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Lead Exposure in Pregnancy: A Review of the Literature and Argument for Routine Prenatal Screening

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Despite a steady decline in average blood lead levels in the U.S. population, approximately 0.5% of women of childbearing age may have blood levels exceeding 10 μg/dl. Strong correlations between maternal and umbilical cord blood lead levels demonstrate that lead is transferred from the mother to the fetus. High lead levels are known to cause neurobehavioral effects in infants and children, and the cumulative effects of low levels of lead exposure *in utero* and after birth can have similar detrimental effects. Modern sources of exposure include occupational exposure during automotive or aircraft paint manufacturing, lead production or smeltering, exposure to stained glass soder, and environmental exposure during home renovation. Prenatal screening for lead exposure may include use of a five-item questionnaire similar to the pediatric questionnaire. Management of prenatal lead exposure focuses on removal of the lead source. Rarely, highly toxic chelation therapy is needed for maternal indications. Recognition and removal of lead sources during the prenatal period can prevent maternal and neonatal morbidity.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader will be able to list the potential sources of lead intoxication in our society, to describe the effects of low level exposure *in utero*, and to outline the management strategy of the lead exposed pregnant patient.

In 1991, the Centers for Disease Control and Prevention (CDC) recommended universal screening of blood lead levels in children at the ages of 6 months and 2 years. This recommendation was amended in 1997 to selective screening of children found to be at high risk for exposure based on zip code or screening questionnaire. Levels >10 μg/dl are regarded as abnormal and require action (1).

Pregnant women often have exposures similar to those of young children, and lead exposure may affect the fetus in a number of detrimental ways. Furthermore, prenatal identification of lead-exposed women would allow for removal of the source and thereby provide a lead-free environment for the newborn and siblings. Several states, such as New York, require that obstetricians provide anticipatory guidance regarding potential sources of lead exposure to pregnant patients and identify high-risk women by using a screening questionnaire (2).

This article provides background information regarding lead poisoning in pregnancy and specifically addresses the toxicokinetics of lead, transplacental transport of lead, sources of exposure, the basis for current guidelines regarding safe levels of exposure, and the epidemiology of exposure. This information is necessary to adequately assess exposure risk for a patient and forms the foundation for anticipatory guidance. The major focus of the article will then turn to the effects of low-level lead exposure *in utero*. This information will be useful to determine whether

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prenatal screening is warranted and, if it is warranted, what the maternal blood lead level of concern should be. Furthermore, this information can be used to educate the lead-exposed mother regarding the risk to her fetus.

BACKGROUND INFORMATION

Although lead is a useful metal outside the human body, it serves no purpose within the body. Contrary to popular belief, ingestion of lead-laden paint chips is not the only method of intoxication. Airborne particles released as industrial by-products or from lead-contaminated soil are frequent vehicles of lead poisoning. Large particles such as those from smelter emissions deposit in the upper respiratory tract. Via mucociliary action, these particles are transported to the buccal cavity and swallowed. Absorption then occurs within the gastrointestinal tract. Small particles, which are most frequent in urban aerosols, can be absorbed directly in the lung. Once in the blood stream, lead binds directly to erythrocytes and can accumulate in the renal tubules and hepatocytes. Eventually, the majority of lead will be deposited in bone and teeth. Ninety-five percent of the total body burden is stored in bone. The half-life of lead is 1 to 2 months in blood and 20 to 30 years in bone. Blood lead levels reflect the active, toxic fraction and suggest acute intoxication (3).

A woman of childbearing age with high blood lead levels is at risk of transmitting that level to her fetus. Lead crosses the placenta throughout gestation (3). The correlation between maternal and umbilical cord blood lead levels ranges from 0.55 to 0.92 (4). These findings suggest that lead freely crosses the placenta (5–7). The concentration of lead was found to be higher in amniotic fluid than in cord blood in one study that compared maternal blood, cord blood, and amniotic fluid lead levels in 19 women at delivery. These data suggest that fetal membranes, which showed high concentrations of lead, may participate in the elimination of this toxic metal by absorbing lead from the amniotic fluid (8). Fetal lead uptake is constant and cumulative until birth (9). Lead is stored mainly in bone, blood, and liver in the fetus (10).

Because lead is readily transmitted from mother to fetus via the placenta, maternal exposure must be reduced to protect the fetus. Therefore, information regarding the environmental sources of lead is important. The Motherisk Program in Canada examined the three most common occupational exposures reported by pregnant women. After radiation and organic solvents, lead exposure was most often reported. Specifically, the vast majority of lead exposures occurred among artists who used stained glass or workers involved in paint manufacturing for the automotive and aircraft industries (11). Rempel (12) examined occupational lead exposure in the entire population and found that the following occupations put employees and their families at risk of lead exposure: lead production or smeltering, production of illicit whiskey, brass, copper, and lead foundry work, radiator repair, scrap handling, sanding old paint, lead soldering, cable stripping, instructor or janitor at a firing range, demolition of ships and bridges, battery manufacturer, machining or grinding lead alloys, welding of old painted metals, thermal paint stripping of old buildings, and ceramic glaze mixing. Indirect maternal exposure can occur when a worker brings lead dust home on clothing, skin, and hair. Therefore, paternal employment in the lead industry must be regarded as an indirect risk to the fetus (13, 14).

Nonoccupational exposure to lead is also significant. A common source of childhood plumbism is lead-based paint. Before 1955, white house paint could consist of up to 50% based, and 70% of houses built before 1960 contained lead-based paint. Finally, in 1977, lead levels in indoor paint dropped to 0.06%. The latest cases of plumbism derive from young families who are renovating older homes. Such renovations release lead dust into the dwelling and surrounding ground (15). Therefore, pregnant women living in homes built before 1977 undergoing renovation are thought to be at risk for lead exposure. Also, because lead is nonbiodegradable, it accumulates in soil and dust particularly near highly industrialized areas. For example, a survey of backyards on Staten Island downwind from a secondary smelter in Cartaret, NY revealed lead levels of 1000 to 4000 ppm (16). This finding emphasizes that persons who live near smelters and highly industrialized areas are at risk for significant lead exposure.

Unfortunately, water, food, and common home remedies are also potential sources of lead intoxication. Water accounts for approximately 20% of exposures. Acidic “soft” water may leach lead from lead pipes installed in the 1920s. These pipes are still found in older homes and buildings (15). Newer pipes continue to contain a small amount of lead that can allow lead exposure particularly with first draw or intermittent use (16). To reduce exposure via tap water, the 1992 Environmental Protection Agency guidelines for household tap water called for a reduction in lead levels from 50 ppm to 15 μg/liter (15). Acidic food such as orange juice that is stored

in lead-soldered cans, antique pewter, and ceramic pottery containers may leach lead into the beverage. The U.S. Standard Compliance Policy Guide 1988 sets limits for the amount of lead that may leach from ceramic foodware. However, uninspected foreign foodware may exceed these levels and, therefore, should be avoided (15). Ethnic home remedies can also be a significant source of lead exposure. Azarcon and greta are brightly colored powders made of 100% lead that are used in the Hispanic community to treat children with gastrointestinal distress. Payloo-ah is a red or orange powder used in the Hmong community to cure childhood rashes or fever. Ghagard, Bala Goli, and Kandu are Asian Indian remedies used for stomach ailments. Kohl or surma are used by Arab communities for cosmetic and medicinal purposes. All of these agents contain significant amounts of lead (17).

The ubiquitous presence of lead in our environment suggests that much of the population is exposed to some amount of lead. To assess the number of clinically significant exposures that occur in pregnant women, a threshold blood lead level must be defined. In 1988, the U.S. Public Health Service Report to the U.S. Congress acknowledged no safe level of lead, but for practical purposes recommended a critical level reduction from 25 μg/dl to 10 μg/dl in children and women of childbearing age (18). In 1991, the Centers for Disease Control followed suit and adopted a blood lead level of 10 μg/dl as the threshold for concern (19).

With an established benchmark of 10 μg/dl, it becomes possible to assess the size of the population that is at risk and thus the magnitude of the problem of lead poisoning. In 1990, a congressionally mandated study was conducted by the U.S. Agency for Toxic Substances and Disease Registry to estimate the number of American women of childbearing age and the number of American pregnant women whose lead exposure was significant enough to pose a risk of intrauterine toxicity. This risk was determined to exist at blood lead levels >10 μg/dl. The study generated projected 1984 prevalence rates of elevated lead levels in white and black women of childbearing age in two groups: ages 15 to 19 years and 20 to 40 years. A total of 9.2% of white women aged 15 to 19 years and 9.7% of white women aged 20 to 40 years had lead levels >10 μg/dl. Of black women, 8.2% of 15 to 19 year olds and 19.7% of 20 to 40 year olds had lead levels >10 μg/dl. Applying these percentages to standard metropolitan statistical areas, 4.4 million U.S. women of childbearing age were estimated to have blood lead levels >10 μg/dl. Furthermore, 403,200 pregnant women were estimated to have blood lead levels >10 μg/dl. Thus, during 10 years, 4 million fetuses would be at an increased risk from lead exposure (20). Despite a steady decline in average blood lead levels in the U.S. population in recent years, approximately 0.5% of women of childbearing age may have blood lead levels >10 μg/dl according to the Third National Health and Nutrition Examination Survey (1988–1991) (21). Thus, a significant number of pregnant and potentially childbearing women are at risk for high-dose lead exposure.

Although a blood lead level of 10 μg/dl is now regarded as "high risk" for fetal health effects, this level is low compared with levels studied 20 years ago. In 1976, Rom (22) reviewed the literature regarding high-dose effects and concluded that occupational exposure of women and men to high lead levels impaired fertility and increased the risk of spontaneous abortion. Increasing awareness of the environmental risk factors for lead exposure, banning of leaded gasoline and lead-based house paint, and stricter tap water guidelines have led to a decrease in exposure risk. Many studies performed before 1991 studied the effects of blood lead levels of <25 μg/dl as "low dose." Once 10 μg/dl was adopted as the threshold for concern in 1991, studies began to focus on the adverse effects of even lower lead levels (16). An interesting and divided body of information has grown regarding adverse effects of *in utero* exposure to low lead levels, loosely defined for the purposes of this article as a blood lead level <10 μg/dl.

ADVERSE EFFECTS OF FETAL LEAD EXPOSURE

The majority of lead-exposed patients seen by obstetricians will have lead levels <10 μg/dl. Potential adverse fetal outcomes in these patients include intrauterine growth restriction, congenital anomalies, adverse obstetrical outcome, and neurotoxicity.

Neonatal Size and Growth

Birth weight is one of the most frequently measured outcome variables in studies of fetal risk. Although several studies suggest that intrauterine low-level lead exposure alone adversely effects fetal size (23–25), the majority of studies have revealed no correlation (7, 26–29).

Of the three studies that suggest an association between lead levels and neonatal size, the findings of one are not statistically significant and two may have

underestimated confounding variables. Bellinger et al. (23) used data from 4000 newborns to assess the extent to which maternal low-level lead exposure is associated with disturbed fetal growth in a large urban, socioeconomically disadvantaged sample. After controlling for gestational age and maternal smoking, they found that infants with cord blood lead levels >15 μg/dl (regarded as high by today's standards) had a 1.5 to 2.5 times greater risk of being small for gestational age, intrauterine growth restricted, or low birth weight than infants with lead levels <5 μg/dl. However, because of the small number of infants with such high lead levels, the finding did not reach statistical significance. Dietrich et al. (24) reported a significant association between maternal blood lead levels at gestational weeks 6 through 28 and birth weight. Although cofactors were accounted for in the statistical analysis, the prevalence of maternal smoking and alcohol use may have been underestimated (4). Irgens et al. (25) found an association with occupational lead exposure and birth weight of <2500 gm but did not directly measure lead levels or control for smoking status, which is a common confounding variable.

Although prenatal lead exposure may not affect growth as an isolated factor, the cumulative effects of prenatal and postnatal lead exposure may affect extrauterine growth. Investigators in Cincinnati focused on extrauterine growth of children and investigated whether two episodes of lead exposure were necessary for growth restriction (30). They hypothesized that the effect of lead on growth would be most pronounced among infants exposed to both high intrauterine and high postnatal lead levels. A cohort of 260 infants was followed from birth to 15 months of age. The mean prenatal maternal lead level was 7.5 μg/dl and ranged from 1 to 27 μg/dl. The study showed that a larger percentage of slow-growing infants belonged to the group with high prenatal and postnatal blood lead exposure. Maternal lead exposure suppressed normal growth early in life. However, if the infant escaped continued high postnatal exposure, the infant experienced a higher than expected growth rate, indicating growth catch-up. Increased postnatal blood lead concentration was negatively correlated with growth rate only in those infants whose mothers had high lead levels during pregnancy.

When these infants were followed up at 18 to 33 months of age, the results further supported the reversibility of growth restriction secondary to prenatal and early postnatal lead exposure (31). Prenatal blood lead level was no longer a predictor of growth restriction, confirming that prenatal lead exposure does not cause a permanent detriment in growth. The growth-restricting effect of lead during this age period was found to depend on continued lead exposure in the early postnatal period. The investigators concluded that lead affects growth only with prolonged periods of exposure, e.g., prenatal exposure and early postnatal exposure at age 3 to 15 months or prolonged postnatal exposure from ages 3 to 15 months through 18 to 33 months.

In summary, most studies have revealed no significant association between isolated *in utero* lead exposure and extrauterine growth. Reports that document a significant association may not have adequately controlled for confounding variables. Clearly, further investigation is warranted. Prenatal lead exposure does seem to be a significant factor in postnatal growth when lead exposure continues postnatally. Additionally, in studies that show growth effects of *in utero* lead exposure the effect seems to be reversible if lead exposure is curtailed. Evidence from the Cincinnati study suggests that by identifying exposure risk and removing the lead source, long-term growth effects may be avoided (31).

Congenital Anomalies

Lead is a biologically plausible teratogen. Teratogens generally act via germinal or somatic mutations, interference with mitosis, chromosomal alterations, membrane changes, or disturbance in nutrition or energy sources. Lead acts on many of these mechanisms. *In vitro*, lead can affect DNA synthesis (32), increase the incidence of dicentric chromosomes, and cause defects in centralization during mitosis (33). Using a rat model, Choie and Richter (34) confirmed that lead exposure altered DNA synthesis *in vivo*. Lead interferes with nutrition and energy supply by competing with other cations such as zinc, iron, and calcium to limit their supply at critical sites (35) and by interfering with mitochondrial function and the synthesis of cytochromes (36).

Despite the plausibility of lead as a teratogen, there is no evidence that exposure to low levels of lead produces major malformations in the human fetus (4). Controversy exists regarding the association of intrauterine lead exposure and minor malformations. Needleman et al. (28) found that cord blood lead levels from 5183 deliveries were associated with an increased risk of minor anomalies in a dose-related fashion. These anomalies included hemangiomas, lymphangiomas, hydrocele, minor skin abnormalities such as skin tags and papillae, and undescended

testes. The relative risk of a child demonstrating a malformation at birth increased by 50% as cord lead levels rose from 0.7 μg/dl to the mean of 6.3 μg/dl and increased by another 50% at 24 μg/dl. Multiple or major malformations did not show this pattern. Needleman and co-workers (28) note several limitations of their study including the fact that no particular type of minor malformation was associated with lead exposure. This suggested to the authors that lead might interact with other teratogenic risk factors to cause abnormalities. Also, rotating pediatric residents rather than trained teratologists conducted the neonatal examinations during the first days of life. Many minor anomalies, therefore, may have been missed.

In contrast, Ernhart's literature review (4) demonstrated that minor anomalies were unrelated to *in utero* lead exposure in most studies. Furthermore, she criticized the above study for failing to adequately control for alcohol effects because self-reports of alcohol consumption were gathered by using a questionnaire. Self-reports may underestimate actual alcohol use.

At present, additional studies need to be undertaken to assess the association between *in utero* lead exposure and minor malformations. If Needleman's results are replicable, a strong argument for preventing even very low lead exposure during pregnancy could be made.

Adverse Obstetrical Outcome

Because exposure to lead levels >25 μg/dl has been associated with increased frequency of abortion and preterm birth, many studies have attempted to assess obstetrical outcome in women exposed to lower, urban lead levels of approximately 9 μg/dl (37). Most studies have found no statistically significant differences in mean concentration of lead in cord blood between women with complications such as premature rupture of membranes, preterm delivery, preeclampsia, or meconium staining and women who did not suffer these complications (4, 23, 27, 28, 37). Additionally, no association between lead levels and breech presentation, placenta previa, abruptio placentae, fetal distress, or low Apgar scores has been elucidated (28). Only one study showed a statistically significant increase in preterm delivery of babies with cord blood lead levels averaging approximately 10 μg/dl (38). In summary, the majority of studies that investigated adverse obstetrical outcome and elevated but relatively low lead levels revealed no statistically significant relationship between lead and obstetrical outcome.

Neurotoxicity

Perhaps the most critical sequela of low-to-moderate lead exposure is neurotoxicity. High levels of lead *in utero* have been associated with mental retardation and developmental problems (3). Many prospective studies evaluated the short- and long-term developmental sequelae of low dose *in utero* lead exposure at various ages. Although results were mixed, there seemed to be a trend toward normalization of an early developmental deficit associated with low lead exposure *in utero* if lead exposure was discontinued.

A prospective study of fetal lead exposure on neurodevelopment in 3- and 6-month-old children whose lead levels were sampled prenatally (mean 8.0 μg/dl), at birth (mean 6.3 μg/dl), at day 10 (mean 4.6 μg/dl), and at 3 months (mean 5.9 μg/dl). Development was assessed with the Bayley Mental Developmental Index (MDI) at 3 and 6 months, controlling for birth weight and gestational age. Results showed an inverse relationship between prenatal and neonatal blood lead levels and performance on the MDI at both ages. The effect was greatest in boys and in infants with low socioeconomic status (24). Shen et al. (39) performed a similar study by using a Chinese cohort with a mean fetal cord blood lead level of 9.2 μg/dl. The difference in mean adjusted MDI scores between the low and high lead level groups was significantly different through 12 months of age.

Although development at 3 months and 6 months may be delayed by *in utero* lead exposure, results of studies of children up to 3 years of age are mixed. The 2-year follow-up of the above study found no statistically significant relationships between prenatal or postnatal blood levels and Bayley MDI scores at 3 years of age, suggesting that early developmental delay subsequently normalized (40). Unrelated studies of children at 3 years of age, again with use of the Bayley scales, showed similar findings (29). A study by Ernhart and Greene (41), which used language skills as the index of development, was also consistent with these findings. They examined the relationship of blood lead levels at birth (mean approximately 6 μg/dl), 6 months, 2 years, and 3 years with language measures at 1, 2, and 3 years of age. Multivariate analyzes revealed no significant relationship between prenatal lead level or early preschool lead level and language measures after controlling for cofactors.

In contrast, a study performed in Boston that followed 249 children from birth to 2 years and used methods similar to those described above found that MDI scores were inversely related to cord blood lead level during the first 2 years of life (42). However, when these children were followed up at 57 months of age, they no longer showed developmental deficits (43). In an effort to identify variables related to developmental improvement, investigators found that children with high (>10 μg/dl) prenatal lead exposure had greater recovery of function with lower blood lead levels at 57 months of age, higher socioeconomic status, higher maternal IQ, and female gender. Subsequent studies have also revealed a diminished association between prenatal lead exposure and cognitive function at 57 months of age except among children with higher concurrent lead exposure (44). Although socioeconomic status, gender, and maternal IQ are not modifiable, postnatal lead levels can be lowered; a goal that seems worthwhile and attainable.

Additional evidence for a cumulative effect of lead exposure as the key to long-term developmental deficits was derived from the Port Pirie cohort study (45). The study used the McCarthy Scales of Children's Abilities to examine the neurodevelopmental effect of environmental exposure to lead. Investigators found that blood lead level from birth to 4 years of age showed the strongest inverse relationship with the abilities score. Investigators concluded that the adverse effect of exposure to lead on mental development is cumulative during early childhood.

In sum, these studies suggest that low-dose lead exposure *in utero* may cause developmental deficits in the infant. These effects seem to be reversible if further lead exposure is avoided. Importantly, these effects seem to accumulate if high lead levels persist. Obviously, pregnant women should avoid high lead exposure; however, if a woman is found to have low-dose exposure, the prognosis for the infant is good if the infant can be protected from further exposure postnatally.

MANAGEMENT OF THE LEAD-EXPOSED PREGNANT PATIENT

Removal from the exposure is crucial in the treatment of lead toxicity in pregnancy because the chelating agents used in nonpregnant patients are contraindicated. Dimercaprol (BAL) has been reported to produce skeletal abnormalities in fetal mice (11). Ethylenediamineteraacetate (EDTA) is less toxic but chelates calcium and zinc, thus depriving the fetus of these essential elements. D-penicillamine is less effective and may cause connective tissue abnormalities in the fetus (11). Even when these agents were not toxic to the fetus, the amount that crossed the placenta for treatment of the fetus was not quantified. Only one well-documented case of EDTA therapy during pregnancy exists (46). The mother's blood lead level was 86 μg/dl pretreatment and 26 μg/dl posttreatment. The cord level remained at 79 μg/dl, suggesting nonpassage of the chelator. Even with use of a chelator with good fetal penetration, transplacental chelation is difficult due to the prolonged courses required. This would cause the fetus to lose essential trace elements. Therefore, maternal indications are the only valid reason for administration of chelators during pregnancy (46).

Indirect methods to prevent elevated lead levels may be worthwhile. Poor nutrition resulting in diets deficient in calcium, iron, and zinc enhance lead toxicity (47). Iron deficiency increases lead absorption (13). Women taking iron and folic acid supplements have been found to have lower lead levels than matched cohorts (48). Therefore, improved diet and vitamin supplementation may lower lead levels (13). Studies of factors that affect lead levels found that tobacco and/or alcohol use were related to higher prenatal blood lead values by an unknown mechanism (25, 29, 48–50). Thus, reiteration of the importance of abstinence from alcohol and tobacco during pregnancy is warranted in women who are at risk for lead exposure.

Finally, counseling the mother with an elevated but low blood lead level regarding the relatively good prognosis for her pregnancy and infant is important. Identification of ongoing lead exposure that poses a threat to the mother and her child is imperative. To prevent possible developmental deficits, the newborn should be raised in a home with minimal risk of lead exposure.

CONCLUSION

Considering the high number of women of childbearing age exposed to significant levels of lead and the possible toxic effects to the fetus, identification of high lead exposure is warranted. The current CDC critical level of 10 μg/dl seems reasonable considering the lack of evidence for irreversible damage at lower blood lead levels. However, administration of a questionnaire that would identify patients at risk for even lower doses of lead exposure may be useful in a general obstetrical practice. Blood lead levels below 10 μg/dl can be associated with growth and

developmental delay if exposure is continued postnatally. By identifying low-dose exposure early in the course of pregnancy, further exposure could be avoided, thereby protecting the fetus. Equally important, the identified lead source could be removed to allow the newborn to be brought home to a lead-free environment and prevent the detrimental effects of cumulative lead exposure.

An appropriate screening questionnaire should identify the majority of women who are at high risk for significant lead exposure. The pediatric screening questionnaire can serve as the foundation for a prenatal screening tool. The CDC recommends use of a five-item questionnaire to assess a child's risk of lead exposure: 1) Does your child live in or regularly visit a house built before 1960 with peeling or chipped paint? 2) Does your child live in or regularly visit a house built before 1960 with recent, ongoing, or planned renovation or remodeling? 3) Does your child have a brother, sister, or housemate who has been observed or is being treated for lead poisoning? 4) Does your child live with an adult whose job or hobby involves exposure to lead? 5) Does your child live near an active lead smelter, battery recycling plant, or other facility that is likely to release lead? (19) Stefanak et al. (51) assessed the accuracy of this questionnaire to identify pregnant women with blood lead levels >10 μg/dl. The sensitivity and negative predictive value when used in a geographically and socioeconomically high-risk population are comparable to its reported accuracy in young children. In the future, a questionnaire that includes additional information that integrates dietary habits, socioeconomic status, smoking, and alcohol use could be developed to more accurately identify women who are at risk for lead exposure.

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