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# The relationships between blood lead levels and serum follicle stimulating hormone and luteinizing hormone in the third National Health and Nutrition Examination Survey

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**Abstract**

The relationships between blood lead levels and serum follicle stimulating hormone and luteinizing hormone were assessed in a nationally representative sample of women, 35–60 years old, from the third National Health and Nutrition Examination Survey. The blood lead levels of the women ranged from 0.7 to 31.1 μg/dl. The estimated geometric mean was 2.2 μg/dl, and the estimated arithmetic mean was 2.8 μg/dl. As the blood lead level increased across women, the concentration of serum follicle stimulating hormone increased in post-menopausal women, women who had both ovaries removed, and pre-menopausal women. The concentration of follicle stimulating hormone decreased in pre-menopausal women who were taking birth control pills. The concentration of luteinizing hormone increased as blood lead level increased in post-menopausal women and women who had both ovaries removed. The lowest concentrations of blood lead at which a relationship was detected were 1.7 μg/dl for follicle stimulating hormone and 2.8 μg/dl for luteinizing hormone. The increase in follicle stimulating hormone and luteinizing hormone in women with no ovaries indicates that lead may act at a non-ovarian site in the female reproductive system, along with a possible effect on the ovaries.
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*Keywords:* NHANES III; Blood lead; Follicle stimulating hormone; Luteinizing hormone; FSH; LH

## 1. Introduction

Data from the second and third National Health and Nutrition Examination Survey have been used to identify demographic and other factors related to the blood lead levels of women of reproductive age in the United States. Black (Geronimus and Hillemeier, 1992; Lee et al., 2005) and Mexican-American (Lee et al., 2005) women have higher mean blood lead levels than white women. The mean blood lead level increases with age (Geronimus and Hillemeier, 1992; Lee et al., 2005), and decreases as income and education level increase (Lee et al., 2005). Women who smoke or drink alcohol have a higher mean blood lead level than women who do not (Lee et al., 2005). Women who live in the northeast region of the United States, or who live in a house built before 1946 have a higher mean blood lead level than those who do not (Lee et al., 2005).

Data from the third National Health and Nutrition Examination Survey (NHANES III) have been used to demonstrate that there is an inverse relationship between blood lead level and bone mineral density in women, 40–59 years old, indicating that lead may be released from bone as it resorbs (Nash et al., 2004). The post-menopausal women in this study had higher median blood lead levels than the pre-menopausal women. As women go through menopause, their estradiol levels fluctuate and then decrease (Burger, 1999), and, as a result of the decrease, they lose bone mass (Riggs, 2000).

Data from NHANES III have been used to show a direct relationship between the geometric mean of blood lead levels and serum cotinine levels (Mannino et al., 2005). Lead is a component of tobacco (Jenkins, 1986), and cotinine is a metabolite of nicotine that can be used as a measure of exposure to tobacco smoke (Benowitz, 1996).

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NHANES III data have been used to identify demographic and other factors related to the concentrations of serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) in women, 35–60 years old (Backer et al., 1999). In these women, median serum FSH and LH increased and then leveled off as age increased. Women who smoked had a higher mean FSH concentration than those who did not. Women with one or both ovaries removed had higher mean FSH concentrations than women who had both ovaries.

The increase in FSH as women age is thought to be due to a decrease in the amount of inhibin B produced by the ovarian follicles as their number declines (Laven and Fauser, 2004). There is epidemiological evidence that women who smoke are estrogen deficient (Baron et al., 1990), indicating that a reduction in negative feedback may cause an increase in FSH. FSH levels rise following bilateral oophorectomy, due to the decrease in negative feedback caused by removing the ovaries (Muttukrishna et al., 2002).

In the present study, the NHANES III data are used to assess the relationships between blood lead levels and the concentrations of serum FSH and LH in women, 35–60 years old. Increases in FSH and LH concentrations may indicate that a woman's ovaries are not functioning well. For example, in one study, pre-menopausal women with unexplained infertility had higher mean serum FSH and LH concentrations in the early follicular phase, consistent with there being a reduced number of follicles in their ovaries (Randolph et al., 2003). Previous research on the effects of lead on reproduction has been focused on male reproductive toxicity and the effect of lead on pregnancy (Winder, 1993). The results presented here indicate that the effects of lead on the reproductive systems of non-pregnant women need more attention.

## 2. Materials and Methods

The data and documentation from the survey (adult.exe, exam.exe, and lab.exe from NHANES III Series 11, No. 1A, July, 1997—Interview & Exam Components; lab2.exe from NHANES III Series 11, No. 2A, April 1998—Electrocardiogram, Dietary Recall, Laboratory, Dietary Supplement and Prescription Drug) were downloaded from the NHANES website (http://www.cdc.gov/nchs/nhanes.htm) on August 19, 2005 and September 1, 2005. A reference manual for the laboratory methods (Gunter et al., 1996) and analytical guidelines (National Center for Health Statistics, 1996) are also available at the website.

### 2.1. Subjects

The subjects in NHANES III were civilian, non-institutionalized persons in the United States 2 months of age or older. The survey was conducted from 1988 to 1994. Approximately 40,000 persons were selected to participate in the survey. Of these, 3375 women aged 35–60 were eligible for FSH and LH measurements, of which 92.5% had FSH measurements and 92.4% had LH measurements.

### 2.2. Sampling

The sample design was a stratified, multistage probability design. In the first stage of sampling, 81 primary sampling units (PSUs) were selected. The PSUs were individual counties or adjacent counties. Thirteen of the large PSUs were divided into 21 survey locations and the remaining 68 PSUs had one survey location. The 89 survey locations or 'stands' were randomly divided into two phases. Phase I consisted of 44 locations visited from 1988 to 1991. Phase II consisted of 45 locations visited from 1991 to 1994. Later stages of sampling included area segments, households, and sample persons.

### 2.3. Blood lead

Venous blood samples were taken at mobile examination centers or during home examinations that were given to persons who could not go to a mobile examination center. Blood lead was measured by atomic absorption spectrometry. The limit of detection for the blood lead measurements was 1 μg/dl. Values below the limit of detection were assigned a value of 1 μg/dl divided by the square root of two. Of the measured values of blood lead, 8.7% were below the limit of detection.

### 2.4. FSH and LH

The blood samples of the women whose FSH and LH were measured were all taken at a mobile examination center. A single sample was taken for each woman. In pre-menopausal women, it was taken without regard to the day of their cycle. FSH and LH were measured using an immunoradiometric assay. The limit of detection for serum FSH and LH was 0.15 IU/l. Values below the limit of detection were assigned a value of 0.15 IU/l divided by the square root of two. For FSH, 0.2% of the measured values were below the limit of detection, for LH, 0.1%.

### 2.5. Covariates

*Bone densitometry:* The bone densities of five areas of the proximal femur were measured using dual energy X-ray absorptiometry. Measurements were made on women who were not pregnant and men, 20 years or older. The femoral neck, trochanter, intertrochanter, Ward's Triangle, and the total region were measured. Bone mineral density of the total region ($g/cm^2$) was used in the present analysis. The missing values for pregnant women were set to zero so that they would not be excluded from the analysis.

*Cotinine:* Serum cotinine was measured by an enzyme immunoassay for persons, four years or older, who gave a blood sample. The limit of detection for serum cotinine was 0.05 ng/ml. Values below the limit of detection were assigned a value of 0.05 ng/ml divided by the square root of two. Of the measured values of serum cotinine, 12.3% were below the limit of detection.

*Mobile Examination Center Adult Questionnaire:* Information about alcohol use and reproductive health came from items in the Mobile Examination Center (MEC) Adult Questionnaire that was administered to all persons, 17 years or older, that were examined at a MEC. The questions that were used are listed in Table 1. Positive responses were coded as '1'. 'Blank but applicable' and 'Don't know' were coded as missing. All other values were coded as '0'. A variable called 'status' was created with six levels: post-menopausal, pregnant (pre-menopausal only), currently having a period, both ovaries removed, currently taking birth control pills (pre-menopausal only), and pre-menopausal women. Post-menopausal women were defined as women who had not had a period in the last 12 months. The levels of status were mutually exclusive. The 'post-menopausal' and 'pre-menopausal' categories contained women who were not included in one of the other categories.

*Demographic variable:* The only demographic variable used was age at interview (HSAGEIR). A classification variable called 'age group' was