

**CDC Advisory Committee on Childhood Lead Poisoning Prevention**  
**Lead and Pregnancy Work Group**  
**Subgroup 3 – Management, Treatment and Other Interventions**  
**LITERATURE REVIEW (Draft)**  
October 3, 2005

This group would be asked to review literature including, but not limited to:

- Breast milk exposure including:
  - Amount transmitted to baby
  - Benefits vs. hazards of breast feeding when blood lead levels are elevated.
- Effectiveness of nutritional supplementation during pregnancy and lactation
- Indications/Contraindications/Adverse effects of chelation on:
  - pregnant woman
  - fetus
  - neonate

Based on subgroup findings, this group would address the following questions:

- What is the follow-up testing schedule at various blood lead levels for pregnant and lactating women and for the neonate?
- At what blood lead level, if any, should women not be breastfeeding?
- What nutrition counseling or nutritional supplements should be recommended?
- What chelating agents should be employed?
- What interventions should be provided by public health agencies at various blood lead levels?

Based on subgroup findings (tasks revised by subgroup 3):

1. What are the components of intervention?

This question will be broken down as follows:

- a. Eliminating sources – describe the methods for separating the person from the lead source (not concerned with laws/regulations )
- b. Changing behavior (e.g., pica)
- c. Reducing absorption following exposure (e.g., nutrition)
- d. Decreasing retention and toxicity/increasing excretion (e.g., chelation)

2. What is the follow-up and intervention schedule (for clinicians and for public health agencies) at various BLLs for pregnant and lactating women and for the neonate?

3. At what BLL, if any should women not be breastfeeding?

# **EXPOSURE TO LEAD VIA BREAST MILK**

## **Introduction**

Due to the unique nutritional characteristics of human milk, breastfeeding is thought to be the optimal mode of nutrient delivery to term infants. Despite the many well-recognized benefits of breastfeeding for both mothers and infants, detectable levels of environmental contaminants, such as lead, have been documented in population studies of women with no known environmental or occupational exposures (Abadin *et al.*, 1997). Lactation requires a substantial redistribution of maternal calcium that is marked by mobilization of calcium from bone. Mobilization of maternal bone lead stores during pregnancy and lactation has been suggested as a significant potential source of lead exposure to the fetus and neonate (Silbergeld, 1991). However, there is limited information regarding the hazard that this represents for the developing fetus and infant.

## **Importance of Breastfeeding**

The USPHS Technical Information Bulletin *A Review of the Medical Benefits and Contraindications to Breastfeeding in the United States* (Lawrence, 1997) emphasizes the value of breastfeeding. Human breast milk is specific to the needs of the human infant. Its composition provides the ideal nutrients for human brain growth in the first year of life. The essential nutrients in breast milk are readily transferred into the infant's bloodstream. The ready bioavailability of essential nutrients, including microminerals, from breast milk contrasts with the bioavailability of constituents of modified cow's milk formula, from which only a small fraction of some nutrients is absorbed. Human milk also protects the breastfed infant against certain common infections and reduces the incidence of certain chronic diseases as well as symptoms of allergy. Breastfeeding may also provide the mother herself with health benefits. The benefits of breastfeeding are so compelling that very few situations definitively contraindicate breastfeeding. "The decision to breastfeed in the presence of a possible contraindication should be made on an individual basis, considering the risk of the complication to the infant and mother versus the tremendous benefits of breast feeding" (Lawrence, 1997, p. 5). Specifically and with regard to lead, this report states that breastfeeding is not contraindicated unless the concentration of lead in maternal blood exceeds 40 µg/dL. The American Academy of Pediatrics (AAP, 2005), likewise, has a statement on breastfeeding that confirms that breast milk is the superior food for infants and details the multiple benefits of breastfeeding on the infant and the mother. The paper reviews some of the situations in which breastfeeding is not recommended; generally if the mother has active infections or is taking toxic medication or treatments. The statement does not specifically address the transfer of toxic environmental agents through breast milk nor offer recommendations about this. It does state that before advising against breastfeeding the practitioner should weigh the benefits of breastfeeding against the risks of not receiving human milk.

## Lead in Breast Milk

Studies of lead in human breast milk have found concentrations ranging over three levels of magnitude, from <1 to greater than 100 µg/L (ppb). The sources of this variability include the nature and magnitude of exposure of the sampled population, the accuracy and precision of the lead analytical method itself, and difficulties associated with the collection and preparation of breast milk samples for analysis. Breast milk lead levels from older published studies, especially those reporting extremely high values, should be reviewed with caution due to the high potential for contamination during sample collection, storage, and preparation for analysis and to inaccuracy and imprecision of the laboratory analytical methods. Measurement of lead in breast milk is also complicated by the fat content of human milk, which changes both during feeding and over the course of lactation (Sim and McNeil, 1992).

Given the correlation of breast milk lead levels with maternal and infant blood lead levels, milk lead can be used as an indicator of both maternal and neonatal exposure (Hallen *et al.*, 1995). Since maternal blood is the medium from which lead is transferred to breast milk and ultimately to the nursing infant, the relationship of lead in maternal blood to lead in breast milk is of key importance. Early studies supported the belief that milk lead levels were one-tenth to one-fifth the levels of lead in maternal whole blood (Abadin *et al.*, 1997). Gulson *et al.* (1998) have discussed in detail the analytical difficulties attending the assay of lead in breast milk. In addition to the ubiquitous laboratory concerns for accuracy and precision associated with the analysis of very low concentrations of lead, breast milk presents two further issues. The probability of contamination of milk samples during the collection process is high, as noted in particular by Hu *et al.* (1996). In addition, breast milk is a fatty medium. Its high fat content leads to the danger of either further contamination or loss during the intensive dry ashing procedure frequently used to prepare milk samples for analysis. Gulson *et al.* (1998) reviewed and compared the results of a number of studies of the relationship of breast milk lead to maternal blood lead published over the past fifteen years, and concluded that the line of best fit through the data “that are considered to represent the realistic relationships between lead in maternal blood and breast milk” defines an array of slope of less than 3%.<sup>1</sup> The implication is that the studies not included suffered to a greater or lesser degree from significant contamination.

Recent careful studies of lead in breast milk consistently return milk lead to maternal blood lead ratios of 3% or less. For example, in a well-designed and well-executed study with rigorous contamination control, Ettinger *et al.* (2004) showed that breast milk lead was significantly correlated with maternal blood lead at one month postpartum in 310 lactating women in Mexico City. The ratio of the geometric mean milk lead concentration to the geometric mean maternal blood lead concentration was .013, or 1.3%. The highest observed blood lead concentration was 29.9 µg/dL. Breast milk analyses were carried out by isotope dilution mass spectrometry. Counter *et al.* (2004) reported ratios of milk lead concentration to maternal blood lead concentration in thirteen nursing mothers from Ecuadorian Andean villages. The ratios ranged from 0.4% to 3.3% in twelve of the subjects, appearing to increase with

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<sup>1</sup> Earlier in their 1998 paper, Gulson *et al.* made the statement that, “It appears that any data that have a ratio of the concentration of lead in breast milk to the concentration of lead in maternal blood greater than 15% should be treated with caution.” In response to an inquiry, Dr. Gulson has responded in a personal communication to Dr. O’Flaherty dated 23 May 2005, “The 15% is a feel good number looking at Figure 3 of my paper and has no scientific basis. It was more to try and get people aware of how much useless breast milk data there are in the literature . . . less than 3% would cover higher quality results.”

increasing blood lead level. The thirteenth subject, with a blood lead concentration of 27.4 µg/dL, had a milk lead to blood lead ratio of 7.5%. Breast milk samples in this study were analyzed by inductively coupled plasma mass spectrometry. Li *et al.* (2000) evaluated 119 non-occupationally exposed women in Shanghai, reporting a mean maternal blood lead concentration of 14.3 µg/dL and a mean milk lead to blood lead ratio of 3.9%. Lead was measured by atomic absorption spectrometry. Gulson *et al.* (1998) found that the percentage of lead in breast milk compared with whole blood was less than 3% in 15 adult female immigrants to Australia with blood lead concentrations up to 34 µg/dL. Milk lead analysis was carried out in purpose-built low contamination laboratories (clean rooms) by isotope dilution mass spectrometry.

Like the concentration of lead in breast milk, its reported concentration in blood plasma has decreased over time with increasing sophistication of analytical techniques and improved quality control. In perhaps the most rigorous and detailed published recent study, Manton *et al.* (2001), using isotope dilution analysis, observed a linear relationship of serum lead concentration (y) to whole blood lead concentration (x),  $y = 0.00030 + 0.00241x$ , in 73 Los Angeles women of childbearing age with blood lead concentrations up to 6 µg/dL. The observed serum lead to whole blood lead ratio was therefore 0.24%.<sup>2</sup> Earlier well-controlled analytical studies (Manton and Cook, 1984; Schütz *et al.*, 1996; Hernandez-Avila *et al.*, 1998) had reported slightly higher values, but none greater than about 3%. Thus, the concentration of lead in breast milk is comparable to its concentration in blood plasma, as pointed out by Gulson *et al.* (1998). Physiologically, this relationship is reasonable, since it is consistent with the concept that plasma is the compartment from which lead is transferred to other fluids and tissues (O'Flaherty, 1993).

At higher blood lead concentrations, the relationship between the concentration of lead in plasma and its concentration in whole blood becomes nonlinear (Manton *et al.*, 2001). Plasma lead increases as a fraction of whole blood lead, and it could be posited that where lead exposure is very high, breast milk lead may also be elevated disproportionately to whole blood lead. The reported blood lead concentration at which deviation from linearity in the relationship of plasma lead to whole blood lead begins to be clearly apparent depends on the particular data set and the method of fitting a curve to it, but it appears generally that blood lead concentrations above about 40 µg/dL are associated with significant nonlinearity (Manton and Cook, 1984; O'Flaherty, 1993; Schütz *et al.*, 1996; Hernández-Avila *et al.*, 1998; Manton *et al.*, 2001).

Taking breast milk lead concentrations to be 3% or less of maternal blood lead concentrations below about 40 µg/dL, it is possible to estimate the intake of lead by nursing infants from breast milk. Infants' total fluid requirements can be estimated by the Holliday-Segar method (**will have a reference here**) (Table 2a and b). In this calculation, for infants up to 10 kg in weight the requirement is calculated as 100 mL/kg/da; for the next 10 kg, the additional requirement is 50 mL/kg/da; and above 20 kg, for each additional kg the requirement is 20 mL/kg/da.

Actual measurements of breast milk intake by infants have resulted in reported weighted mean average intakes of 702 mL/da at one month, 759 mL/da at 3 months, 765 mL/da at 6 months, and 427 mL/da at 12 months (**will have EPA document reference here**), greater than the total fluid requirement estimated by the Holliday-Segar method for ages up to 3 months. For simplicity, we will assume that daily breast milk intake in both boys and girls is about 700 ml up to age 6 months, and drops off thereafter to about 400 ml at age 12 months. Given these conditions, Table 3 shows what the infant's daily intake of lead from breast milk would be at different maternal blood lead concentrations. These estimated intakes err on the high side

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<sup>2</sup> There was no difference between the lead contents of blood plasma and blood serum.

because the calculations use (1) a relatively high estimate of milk consumption, especially at ages less than 3 months, and (2) a (reasonable) upper limit of 3% for the relationship of maternal plasma lead to maternal blood lead at maternal blood lead concentrations less than 40 µg/dL (and therefore of breast milk lead to maternal blood lead in the same concentration range). (While the upper 95<sup>th</sup> percentile of infants' body weight was used in Table 2 for the same reason, to skew intake toward an upper limit, that figure is not used in the calculations in Table 3.)

**Table 2a.** Calculation of Female Infants' Total Fluid Requirements

Age of Child, months	Upper 95 <sup>th</sup> Percentile of Body Weight, kg (From standardized growth charts)	Total Fluid Requirement, mL/da (Holliday-Segar method)
0	4.5	450
1	5.0	500
2	5.9	590
3	6.7	670
4	7.4	740
5	8.0	800
6	8.7	870
12	11.4	1070

**Table 2b.** Calculation of Male Infants' Total Fluid Requirements

Age of Child, months	Upper 95 <sup>th</sup> Percentile of Body Weight, kg (From standardized growth charts)	Total Fluid Requirement, mL/da (Holliday-Segar method)
0	4.5	450
1	5.5	550
2	6.5	650
3	7.3	730
4	8.1	810
5	8.9	890
6	9.6	960
12	12.4	1120

**Table 3.** Estimated Daily Intake of Lead from Breast Milk at Different Maternal Blood Lead Concentrations

Maternal Blood Lead Concentration, $\mu\text{g/dL}$	Maternal Plasma Lead Concentration, $\mu\text{g/dL}$ (Calculated as 3% of maternal blood lead concentration)	Breast Milk Lead Concentration, $\mu\text{g/L}$ (Numerically equal to maternal plasma lead concentration, but expressed per liter rather than per deciliter)	Infant's Lead Intake from Breast Milk to Age 6 Months, $\mu\text{g/da}$ (Assuming ingestion of 700 mL milk/da)	Infant's Lead Intake from Breast Milk at Age 12 Months, $\mu\text{g/da}$ (Assuming ingestion of 400 mL milk/da)
2	0.06	0.6	0.42	0.24
5	0.15	1.5	1	0.6
10	0.3	3	2.1	1.2
20	0.6	6	4.2	2.4
30	0.9	9	6.3	3.6
40	1.2	12	8.4	4.8

The FDA has set a goal of less than 100  $\mu\text{g/da}$  as the maximum lead intake by children one to five years of age (**will have FDA reference here**). Comparison of the intakes in Table 3 with the 100  $\mu\text{g/da}$  figure shows that the estimated intake of lead from breast milk is consistently small, and less than 10% of the proposed maximum. This calculation is consistent with experimental observations demonstrating a very small impact of breast milk lead on infant blood lead. For example, Ettinger *et al.* (2004) showed that a difference of about 2  $\mu\text{g/L}$  in breast milk lead was associated with an 0.82  $\mu\text{g/dL}$  increase in the blood lead of breast-feeding infants at 1 month of age, adjusting for cord blood lead, infant weight change, and reported breast-feeding status; and Manton *et al.* (2000) showed that the principal source of lead exposure in very young children, irrespective of whether they are breast- or bottle-fed, is hand-to-mouth activity. In an observation differing slightly from that of Manton *et al.* (2000), Gulson *et al.* (1998) found that for the first 60 to 90 days postpartum, the contribution of breast milk lead to infant blood lead varied from 36% to 80%, suggesting that breast milk lead can at times be the principal source of the nursing infant's lead exposure. Nonetheless, the low intakes calculated in Table 3 do not represent a significant health hazard in either case. A number of other investigators have concluded on the basis of experimental observation that because of the normally very low concentrations of lead in breast milk, typical diets consumed by lactating women in most countries should not pose a health hazard to the nursing infant (Osterloh and Kelly, 1999; Gundacker *et al.*, 2002; Téllez-Rojo *et al.*, 2002; Dorea, 2004).

Much higher breast milk lead concentrations have been recorded in women living or working in lead-polluted areas. Li *et al.* (2000) reported a mean breast milk lead concentration of 92  $\mu\text{g/L}$  in 12 occupationally exposed women working in a small battery factory in Shanghai. The highest observed breast milk lead concentration in this group was 291  $\mu\text{g/L}$ . The mean breast milk lead concentration in the 119 non-occupationally exposed women in this study was 5.6  $\mu\text{g/L}$  and the mean milk lead to blood lead ratio was 3.9%, so it is unlikely that these extremely high milk lead concentrations were due to contamination. Namihara *et al.* (1993) published data defining a relationship between matched maternal blood lead/milk lead pairs in 35 women living within 200 meters of one of three smelters in Mexico City. Reported breast milk

lead levels, determined by atomic absorption spectrometry, ranged up to 350 µg/L in these women. The data suggested different slopes for blood lead concentrations less than and greater than about 40 µg/dL. However, it is difficult to interpret these data with any assurance since 54% of the milk samples were below the rather high analytical detection limit of 9.2 µg/L.

The great bulk of adult lead body burden is found in the bone (Barry, 1975). Normal bone turnover feeds lead to the blood, which reflects a mixture of integrated past exposure and current exposure. Indeed, maternal bone lead has been shown to be positively associated with both maternal blood and breast milk lead concentrations (Téllez-Rojo *et al.*, 2002; Ettinger *et al.*, 2004). Bonithon-Kopp *et al.* (1986) found that women over 30 had significantly higher levels of breast milk lead than women between 20 and 30 years of age. Since bone accumulates lead with age, the implication was that the increased maternal bone lead levels had led to increases in breast milk levels. In addition, maternal bone turnover increases during lactation (Osterloh and Kelly, 1999; Moline *et al.*, 2000; Sowers *et al.*, 2002), which has raised the concern that maternal blood lead concentrations might increase significantly during lactation. Experimental evidence on this point is not entirely consistent but does largely alleviate the concern. Manton *et al.* (2003) observed sustained elevations of from 1 to 4 µg/dL in maternal blood lead concentration during the first 6 to 8 months of lactation, after the expected normal postpartum reduction in plasma volume, in 6 nursing mothers with pre-pregnancy blood lead concentrations of less than 2 µg/dL. At a ratio of 3%, this elevation corresponds to an elevation in breast milk lead concentration of 0.3 to 1.2 µg/L. It was followed by a gradual decline over the next year in the two women who continued to breastfeed to 18 months postpartum. Isotope ratio analysis suggested that the additional lead originated from maternal bone. Similarly, Téllez-Rojo *et al.* (2002) observed an increment of 1.4 µg/dL in blood lead concentration in women who were breastfeeding exclusively relative to women who had stopped lactation, based on multivariate regression analysis of measurements taken at 1, 4, and 7 months postpartum. These women had blood lead concentrations up to 23.4 µg/dL at delivery. However, in another longitudinal study, Osterloh and Kelly (1999) found no relationship between bone density changes and changes in maternal blood lead concentration, after the reduction in plasma volume occurring during the first two weeks of lactation, in 58 women with a mean blood lead concentration of 2.35 µg/dL at enrollment in the study (32 to 38 weeks of gestation). It is generally agreed that biologically significant elevations in milk lead concentration do not occur in lactating women at the blood lead concentrations typical of developed countries (Osterloh and Kelly, 1999; Sowers *et al.*, 2002; Manton *et al.*, 2003; Ettinger *et al.*, 2004).

Among the factors that can reasonably be included among those considered in advising a woman whether or not to breastfeed are parity and the projected length of nursing. There is evidence that with closely-spaced multiple pregnancies, baseline maternal blood lead concentrations are lower and the increases occurring in maternal blood lead concentrations during late pregnancy and lactation are damped relative to those in the first pregnancy (Rothenberg *et al.*, 1994; Manton *et al.*, 2003). This observation is consonant with folklore from the lead trades in the nineteenth century and earlier, which held that if a lead-poisoned woman had a child, her symptoms would be alleviated. (ELLEN; I SUGGEST INSERTING THE REFERENCE FOR THIS HERE) Folklore aside, the limited evidence does suggest that the greatest concern for lead exposure of the nursing infant may be during the first pregnancy.

In another observation, lead acquired (not by nursing) through a brief exposure was found to be cleared by the child more rapidly than lead acquired over a more protracted period (Manton *et al.*, 2000). The age of the child at termination of exposure may have been a factor in this study, since the children who had experienced the longer exposures were older (2 to 3 years old

versus 1 to 1½ years old), and the degree of mineralization and turnover of the skeleton, as well as the length of exposure, could have been among the important determinants of clearance. Nonetheless, the inference is the same: the older the child is at cessation of nursing, the more slowly will the lead acquired through nursing be cleared. Therefore, a long periods of breastfeeding by a child whose mother has a very elevated blood lead level (of 40 µg/dL or higher) may lead to a more persistent lead burden for the child.

## Summary

(1) Because of the very low concentrations of lead in breast milk, typical diets consumed by lactating women in most countries should not pose a health hazard to the nursing infant.

(2) Considering the low concentration of lead in breast milk relative to its concentration in maternal blood, the absence of evidence for a biologically significant increase during lactation, and the established benefits of breastfeeding, there is no reason to recommend deviation from the USPHS recommendation that breastfeeding be advised at concentrations of lead in maternal blood up to 40 µg/dL.

(3) Maternal whole blood lead level should be used as the basis for making this determination. The measurement of breast milk lead levels is not recommended. There are many methodological difficulties with breast milk lead analysis, and its accuracy could not be guaranteed, whereas an approximate breast milk level can be estimated based on the whole blood lead level.

(4) At maternal blood lead concentrations much exceeding 40 µg/dL, the observations and calculations on which these recommendations are based do not apply. In this very high range, the concentration of lead in breast milk may be higher relative to its concentration in maternal blood than it is at maternal blood lead concentrations less than 40 µg/dL.

(5) Given all of the above considerations, we recommend that if a woman's blood lead level is equal to or greater than 40 µg/dL, breastfeeding be stopped until further blood lead measurements are below 40 µg/dL. It is also recommended that the infant's blood lead level be checked. If the maternal blood lead level is below 40 µg/dL and the infant's blood lead level is maintained below 10 µg/dL, then the advantages of breastfeeding outweigh the risks of lead exposure. In situations where a breastfed infant has a venous lead level of 10 µg/dL or higher, irrespective of the mother's blood lead level, a thorough investigation of the child's environment should be performed to evaluate the possibility of additional lead sources. The results of this investigation should be factored into the decision to continue or discontinue breastfeeding.

Followup of infant blood lead levels should be based upon the guidelines presented in Table X.

# **EFFECTIVENESS OF NUTRITIONAL SUPPLEMENTATION DURING PREGNANCY AND LACTATION**

## **Introduction**

The potential role of nutritional status in altering susceptibility to lead exposure and toxicity has long been recognized (Mahaffey 1980, 1990, 1995). There is increasing evidence that suggests several nutrients may interact with lead absorption, deposition, and excretion of lead from the body. This may be particularly true at times, such as pregnancy and lactation, when nutrient requirements are increased in comparison to other periods of life. These relationships are of particular interest due to the concern for fetal and infant exposure to circulating maternal lead. Since over 95% of lead is stored in bone, nutritional intervention may be an important strategy for preventing trans-generational exposures from lead-exposed women during the reproductive years.

In a study of maternal diet during pregnancy, iron and vitamin D intake were negatively associated with neonatal blood lead level (Schell, et al. 2003). In another study, higher maternal hemoglobin and sickle cell trait were associated with lower cord blood lead (Harville, et al. 2005), suggesting that iron status may be an important factor in the maternal-fetal transfer of lead across the placenta. There is some evidence supporting low dietary calcium and vitamin D as risk factors for elevated bone lead levels (Cheng et al., 1998). Calcium, phosphorus, magnesium, fluoride, and vitamins D and K are known to be essential to bone health, but the effect of diet on the mobilization of previously-accumulated bone lead stores between osseous and non-osseous tissues has not been fully investigated. Among postpartum women in Mexico City, lower levels of bone lead were associated with higher intakes of calcium, vitamin D, phosphorus, magnesium, iron, zinc, and vitamin C, though these relationships showed inconsistent trends (Ettinger, et al., Submitted 2005).

Dietary factors concurrent to the time of exposure are known to have an impact on lead dynamics, particularly with respect to the absorption of lead from the gastrointestinal tract (Mahaffey 1990, 1995) where nutrients may interact with lead by several potential mechanisms. Dietary nutrients potentially interact with lead by: binding lead in the gut, competing with lead for absorption, altering intestinal cell avidity for lead, or by altering affinity of target tissues for lead (Ballew and Bowman, 2001). Calcium deficiency has been shown to increase lead absorption (Heard and Chamberlain, 1982) and lead retention (Six and Goyer, 1970). Higher milk intake during pregnancy has been associated with lower maternal and umbilical cord lead levels in postpartum women in Mexico (Hernández-Avila et al., 1997). Iron deficiency has been associated with increases in absorption and deposition of lead (Barton et al., 1978). Baltrop and Khoo (1975) also observed that lead absorption is dependent upon both the quantity and type of dietary fat consumed. Ascorbic acid (vitamin C) has been suggested as acting as a natural chelating agent that enhances the urinary elimination of lead from the body (Simon & Hudes, 1999).

Lead may also modify the metabolism of nutrients (Sauk and Somerman, 1991; Pounds, 1991). Lead also impacts on a wide variety of biological activities at different intracellular levels at the voltage-gated channels and on the first, second and third messengers (Finkelstein et al., 1998). Lead can substitute for calcium ( $\text{Ca}^{2+}$ ) and zinc ( $\text{Zn}^{2+}$ ) as a second messenger in ion-dependent events at synapse. There is also evidence that lead, like other divalent metal toxins, is an oxidative toxin that can both directly and indirectly cause cell damage (Adonaylo and Oteiza, 1999).

## Nutritional Aspects of Pregnancy & Lactation

### Calcium Requirements of Pregnancy and Lactation

Profound changes in calcium metabolism and bone mineral status accompany pregnancy both during gestation and after delivery. Calcium requirements are increased substantially during pregnancy and lactation in order to meet the calcium needs of the developing fetus and nursing infant for skeletal mineralization and growth (Prentice, 1994; 2000). Levels of calcium in plasma are under strict hormonal control (Kovacs and Kronenberg, 1997). Calcium homeostasis is maintained by controlling intestinal calcium absorption, renal calcium excretion, and skeletal calcium release (IOM, 1997). It is recommended that pregnant and nursing women adjust their dietary calcium intake to 1,200-1,500 milligrams per day depending on their age (IOM, 1997). The role of dietary calcium and mineral adequacy on skeletal changes of pregnancy and lactation is still controversial. Other nutrients (vitamin D, phosphate, magnesium) remain relatively unexplored.

The first half of pregnancy is a time of preparation for the demands of rapid fetal growth that occur in the later stage when >90% of fetal growth occurs and the calcium demand reaches about 300 mg/day in the last quarter of gestation (King, 2000). During pregnancy approximately 25 to 30 grams of calcium are transferred to the fetus (IOM, 1990). Lactation also has discernible effects on calcium homeostasis. Approximately 210 milligrams of calcium per day is utilized for milk production during lactation (IOM, 1991). Biochemical markers and bone density measurements indicate that bone resorption is increased during lactation (Kalkwarf et al., 1995; Sowers et al., 1995). Renal conservation of calcium occurs during lactation (Kent et al., 1993; Specker et al., 1994). Maternal calcium loss during lactation is estimated at 280-400 mg/day (up to 1,000 mg/day) approximately four times higher than during pregnancy (Sowers, 1996). Calcium supplementation has been shown to have little effect on lactation-induced changes in bone turnover (Kalkwarf et al., 1997; 1999). However, baseline dietary intake and levels of calcium supplementation in recent studies have been relatively low. It is possible that very high levels of calcium are needed to counterbalance the nutritional needs of the developing fetus (Johnson, 2000).

### **Lead and Micronutrient Supplementation to Reduce Exposure**

Animal studies have found an association between various micronutrients and BLLs and suggest that micronutrients may be helpful in minimizing lead toxicity. Results of animal studies indicate that micronutrients such as vitamins C, E, and B6; beta-carotene; and selenium may play a role in reducing oxidative damage induced by lead **Hsu P, Guo Y (2002) Antioxidants nutrients and lead toxicity Toxicology 180:33-44** **Flora S, Pande M, Mehta A (2003) Beneficial effect of combined administration of some naturally occurring antioxidants (vitamins) and thiol chelators in the treatment of chronic lead intoxication. Chemico-Biological Interactions 145:267-280.** While other micronutrients, such as zinc, iron, and calcium, are thought to compete with lead for binding sites thereby minimizing initial uptake through the gut and subsequent uptake into various organs **Hsu P, Guo Y (2002) Antioxidants nutrients and lead toxicity Toxicology 180:33-44.**

These findings have prompted researchers to investigate whether micronutrients could also play a role in the prevention or treatment of lead poisoning in humans. A wide range

of micronutrients could potentially affect lead kinetics, including calcium, iron, vitamin C, vitamin E, selenium, and zinc. Increasing the intake of key nutrients either by improving diets or adding supplements has been suggested as a way to prevent lead poisoning and to improve outcomes in those who already have a high lead burden, either by reducing absorption, by “chelating” lead, or by countering the toxic effects of lead. Supplementation with calcium, zinc, or iron may minimize absorption from the gut or uptake into organs, whereas Vitamin C has been suggested to reduce BLLs by promoting excretion. Supplementation with vitamin C and other antioxidants such as vitamin E and selenium may prevent lead-induced oxidative damage due to lead exposure and bolster the anti-oxidant defense system.

Unfortunately the research to date is insufficient in either quality or quantity to evaluate many of these hypotheses. Cross-sectional studies have found inverse relationships between vitamin E, vitamin C, thiamine, zinc, selenium, calcium, and iron and BLLs (**IRON: Wright RO (1999) The role of iron therapy in childhood plumbism. Current Opinion in Pediatrics 11 (3) 255-258, Wright R. (1999) Association Between Iron Deficiency and Low Level Lead Poisoning in an Urban Primary Care Clinic American Journal of Public Health, 89(7):1049. SELENIUM AND IRON: Osman K, SCHU TZ A, ÅKESSON B, MACIAG A, VAHTER, M (1998) Interactions Between Essential and Toxic Elements in Lead Exposed Children in Katowice, Poland Clinical Biochemistry, Vol. 31, No. 8, 657–665, 1998 : VITAMIN C AND E West 1994, Simon, VITAMIN C AND THIAMINE Lee Cite, cite**). However, only a few studies are available that evaluate whether supplementation or a diet enriched with these nutrients affects BLLs or improves outcomes. These studies focus primarily on three nutrients: iron, calcium, and vitamin C.

## **Iron**

The relationship between iron and lead is complex and not completely understood. Most of the research to date has focused on children, not adults. Analysis of this research suggests that supplementation with Fe is beneficial only in the presence of iron deficiency. A study of 42 children undergoing chelation therapy for elevated BLLs found that children with iron deficiency anemia had significant improvements in cognitive and perceptual-motor scores after iron supplementation while iron replete children did not (**Ruff HA, Markowitz ME, Bijur PE, Rosen JF. (1996) Relationships among blood lead levels, iron deficiency, and cognitive development in two year old children. Environmental Health Perspectives 104(2): 180-185**). Studies have also found that while iron may limit lead absorption, it also seems to inhibit lead excretion. (**Ruff, Kwong WT. Friello P. Semba RD. Interactions between iron deficiency and lead poisoning: epidemiology and pathogenesis. [Review] [104 refs] [Journal Article. Review. Review, Tutorial] Science of the Total Environment. 330(1-3):21-37, 2004 Sep 1;**) Iron supplementation in iron-replete children undergoing chelation could potentially worsen outcomes if excretion is delayed and elevated BLLs are sustained longer than usual with chelation. However, other studies suggest that supplementation with iron in children undergoing chelation therapy has led to slightly higher levels of urinary excretion of lead. **Markowitz ME, Rosen JF, Bijur PE Effects of iron deficiency on lead excretion in children with moderate lead intoxication J Pediatrics 1990 116: 360-364--** Whether changes in urinary excretion impact neurobehavioral outcomes in lead-poisoned children is unknown. Therefore, until further research is available that can elucidate these relationships more clearly, many experts recommend that iron supplementation only in iron deficient children, irrespective of lead exposure, and do not recommend iron supplementation for the prevention or treatment of lead

poisoning (**Wright RO (1999)The role of iron therapy in childhood plumbism. Current Opinion in Pediatrics 11 (3) 255-258 (CDC BLUE book).**

Most studies, but not all, have found lower BLLs in adults with better markers of iron status. These studies have generally used dietary intake or laboratory tests, such as serum iron or ferritin, to determine iron status. As with children, cross-sectional studies of lead exposed adult populations have found lower serum iron markers and lower dietary intake, as well as increased rates of iron deficiency anemia, associated with higher BLLs (**Kim H, Lee S, Hwangbo Y, Ahn K, Lee B (2003) Cross sectional study of blood lead effects on iron status in Korean Lead Workers Nutrition 19: 571-576. Graziano J, Popovac D, Factor-Litvak P, Shrout P, Kline J, Murphy M, Zhao Y, Mehmeti A, Ahmedi X, Rajovic B, Zvicer Z, Nenezic D, Lolacono N, Stein Z (1990) Environmental Health Exposures 89, 95-100, Baghurst P, McMichael A, Vimpani G, Robertson E, Clark P, Wigg N. (1987) Determinants of blood lead concentrations of pregnant women living in Port Pirie and surrounding areas. Med J, 146:69-73).** However, the largest cross-sectional study of reproductive aged women to date (N=4394 women aged 20 to 40 years) contradicts these findings. In this study, there was a positive association between dietary iron intake and BLLs (**Lee M, Chun O, song W. (2005) Determinants of the Blood Lead Level of US Women of Reproductive Age. Journal of the American College of Nutrition, 24(1) 1-9.**)

Whether ensuring that women meet the dietary recommendations for iron intake during pregnancy lowers maternal or neonatal BLLs is currently unclear. Only two studies were found that described the relationship between maternal diet **Schell 2003** or use of vitamin supplements **West 1994** and maternal and/or neonatal BLLs. Schell followed 220 mother-infant pairs from early to mid-pregnancy until delivery. A maternal composite dietary score was derived from monthly dietary assessments. Maternal BLLs were obtained in each trimester of pregnancy. Neonatal BLLs were obtained via cord bloods at delivery in 90% of the cases and by a venous blood sample drawn from the neonate within 3 days of life for the remainder. An analysis of maternal intake of iron, calcium, and vitamin D found that of these nutrients iron had the largest impact on newborn lead levels. A 2 standard decrease in maternal iron intake was associated with a 0.51 Mcg/dl increase in newborn lead. **Schell L, Denham M, Stark A, Gomez M, Ravenscroft J, Parsons P, Aydermir A, Samelson R (2003) Maternal blood lead concentration, diet during pregnancy, and anthropometry predict neonatal blood lead in a socioeconomically disadvantaged population. Environmental Health Perspectives volume 111(2): 195 (PDF ON DISC).** However, it should be noted that more than 50% of mothers in this study had intakes below the recommended dietary allowance for iron in pregnancy. Since this study did not analyze whether the inverse relationship found between dietary intake of iron and BLLs differed according to maternal baseline iron status, it is unclear whether this same relationship would hold in both iron-deficient and iron-replete women.

**West (1994)** investigated the relationship between supplementation with prenatal vitamins and maternal BLLs and pregnancy outcomes in 349 African American women. Supplement users had significantly lower BLLs than those who did not use supplements. However, this study did not describe the content of the supplements consumed, provide adherence data, or address iron status.

**Need to look for other articles on Fe supplementation.** Schell gives good evidence that increased iron intake associated with lower neonatal BLLs but many in sample were iron deficient so it may be that same applies: only needed if iron deplete but since most pregnant women are, I think supplementing would be best.

In summary, the research data is too scanty to determine the relationship between maternal intake of iron and maternal or neonatal BLLs, although it suggests that iron supplementation may be proven to be of benefit in future larger and better controlled trials. However, given that the dietary intake of many pregnant women is low in iron, until further data is available, all women should be evaluated for the adequacy of their iron intake and be provided with appropriate nutritional advice and supplements if deficiencies exist.

## ***Vitamin C***

Two large cross-sectional studies in adults have found associations between BLLs and dietary intake or serum levels of vitamin C (**Simon J, Hudes E (1999) Relationship of ascorbic acid to blood lead levels JAMA 281(24) 2289-2293. Lee M, Chun O, Song W. Determinants of the Blood Lead Level of US Women of Reproductive Age Journal of the American College of Nutrition, Vol. 24, No. 1, 1–9 (2005).** In an analysis of nutritional data provided by over 15,000 adult participants in NHANES III, Simon and Hudes (1999) found that adults in the highest 2 serum ascorbic acid tertiles had a 65% to 68% lower prevalence of elevated BLLs compared to adults in the lowest tertile ( $p=0.03$ ). In another analysis of NHANES III data, **Lee (2005)** described the relationship between serum ascorbic acid and BLLs in over 4000 reproductive aged women. Women with high serum ascorbic levels had a 2.5 lower odds of having BLLs in the highest decile ( $\geq 4$  mcg/dl).

These cohort studies suggest that assuring adequate vitamin C intake may help reduce BLLs in women. The protective effect of vitamin C has been confirmed in several small intervention trials. **Dawson et al** randomized 75 male smokers with BLLs ranging between 1.5 to 3.3 mmol/L into three treatment groups. Subjects were given supplements containing either 1) placebo, 2) 200 mg ascorbic acid, or 3) 1000 mg ascorbic acid for four weeks. BLLs fell by 81% in the group receiving 1000 mg ascorbic acid a day but were unchanged in those receiving placebo or 200 mg ascorbic acid. Since urinary excretion remained unchanged, the authors postulate that lower BLLs resulted from reduced absorption from the gut due to the enhanced bioavailability of iron in the presence of vitamin C. Similar result were found in a small study of lead workers. Twenty-four workers who were occupationally exposed to lead were divided into two groups. Mean BLLs in this study was  $32.84 \pm 1.78$  mcg/dl. One group received Vitamin B<sub>1</sub> 75 mg once a day for a month; the other received Vitamin C 250 mg twice a day for a month. Pre and post-treatment levels of BLLs, Cu, Fe, Hb, ALAD, ascorbic acid, and pyruvic acid were obtained. Both supplements significantly lowered BLLs, raised Cu and Fe levels, and reduced blood thiamine and copper deficiencies. **Tandon 2001**. Only one study was found that investigated the impact of vitamins on BLLs in pregnant women **West (1994)**. In this study, 97 women were asked whether they complied with their physician's recommendation to consume a standard formulation of prenatal vitamin. Those who reported "yes" had significantly lower BLLs than those who did not ( $5.11 \pm 0.20$  mcg/100 ml vs.  $7.53 \pm 0.34$  mcg/100 ml  $p=0.0001$ ). However, these results must be interpreted with caution since exposure variables, compliance data, and the content of the recommended vitamin regimes was unspecified.

Animal studies have shown that supplementation with vitamin C reduces markers of oxidative stress in the brains, liver, and testes of supplemented rats as well as lowered lead levels in blood, liver, and renal tissue. (**Hsu, Ping-Chi 2002**). Human studies have also found supplementation with vitamin C reduced lead Levels (**Dawson and Harris, 1997**) **read this study and double check. Article from bib list .. Also Dawson 1999 I have and it shows lower lead levels.** One study randomly assigned non-occupationally exposed male smokers into three

treatment groups (placebo N=25, Vitamin C 200 mg daily N=25, and Vitamin C 1000 mg daily N=25). Baseline BLLs were low and similar to that reported by other studies of the general population. Supplementation with 1000 mg of Vitamin C (but not 200 mg) reduced BLLs by 81%. **(Dawson 1999)** Another small study of 12 occupationally exposed silver workers also had significant reductions in mean whole BLLs after one month supplementation of Vit C 500 mg daily (Pretreatment 38.50mg/dl  $\pm$  3.48, post treatment 23.58mg/dl  $\pm$  2.86 p<0.01) **Hernandez-Avila et al., 1997 orange juice consumption associated with lower vitamin C (Barbara, I think this should be blood lead?) levels**

However, according to a literature review by **Hsu, Ping-Chi 2002**, the benefit of vitamin C supplementation seems to be found most consistently in studies with subjects with lower lead levels. Human and animal studies with higher BLLs in general tend to show minimal to no improvement with vitamin C supplementation. **I CANNOT FIND ANY SUPPORTING LITERATURE FOR THIS STATEMENT AND THE ARTICLE DOES NOT REFERENCE THIS POINT**

In summary, the research to date suggests that vitamin C may significantly lower BLLs and holds the promise that ensuring adequate intake may be protective against, or an adjunct treatment for, lead poisoning. However, further research is needed to confirm these conclusions, since the studies conducted to date are small and do not include pregnant or lactating women. Nor do they evaluate what “dose” of vitamin C is needed to lower BLLs. BLLs were lowered only in those studies which exceeded AIs and the safety of exceeding these levels is unclear.

## *Calcium*

In general, most cross sectional studies have found inverse relationships between various measures of calcium status and BLLs. However, one notable exception is a cohort study which analyzed a subset of NHANES III data in order to investigate the relationship between BLLs of reproductive aged women (N=4394 women aged 20 to 49) and various modifiable lifestyle factors **(Lee 2005)**. In this study, no relationship was seen between dietary calcium and BLLs. However, intake was generally low in this study; mean dietary consumption of calcium was only 718.6  $\pm$  12.3 mg/d compared to the AI of 1000 mg/d.

The role of calcium supplements in altering maternal responses to fetal demand for calcium is not fully understood. Calcium supplementation (1200mg calcium supplement at bedtime) during the third trimester of pregnancy reduced maternal bone resorption, as reflected by urinary NTX levels, by an average of 13.6 nM BCE/mM creatinine (14%) in comparison to placebo, suggesting that calcium supplements can reduce maternal skeletal bone turnover during the third trimester of pregnancy (Janakiraman et al., 2003). The factors controlling skeletal changes of pregnancy and lactation are still largely unknown.

In a randomized, double-blind, placebo-control trial of calcium supplementation during lactation, Hernández-Avila et al. (2003) showed that supplementation with 1200mg calcium among lactating women reduced maternal blood lead levels 15-20% over the course of lactation. Supplementation with 1200 mg calcium led to modest reduction in lead levels with supplementation for 6 mths **(Hernandez-Avila M (2003) in a randomized clinical trial of over 600 lactating women)** However, the overall improvement was not significant however become significant if supplementation extended to 6 months, if body lead burden high, and good adherence. Reductions in BLLs were modest.

Dietary calcium supplementation also increased the rate of decline in breast milk lead by 5-10% over the course of lactation in comparison to placebo suggesting that calcium

supplementation may be an important potential intervention strategy to reduce lead in breast milk from both current and previously-accumulated sources (Ettinger, et al. 2005).

Mexico “Cohort 3” preliminary results of calcium trial in pregnancy – need to get permission to use data not available yet, but this is a placeholder (Hu & Hernández-Avila)

### ***Vitamin E***

Supplementation with vitamin E has also been shown to reduce markers of oxidative stress in the liver, brain, and testes of treated rats **Hsu, Ping-Chi 2002**.

### ***Multiple vitamins, minerals***

Supplementation with other antioxidants such as vitamin B6 and beta-carotene seem to be less well studied. **Hsu, Ping-Chi 2002** makes reference to an article with an antioxidant cocktail to lead workers. **Need to get this article. Machartova, V., Racek, J., Kohout, J., Senft, V., Trefil, L., 2000. Effect of antioxidant therapy on indicators of free radical activity in workers at risk of lead exposure. Vnitřní Lekarství 46, 444 /446**

### ***Zinc***

Zinc does not seem to have antioxidant action but competes with lead for uptake in the gut and other organs. Supplementation in rat studies thought to reduce markers of oxidative stress by reducing uptake of lead. **Hsu, Ping-Chi 2002**. Cross sectional study in children showed lower levels of zinc associated with higher levels of lead. **Osman 1998**

### ***Selenium***

One cross sectional study shows that lower levels of selenium associated with increased lead levels **Osman 1998**. Selenium has not been studied alone but in combination with other antioxidants has been found to reduce markers of antioxidative stress in animal studies **Hsu, Ping-Chi 2002**. It may be that supplementation with multiple micronutrients might be more effective than any one single agent.

## **Micronutrients and Lead - Summary of Literature**

- 1) Both animal and human studies have found an association between micronutrients and BLLs (**Lee, Mi-Gyung 2005, Hsu 2002, animal studies, add others**) .
- 2) Some micronutrients are thought to play a role in reducing oxidative damage induced by lead. Others are thought to compete with lead for binding sites thereby minimizing initial uptake through the gut and subsequent uptake into various organs (**Hsu, Ping-Chi 2002**) .
- 3) Both human and animal studies have demonstrated an inverse association between BLLs and various micronutrients(**Lee, Mi-Gyung 2005, Hsu 2002**). In a cross-sectional study of over 3700 reproductive aged women with a baseline BLL of 1.78  $\mu\text{g/dL}$  geometric mean, lead levels were higher in the presence of lower thiamine intake, serum ascorbic acid, and serum folate levels (**Lee, Mi-Gyung 2005**). Other cross-sectional studies have also found an inverse relationship between BLLs and serum ascorbic acid (**West 1994, Simon and Hudes, 1999**).
- 4) Most, but not all (**Lee, Mi-Gyung 2005**), studies have found that higher calcium( **Schell, Hernandez-Avila (preg women) 1997, Hernandez-Avila 1997 lactating women, West 1994, Johnson**) and iron intake (**Simon and Hades 1999 think this is trend only**)

though)(Schell L Maternal blood lead concentration get from disc) or serum iron (Wright 1999) is associated with lower BLL. However, supplementation with Fe thought only to be of benefit if iron deficient. Children with iron deficiency anemia who also had lead poisoning had improved Bayley scores after iron supplementation although some evidence that iron inhibited lead excretion. (literature review)

- 5) **Thought here....Need advice....**Need to look carefully at how measure micronutrients in the literature (serum vs. dietary). Intake data in one of the largest studies in humans (Lee 2005) contradicts other smaller studies which show that intake of key micronutrients is associated with lower BLLs. However dietary intake data is hard to quantify well and this larger study estimates that approximately 29% of diets were underreported and many of those for which data was available did not meet RDAs. It may be that serum markers are a more accurate marker of intake than dietary variables. But not sure if this is true???
- 6) Increasing the intake of key nutrients either by improving diet or adding supplements has been suggested as a way to prevent lead poisoning and to improve outcomes in those who already have a high lead burden, either by “chelating” lead, by reducing lead-related oxidative damage, or reducing absorption. Supplementation with antioxidants such as vitamin C, vitamin E, and selenium, may prevent lead-induced oxidative damage due to lead exposure and bolster the anti-oxidant defense system. Supplementation with calcium, zinc, or iron may minimize absorption from the gut or uptake into organs.

### **Problems with the research**

- What is best way to determine adequate intake: Dietary vs serum markers
- What is considered to be adequate and how is this determined
- Nutrient levels that seem to lower BLLs higher than those usually recommended, what is the safety if exceed AIs?

### **Recommendations**

- Diets/supplements at least meet the AI of key nutrients, in particular since many pregnant women seem to be deficient in many nutrients.
- Vitamins of particular concern are vitamin C, iron and calcium. Maybe B vitamins as well?

### **Future Research Needed**

- Randomized large clinical trials!!!
- Need trials on supplements alone, enhanced dietary intake, and combination of diet and supplements.
- Impact on BLLs in pregnancy, postpartum in both lactating and non-lactating women.
- Is there evidence of more lead flux postpartum than in pregnancy? If so, should supplementation/dietary intake be higher in the first six months postpartum than during the pregnancy?
- Basic nutrition research: determination of AIs, most reliable way to measure intake, what outcome measures of concern, usually use BLLs, but is that the way to go?
- Do recommendations change according to body burden of lead and/or during chelation?

# **INDICATIONS, CONTRAINDICATIONS, AND ADVERSE EFFECTS OF CHELATION ON PREGNANT WOMAN, FETUS, AND NEONATE**

## **The role of chelation therapy for lead poisoning during pregnancy**

1. Definition of chelation
2. Drugs available in US
3. Utility of these drugs in other populations
4. Concerns about chelation during pregnancy
5. Evidence in pregnancy and in the neonate
6. Summary and recommendations

### **1. An overview of chelation:**

Chelation is defined as “the bond formation between a metal ion and two or more polar groupings of a single molecule” (Stedman’s Medical Dictionary). Notice that this definition does not indicate the fate of the chelated metal. Possibilities include excretion of the chelate, persistence in the tissue where the bonding occurred or redistribution to other tissues. Ideally, the drug should effectively increase Pb excretion, be easily administered, be affordable and be safe. The consequences of Pb removal should be to halt further toxicity and to reverse previous Pb effects (Markowitz, Pediatrics in Review, 2000).

### **2. Drugs available in the US**

There are 4 drugs in use for Pb chelation in the US and others are in use elsewhere. These are  $\text{CaNa}_2\text{EDTA}$ , BAL, DMSA, and PCA. None of these drugs specifically bind only Pb; their toxicity profiles differ (Table 1). Two are administered orally (DMSA, PCA) and two must be given parenterally (BAL im only;  $\text{CaNa}_2\text{EDTA}$  im or iv). The latter two require expert nursing care and are always used in the hospital. The former two are used in both in- and out-patient settings.

All of these drugs increase Pb excretion, primarily through the kidneys (Graziano, Aposhian). There may also be tissue redistribution during or as a consequence of chelation. The current regimen for the drugs BAL and  $\text{CaNa}_2\text{EDTA}$  in the treatment of high BPb levels begins with BAL treatment shortly before the first dose of  $\text{CaNa}_2\text{EDTA}$ . This developed in response to the following observation: symptomatic children treated with  $\text{CaNa}_2\text{EDTA}$  alone sometimes deteriorated clinically with a worsening of their Pb induced encephalopathy. The introduction of BAL with  $\text{CaNa}_2\text{EDTA}$  appeared to lower the risk of this complication of chelation treatment and was attributed to the prevention of Pb flux into brain that could occur during  $\text{CaNa}_2\text{EDTA}$  treatment alone (Chisolm, J. Pediatrics 1968). There are no clinical studies to test this hypothesis in humans. However, in animal models, some but not all studies indicate that this drug,  $\text{CaNa}_2\text{EDTA}$ , is associated with either a failure to decrease brain Pb levels or to temporarily increase those levels during treatment.

The introduction of chelating agents for the treatment of severe lead poisoning, BPb >70 ug/dL, was associated with a marked decline in lead related mortality in children, from 30% to <1% (Piomelli in Pediatrics text, Chisolm 1968). Chelation treatment at lower BPb levels, where mortality is not a major concern, is associated with a fall in BPb levels and an improvement in biochemical markers of Pb toxicity such as erythrocyte protoporphyrin (EP) levels and delta-

amino levulinic acid dehydratase (ALAD) activity (Piomelli, Graziano). Depending on the amount of Pb in the body prior to chelation, the effect of treatment on BPb is generally temporary, with levels increasing within 2 weeks after the conclusion of a course of treatment in many patients. The effect on the biochemical markers of toxicity is disparate: ALAD activity declines as BPb rebounds whereas EP levels tend to fall if no further Pb absorption occurs despite the rebound in BPb.

All of the drugs increase the excretion of essential metals, but to differing degrees. DMSA appears to be the most specific for binding heavy metals such as Pb and Hg. The excessive loss of essential metals has been postulated to account for the observed teratogenicity associated with all the agents in animal studies.

### **3. Utility of these drugs in other populations**

Candidates for chelation therapy differ by age group. Previous CDC guidelines established a BPb level of  $\geq 45$  ug/dL as the indication for treatment of children regardless of symptoms (1991). At these levels, biochemical toxicity is demonstrable in the majority of children (elevated EP level, decreased ALAD activity); sub-clinically, cognitive scores are likely lower and gastrointestinal symptoms may occur in a substantial plurality. Additionally and of importance, such children are very likely to excrete large amounts of Pb in response to chelation treatment; much greater amounts than they would spontaneously excrete over periods of time comparable to a course of chelation. Though symptoms and biochemical markers of toxicity may improve post chelation there is no documentation of cognitive improvements in nonencephalopathic children.

Under BPb levels of 45 ug/dL chelation treatment can also lower BPb levels and improve biochemical markers of toxicity temporarily. However, there is no evidence that Pb excretion is substantially increased for the majority of children.

There are no published guidelines identifying a specific BPb level as requiring chelation therapy in adults. Nor is there a universal protocol for which agents to use, dose or duration of treatment.

### **4. Concerns about chelation during pregnancy**

Consideration of chelation therapy during pregnancy must first identify the targeted beneficiary. If it is the fetus, can the risks and benefits of treatment of lead poisoned children be extrapolated? If so, then a BPb  $\geq 45$  in the mother's blood would trigger treatment, since the correlation between maternal and newborn BPb levels is very high as indicated by cord and maternal BPb levels determined at delivery. If it is the adult childbearer, then the selection for treatment by BPb level in the absence of symptoms is not defined.

There are a number of concerns regarding the use of chelating agents in pregnant women besides selection of candidates. Are the drugs teratogenic? How is the drug to be delivered, i.e., can administration of drug to the woman benefit both her and her fetus or does the fetus require its own separate drug administration? Does maternal treatment remove Pb from her and concomitantly from her fetus or does it deliver more Pb to the fetus. Do the drugs cross the placenta and return with Pb or does the chelate simply remain. Does treatment result in redistribution of Pb within the fetus? Does chelation improve the clinical and/or biochemical toxic effects of Pb for either mother or fetus?

In summary, the following questions need to be addressed:

Who should be treated and when?

What drug(s) can be used?

What regimen for treatment should be followed, i.e., dose and duration?

Are they effective at removing Pb from the dyad?

Is there improved health as a consequence of treatment?

What toxicities may occur? For the host? For the fetus?

## 5. Evidence in pregnancy and in the neonate

The clinical data to address these questions are minimal. The literature identified to date includes case reports about 7 women (Table 2). The women were selected for chelation based on their BPb levels with the lowest level pretreatment reported as 44 ug/dL although in that case a prior BPb of 62 ug/dL was found. All appeared to be treated during the second half of pregnancy. All but 1 were treated with varying amounts and for varying durations with CaNa<sub>2</sub>EDTA. A single patient also received BAL in addition to CaNa<sub>2</sub>EDTA. A single case reported the exclusive use of DMSA.

In all cases, CaNa<sub>2</sub>EDTA therapy was associated with a decline in maternal BPb levels. There was no change in maternal BPb after the one case of treatment with DMSA (18 day course). However, she was treated as outpatient without apparent oversight for either compliance or ongoing exposure. In all but one case, when reported, a healthy newborn was delivered. The exception occurred in a case where maternal BPb pretreatment was 104 ug/dL. She received CaNa<sub>2</sub>EDTA and BAL. The 1.6 kg infant was born prematurely after antepartum hemorrhage 36 hours into treatment. This baby was later noted to have developmental delay and hearing deficit.

No consistent pattern in cord BPb levels was apparent in the few cases where they were reported. The interval between chelation and delivery also varied from months to minutes. Cord BPb levels were higher than maternal BPb in the case treated with DMSA and in that of the sick premature infant described. In the other cases cord BPb levels were lower than maternal pre-chelation levels.

In several reports, chelation treatment was not initiated until shortly before or soon after delivery and was directed towards the neonate. Various drugs at full dosages have been used singly or in combination: CaNa<sub>2</sub>EDTA alone, CaNa<sub>2</sub>EDTA and BAL, CaNa<sub>2</sub>EDTA and DMSA, and DMSA alone. In general chelation was well tolerated by the infants.

A non chelation strategy to lower the neonate's BPb level was described in several other case reports. Exchange transfusion successfully lowered neonatal BPb from 100 to 28 ug/dL. On day 2 the infant was chelated with a combination of BAL and CaNa<sub>2</sub>EDTA for 5 days at the end of which the BPb was 37 ug/dL. Chelation was continued for 19 days with DMSA at the end of which the infant's BPb was 38 ug/dL. Both the exchange and chelation treatments were described as "well tolerated" (Mycyk, Ann Pharmacother 2004). Of particular interest in this case is that maternal BPb at preconception was 117 ug/dL and declined to 72 ug/dL by the third trimester. The mother was not chelated during her pregnancy. The baby was delivered at 40 weeks and weighed 3.7 kg and achieved normal developmental milestones at 1 month of age..

## 6. Summary and conclusions

A list of questions was developed in section 4. Limited information is available to address them:

*Who should be treated and when?* Pb poisoning may be life threatening at levels greater than 100 ug/dL though many cases have been described where patients with such levels were asymptomatic. Encephalopathic pregnant women should be chelated regardless of trimester. In all other cases chelation should be delayed until the completion of organogenesis. Since a level  $\geq 45$  ug/dL is the indication for chelation in children and the fetus is apparently also susceptible to Pb effects, then chelation should be considered for women in the second half of pregnancy with a BPb  $\geq 45$  ug/dL.

*What drug(s) can be used?* Three of the four available chelating agents have been used during pregnancy. Data for penicillamine are unavailable.

*What regimen for treatment should be followed, i.e., dose and duration?* The most experience, little as it is, has been with CaNa<sub>2</sub>EDTA. This drug may be used intravenously at regular doses for 5 days. It appears to be safe for mother and fetus.

*Are they effective at removing Pb from the dyad?* Maternal BPb levels decline after a course of chelation. In general, neonatal BPbs at birth are also lower than peak maternal levels during the pregnancy. Measures of bone Pb are unavailable.

*Is there improved health as a consequence of treatment?* Very limited information is available to determine if any long term benefit is derived from in utero treatment. In the few case reports babies appeared to be normal developmentally when tested 1 month to 4 years of age. There are no long term outcome studies of the effects of chelation on the mothers.

*What toxicities may occur? For the host? For the fetus?* No chelation attributable toxicities have been reported.

In all situations, given the lack of controlled studies and the paucity of even published case reports or series chelation should only be undertaken with advice from experts in this field.

Table 1.

Name	Synonym	Dose	Toxicity
Succimer	Chemet, DMSA	350 mg/m <sup>2</sup> /dose q 8 hrs for 5 days; then q 12 hrs for 14 days; oral	GI distress, rashes; elevated LFTs, depressed WBCs
Edetate	CaNa <sub>2</sub> EDTA, versenate	1000-1500 mg/m <sup>2</sup> /day; iv infusion- continuous or intermittent; im divided q 6 or q 12 hrs. For 5 days	Proteinuria, pyuria, rising BUN/Creatinine- all rare Hypercalcemia if too rapid an infusion. Tissue inflammation if infusion infiltrates
BAL	dimercaprol, British AntiLewisite	300-500 mg/m <sup>2</sup> /day; <b>im</b> only divided q 4 hrs. For 3-5 days. Only for BLL $\geq$ 70.	GI distress, altered mentation; elevated LFTs, hemolysis if G6PD deficiency; no concomitant iron Rx
D-Pen	Penicillamine	10 mg/kg/d for 2 weeks increasing to 25-40 mg/kg/d; oral, divided q 12 hrs. For 12-20 weeks	Rashes, fever; blood dyscrasias, elevated LFTs, proteinuria. Allergic cross-reactivity with penicillin.

Table 2. Case Reports of Chelation during Pregnancy

Study	location	population	study type	biological measure/ Rx	outcome	chronic vs acute	sample size	Pb level	Pb results	clinical outcome
Ausgezeichnete wirksamkeit .. Abendroth K 1971; Dtsch.Ges.wesen26:2130	Germany	pregnant woman 5th mo	case report	BPb 80 ug/dL; Rx EDTA .5 g/day iv 3x/wk wkly;4wks	Decline in BPb-->30 ug/dL	acute	1	80	healthy baby at 4 years	healthy baby at 4 years
Lead Poisoning During Pregnancy. Angle CR AJDC 1964	Nebraska	pregnant woman 8th mo	case report	BPb 240 ug/dL; Rx EDTA 75 mg/kg/d for 7d	at delivery 4 wks post Rx: urinary copropor. negative in mother and baby	chronic	1 ??		healthy baby at 4 years	healthy baby at 4 years
Congenital lead intoxication. Timpo A. JPeds 1979	New York	pregnant woman 8th mo	case report	BPb 86 ug/dL; amniotic fluid Pb; Rx EDTA 1g bid for 3 days; BPb-->41 2d postRx	at delivery 8 days post RX: gestation, nl ht wt; cord Pb 60-->72 at 2 wks	chronic	1	86		healthy at 18 months of age
Lead poisoning and chelation in a mother-neonate pair. Horowitz B. Clinical Toxicology 2001	Oregon	pregnant woman 6th mo	case report	BPb 44 ug/dL; Rx DMSA 30mg/kg for 5d & 20 mg/kg for 13d with no change in Pb (44)	term healthy infant with cord Pb 126 ug/dL	chronic	1	62		healthy term newborn
Lead opisoning in late pregnancy due to maternal pica. Olmedo RE. Clinical Toxicology 1999,	New York	pregnant woman 32 wk	case report	BPb 130 ug/dl; Rx EDTA 1g/d;baby delivered after 2 d	healthy premie with cord Pb 78 ug/dl	acute	1	130		healthy premie
Severe congenital lead poisoning in a preterm infant due to a herbal remedy. Tait P., MJA 2002	Australia	pregnant woman 30 wk	case report	BPb 104 ug/Dl; Rx EDTA/BAL; baby delivered 36 hr later after antepartum hemorrhage at 30 wks gestation	sick flaccid premie; cord BPb 152 ug/dL when maternal BPb 46	chronic	1	104		dev. Delay unilateral deafness
Lead poisoning among pregnant women in NY City: Risk factors and screening practices. Klitzman S., JUrbanHealth 2002. NY City		pregnant women	case series	BPb: 2 women with >45: 53,130. Both Rx EDTA, the last with DMSA added after 2d and delivery of neonate	all infants survived; BPb declined 53-->20 1 month later at delivery (not reported in article-per.comm)	first chronic; last case acute with EP initially 25 ug/dL		case of BPb 130 same as Olmeda during pregnancy	2 above	healthy newborns

## **Interventions: Pica**

Pica has been practiced by peoples worldwide for medicinal, religious, and cultural reasons since antiquity (Hunter, Abrahams 1996). However, while Western medicine has viewed pica as aberrant and unhealthy behavior, it was widely accepted by the Greeks and Romans and used to treat various medical conditions. Its use has been condoned by Catholic sects in Central America where clay tablets inscribed with Christian scenes have been sold for consumption for centuries. These clay tablets, known as Tierra Santa, are blessed before sale and are available throughout Mexico and Central America. They are thought to have health giving properties. Clay tablets are also sold throughout parts of Africa. While pica appears to be declining in the United States, it is still a common practice in many parts of the world, particularly in Africa, Asia, and Central America. In the United States, it appears to more frequently occur in sections of the South and in immigrant communities. Prevalence rates have been reported to be as high as 50% to 74% in parts of Africa (Nichito 2004, Sule 2001), 23% to 44% in Latin America (Lopez 2004), 34% in Mexican-born women living in California (Simpson 2000), and 14% (Simulian) to 38% (Corbett 2003) in low-income rural African-American women.

### ***1. What is the health impact of pica behavior?***

Materials ingested as pica can be benign or potentially harmful and include ice, paper, dirt, clay, starch, ashes, and small stones as well as substances contaminated with lead or other toxic substances.. For example, cases of lead poisoning have been reported after the consumption of lead glazed pottery and lead contaminated soil. See the work of Subgroup 1 for further details.

What impact the consumption of non-toxic pica substances has on an individual's health is controversial. Pica has been theorized to promote health by helping to detoxify food, to provide extra minerals to nutrient-poor diets, to relieve common early pregnancy symptoms such as nausea, and to protect the fetus by coating the maternal GI tract, thereby minimizing absorption of teratogens. However, pica could also jeopardize health by causing nutritional deficiencies, blockages in the GI tract, and poisoning if ingested materials contain toxic materials such as lead. Descriptive studies have found associations between nutritional deficiencies and pica. Several reported lower serum ferritin levels (Edwards 1994, Geissler 1998), lower Hemoglobin or Hematocrit levels (Corbet 2003, Edwards 1994, Rainville 1998, Geissler 1998), or higher rates of anemia (Kettaneh 2005) in those who engage in pica, while others have found no health affects from pica (Smulian 1995). In one of the largest descriptive cohort study which included 553 African American women, Edwards (1994) found that dietary intake of iron and calcium tended to be lower in those women who practiced pica and that serum ferritin and vitamin B 12 levels were significantly lower in pica than non-pica women. Infants born to pica mothers had smaller head circumference ( $p=0.003$ ) despite no differences in gestational age, birth weight, or birth length between pica and non-pica groups. In general, however, these studies had small sample sizes, ranging from 125 (Simulian 1995, Corbett 2003) to 150 (Kattaneh) to 225 (Simpson 2000).

### ***2. What interventions have been shown to help reduce or eliminate pica behavior?***

Little is known about antecedents leading to pica behavior. Women report that they consume pica items because they like the taste, smell, and feel of the substance; to feel better and soothe minor complaints such as stomach upset, to promote health; or as part of established

religious and cultural practices. See Appendix 1 for a description of commonly ingested pica substances. Most studies reported in the literature are case reports, although a few descriptive studies are available. Most of these studies lack information on the cultural context in which pica occurs and the health outcomes expected by those who engage in pica. However, in a meta-analysis of 13 studies published between 1950 and 1987, Horner (1991) estimates that the risk of pica doubles in pregnancy if pica is practiced by other family members and is increased six-fold if the woman had a pre-pregnancy history of pica.

Many studies agree that pica is likely to be underreported. Individuals who engage in pica may view it as normal, and therefore not worthy of reporting to a health care provider, or as an important, but misunderstood and undervalued, health promoting behavior. Because pica is viewed negatively by the Western medical community, individuals who engage in pica may be reluctant to disclose that they consume non-food items if asked directly about the practice.

No clinical studies have been conducted on the best way to identify pica, which is a critical first step that must be achieved before any intervention can be carried out. Therefore, identifying pica in a clinical setting may best be accomplished using a similar approach found to be effective in identifying other sensitive issues: proceeding from general to more specific questions, from less intrusive to more intrusive questions. In the case of pica, a more productive clinical approach is likely to be one that initially focuses on the strategies women use to cope with discomforts of pregnancy. Pica has been commonly reported to be used in pregnancy to help relieve abdominal pain, diarrhea, and nausea; to assuage cravings and to improve appetite; and to impart a sense of well-being. Obstetrical providers need to ask women specifically about these symptoms and the techniques women are using to minimize them.

Obstetrical providers also need to inquire about cravings. Ice pica is particularly common and is often accompanied by pica to other less benign substances. Therefore inquiring first about general cravings in pregnancy, then about specific cravings for ice, and finally cravings for other less commonly ingested non-food items may be more likely to uncover pica behavior. Follow-up questions inquiring about the ingestion of other substances commonly used by members of a woman's community may also help elicit a history of pica. Other factors that may influence whether women are comfortable disclosing pica use include being able to converse in their native language, to be able to discuss the practice in private, and to be questioned about the practice in an accepting manner by someone from their own community (Simpson 2000).

Once pica is identified, other information is needed in order to understand the cultural context in which pica occurs and to determine whether the practice poses any health concerns. The health impact will vary depending on the specific substance consumed: whether it is contaminated with heavy metals, microbes, or other noxious substances, the dose received; and when pica occurred during the course of pregnancy. Equally important, is to understand the context in which pica occurs: what is the expected outcome, who recommends its use, how the substance is obtained, and whether any other family members also ingest the substance. A better understanding of the cultural milieu in which pica occurs can be used to develop more effective approaches in identifying, as well as modifying or eliminating, the practice if the substance consumed poses health risks. See Appendix 1 for an outline of a suggested standardized history.

Only a few studies are available which evaluate the effectiveness of interventions designed to reduce or eliminate pica behavior; none of these include pregnant women. Most of these studies evaluated the impact of interventions on pica behavior in developmentally-delayed individuals or those with Obsessive-Compulsive Disorders (Piazza 1998, Goh 1999, McAdam

2004). Effective strategies for these individuals involve evaluating the meaning and context of the behavior for a specific individual, modifying the social environment accordingly and substituting more acceptable materials for the original pica item. The most effective substitutions seem to be those which continue to provide oral stimulation and mimic the texture of the original pica item. The impact of social interactions on the amount of pica behavior varied by individual; in some the same type of interaction reduced pica behavior, but had no effect in others. These studies underscore the importance of developing strategies that consider the social context of pica behavior for individuals, as well as specific characteristics of the substance that is consumed.

Other studies have attempted to reduce pica behavior by providing vitamin supplements and improving the quality of the diet. While this approach appears to be effective in some case reports (Pace 2000, Bugle 1993), a randomized, double blind, placebo-controlled study found that micronutrient supplementation did not affect geophagy in 220 school-aged children in Zambia (Nchito 2004). Geophagy was common in this population; 74% of children enrolled in this study reported consuming dirt daily. Clays sold in the market (brown and white) were consumed by all children who practiced geophagy. Other sources included dirt from termite mounds, “grey dirt”, and dirt from plastering of the house. Children who practiced geophagy were more likely to have relatives who also consumed dirt (79% vs. 1.9%,  $p < 0.001$ ). Children reported that they consumed dirt because they liked the taste (88%) or because it relieved nausea and vomiting (8%) or hunger (2.6%). Children were randomized into four treatment groups who received different supplements: iron, placebo iron, multivitamins, or placebo multivitamin. No differences were found after 10 months of follow-up in the prevalence of geophagy or in the amount of earth consumed. The authors conclude that the results of their study support that premise that geophagy is a learned activity and that nutritional deficiencies associated with geophagy are more likely to be a result, not a cause, of this practice.

### **Summary of the Evidence**

Pica appears to be relatively uncommon in the general population in the United States but has been reported to have a prevalence rate of 30% to 75% in certain subpopulations. However, studies indicate that women are reluctant to disclose pica behavior making prevalence data unreliable. Even less is known about the cultural context or meaning that pica may hold for pregnant women. Pica behavior clearly poses health dangers if the materials consumed contain lead or other toxic substances. Whether the consumption of non-toxic substances has a significant health impact is controversial. Cross-sectional studies have found an association between pica and nutritional deficiencies such as anemia and low intake of key nutrients such as calcium, iron, and vitamin B. Nutritional deficiencies are thought to enhance the absorption of lead and raise blood lead levels and have been theorized to cause cravings and lead to pica behavior. The limited research that is available to date seems to indicate that pica is learned behavior and not a result of nutritional deficiency. Therefore, correcting nutritional deficiencies is unlikely to reduce pica behavior, but it may optimize fetal and maternal health by limiting exposure to lead if absorption is reduced with supplementation, as well as by providing essential nutrients to the pregnant woman. Further studies are needed to confirm these relationships. Additional research is also needed on how to more effectively identify, and eliminate, pica of toxin containing substances. Since pica behavior differs within subpopulations a better understanding of the cultural context in which pica occurs is critical in developing effective interventions.

## RECOMMENDATIONS

### 1) *Strategies to Identify and Evaluate the Health Impact of Pica*

- A. A standardized data collection tool on pica needs to be developed. Identification of pica behavior is difficult because pica is relatively uncommon in the United States and individuals who engage in the practice may be reluctant to discuss it. The few studies that are available are small and use different definitions of key variables and outcome measures, making it difficult to draw any firm conclusions about the impact pica has on maternal and fetal health. Using a standardized format will make it easier to get a large enough sample size to adequately evaluate these concerns. This data collection tool needs to be comprehensive and include the items outlined in Appendix 1 and 2. Questionnaires already available in the literature, such as the one developed by Corbett, could be used as a model.
- B. A standardized questionnaire should be made widely available. The CDC should promote use of this data collection tool by all health departments and poison control centers during investigations of elevated lead levels. Health providers should be encouraged to use this tool in their own practices and to screen all pregnant women for pica, particularly those at higher risk. Women who live in immigrant communities or in rural areas of the South or who are of African descent are more likely to engage in pica. The presence of medical conditions, such as persistent anemia, nutritional deficiencies, or elevated lead levels, should raise the suspicion that pica may be present and prompt screening.
- C. In addition to the use of a standardized data collection tool, the CDC should recommend that micronutrient status and dietary quality be evaluated for individuals who engage in pica behavior. Studies suggest that the health consequences of pica might vary depending on what substance is consumed. Nutritional deficiencies are commonly associated with pica. Calcium, vitamin C, and iron deficiencies are thought to increase lead absorption. If these deficiencies are confirmed in larger better designed studies, pica may increase the risk of lead poisoning, not only by consumption of lead-contaminated substances, but by causing nutritional deficiencies which can increase absorption of lead from the environment or release from the bone.
- D. A national registry should be established in order to analyze this data looking for associations between specific substances and adverse outcomes as well as patterns and meaning of use by different cultural groups. As with other national registries case reports should be accepted from all sources: the general public, health care providers, health departments, and poison control centers.

Because pica is uncommon generally in the United States, is more prevalent in certain subgroups, and includes consumption of a wide range of substances, it is likely that only a co-coordinated national approach will result in enough data to be able to accurately evaluate the health impact of pica.

### 2) *Strategies Needed Reduce or Eliminate Pica*



		Benditos Cipula, Kipula, Akipula, Askipula	Belize  <b>North America</b> US	African- Americans  Immigrants	South, particularly rural areas
Ice/Refrige rator Frost		Relief thirst and cool down	US  Mexico	African- Americans	South
Argo Starch	Nausea and GI upset		US	African- Americans	South
Clay Pottery			Mexico		

<b>Appendix 2: Components of Pica History</b>	
Pica Behavior	Age at onset? Use affected by hormonal changes (menses, pregnancy, lactation) or stress? Substitution if usual pica substance not available?
Reason for Use	Reason(s) for use: treatment for specific symptom, general health, or spiritual or emotional well-being
Substance	What substance(s) consumed? Dose consumed (amount and frequency)? Where obtained? (Be as specific as possible in case a sample needs to be obtained for testing for contamination)
Community Context	Who else consumes substance in community (family, neighbors)? What quality(ies) about the substance is important? What problems are thought to be associated with its use?

Community	Race, ethnicity? Country and region of origin? Current community?
General Health	Underlying medical conditions?
Pregnancy	Substance consumed throughout pregnancy? Current Pregnancy: Gestational age at delivery, birth weight of child, preeclampsia, gestational diabetes Previous pregnancy history: spontaneous abortions, preterm births, low-birth weight or macrosomia
Demographics	Age

# **FREQUENCY OF FOLLOW-UP TESTING IN THE PREGNANT WOMAN, PRENATALLY-EXPOSED NEONATE, LACTATING MOTHER AND NURSING INFANT**

## **Introduction**

An important component of the management of lead exposed individuals is follow-up testing. This ensures that blood lead levels are declining once interventions, such as removal from the source of exposure, nutritional supplementation and, possibly, chelation take place. Measurement of BLLs is the main method of determining whether significant absorption of lead has occurred, how urgently intervention is needed, and how successful case management has been. When the patient's BLL does not fall within a reasonable amount of time, the cause of the failure must be determined. A continuing increase in the measured venous BLL during the follow-up period may indicate continuing or possibly increased exposure to lead and indicates a need for further environmental investigation. Potential causes of rising BLLs in pregnant women include the failure to address the source of the lead, inappropriate management of the lead source, continued use of lead contaminated products such as spices, foods, cosmetic or folk remedies that were not revealed during the initial investigation and the continued use of lead-glazed ceramics. Additionally, prevention of exposure to lead from occupational sources may not be adequate to maintain a BLL below the level of concern. Potential causes of rising BLLs in newborns and infants under the age of 6 months include environmental sources of lead exposure such as environmental contamination from deteriorating lead-based paint. Not enough is known about the behavior of lead in the body of a newborn exposed in-utero and may still be the primary source of lead in an infant with rising BLLs.

There is no clear formula to estimate the rate of decline of BLLs in exposed women or their offspring. Several factors play a role and include chronicity of the exposure, presence of physiological stressors affecting bone turnover rates, nutritional status and medical interventions. Chronic lead exposure results in increased soft and hard tissue accumulation. Lead that remains in the body accumulates mostly in bone. In adults, more than 90% of the lead found in the body is in the skeleton; in children, about 65% is found in the skeleton. The half-life in this compartment is measured in years to decades, unless there is a physiological stressor leading to an increase in bone turnover. The body's increased need for calcium during pregnancy and lactation is one example. Blood lead levels rise as bone stores are released. Once in the blood, the half-life of lead in adults is about 3 weeks. Little is known about the half-life of lead in the blood of pregnant women, lactating women and newborns.

Blood lead levels in pregnancy follow a "U" shaped curve. Three studies where measurements were made in all three trimesters for the same women in the cohort demonstrated a clear U-shaped curve, with a nadir at 20 weeks (Rothenberg et al., 1994; Hertz-Picciotto et al., 2000; Schell et al., 2000). The peak blood lead level appears to be at or near delivery. Assuming unchanging lead intake, the combination of hemodilution, increased weight of organs and enhanced metabolic activity could account for much of the observed decrease in whole blood lead between 12 and 20 weeks gestation. Accelerated absorption of dietary lead and decreased elimination of lead from the body, perhaps following the calcium conservation strategies of late pregnancy and release of bone lead may all operate to yield the observed pattern of lead during pregnancy. The type of bone resorption taking place may also play a role in these dynamics where only trabecular bone (presumably of low lead content) is resorbed in early pregnancy,

causing blood leads to fall more than expected from hemodilution alone. In late pregnancy, the sites of resorption move to cortical bone of higher lead content and blood leads rise (Manton et al., 2003). The implications for follow-up testing are two fold. Pregnant women who have an initial blood lead level in the first trimester that is greater than the level of concern may have a lower BLL on repeat testing regardless of interventions. This blood lead level may increase prior to delivery and may in fact be higher than the initial level. Additionally, the measured BLL of pregnant women in the 2<sup>nd</sup> and late 1<sup>st</sup> trimesters may be an underestimation of the actual body lead burden.

The literature estimates that umbilical cord BLLs are 80-90% of maternal BLL at the time of delivery (Gulson et al., 1997; Lagerkvist et al., 1996; Baghurst et al., 1992; Silbergeld EK, 1991). This is fairly consistent across studies. Therefore, the two levels are considered to be interchangeable for clinical management. Post-partum blood lead levels are expected to increase by 1 month after delivery (Rothenberg et al., 2000). This increase is thought to be greater in lactating women than in women who bottle feed their infants (Tellez-Rojo et al., 2002). This finding confirms earlier reports where blood lead levels rose significantly 6 months post-partum (Ernhart and Green, 1992). These findings illustrate the importance of understanding that a slight increase in blood lead level after delivery may not be associated with a new source of exposure. However, it is difficult from the literature to draw a conclusion about the magnitude of the change warranting concern. Based on the above cited studies the amount of the increase is probably no more than 2 or 3 µg/dL and may be slightly higher in breastfeeding women.

## **Follow-up Venous Blood Lead Testing**

Medical management includes follow-up blood lead testing. The tables below are to be used as guidance. Case managers and primary care providers should consider individual patient characteristics and caregiver capabilities and adjust the frequency of follow-up tests accordingly. These important factors include the initial BLL, the chronicity of exposure, risk factors for continued, repeat or future exposure, and types of clinical interventions. The frequency of follow-up blood lead testing of the neonate exposed in utero fills a gap left by the CDC recommendation for the follow-up testing of lead exposed children. All testing should be done in conjunction with anticipatory guidance, patient education and distribution of educational materials.

**Table 1: Frequency of Maternal BLL Follow-Up Testing**

<b>Initial Venous Blood Lead Level (µg/dL)</b>	<b>Perform a follow-up test:</b>
5-14	Once at least 30 days from the initial test to assess the trend, efficacy of education, investigation, and interventions. Repeat test only if the BLL is rising.
15-44	Within 2 weeks and then monthly to assess the efficacy of investigation and interventions. Obtain a BLL at delivery (maternal or UCLL).
≥45	Within 24 hours and then at frequent intervals depending on clinical interventions and trend in BLLs. Consultation with a clinician experienced in the management of pregnant women with BLLs in this range is strongly advised. Obtain a BLL at delivery (maternal or UCLL).

**Table 2: Follow-Up Blood Lead Testing of the Newborn (0-6 months of age) Exposed In Utero**

<b>Blood Lead Level<sup>a</sup> (µg/dL)</b>	<b>Initial Post-Partum Venous Blood Lead Testing in the Newborn</b>	<b>Frequency of Retesting Based on Initial Post-Partum BLL of the Newborn</b>
5-14	< 1 month	Every 3 months <sup>b</sup>
15-24	< 1 month	Every 1-3 months <sup>b</sup>
25-44	< 2 weeks	2 weeks – 1 month
>45	As soon as possible	Depends on Clinical Intervention <sup>c</sup>

- a. The initial blood level may be either a maternal BLL at the time of delivery or an umbilical cord BLL.
- b. Repeat blood lead testing at these BLLs is performed mainly to assess the trend. Once the BLL of the newborn is declining, repeat testing may be unnecessary.
- c. The frequency of retesting should be based on the clinical interventions performed in consultation with a specialist.