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Research Strategy

Lead Exposure in Female Workers Who are Pregnant or of Childbearing Age

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Abstract: In adults, high-level lead exposure often occurs in the lead-related industries. Acute lead poisoning has become rare, but chronic exposure to low-level lead remains a public health issue. With recent advances in our understanding of lead toxicity at low-levels, researchers have shifted their focus to studying lead at concentrations below those currently recommended as 'acceptable' in worker protection. As gender plays an important role in the storage, biokinetics, and toxicity of lead, it seems inappropriate to extrapolate findings of lead exposure in men to women. Women's bones release lead more slowly to the bloodstream, so blood levels remain increased for a long time after cessation of high exposure, reflecting the endogenous source of the lead. Particularly in pregnant women, bone lead release could influence health in pregnancy and be extremely harmful to the rapidly growing and developing fetus. Accordingly, female workers of childbearing age should avoid excessive lead exposure. However, because studies of pregnant workers encounter many difficulties and inconveniences, sufficient research has not been conducted in this area. As an alternative, a group of non-occupationally exposed women, matched as well as possible for anthropometric and reproductive variables and with almost the same levels of blood lead, could be recruited for survey.

Key words: Lead, Female, Childbearing age, Pregnancy, Occupation

Introduction

Society's industrialization and constant need for new products and components have increased the number and concentration of toxic substances that we are exposed to in the environment in general and in the workplace. Because lead has high malleability, a low melting point, and the ability to form numerous compounds, it has been widely used in hundreds of products such as paints, pipes, cables, ceramics, stained glass, and batteries. However, this very useful metal is also a well-known poison that affects many systems in the body. Toxicity ranges from subclinical effects to symptomatic poisoning, clinically obvious toxicity, and acute poisoning[1, 2]. Although acute lead poisoning has become rare, chronic low-level exposure to lead remains a public health issue[3]. People of all ages encounter lead in the air, dust, soil, and drinking water[4], but for adults most high-level exposure occurs in lead-related jobs. Workers are usually exposed via inhalation[2]. However, in the general population, toxicity mostly occurs via oral ingestion and absorption through the gut[4], and exposure levels are generally lower than those incurred in the workplace.

In recent decades, the prevalence of elevated blood lead levels has continued to decline[5], although there is substantial variation among different communities and populations. For instance, a Japanese study showed that blood lead concentrations in women reduced from 3.17 μg/dl in 1977–1981 to 2.02 μg/dl in 1991–1997[6]. More recently, values for Japanese female subjects from both urban and rural areas have declined further to 1.9 μg/dl[7]. Low concentrations of blood lead (<10 μg/dl) are typical of environmental exposures in many developing countries[8, 9] and of occupational exposure in some developed countries[10]. Accordingly, contemporary research has shifted to the

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study of low levels of lead exposure, at levels that are currently 'acceptable' by international and national standards (generally < 10 μg/dl) but still adversely affect health[11, 12]. Despite awareness of the adverse effects of lead on human health at these concentrations, morbidity and mortality from this level of exposure remains a major public health problem in many societies[3, 12–14].

Since no lead level has been proven safe[15], scientists' focus has shifted from high-dose toxicity and clinically symptomatic individuals to lower-dose exposures which cause subclinical problems. This has led to support for a reappraisal of the 'safe' levels for lead exposure[16, 17]. For example, many studies in different populations and with various designs have reported lead toxicity at concentrations lower than 5 μg/dl, including associations with male reproductive disorders[18] and several aspects of behavioral dysfunction during infancy[19]. In addition, a significant association between much lower blood lead levels (≤2 μg/dl) has been demonstrated with both myocardial infarction and stroke mortality[14]. Similarly, studies on experimental animals exposed to low levels of lead have demonstrated significant relationships with adverse outcomes such as chronic renal disease, hypertension, acceleration of microvascular and tubulointerstitial injury, and morphological changes in the brain[20, 21]. Therefore, health surveillance including the assessment of adverse effects on various organs in lead-exposed workers should always be recommended.

Our understanding of lead toxicity has advanced substantially over the past decades, on account of the aim of improving measures regarding its control[22]. However, one sensitive and at high risk population to the adverse health effects of lead exposure is female workers of childbearing age that they have not been sufficiently studied. The present paper reviews gender differences in body lead accumulation and toxicity, in particular changes in levels during pregnancy, and then introduces an alternative study method for investigating the effects of lead in pregnant workers.

Gender and Lead Toxicity

Studies have shown that the adverse health effects of metals vary in prevalence according to gender. Like many toxic substances, the health risk assessment of lead has largely been based on data from exposed men[23], and women have mainly been investigated in mixed-gender studies. However, studies of men exposed to lead have many limitations when trying to understand the effects in women because of differences in organs, hormones, and other aspects such as lead metabolism and biokinetics[24–26], dose-response relationships, thyroid function, and accumulation of lead in the liver[27–29].

Studies on animals have also shown gender is a significant factor influencing the bioaccumulation of metals, for example, an increased lead concentration in the lung of female mice exposed to lead acetate was demonstrated[30]. On the other hand, a gender difference in organ dysfunction in animals exposed to lead could be a response to differing lead accumulation in those organs[31, 32]. For instance, studies on the immune system of rats administered lead have shown elevations in IL-10 production, absolute monocyte numbers, neutrophil numbers, relative thymus weights, and increased functional disorder of delayed-type hypersensitivity in female animals that were greater than those observed in males[33, 34].

In short, gender seems to play an important role in lead toxicity and biometabolism. These differences might be explained by variation in particle clearance, reactive oxygen species production, cytokine pathway activation, and cytochrome P450 enzyme activity induced by sex hormones[30]. Therefore, extrapolation of findings regarding lead exposure in men to women appears to be inappropriate.

Differences in blood lead levels between men and women

The appropriate measurement of the lead exposure level is a critical factor for health care management and primary prevention activities. Blood lead concentration is the primary biomarker used for monitoring exposure levels, and reflects an individual's current body lead burden[35]. However, blood metal concentrations reflect not only exposure in both genders, as previously believed, but are also influenced to a considerable extent by genetic factors possibly related to uptake and storage[26]. For example, although the biological half-life of lead in the blood compartment is about 40 d[36], blood lead level has been reported to be increased in pregnant women than in non-pregnant women, because of bone remodeling[37].

Several epidemiological studies of occupational and environmental exposure have shown that men generally have higher concentrations of blood lead than women[12, 27, 38–40]. Similarly, blood lead levels exceeding 10 μg/dl —the level that the Centers for Disease Control and Prevention recommends 'not to be exceeded'— were found several times more frequently among men than among women[40, 41]. There are two known reasons for higher blood lead levels in men: first, men are generally at higher risk of exposure to increased levels of lead than women[42], and second, higher blood hematocrit in men causes accumulation of more lead in men's blood because a large proportion of lead binds to erythrocytes[43].

Storage and release of bone lead into the bloodstream in women

Like many other "bone-seeking" elements, blood lead becomes incorporated into calcified tissues such as bone and teeth, where it remains for several years; the half-life ranges from 10 to 30 yr depending on the type of bone (trabecular or cortical). The bone lead level is higher in men than in women[25, 44]. For example, the lead concentration in tibial bone was reported to be 9.7 μg/g higher in men than in women[45]. In addition, lead stored in bone is released more slowly into the bloodstream in women than in men[25], so blood lead levels remain high much longer after the cessation of occupational/environmental exposure, reflecting the endogenous source of lead in women[37]. The accumulated lead in women's bones is released more quickly during periods of increased bone turnover, particularly in pregnancy and menopause. In addition, bone lead has greater bioavailability in younger women than in older women, and this could strongly contribute to higher blood lead concentrations in women of childbearing age[46, 47].

Because lead stays in women's bone for years to decades, its mobilization during pregnancy may pose a significant fetal exposure risk long after maternal lead exposure has ceased[48]. In pregnancy, bone lead released into the blood stream varies from subject to subject but there is an overall estimated 20% increase in blood lead[49], leading to speculation that during pregnancy lead is released from the skeleton and potentially available to the fetus. However, multiparous women tend to have lower lead concentrations than women delivering for the first time[50]. Blood lead concentrations significantly decrease in a stepwise manner from pregnancy to pregnancy in multiparous women, implying that the greatest risk of lead toxicity lies with the first pregnancy[47]. Since the placenta only partially prevents lead diffusion[51], the released lead crosses the fetal membrane and blood lead concentrations in the umbilical cord reach about 80% of those in the maternal circulation[49].

Epidemiological and experimental studies have shown variation in blood lead concentrations during gestation with a substantial increase in late pregnancy[46, 52]. This increase may be linked to increased calcium demand and changes in calcium-related regulatory factors which affect lead compartmentation. Also, bone lead tends to move to the maternal circulation (greater bioavailability), and this potentially increases toxicity for the mother and fetus[53]. Furthermore, elevated maternal levels of blood lead are linked to decreased calcium uptake by syncytiotrophoblasts, suggesting that exposure to lead can modify calcium transfer in these cells[54].

Lead and pregnancy outcome

Pregnancy is an important and unique period of a woman's life in which there is high sensitivity to toxic substances. Increased blood lead, either endogenous (bone saved) or from ambient pollution, affects health in pregnancy and could be extremely harmful to the rapidly developing central nervous system of the fetus[55, 56]. For instance, pregnant rats administered 200 mg/l lead in drinking water, resulting in a peak blood lead of 60–80 μg/dl, showed a developmental delay in the fetal cerebral cortex[52]. Lead not only adversely influences the nervous system, but also has many other effects including defects in hematopoietic and renal impairment, pregnancy induced hypertension/pre-eclampsia, spontaneous abortion, alteration of fetal anthropometric characteristics and birth weight, and preterm labor[57–62]. In addition, women exposed to lead at work before pregnancy have increased rates of miscarriages, stillbirths, and low birth weight infants[63]. Thus, long-term exposure to this toxic metal stored in and released from the mother's bone is particularly harmful to fetal growth and development.

Difficulties in Studying Pregnant Workers

As mentioned above, lead adversely affects pregnancy outcomes. However, in addition to the general epidemiological difficulties such as pregnancy follow up, changes in the prenatal care unit, refusal of subjects to collaborate, and low accessibility to women at delivery, there are many obstacles to studying the effects of lead in pregnant Japanese workers:

A) poor collaboration by factories; pregnancy follow-up takes several months, so many factories are not interested in collaborating in such research
B) changes in the pregnant woman's job or workplace
C) historical differences in occupational lead exposure
D) a low birth rate in Japan has resulted in lower numbers of pregnant workers for survey.

Thus, studies on the pregnant workers need to resolve these difficulties or to use alternative sampling methods. The first choice of sampling might be pregnant women with non-occupational exposure with the same levels of blood lead, matched as closely as possible for demographic and reproductive variables such as age, parity, and other pregnancy-related and reproductive conditions. However, the general Japanese population often has several times lower concentrations of blood lead than workers in factories using lead; therefore, the appropriate subjects are difficult to find in the general Japanese population. Thus, we need a population with

higher environmental exposure to lead, in which average blood lead concentrations in non-occupationally exposed women are close to those in female Japanese lead workers. The substitute subjects, non-occupationally lead-exposed women, would need to be of the same gender and almost the same age (childbearing age). Also, they would need to be matched for reproductive characteristics (parity, gravidity, gestational age, type of delivery, and so on) with the women workers in Japan, and be free from any medical condition that affects pregnancy outcomes.

In an epidemiological study by Saito and colleagues (2006) of 2,216 Japanese women workers, the geometric mean blood lead level was 3.7 μg/dl (0.1–48.1 μg/dl)[10]. Our previous study (2006) in Iran of 396 environmentally exposed healthy women at the time of delivery showed an average blood concentration of 4.8 μg/dl (1.7–24.6 μg/dl), close to that of female Japanese lead-plant workers[64]. Although the average blood lead level in both studies was classified as acceptable, several studies have reported adverse pregnancy outcomes occurring at these blood levels or even lower[9, 16, 64, 65]. In addition, some of the subjects in both studies had blood lead levels greater than 20 μg/dl, suggesting a high risk of adverse pregnancy outcomes[66–68].

As discussed in the preceding paragraphs, bone lead storage is an important endogenous source that can increase blood lead concentration during pregnancy. Therefore, women's bone lead as well as blood lead should be considered as a biomarker for the exposure assessment and health effects on pregnant women and their fetuses. However, there are no published data of bone lead measurements of Japanese and Iranian women. Females environmentally exposed to lead are considered to receive low levels of lead during a long exposure period. In contrast, female workers engaged in lead-related jobs are generally exposed to high levels of lead during a short period. Therefore, the body burden of lead of females with environmental exposure to lead at low levels for a long time period might not be much different from that of female workers with occupational exposure to lead at relatively high levels for a short time period. This leads to speculation that there is no essential difference in bone lead levels between these two populations. In addition, gestational blood lead levels of Iranian females may change in the same manner as those of Japanese pregnant workers, since bone exchange of calcium and lead, and a substantial increase in blood lead during late pregnancy would take place under the similar biokinetic pathways in the two populations. Thus, it can be inferred that Iranian women with environmental exposure to lead are a suitable surrogate for pregnant Japanese workers in lead plants, setting aside minor variations between the two populations.

Conclusion

As lead levels have sharply fallen, researchers concerns about lead toxicity at lower levels have increased. New findings of lead-related adverse reproductive outcomes have led to recommendations for women who are pregnant or of childbearing age to avoid occupational lead exposure, even at blood lead concentrations <10 μg/dl[16, 65]. A growing body of scientific evidence suggests that occupational exposure to 'safe' lead levels may not prevent toxicity, both in the acute setting and from cumulative doses[69]. In addition, there is no evidence of a threshold below which lead has no adverse health effects[70]. Therefore, particularly for high-risk groups such as pregnant women, it is preferable that blood levels be minimized and, optimally, approach zero[17]. Moreover, the data supports a reappraisal of lead exposure standards for levels not to be exceeded in female workers of childbearing age.

Since gender plays an important role in body lead accumulation and biokinetics, it is inappropriate to extrapolate the findings of studies of men to women. However, studies of pregnant workers encounter many difficulties and inconveniences; therefore, lead toxicity in this population has not been sufficiently studied in Japan. In the current paper, we have described an alternative method for research into the relationship between blood lead concentrations and pregnancy outcomes using a group of non-occupationally exposed women with similar levels of blood lead to female Japanese lead workers. We hope that the alternative study method presented in this paper provides a new methodology for future studies of lead-exposed workers of childbearing age both in Japan and overseas.

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