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Increased urinary cobalt and whole blood concentrations of cadmium and lead in women with uterine leiomyomata: Findings from the ENDO Study

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Abstract

Multiple trace elements have estrogen receptor activity, but the association of these elements with uterine leiomyoma has not been defined. A cohort of 473 women aged 18–44 undergoing surgery for benign gynecologic indications provided whole blood and urine specimens for trace element analysis, which was performed by inductively coupled plasma mass spectrometry. The surgeon documented whether fibroids were present. Geometric mean concentrations were compared between women with and without fibroids, and logistic regression models were generated to assess the impact of the concentration of each trace element on the odds of fibroids. In multivariate regressions, odds of a fibroid diagnosis was higher with increased whole blood cadmium (AOR 1.44, 95% CI 1.02, 2.04) and lead (AOR 1.31 95% CI 1.02, 1.69), and urine cobalt (AOR 1.31, 95% CI 1.02, 1.70). Increased exposure to trace elements may contribute to fibroid growth, and fibroids may serve as a reservoir for these elements.

Keywords

Cadmium; Fibroids; Lead; Leiomyoma; Mercury; Metals; Trace Elements; Toxic Exposures

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1. Background

Uterine leiomyoma are smooth muscle neoplasms that arise from a single myometrial cell, and are estimated to affect 20–50% of women of reproductive age [1, 2]. Uterine fibroids are more common in black than white women [3]. The cumulative incidence increases between 35 and 50 years of age, from approximately 60% to 80%, and 35% to 60% in black and white women, respectively [2]. Overweight and obesity increase the likelihood of uterine leiomyoma, while smoking has been associated with a decreased risk [4].

A variety of growth factors have been implicated in the development of leiomyomas, including acidic fibroblast growth factor (aFGF), activin, basic fibroblast growth factor (bFGF), heparin-binding EGF (HB-EGF), insulin-like growth factor (IGF), myostatin, platelet-derived growth factor (PDGF), transforming growth factor-α (TGF-α) and TGF-β, platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) [5]. The primary signal activating transcription of these growth factors comes via steroid hormone receptors. The importance of sex steroids in sustaining leiomyoma volume is demonstrated by the decrease in leiomyoma and uterine volume seen with administration of gonadotropin releasing hormone agonists [6].

It has, therefore, been postulated that endocrine disrupting chemicals may contribute to fibroid development. Multiple trace elements have been shown to bind to and activate estrogen receptor α. These elements include cadmium, chromium, cobalt, copper, lead, mercury, nickel and tin [7–9]. Moreover, cadmium has estrogenic activity shown by bioassay demonstrating increased uterine weight [10]. Exposure to non-essential metals such as cadmium and mercury may, therefore, contribute to the pathophysiology of uterine fibroids.

However, the limited research on this topic has yielded inconsistent findings with regards to the relationship between trace elements and uterine fibroids. In the largest study to date comprising 1,425 women who participated in the 1999–2002 NHANES cross-sectional survey, no significant association between whole blood cadmium, lead, or mercury levels and self-reported uterine myomas was observed even after adjusting for potential confounders [11]. A key limitation of the NHANES survey is its reliance on self reported uterine myomas, a diagnostic method with poor sensitivity.

The NHANES study reflected a prevalence of 8% well below that reported by authors utilizing ultrasonography for the detection of fibroids (35% to 60% for women of similar ages) [2]. Smaller studies have suggested possible associations between certain trace elements and leiomyoma. For example, Tantchev et al. demonstrated lower levels of plasma iron and copper but not zinc in women with leiomyomas (n=25) in comparison to women without (n=22) [12]. In the same study, plasma selenium was lower in women with leiomyoma, while manganese was similar to that for unaffected women [13]. Lower serum iron has been noted preoperatively for women with leiomyoma in comparison to unaffected women, which has been interpreted to reflect greater menstrual blood loss in women with leiomyoma [14]. He et al. found lower serum levels of zinc but higher levels of copper and chromium in women with than without leiomyoma [15].

The aim of this study was to assess the relationship between metals and trace elements in relation to an incident diagnosis of leiomyoma in a large, well defined population with adequate ascertainment of the fibroid diagnosis.

2. Materials and Methods

2.1 Study population

This study population comprised the operative cohort of the Endometriosis: Natural History, Diagnosis and Outcomes (ENDO) Study. The detailed methodology for this study has been previously published [16]. The study recruited 495 women aged 18–44 years in the operative cohort who were undergoing diagnostic and/or therapeutic laparoscopy or laparotomy for benign gynecologic indications at one of 14 clinical sites in the Salt Lake City, Utah, or San Francisco, California geographic areas. By design, the cohort was intended to be inclusive and only excluded women with a prior surgical diagnosis of endometriosis or cancer other than non-melanoma skin cancer, unable to communicate in English or Spanish, currently breastfeeding for >6 months, or having used injectable hormone therapy within the past two years. The latter two exclusion criteria were required, given the ENDO Study's interest in persistent lipophilic chemicals and gynecologic pathology. Surgical indications included: pelvic pain (n=206, 42%), pelvic mass (n=74, 15%), menstrual irregularities (n=60, 12%), fibroids (n=49, 10%), tubal ligation (n=48, 10%), and infertility (n=35, 7%).

2.2 Recruitment and informed consent

Full institutional Review Board approval was obtained from all participating clinical sites. Women scheduled for surgery at participating clinical centers were contacted by research nurses and informed about the ongoing study. If women agreed, they were screened for eligibility (minimal criteria consistent with the inclusive nature of this study design). If eligible, women provided informed consent when they arrived at the clinical centers for their interview and anthropometric assessment followed by the collection of biospecimens. No data or biospecimens were obtained before consenting women.

2.3 Data and biospecimen collection

Following the baseline interview that captured information on lifestyle, medical and reproductive history, an anthropometric assessment was completed with all women. This included the measurement of height and weight using standardized stadiometers and electronic scales using an established protocol [17]. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared (kg/m^2).

A urine specimen (120 ml) was collected from all women upon completion of the baseline interview that was conducted by trained research nurses and associates at all sites. An aliquot of urine was transferred from the baseline collection container into a 2.0-mL cryovial for trace element analysis. A second aliquot was transferred into another cryovial containing a preservative to stabilize mercury thus preventing its loss as Hg^0. The samples were immediately refrigerated and processed by the lab, while being stored at −20° C or lower

until shipment with sufficient dry ice to the New York State Department of Health's (NYSDOH) Wadsworth Center for trace element analysis.

Whole blood specimens were collected into an EDTA tube precertified for trace element analysis. Blood specimens were also collected into glass tubes without preservative, and serum harvested for determination of serum cotinine. Blood and serum were aliquoted into 2.0-mL cryovials for shipment on dry ice to Wadsworth.

2.4 Trace Element Analyses of Blood and Urine

Inorganic biomonitoring analyses were performed in the Clinical Trace Elements Section of the Laboratory of Inorganic and Nuclear Chemistry at the Wadsworth Center NYSDOH, Albany NY. The Wadsworth Center holds a NYSDOH clinical laboratory permit for trace element analysis, and is a fully certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA' 88). The laboratory participates successfully in several proficiency testing (PT) programs and external quality assessment (EQA) schemes for trace elements including those operated by: the NYSDOH; L'Institut National de Santé Publique du Québec, Le Centre de Toxicologie du Québec; the Trace Elements External Quality Assessment Scheme, at the University of Surrey, UK; and the German External Quality Assessment Scheme, operated by the Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine of the Friedrich-Alexander University, Erlangen-Nuremberg, Germany. All clinical specimens were prepared for analysis in a SterilGARD(R) e3 Class II, Type A2 Biological Safety Cabinet (The Baker Company, Sanford, MA, USA) which was determined to meet Class 100 clean standards. All other preparation work was performed under Class 100 clean room conditions or better (Terra Universal, Fullerton, CA, USA).

Cadmium, lead, and mercury, were measured in whole blood on a PerkinElmer Elan DRC Plus inductively coupled plasma mass spectrometer (ICP-MS), using a biomonitoring method [18] that has been validated for low level exposure assessments in human populations [19]. Method accuracy was assessed during the study by analysis of NIST Standard Reference Material (SRM) 955c Toxic Metals in Caprine Blood. Method LODs for lead, cadmium and mercury in whole blood were 0.05 μg/dL, 0.14 μg/L and 0.3 μg/L respectively. Complete details of performance data for this assay have been published previously [20].

Trace element analysis of urine was performed on a PerkinElmer DRC II ICP-MS, equipped with dynamic reaction cell (DRC) technology to correct for polyatomic interferences. The method for trace elements in urine has been optimized for the DRC instrument[21] and has now been validated for the determination of up to 21 trace elements: total arsenic (As), barium (Ba), beryllium (Be), cadmium (Cd), cobalt (Co), chromium (Cr), cesium (Cs), copper (Cu), manganese (Mn), molybdenum (Mo), nickel (Ni), lead (Pb), platinum (Pt), antimony (Sb), tin (Sn), tellurium (Te), thallium (TI), uranium (U), vanadium (V), tungsten (W), and zinc (Zn) for biomonitoring studies [22]. The measurement of ^{75}As and ^{52}Cr in urine requires use of the DRC mode to attenuate major polyatomic interferences at *m/z* 75, caused by $^{40}Ar^{35}Cl$, and at *m/z* 52 caused by $^{40}Ar^{12}C$. Cadmium measurements in urine by ICP-MS can be affected by the presence of high levels of Mo due to various polyatomic interferences from oxides of Mo. In this study, the interference from high levels of Mo on

low levels of Cd was corrected using an empirical model similar to that used previously for the NHANES data [23]. Urinary Hg concentration was assessed by a separate ICP-MS method [24] that was optimized and validated for previous biomonitoring studies [25, 26] . Method accuracy was assessed during the course of the study by analysis of NIST SRMs 2670a Toxic Elements in Urine (Freeze-Dried), 2668 Toxic Elements in Frozen Human Urine, and 3668 Mercury, Perchlorate, and Iodide in Frozen Human Urine. Complete details related to method detection limits and quality control procedures for this method have been described elsewhere [20].

For both blood and urine, we used all machine observed concentrations in the analysis, including those below the LOD, consistent with current practice to avoid introducing bias when estimating human health effects [27].

2.5 Urinary creatinine and serum cotinine analysis

Creatinine content was determined in urine using an automated spectrophotometry procedure based on the method of Jaffe [28]. Creatinine data (reported in ng/mL) were used to adjust trace element concentrations in spot urine specimen (reported in mg/dL) to yield results in μg/g creatinine.

Serum cotinine was quantified using high-performance liquid chromatography/tandem MS using an isotope dilution method and external standard calibration plots and reported as ng/mL [29], and subsequently categorized to reflect active (≥10.0 ng/mL) versus passive (<9.99 ng/mL) cigarette smoke exposure [30].

2.6 Fibroid ascertainment

Fibroid status was based upon postoperative diagnoses. Participating surgeons completed standardized data collection forms developed for notebooks and intended to capture postoperative diagnoses and other related pathology (or its absence) immediately following surgery. All surgeons were blinded to women's metal and trace element concentrations.

2.7 Statistical analyses

Descriptive analyses included the inspection of data completeness and the comparison of women with and without fibroids in relation to sociodemographic, medical and reproductive history characteristics. Statistical significance was determined using the non-parametric Wilcoxon test for continuous variables and the Chi-square statistic for categorical variables. Geometric means and corresponding 95% confidence intervals (CIs) were calculated for whole blood and creatinine-adjusted (element concentration *100/urine creatinine in ng/mL) urine trace element concentrations by fibroid status. In the analytic phase, logistic regression was used to estimate the odds of a fibroid diagnosis in relation to each blood and urine trace element and, subsequently, adjusting for *a priori* defined confounders. These possible confounders included: age as defined in years and left continuous, race that was dichotomized as black or other, BMI categorized as <29.9 or ≥30.0 (obese or non-obese), serum cotinine dichotomized as no versus passive/active exposure (≤9.99 versus ≥10.0 ng/mL, respectively), and research site (California or Utah). All metals and trace elements were log (x+1) transformed then rescaled by their standard deviations to enhance

interpretation of the point and interval estimates. This transformation normalized the distribution while allowing inclusion of zero or negative values. Specifically, odds ratios denote the change in the odds of a fibroid diagnosis per one standard deviation change in concentration of the compounds under study. Separate models were run for each metal and element and by biologic media. Models for urinary trace elementsalso included urine creatinine (ng/mL) as a covariate. Sensitivity analyses were performed excluding women with endometriosis to avoid confounding by comorbidity [20]. For exposures that remained statistically significantly associated with the odds of a fibroid diagnosis in multivariate analysis, we assess the relationship of quartile of trace element concentration and odds of a fibroid diagnosis using univariate and multivariate models adjusting for the same confounding variables. For all analyses, p-values less than 0.05 were considered statistically significant, as were CIs that excluded one. In this exploratory work, results are reported without adjustment for multiple comparisons.

3. Results

Ninety-nine (20%) of women in the operative cohort had a postoperative diagnosis of fibroids. Of the 495 women enrolled in the operative cohort, 22 (4%) were excluded from analysis due to cancelation of their surgeries. As Table 1 reflects, women with a postoperative fibroid diagnosis were significantly older and more likely to self identify as black race and to be gravid than women without a fibroid diagnosis. The majority of women with fibroids were undergoing surgery for this indication (48/75), while fibroids were relatively rare for women with other surgical indications (0–11%).

Geometric mean concentrations of trace elements in whole blood and urine were systematically higher for women with than without fibroids with the exception of Mo, Sb, Te, Zn, and W (Table 2). However, only urinary W was significantly lower in women with fibroids. Of note are the consistently higher concentrations of both blood and urinary Cd and Pb for women with than without fibroids, with all differences achieving significance in addition to higher concentrations of urinary Co, Cs, Mn, and Tl in the former group of women. Of note is the lack of an association between creatinine and fibroid status.

Multivariate logistic regression results reflected approximately a 30%-40% higher odds of a fibroid postoperative diagnosis per one standard deviation increase in blood Cd or Pb concentration and similarly so for urinary Co concentration. However, all CIs are relatively wide (Table 3). Whole blood Cd and Pb concentrations by quartile were also evaluated in relation to the odds of a fibroid diagnosis. For Pb, results were consistent across quartiles; for Cd, odds ratios for a fibroid diagnosis increased across quartiles, but only the 4^{th} quartile had a statistically significantly different odds of fibroids compared to the first. Results from our sensitivity analysis reflected that when excluding women with a postoperative diagnosis of endometriosis to remove potential comorbidity associated with exposure, blood Pb remained significantly associated with approximately a 50% higher odds of a fibroids diagnosis per one standard deviation increase in concentration (Table 4). Of note are the elevated ORs for blood Cd and urinary Co despite CIs inclusive of one, perhaps a reflection in the loss of statistical power with the removal of 190 women with endometriosis from the operative cohort.

4. Discussion

Our findings are the first known to us to report an increased odds of a postoperative fibroids diagnosis in women with higher blood concentrations of Cd and Pb and urinary Co compared to women without such a diagnosis. Our findings are in contrast to those of the 1999–2002 NHANES cohort, in which no associations between metal concentrations and fibroids persisted after adjustment for confounders. In our population, geometric mean concentrations of Cd, Hg, and Pb were somewhat lower than in the NHANES study, which may relate to geographic differences and the slightly younger age of our study population. The more complete ascertainment of fibroids in our study likely accounts for our ability to detect a significant association.

The relatively consistent pattern of significantly higher concentrations of trace elements including those that are both essential and nonessential is intriguing, and may be suggestive of a possible role of environmental agents in the development of common gynecologic pathology such as fibroids. We noted an association between blood Cd and Pb and fibroids, but the same association was not noted with urinary concentrations of these elements. This is not surprising as blood and urine reflect different timing and duration of exposure, and spot urines, despite correction for creatinine, may be subject to greater variability in concentration, which would limit our ability to detect an association.

Our findings are strengthened by the inclusive nature of the operative cohort, the surgical visualization of fibroids in a manner blinded to trace element concentrations and the sophisticated methods for quantifying individual exposures for a spectrum of compounds. Still, our findings await corroboration and need to be carefully interpreted in light of important study limitations. Of particular note is the possibility that some fibroids may have escaped detection, particularly small submucosal or intramural fibroids that are best detected with imaging modalities such as ultrasonology or magnetic resonance imaging [31–33]. Women in the operative cohort did not undergo such imaging techniques, and histopathology was not performed on fibroids, as in many cases they were left in situ at surgery. Still, the 20% prevalence observed in our study is consistent with the earlier reports [34] and suggests that most clinically significant fibroids were captured by surgeons. Another important consideration is the relative lack of significant ORs for urinary trace elements (with the exception of Co) in relation to the odds of a fibroid diagnosis. This observation may denote that, for some trace elements, untimed urinary measurements do not adequately capture long-term exposure or during sensitive windows for the development of fibroids. Finally, in this exploratory analysis, designed to generate directions for future research, we did not adjust for the multiple comparisons made.

We are unaware of any past research that is directly comparable with our study design and methods, making it difficult to integrate evidence. Still, past research has demonstrated a correlation between estrogen receptor expression and cadmium concentration within uterine myomas, suggesting this metal may contribute to the growth of fibroids through estrogen receptor activation. Whole blood cadmium concentrations have correlated well with concentrations in leiomyoma tissue [35].

In working to provide a plausible explanation for our findings, we offer two possible mechanisms. Firstly, increased exposure to cadmium, lead and/or cobalt may contribute to the pathophysiology of leiomyoma, through binding to estrogen receptors [7, 9, 36]. Lead-based paint is still the primary source of environmental exposure to lead, despite being banned decades ago, while cigarette smoke and air pollution provide cadmium exposure [11]. However, the negative association between cigarette smoking and leiomyomata suggests another mechanism [37]. Secondly, leiomyoma may possess a characteristic of neoplastic solid tumors described by Maeda as the “enhanced vascular permeability and retention (EPR) effect” which could explain increased levels of cadmium and lead after chronic exposure but not be related to a causal effect [38]. Multiple factors influence the degree of EPR, including bradykinin, carbon monoxide, collagenase, nitrous oxide, local physiological milieu, peroxynitrite, pH, matrix metaloproteinases, prostaglandins, and VEGF [39] . Recent supportive studies for EPR include the documentation of abnormal vascular architecture and evidence of extravascular diffusion in leiomyoma [40, 41]. We posit that due to the possibility of enhanced permeability and retention in fibroids, they may serve as a tissue reservoir of some environmental exposures. Given their abnormal vascularity and extravascular diffusion, fibroids may accumulate trace elements after chronic exposure to increased blood concentrations. Thus, fibroids may provide a new, accessible sampling source as well as reservoir for chronic exposure. While it is feasible that fibroids may serve as tissue reservoir, at present there are no data on trace element uptake within leiomyomas to corroborate this hypothesis. One small study found decreased concentrations of cadmium [35] and iron in leiomyomata compared with normal uterine muscle, and increased magnesium and Mg/Ca ratio [42]. Concentrations of zinc and copper in leiomyoma were not significantly different from those in surrounding normal myometrium [43]. Promising new technology may ultimately allow this assessment [44]. Studies to confirm the EPR effect in fibroids are in progress. Thus, our second hypothesis suggests that the increased levels of cadmium and lead found in association with a diagnosis of fibroids may indicate only accumulation due to the possibility of enhanced permeability and retention after chronic exposure and have no causal association.

5. Conclusions

Higher blood concentrations of cadmium and lead, and higher urinary cobalt concentrations were associated with higher odds of a postoperative fibroid diagnosis. We propose two hypothetical explanations: a bidirectional mechanism, in which increased exposure stimulates leiomyoma growth, and in turn an enhanced permeability and retention effect, such that leiomyomata may then serve as tissue reservoirs for cadmium, lead, and cobalt, ultimately leading to increased blood and urine concentrations, respectively, and whole body exposure to these potentially toxic metals. Alternatively, fibroids may simply allow a reservoir effect for cadmium, lead, and cobalt due to an enhanced permeability and retention effect found in the abnormal vasculature of leiomyoma and have no causal association. In this scenario, the tissue reservoir effect would also lead to extended whole body exposure to these metals. Thus, with or without a causal effect, the association between fibroids and the metals cadmium, lead, and cobalt found in this study deserve further investigation.

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References

1. Wallach EE, Vlahos NF. Uterine myomas: an overview of development, clinical features, and management. Obstet Gynecol. 2004; 104(2):393–406. [PubMed: 15292018]
2. Baird DD, et al. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol. 2003; 188(1):100–7. [PubMed: 12548202]
3. Marshall LM, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol. 1997; 90(6):967–73. [PubMed: 9397113]
4. Templeman C, et al. Risk factors for surgically removed fibroids in a large cohort of teachers. Fertil Steril. 2009; 92(4):1436–46. [PubMed: 19019355]
5. Ciarmela P, et al. Growth factors and myometrium: biological effects in uterine fibroid and possible clinical implications. Hum Reprod Update. 2011; 17(6):772–90. [PubMed: 21788281]
6. Carr BR, et al. An evaluation of the effect of gonadotropin-releasing hormone analogs and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double blind, placebo-controlled, crossover trial. J Clin Endocrinol Metab. 1993; 76(5):1217–23. [PubMed: 8496313]
7. Stoica A, Katzenellenbogen BS, Martin MB. Activation of estrogen receptor-alpha by the heavy metal cadmium. Mol Endocrinol. 2000; 14(4):545–53. [PubMed: 10770491]
8. Fechner P, Damdimopoulou P, Gauglitz G. Biosensors paving the way to understanding the interaction between cadmium and the estrogen receptor alpha. PLoS One. 2011; 6(8):e23048. [PubMed: 21829690]
9. Martin MB, et al. Estrogen-like activity of metals in MCF-7 breast cancer cells. Endocrinology. 2003; 144(6):2425–36. [PubMed: 12746304]
10. Johnson MD, et al. Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. Nat Med. 2003; 9(8):1081–4. [PubMed: 12858169]
11. Jackson LW, Zullo MD, Goldberg JM. The association between heavy metals, endometriosis and uterine myomas among premenopausal women: National Health and Nutrition Examination Survey 1999–2002. Hum Reprod. 2008; 23(3):679–87. [PubMed: 18192673]
12. Tantchev L, Tantchev S, Mutaftchiev K. Content of iron, copper and zinc in plasma of women with leiomyoma of the uterus. Akush Ginekol (Sofiia). 2011; 50(6):25–7. [PubMed: 22452064]
13. Mutafchiev K, Popov I, Tsafarov M. Manganese and selenium content in plasma of women with uterine myoma. Akush Ginekol (Sofiia). 2007; 46(9):43–5. [PubMed: 18646308]
14. Brodzinski W, Wozikowski B, Dzwoniarkiewicz Z. Levels of ferritin and iron in women with leiomyoma of the uterus treated surgically. Ginekol Pol. 1992; 63(6):296–9. [PubMed: 1305130]
15. He Q, Ma RH, Tang Y. Determination of trace element Cu, Zn, Mg, Cr in serum of women with barrenness and hysteromyoma disease. Guang Pu Xue Yu Guang Pu Fen Xi. 2002; 22(4):685–6. [PubMed: 12938400]
16. Buck Louis GM, et al. Incidence of endometriosis by study population and diagnostic method: the ENDO study. Fertil Steril. 2011; 96(2):360–5. [PubMed: 21719000]
17. Lohman, TG.; Roche, F.; Martorell, R. Anthropometric Standardization Reference Manual. Human Kinetics Books; Champaign, IL: 1988.
18. Palmer CD, et al. Determination of lead, cadmium and mercury in blood for assessment of environmental exposure: a comparison between inductively coupled plasma-mass spectrometry and atomic absorption spectrometry. Spectrochimica Acta Part B-Atomic Spectrometry. 2006; 61(8):980–90.
19. McKelvey W, et al. A biomonitoring study of lead, cadmium, and mercury in the blood of New York city adults. Environ Health Perspect. 2007; 115(10):1435–41. [PubMed: 17938732]

20. Pollack AZ, et al. Trace elements and endometriosis: The ENDO Study. Reprod Toxicol. 2013; 42C:41–48. [PubMed: 23892002]
21. Minnich MG, Miller DC, Parsons PJ. Determination of As, Cd, Pb, and Hg in urine using inductively coupled plasma mass spectrometry with the direct injection high efficiency nebulizer. Spectrochimica Acta Part B: Atomic Spectroscopy. 2008; 63:389–95.
22. Kim K, et al. Biomonitoring for exposure to multiple trace elements via analysis of urine from participants in the study of metals and assisted reproductive technologies (SMART). J Environ Monit. 2011; 13(9):2413–9. [PubMed: 21773592]
23. Jarrett JM, et al. Eliminating molybdenum oxide interference in urine cadmium biomonitoringusing ICP-DRC-MS. Journal of Analytical Atomic Spectrometry. 2008; 23:962–7.
24. Parsons, PJ., et al. Determination of total mercury in urine by inductively coupled plasma mass spectrometry (ICP-MS). In: Holland, G.; Bandura, D., editors. Plasma Source Mass Spectrometry: Proceedings of the 9th International Conference on plasma source mass spectrometry. Royal Society of Chemistry; London: 2005. p. 59-71.
25. McKelvey W, et al. Population-based inorganic mercury biomonitoring and the identification of skin care products as a source of exposure in New York City. Environ Health Perspect. 2011; 119(2):203–9. [PubMed: 20923743]
26. Geer LA, et al. Assessment of prenatal mercury exposure in a predominately Caribbean immigrant community in Brooklyn, NY. J Environ Monit. 2012; 14(3):1035–43. [PubMed: 22334237]
27. Guo Y, Harel O, Little RJ. How well quantified is the limit of quantification? Epidemiology. 2010; 21(Suppl 4):S10–6. [PubMed: 20526201]
28. Junge W, et al. Determination of reference intervals for serum creatinine, creatinine excretion and creatinine clearance with an enzymatic and a modified Jaffe method. Clin Chim Acta. 2004; 344(1–2):137–48. [PubMed: 15149882]
29. Bernert JT, et al. Interlaboratory comparability of serum cotinine measurements at smoker and nonsmoker concentration levels: a round-robin study. Nicotine Tob Res. 2009; 11(12):1458–66. [PubMed: 19933777]
30. Wall MA, et al. Cotinine in the serum, saliva, and urine of nonsmokers, passive smokers, and active smokers. Am J Public Health. 1988; 78(6):699–701. [PubMed: 3369604]
31. Dudiak CM, et al. Uterine leiomyomas in the infertile patient: preoperative localization with MR imaging versus US and hysterosalpingography. Radiology. 1988; 167(3):627–30. [PubMed: 3283833]
32. Scoutt LM, et al. MR evaluation of clinically suspected adnexal masses. J Comput Assist Tomogr. 1994; 18(4):609–18. [PubMed: 8040448]
33. Bradley LD, Falcone T, Magen AB. Radiographic imaging techniques for the diagnosis of abnormal uterine bleeding. Obstet Gynecol Clin North Am. 2000; 27(2):245–76. [PubMed: 10857118]
34. Buttram VC Jr, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertil Steril. 1981; 36(4):433–45. [PubMed: 7026295]
35. Nasiadek M, et al. The effect of cadmium on steroid hormones and their receptors in women with uterine myomas. Arch Environ Contam Toxicol. 2011; 60(4):734–41. [PubMed: 20711721]
36. Deegan BJ, et al. Structural and thermodynamic consequences of the replacement of zinc with environmental metals on estrogen receptor alpha-DNA interactions. J Mol Recognit. 2011; 24(6): 1007–17. [PubMed: 22038807]
37. Parazzini F, et al. Uterine myomas and smoking. Results from an Italian study. J Reprod Med. 1996; 41(5):316–20. [PubMed: 8725755]
38. Maeda H. Macromolecular therapeutics in cancer treatment: the EPR effect and beyond. J Control Release. 2012; 164(2):138–44. [PubMed: 22595146]
39. Maeda H, et al. Vascular permeability enhancement in solid tumor: various factors, mechanisms involved and its implications. Int Immunopharmacol. 2003; 3(3):319–28. [PubMed: 12639809]
40. Verret V, et al. IL6 and TNF expression in vessels and surrounding tissues after embolization with ibuprofen-loaded beads confirms diffusion of ibuprofen. Eur J Pharm Sci. 2011; 42(5):489–95. [PubMed: 21329755]

41. Chen CL, et al. Characteristics of vascular supply to uterine leiomyoma: an analysis of digital subtraction angiography imaging in 518 cases. Eur Radiol. 2013; 23(3):774–9. [PubMed: 23001578]

42. Nasiadek M, Krawczyk T, Sapota A. Tissue levels of cadmium and trace elements in patients with myoma and uterine cancer. Hum Exp Toxicol. 2005; 24(12):623–30. [PubMed: 16408615]

43. Salkie ML, Honore LH, Jajczay FL. Copper and zinc content of human leiomyomas. Gynecol Obstet Invest. 1986; 21(4):208–12. [PubMed: 3721318]

44. Ekinci N, Ingec M. The analysis of leiomyomata uteri and uterus using energy-dispersive X-ray fluorescence spectrometry. Appl Radiat Isot. 2008; 66(8):1117–22. [PubMed: 18291662]

Highlights

- Women undergoing benign gynecologic surgery were assessed for uterine fibroids.
- Whole blood and urine concentrations of trace elements were determined.
- Women with higher whole blood cadmium and lead were more likely to have fibroids.
- Increasing urinary cobalt was also positively associated with the odds of fibroids.

Table 1

Baseline characteristics by postoperative fibroid diagnosis

Baseline Characteristic	Fibroids 99 (21%) Mean (SD) or N (%)	No Fibroids 374 (79%) Mean (SD) or N (%)
Age (years) Mean (SD)*	37.83 (4.88)	31.68 (6.91)
Race and ethnicity*		
Hispanic	15 (23.8)	48 (76.2)
White	61 (17.2)	293 (82.8)
Black/ Asian/ Multi/Other	23 (41.1)	33 (58.9)
BMI (kg/m^2) Mean (SD)	28.42 (7.78)	27.95 (8.12)
Parity conditional on gravidity*		
Nulligravid	32 (20.6)	123 (79.4)
Gravid/Nulliparous	17 (36.2)	30 (63.8)
Parous	49 (18.2)	220 (81.8)
Serum Cotinine		
No exposure (≤9.99 ng/ml)	91 (22.6)	311 (77.4)
Passive/ Active/ Heavy	8 (11.3)	63 (88.7)
smoking (≥10.0 ng/ml)		
Primary Reason for Surgery*		
Tubal ligation	2 (4.2)	46 (95.8)
Pelvic pain	22 (10.7)	184 (89.3)
Pelvic mass	15 (20.3)	59 (79.7)
Infertility	1 (2.9)	34 (97.1)
Fibroids	49 (100)	0 (0.0)
Menstrual irregularities	9 (15.0)	51 (85.0)

* $P<0.05$

Table 2

Geometric mean comparison of trace element concentrations and creatinine by biologic media and postoperative fibroid diagnosis (n=473)

Trace Element or Compound	Fibroids (n=99) Mean (95% CI)	No Fibroids (n=374) Mean (95% CI)	LOD value	% below LOD
Metals in blood				
Cadmium (Cd) (μg/L)*	0.37 (0.32, 0.43)	0.30 (0.28, 0.32)	0.1900	26
Mercury (Hg) (μg/L)*	0.93 (0.73, 1.17)	0.55 (0.49, 0.62)	0.2400	19
Lead (Pb) (μg/dL)*	0.83 (0.75, 0.92)	0.61 (0.57, 0.64)	0.3400	8
Trace elements in				
urine (μg/g creatinine)				
Arsenic (As)	10.19 (8.25, 12.59)	7.96 (7.30, 8.68)	4.0000	23
Barium (Ba)	2.14 (1.79, 2.56)	2.02 (1.86, 2.20)	0.2000	1
Beryllium (Be)	0.04 (0.03, 0.06)	0.04 (0.03, 0.05)	0.3000	100
Cadmium (Cd)*	0.31 (0.27, 0.35)	0.22 (0.21, 0.24)	0.1000	16
Cobalt (Co)*	0.68 (0.58, 0.80)	0.49 (0.47, 0.52)	0.0800	3
Chromium (Cr)	1.08 (0.86, 1.35)	0.99 (0.88, 1.13)	3.0000	92
Cesium (Cs)*	6.00 (5.37, 6.71)	4.34 (4.14, 4.54)	0.4000	0
Copper (Cu)	10.68 (9.71, 11.76)	10.39 (9.94, 10.87)	3.0000	9
Mercury (Hg)	0.38 (0.28, 0.51)	0.33 (0.28, 0.40)	0.3000	54
Manganese (Mn)*	1.62 (1.43, 1.83)	1.35 (1.26, 1.43)	0.4000	9
Molybdenum (Mo)	43.42 (37.38, 50.43)	44.83 (42.16, 47.67)	1.0000	0
Nickel (Ni)	4.51 (3.80, 5.36)	4.11 (3.81, 4.43)	2.4000	27
Lead (Pb)*	0.47 (0.33, 0.68)	0.33 (0.28, 0.38)	0.5000	73
Antimony (Sb)	0.06 (0.05, 0.08)	0.06 (0.06, 0.07)	0.0500	44
Tin (Sn)	0.75 (0.60, 0.93)	0.68 (0.62, 0.74)	0.4000	35
Tellurium (Te)	0.10 (0.07, 0.16)	0.11 (0.09, 0.13)	0.4000	93
Thallium (Tl)*	0.18 (0.16, 0.20)	0.14 (0.14, 0.15)	0.0300	5
Uranium (U)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.0050	32
Tungsten (W)*	0.07 (0.06, 0.10)	0.09 (0.08, 0.10)	0.0600	52
Zinc (Zn)	266.51 (226.30, 313.87)	279.18 (257.26, 302.96)	17.000	1
Urine creatinine (mg/dL)	80.19 (68.26, 94.20)	91.16 (84.57, 98.27)		

NOTE: Urinary trace elements were normalized to creatinine (mg/dL) excretion.

Geometric means and 95% confidence intervals (CIs).

*P<0.05

Table 3

Trace elements and odds of a postoperative fibroid diagnosis (n=473)

Trace Element	OR (95% CI)	AOR (95% CI)
Metals in blood		
Cd (μg/L)	1.18 (0.95, 1.46)	1.44 (1.02, 2.04)
Hg (μg/L)	1.21 (0.95, 1.53)	0.98 (0.75, 1.28)
Pb (μg/dL)	1.43 (1.15, 1.77)	1.31 (1.02, 1.69)
Trace elements in urine (μg/g creatinine)		
As		
Ba	0.95 (0.74, 1.21)	0.91 (0.70, 1.18)
Be	0.94 (0.74, 1.20)	0.98 (0.75, 1.30)
Cd	1.12 (0.85, 1.46)	1.20 (0.88, 1.63)
Co	1.11 (0.87, 1.42)	0.99 (0.77, 1.29)
Cr	1.29 (1.02, 1.61)	1.31 (1.02, 1.70)
Cs	1.06 (0.82, 1.38)	1.03 (0.77, 1.37)
Cu	1.05 (0.83, 1.34)	0.99 (0.76, 1.27)
Hg	0.83 (0.65, 1.06)	0.87 (0.67, 1.13)
Mn	0.92 (0.69, 1.21)	0.86 (0.63, 1.18)
Mo	1.05 (0.82, 1.33)	1.02 (0.79, 1.31)
Ni	0.86 (0.68, 1.10)	0.94 (0.72, 1.23)
Pb	0.94 (0.73, 1.19)	0.95 (0.73, 1.25)
Sb	0.91 (0.72, 1.15)	0.89 (0.68, 1.18)
Sn	1.02 (0.81, 1.29)	1.09 (0.86, 1.38)
Te	1.17 (0.93, 1.46)	1.12 (0.87, 1.43)
Tl	1.22 (0.89, 1.67)	1.16 (0.81, 1.64)
U	1.05 (0.83, 1.33)	1.02 (0.80, 1.29)
W	0.95 (0.67, 1.34)	1.07 (0.75, 1.52)
Zn	0.76 (0.54, 1.07)	0.85 (0.60, 1.21)
	0.82 (0.65, 1.04)	0.85 (0.66, 1.11)

NOTE: All chemicals were log (x+1) transformed then rescaled by their standard deviation for analysis. Unadjusted model includes the element, creatinine for urinary elements and research site. Adjusted model also includes age (years, continuous), race (black/other), BMI (<29.9/≥30.0), and serum cotinine (<9.99/≥10.0 ng/mL).

OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval

Table 4

Trace elements and odds of a postoperative fibroid diagnosis restricted to women without endometriosis (n=283)

Trace Element	OR (95% CI)	AOR (95% CI)
Metals in blood		
Cd (μg/L)	1.22 (0.92, 1.61)	1.50 (0.98, 2.28)
Hg (μg/L)	1.21 (0.87, 1.68)	1.05 (0.73, 1.51)
Pb (μg/dL)	1.65 (1.24, 2.20)	1.53 (1.12, 2.10)
Trace elements in urine (μg/L)		
As	0.90 (0.66, 1.23)	0.85 (0.60, 1.19)
Ba	0.87 (0.63, 1.20)	0.97 (0.68, 1.39)
Be	1.37 (0.88, 2.13)	1.45 (0.90, 2.34)
Cd	1.15 (0.84, 1.57)	1.02 (0.72, 1.44)
Co	1.28 (0.97, 1.69)	1.30 (0.95, 1.79)
Cr	1.12 (0.79, 1.59)	1.03 (0.69, 1.55)
Cs	1.12 (0.81, 1.54)	1.02 (0.73, 1.43)
Cu	0.84 (0.61, 1.16)	0.88 (0.62, 1.25)
Hg	0.84 (0.57, 1.23)	0.85 (0.55, 1.30)
Mn	0.94 (0.68, 1.29)	0.89 (0.63, 1.26)
Mo	0.92 (0.67, 1.25)	1.00 (0.70, 1.41)
Ni	0.87 (0.64, 1.18)	0.88 (0.62, 1.26)
Pb	0.79 (0.56, 1.12)	0.81 (0.54, 1.20)
Sn	1.14 (0.86, 1.51)	1.08 (0.79, 1.47)
Sb	1.14 (0.72, 1.82)	1.43 (0.82, 2.49)
Te	1.35 (0.81, 2.25)	1.21 (0.70, 2.06)
Tl	1.14 (0.85, 1.53)	1.08 (0.80, 1.46)
U	0.93 (0.62, 1.40)	1.05 (0.68, 1.60)
W	0.91 (0.64, 1.29)	1.01 (0.73, 1.40)
Zn	0.85 (0.62, 1.16)	0.87 (0.62, 1.22)

NOTE: All chemicals were log (x+1) transformed then rescaled by their standard deviation for analysis. Unadjusted model includes element, creatinine for urinary elements and research site. Adjusted model also includes age (years, continuous), race (black/others), BMI (<29.9/≥30.0), and serum cotinine (<9.99/≥10.0 ng/mL).

OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval