Original Article

Association between the concentrations of some toxic metals and the risk of uterine fibroids among Nigerian women

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Abstract

Background: Uterine fibroids are a major health challenge to some women in the world, especially women of African descendants. The etiology of uterine fibroids and the mechanisms of their growth are not fully understood, and those factors that make women to be susceptible to fibroid development are subjects of investigation. Environmental toxicants such as toxic metals exposure have been implicated, but the results have not been consistent. This study seeks to determine the association between blood cadmium (Cd), arsenic (As), and lead (Pb) levels and the risk of uterine fibroids among women of reproductive age.

Materials and Methods: This case–control study comprised 100 women of reproductive age (age range, 20–50 years) with uterine fibroid and 50 age-matched women without uterine fibroids. Fibroids were diagnosed using abdominal scan by attending physicians. Furthermore, the control subjects were screened for fibroids using abnormal scan. Blood Cd, As, and Pb were determined using an atomic absorption spectrophotometer, and the risk of association was calculated.

Results: The mean blood Cd, As, and Pb were significantly higher ($P < 0.001$) among women with fibroid than those without fibroid (controls). The odds ratio for Cd 2.62 (confidence interval [CI]: 0.02–0.05), As 1.02 (CI: 0.02–0.030), and Pb 1.42 (CI: 0.04–0.129) was greater among women with uterine fibroids than controls.

Conclusions: Exposure to cadmium and lead might be a risk factor for developing uterine fibroids among Nigerian women.

Keywords: Female, humans, leiomyoma, Nigeria

INTRODUCTION

Uterine fibroids, also called leiomyoma, are a major health challenge to some women in the world, especially women of African descendants. Uterine fibroids are gynecological disorders that affect 70%–80% of women throughout their lifetime.[1] Uterine fibroids are noncancerous growths that are formed in the smooth muscle of the uterus.[2] They are characterized by increase in smooth muscle cell proliferation and an excessive deposition of extracellular matrix.[3] The most common symptoms are uterine bleeding and pelvic pain that may be severe, leading to infertility. The etiology of uterine fibroids and the mechanisms of their growth are not fully understood, and those factors

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that make women to be susceptible to fibroid development are subjects of continuous investigation. Nonmodifiable risk factors include age, race, and family history, but modifiable risk factors that influence the rate of fibroid development are elevated blood pressure (BP),[4] due to altered atherogenesis.[5] Elevated serum lipids and metabolic syndrome have been associated with risk of fibroids, suggesting cardiometabolic mechanisms.[6] Low Vitamin D circulating levels may also increase risk for fibroids.[7]

African women have been reported to be highly susceptible to fibroids development than other races and fibroids symptoms are likely to be more severe among black Africans.[8] According to Stewart *et al.*,[9] the proportion of women affected by fibroid range from 4.5% to 68.6% depending on the study population and diagnostic methods used. The National Institute of Health 2013 report has established that 25%–80% of women suffer from uterine fibroid.[10] The incidence of fibroid can be observed in women between the ages of 30 and 39 years.[11] The prevalence of uterine fibroids recorded in some part of Nigeria varies from one region to another. The prevalence of 9.8% was reported in Lokoja, 7.8% in Ilesa, 8.3% in Zaria, and 6.58% in Ile-Ife,[12] while 3.2% was observed in Sagamu,[13] 13.6% in Ebonyi,[14] 19.75% in Irrua, 25.9% in Enugu,[15] and 10% in Nnewi.[16]

Environmental toxicants especially toxic metals might play some roles in the development of fibroids. Elsewhere, some studies have reported the associations between blood toxic metal concentrations and the development of uterine fibroids even though the results are not consistent.[17,18] It is of public interest to know whether association exists between blood toxic metal levels and presence of fibroids among women of reproductive age in our setting. This may help formulate policy that might guide against the development of fibroid with its accompanied complications and economic loss.

Emerging evidence indicates that Cadmium (Cd) may be associated with several adverse outcomes in women's reproductive health including uterine fibroids. The association between uterine fibroid volume and blood Cd concentrations has been reported.[19] Cd is a nonessential toxic metal with ubiquity exposure. It is the seventh most toxic metal as per ATSDR ranking and a by-product of zinc production.[20] Individuals are exposed to Cd through cigarette smoking and diets such as seafood (shellfish), cereal, leafy green, and root vegetables. Cd is toxic, carcinogenic, nonbiodegradable metal, which can induce elevated reactive oxygen species formation, and successively induces DNA damage, in addition to its ability to interfere with cell signaling.[13,20]

Arsenic (As) is a nonessential, natural-occurring metal that is carcinogenic and ubiquitously distributed in the environment and is highly toxic to all forms of life.[20] It is classified as group I carcinogen which is a contaminant of drinking water and humans are exposed to As through soil, water, and food.[21]

Lead is a naturally occurring toxic metal that is widely distributed in the environment and biological system through human activities. It is a nonessential metal that is highly toxic even at low levels of human exposure. Furthermore, it is nonbiodegradable and tends to accumulate in living organism.[22]

Fibroids are estrogen-dependent diseases, where the affected tissues demonstrate more estrogen receptor-α (ERα) than nonaffected tissues. Since fibroids are associated with estrogen hormone, some authors have suggested that exposure to exogenous estrogens may exacerbates their development.[1,3,17] Metalloestrogens such as Cd, As, and Pb are known to activate the ER in the absence of estradiol. The objective of this study was to determine the association between some blood level of toxic metals and risk of uterine fibroids among women of reproductive age in Owo, Ondo Sate, Nigeria.

MATERIALS AND METHODS

Study design

This was a case–control study conducted among 100 females (age range 20–50 years) with uterine fibroid and 50 age-matched females without uterine fibroids attending the Obstetrics and Gynaecology clinic of Federal Medical Centre, Owo. The abdominal scan (Acuson Sequoia 512) was used to screen the women into fibroids and controls. Women with fibroids were duly diagnosed by the attending physicians in the facility. The study participants live in the same geographic region (South-West) of Nigeria. The sociodemographic data were obtained using a semistructured questionnaire.

Inclusion and exclusion criteria

Any subjects whose age did not fall within the range and pregnant women who have fibroids were excluded. Furthermore, pregnant women without fibroids and postmenopausal women were excluded from the study. Women who refused to give consent were also excluded from the study.

Ethical consideration

Approval for this study was obtained from Ethical Review committee of the Federal Medical Centre, Owo, with registration reference number: FMC/OW/380/

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VOL. CIX/69, issued on the December 14, 2020. A semistructured questionnaire was used to obtain sociodemographic (age, parity, education, and marital status) and medical information of the study participants.

Sample size determination

The sample size for the study was determined using the sample size determination for health studies ($n = Z^2Pq/d^2$)[23] and 6.58% prevalence of fibroids among women of reproductive age reported from Ile-Ife, Osun State.[12] The calculated sample size was 95, but for the purpose of this study, 100 subjects with uterine fibroids and 50 age-matched controls were enrolled.

Anthropometric measurement

The BP, weight, and height were measured by a trained nurse using a standard sphygmomanometer, Suvarna Electro-Digital Body Weighing Scale (Suvarna, India) and Seca 213-Scale Galore Metric Stadiometer (USA) attached to a wall. The measurements were taken with the subjects standing as their head, shoulder blades, buttocks, and heels touch the measuring rod on the stadiometer and facing forward. Body mass index (BMI) was calculated by dividing the weight (kg)/height (m^2).

Sample collection

Exactly, 5 ml of venous blood samples was collected from women with fibroids and controls into ethylenediaminetetraacetic acid bottle and stored at − 20°C for toxic metals determination.

Laboratory analysis

Blood As, Cd, and lead (Pb) were determined using atomic absorption spectrophotometric technique. An aliquot (1 ml) of whole blood sample was measured and poured into the khedjahl digestion tube, 5 ml of the mixed acid (Nitric-Perchloric acid mixture (Ratio 2:1)) was added. Digestion tube was brought to the heater and heated. When dense white fume occurred, heating continues until a clean solution was obtained. It was removed from the heater, cooled, and a small amount of deionized water was added. The solution was filtered with Whiteman number 42 filter paper into a 25 ml volumetric flask, and the volume was made up with deionized water to 25 ml. A reagent blank was prepared identically but without the blood sample. The metal concentrations were determined by an atomic absorption spectrophotometer (BUCK Scientific, Norwalk, CT, USA) according to the manufacturer's protocol.

Standard preparation (QC)

The AAS was first calibrated using Buck certified atomic absorption standards for the respective metals to obtain a calibration curve. The reagent blank was run at intervals of every 10 samples of analysis to eliminate equipment drift. All samples were analyzed in duplicate for reproducibility and precision and to ensure accurate checks.

Statistical analysis

The statistical analysis was done using IBM Statistical Package for the Social Science (IBM SPSS, Armonk, NY, USA) version 21.0. The Student's *t*-test was used for comparison within the groups. Spearman's correlation (of log transformed toxic metal levels) was used to test the association between variables. The level of significance was taken at 95% confidence interval (CI) and $P < 0.05$ was considered statistically significant.

RESULTS

The findings from this study are presented in Tables 1-3. Table 1 shows the sociodemographic and anthropometric variables of the study participants. There were no significant differences between two groups in the distributions of age, education status, and parity ($P > 0.05$). The mean

Table 1: Comparison of demographic and anthropometric characteristics between women with uterine fibroids and control subjects

Parameters	Women with uterine fibroids, *n* (%)	Women without uterine fibroids, *n* (%)	χ^2/P
Age (years)			
20-30	38 (38.0)	16 (32.0)	0.565 (0.754)
31-40	45 (45.0)	24 (48.0)	
41-50	17 (17.0)	10 (20.0)	
Educational status			
Literate	65 (65.0)	31 (62.0)	0.130 (0.719)
Illiterate	35 (35.0)	19 (38.0)	
Parity			
0	35 (35.0)	18 (36.0)	4.412 (0.492)
1	22 (22.0)	13 (26.0)	
2	21 (21.0)	10 (20.0)	
3	11 (11.0)	8 (16.0)	
≥4	11 (11.0)	1 (2.0)	
BP			
Systolic	118.80±13.36	119.00±10.55	0.926
Diastolic	76.60±11.30	77.20±12.62	0.769
BMI	25.65±4.26	25.13±4.15	0.476

BP: Blood pressure, BMI: Body mass index

Table 2: Comparison of measured blood toxic metals between women with uterine fibroids and control subjects without uterine fibroids (median±standard deviation)

Toxic metals	Women with uterine fibroids	Women without uterine fibroids	*P*
Cadmium (mg/L)	0.028±0.02	0.005±0.00	0.001
Arsenic (mg/L)	0.040±0.02	0.006±0.00	0.001
Lead (mg/L)	0.089±0.04	0.014±0.01	0.001

Table 3: Association between toxic metals and presence of uterine fibroids

Toxic metals	Unadjusted OR	95% CI
Cadmium (mg/L)	2.62	0.026-0.050−1.59-−1.30
Arsenic (mg/L)	1.02	0.02-0.030−1.70-−0.52
Lead (mg/L)	1.42	0.04-0.129−1.40-−0.89

OR: Odd ratio, CI: Confidence interval

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systolic BP of women with fibroid was not significantly different ($P > 0.05$) compared with the control subjects. Similarly, the mean diastolic BP was not significantly different ($P > 0.05$) compared with the control subjects. Furthermore, the mean BMI of the women with fibroid was not significantly different ($P > 0.05$) compared with controls.

Table 2 shows the comparison of mean blood Cd, Ar, and Pb between women with fibroid and those without fibroid. The mean blood Cd, As, and Pb were significantly higher ($P < 0.001$) among women with fibroid than those without fibroid (controls).

Table 3 indicates the odds ratio of the association of toxic metal concentration with the development of uterine fibroids among the study participants. The odds ratio for Cd 2.62 (CI: 0.02–0.05), As 1.02 (CI: 0.02–0.030), and Pb 1.42 (CI: 0.04–0.129) was greater among women with uterine fibroids than controls.

DISCUSSION

Environmental toxicants including toxic metals have been suggested to play some roles in the development of fibroids. Some authors elsewhere have associated blood toxic metal concentrations with the development of uterine fibroids even though the results are conflicting.[17,18] Toxic metals exposure is a modifiable factor and awareness of their contribution to the development of fibroids may be of public interest to prevent the occurrence of fibroids among Africans. This is particularly important beacuse African women are highly susceptible to fibroids development than other races and fibroids symptoms are reported to be more severe among Africans than other racial groups.[8]

In this study, we demonstrated that the blood levels of Cd, As, and lead were significantly higher among women with fibroid than those without fibroids. The risk of developing fibroids was 2.62, 1.02, and 1.42 folds higher among women with significantly higher blood Cd As and lead, respectively. This observation was consistent with previous studies.[24,25] Johnstone *et al.*[24] reported significantly higher levels of blood and urine lead and Cd but not As among women with fibroids. The authors suggested that toxic metal exposures may contribute to the pathogenesis of uterine fibroids and fibroids may serve as a reservoir for the bioaccumulation of toxic metals among women. Fibroids development has been suggested to be associated with the exposure to exogenous substances that mimic estrogens action such as Cd, lead, and other toxic metals.[5,6] These metalloestrogens such as Cd, lead, and mercury could activate the ER in the absence of estradiol.[26] This has been demonstrated in both *in vitro* and *in vivo* studies where metalloestrogens resulted in the activation of ERα receptors.[7-9] The main sources of human exposure to these toxic metals include consumption of sea foods, drinking of contaminated water, contaminated soil and dust, hair relaxers, and cosmetics and air pollution.[19] Furthermore, fibroid tissues are reported to exhibit increased expression of ER-α gene and protein than nonfibroid cells in the surrounding tissues.[27] Although a good number of women with fibroids are asymptomatic, the symptomatic disease can cause substantial adverse effects, thus reducing the quality of life of women.

Similarly, the findings of significantly higher concentrations of Pb and As among women with uterine fibroids align with previous studies.[17,24] It was reported that Pb levels in women with uterine leiomyoma are higher than those of the healthy controls without uterine fibroid.[24] Some of the reported mechanisms are that toxic metal acts as metalloestrogen, enhance free radical generation leading to oxidative stress, exacerbates inflammation, impairs endothelial function and increases the risk of peripheral arterial disease.[6,17,24]

Conversely, some authors reported no association between the measured toxic metal concentrations and the development of uterine fibroids.[25] They, however, observed that the odds of women having fibroids were higher with significantly higher blood concentrations of Cd, lead, and mercury. The authors also reported an association between Cd levels with fibroids volume but not with lead and mercury.[25]

Toxic metals do not only encourage the development of fibroids but could exacerbate the transformation of benign fibroids to malignant tissues. A study conducted to determine the role of toxic metal in the transformation of benign human uterine fibroid cells to malignant tumor reported that continuous Cd exposure can cause a significant inhibition of transforming growth factor-beta 1 signaling, leading to increased proliferation and attenuated fibrosis. Continuous Cd exposure can change the phenotypic characteristics and dysregulated genes in fibroid cells, thus suggestive of progression toward a cancer phenotype.[19]

Most of the women with fibroids in this study were below 40 years old; 38/100 (38%) were between 20 and 30 years, while 45/100 (45%) were between 31 and 40 years. This is consistent with the observations made in previous study that Black women have higher incidences of fibroids at younger ages than Caucasian women. This is an indication

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of racial variations in fibroid development as well as disease pathogenesis.[27] Some authors suggested that that the use of hair relaxers among Black women may be a contributing factor to the higher risk for uterine fibroids and that this increased risk was further heightened among women who relaxed their hair frequently.[28] Hair relaxers and other personal care products frequently used by Black women may be the sources of the increased risk as they contain a wide variety of compounds with endocrine-disrupting activity.[29] Obviously, apart from the endogenous estrogen, fibroid growth may also be influenced by exogenous estrogen mimicking substances which are associated with environmental exposures.[27]

In this study, there were no significant differences in the BP and BMI between women with fibroids and those without fibroids. Although some authors have suggested that the presence of uterine fibroids may be associated with higher BP level, the prevalence of hypertension among women with uterine fibroids was shown to be as high as 40%.[30] Several authors have indicated that women with hypertension have a higher risk for fibroids formation and the risk of hypertension may be greater in women with fibroids than those without fibroids.[31,32]

The proportion of women with fibroids decreased with increasing parity among the subjects. This is consistent with previous study. It may be assumed that pregnancy which is accompanied with high circulating estrogen and progesterone levels would promote fibroid development, but documentary evidence has shown that most fibroids neither grow nor shrink during pregnancy. Furthermore, most epidemiologic studies of fibroids have reported an inverse relationship between parity and fibroids, suggestive of a protective effect.[33] These protective effects were attributed to postpartum involution of the uterus that after each pregnancy the uterus rapidly returns to prepregnancy size by remodeling of the tissue. During this processes, small fibroids may be eliminated.[33]

CONCLUSIONS

Blood Cd, As, and Pb were significantly higher among women with fibroid than those without fibroid. The odds of women having fibroids were higher with Cd and lead levels in blood. Prevention of toxic metal contamination may help reduce the development of uterine fibroids among women and improve premenopausal women's health.

Implications

These results indicated that blood Cd and lead accumulation might exacerbate the development of fibroids among Nigerian women of reproductive age. The need to prevent environmental pollution from toxic metals is emphasized and adequate preventive measures should be adopted by the general population to avoid contamination.

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Conflicts of interest

There are no conflicts of interest.

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