guideline level of the WHO of 1.5 mg/L. The lowest mean concentration of F was 1.46 ± 0.37 mg/L in Moradloo village and highest mean F level was 10.3 ± 1.44 mg/L in Sarisoo village (Table 1). Comparing the women in the low and high F areas, the respective fertility, infertility, and abortion rates were: fertility: 105/1993, 5.3%; 70/1224, 0.5%; infertility without known etiological factors: 17/1993, 0.9%; 24/1224, 2.0%; and abortion without known etiological factors: 6/105, 5.7%; 11/70, 10.0%. (Tables 2–5). We found that there were no statistically significant differences in the reproductive parameters between the low and high F regions when the women were considered by 5-year age groups, but, when the data were pooled and all the age groups were considered together in a group with ages 10–49 yr, those in the low F group were more fertile ($p < 0.05$) and had lower rates of (i) infertility without known etiological factors ($p < 0.001$) and (ii) abortion without known etiological factors ($p < 0.001$).

Table 2. Comparison of the prevalence of fertility (%) in the different age groups in the rural areas with different drinking water fluoride levels

Age group (yr)	Group						Difference	p
	Low F villages (Daiankendi, Eshgabad, Moradloo)			High F villages (Sarisoo, Monikor)				
	Population	n	Prevalence of abortion (%)	Population	n	Prevalence of abortion (%)		
10–14	293	0	0.0%	225	0	0.0%	0.0%	1
15–19	308	14	4.5%	247	11	4.5%	–0.1%	0.843
20–24	347	29	8.4%	199	22	11.1%	2.7%	0.62
25–29	274	30	10.9%	134	25	18.7%	7.7%	0.089
30–34	255	19	7.5%	108	10	9.3%	1.8%	0.73
35–39	178	10	5.6%	108	2	1.9%	–3.8%	0.152
40–44	199	3	1.5%	93	0	0.0%	–1.5%	0.998
45–49	139	0	0.0%	110	0	0.0%	0.0%	1
Total	1993	105	5.3%	1224	70	5.7%	0.5%	<0.001

Table 3. Comparison of the prevalence of infertility (%), without known etiological factors, in the different age groups in the rural areas with different drinking water fluoride levels

Age group (yr)	Group						Difference	p
	Low F villages (Daiankendi, Eshgabad, Moradloo)			High F villages (Sariso, Monikor)				
	Population	n	Prevalence of abortion (%)	Population	n	Prevalence of abortion (%)		
10–14	293	0	0.0%	225	0	0.0%	0.0%	1
15–19	308	0	0.0%	247	0	0.0%	0.0%	1
20–24	347	0	0.0%	199	2	1.0%	1.0%	0.132
25–29	274	2	0.7%	134	11	8.2%	7.5%	0.018
30–34	255	2	0.8%	108	7	6.5%	5.7%	0.002
35–39	178	9	5.1%	108	4	3.7%	–1.4%	0.342
40–44	199	3	1.5%	93	0	0.0%	–1.5%	–
45–49	139	1	0.7%	110	0	0.0%	–0.7%	–
Total	1993	17	0.9%	1224	24	2.0%	1.1%	<0.001

Table 4. Comparison of the prevalence of abortion (%), without known etiological factors, in the different age groups in the rural areas with different drinking water fluoride levels

Age group (yr)	Group						Difference	p
	Low F villages (Daiankendi, Eshgabad, Moradloo)			High F villages (Sarisoo, Monikor)				
	Population	n	Prevalence of abortion (%)	Population	n	Prevalence of abortion (%)		
10–14	0	0	NA	0	0	NA	NA	–
15–19	14	0	0.0%	11	2	18.2%	18.2%	0.183
20–24	29	2	6.9%	22	2	9.1%	2.2%	0.922
25–29	30	1	3.3%	25	4	16.0%	12.7%	0.007
30–34	19	2	10.5%	10	2	20.0%	9.5%	0.257
35–39	10	1	10.0%	2	1	50.0%	40.0%	0.336
40–44	3	0	0.0%	0	0	NA	NA	–
45–49	0	0	NA	0	0	NA	NA	–
Total	105	6	5.7%	70	11	15.7%	10.0%	0.011

DISCUSSION

Some of the F concentration values of the water resources in Poldasht County are higher than the recommended WHO upper limit guideline of 1.5 mg/L. The lowest mean concentration of F was 1.46 ± 0.37 mg/L in Moradloo village and the mean highest F level was 10.3 ± 1.44 mg/L in Sarisoo village (Table 1). Various adverse effects on human tissue of high drinking water F concentrations have been observed^{31–32} but the adverse effects on the reproductive system are still not well understood. The results of the present study showed that there was no statistically significant difference between the low and high F villages when the women were considered by 5-year age groups, but, when the data were pooled and all the age groups were considered together in a group with ages 10–49 yr, those in the low F group were more

fertile ($p < 0.05$), and had lower rates of (i) infertility without known etiological factors ($p < 0.001$) and (ii) abortion without known etiological factors ($p < 0.001$).

A similar epidemiological study by Freni et al. in 1994 in the United States of America examined the effect of F in drinking water on the reproduction rate in women and found that an increased F intake was associated with a reduced reproduction rate.¹⁷

Another study, by Ortiz-Perez et al. in 2003 in Mexico, compared people working at a factory producing aluminum fluoride and hydrofluoric acid that were exposed to F at high doses of 3–27 mg/day to a control group exposed to lower doses of F of 2–13 mg/day.³³ In the high F exposure group there was (i) a significant increase in FSH ($p < 0.05$); (ii) a reduction of inhibin-B, free testosterone, and prolactin in serum ($p < 0.05$); and (iii) a decreased sensitivity in the FSH response to inhibin-B ($p < 0.05$). In addition there was (a) a significant negative partial correlation between urinary F and serum levels of inhibin-B ($r = -0.333$, $p = 0.028$) in the low F exposure group; and (b). a significant partial correlation between a chronic exposure index for F and the serum concentrations of inhibin-B ($r = -0.163$, $p = 0.037$) in the high F exposure group.³³ The authors considered that their results indicated that a F exposure of 3–27 mg/day induced a subclinical reproductive effect that could be explained by a F-induced toxic effect in both Sertoli cells and gonadotrophs.³³

A further study, by Al-Hiyasat and Elbetieha in 2000, conducted on female Sprague-Dawley rats, used F concentrations in drinking water of 0.5, 200, 400, and 600 mg/L.³⁴ The results showed that high concentrations of F had an adverse effect on the reproductive system of the rats with more resorptions and a fetotoxic effect with fewer viable fetuses.³⁴

Other studies in this area on human society have suggested that high concentrations of F cause changes in the reproductive hormones and increase the risk of Down syndrome but these investigations have their limitations.

A case-control study by Diouf et al. in 2012 in Senegal on pregnant women living in a fluorosis endemic area with high water F levels included 108 mothers who gave birth to newborns weighing less than 2500 g (cases) and 216 mothers with newborns weighing greater or equal to 2500 g (controls).³⁵ The proportions of mothers consuming well water, with a higher F concentration, were 62% among the cases versus 43.5% among the controls.³⁵ A score 4 on Dean's Index was reported for 25.9% of the cases versus 6.9% of the controls.³⁵ The water consumed and the modal score on Dean's Index were significantly associated with the occurrence of low birthweight adjusted for gender, consanguinity, anemia, and hypertension.³⁵ The authors concluded that low birthweight was associated with pregnant women living in endemic areas. and that defluoridation programs and access for pregnant women and children to high quality water were necessary in areas of endemic fluorosis.³⁵

An additional clinical study, by Susheela in 2010, was focused on the relationships between drinking water F concentration, premature birth, and anemia.³⁶ The results showed that F lowered the production of red blood cells and eventually caused premature death of red blood cells.³⁶

In general, the existing studies on the relationship between the F content in drinking water and human reproduction are few in number and they have significant deficiencies in their design and power, thus restricting the ability to draw conclusions from them.

CONCLUSIONS

The present study indicates that the groundwater of Poldasht is highly deteriorated due to pollution with the fluoride ion. Eighty-five % of the samples in the five villages studied had a F level higher than the WHO recommended upper limit guideline for drinking water F of 1.5 mg/L. We found that there were no statistically significant differences in the reproductive parameters between the low and high F regions when the women were considered by 5-year age groups, but, when the data were pooled and all the age groups were considered together in a group with ages 10–49 yr, those in the low F group were more fertile ($p < 0.05$) and had lower rates of (i) infertility without known etiological factors ($p < 0.001$) and (ii) abortion without known etiological factors ($p < 0.001$). Finally, the authors declare that ultimate conclusions about the association of fluoride and fertility, infertility without known aetiological factors, abortion without known aetiological factors, and other effects on reproductive health will require more experimental and epidemiologic studies, including a better control of confounding factors.

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