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CDC Lead and Pregnancy Work Group
Subgroup 2 – Maternal, Pregnancy, and Child Outcomes
LITERATURE REVIEW (Draft)
October 3, 2005
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This group would be asked to review literature including, but not limited to:

- Impact of lead exposure on –
    - fertility and reproductive system integrity (time-to-pregnancy, etc.)
    - maternal health (gestational hypertension)
    - pregnancy outcomes (early fetal loss – i.e. spontaneous abortion & stillbirth, preterm delivery, gestational age, birth weight, birth length, head circumference, congenital malformations)
    - infant growth and neurodevelopmental (cognitive, motor, behavioral) outcomes due to prenatal exposure

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

- At various blood lead levels, what guidance should medical providers be providing to
    - women of child-bearing age regarding delaying of pregnancy?
    - pregnant women about potential outcomes?

Introduction

The reproductive toxicity of high dose prenatal lead exposure has been recognized for over a century, being associated with reduced fertility, early fetal loss, and adverse postnatal outcomes (Rom, 1976). Early reports from the occupational health literature suggested that women employed in the lead industries become pregnant so that the miscarriage would rid them of their lead burden (reference needed). Several authors have since reported on the presence of lead in human fetal tissues (Kehoe et al., 1933; Thompsett and Anderson, 1935; Barltrop, 1969). Barltrop related findings in the mother to the cord blood lead concentration. Maternal blood lead concentration was highly correlated with umbilical cord lead suggesting the transplacental movement of lead to the fetus. In fact, lead crosses the placenta by passive diffusion and lead has been measured in the fetal brain as early as the end of the first trimester (13 weeks)(Goyer, 1990). The role of fetal lead exposures in producing less severe adverse outcomes has been investigated since the 1980's (Bellinger, 1994). There is some evidence that maternal physiologic parameters in pregnancy can be modulated by low levels of lead exposure (Takser, et al., 2005; Tellez-Rojo, et al., 2004; Tabacova, et al. 1994). In addition, prenatal lead exposure has known influences on maternal and infant birth and neurodevelopmental outcomes (Bellinger, 2005).

Add paragraph covering human epidemiologic studies and biological plausibility.
*Note: Need to consider biological markers of dose/exposure measures used in studies:

- Paternal blood lead level, semen lead level (pre-conception)
- Maternal blood lead level (pre-conception)
- Maternal blood lead during pregnancy or at delivery (represents maternal & fetal exposure)
- Umbilical cord blood lead at delivery (represents fetal exposure)
- Placental lead
- Maternal bone lead levels (represents cumulative maternal lifetime exposures)

- Area Under the Curve (AUC) blood lead versus time (estimates lifetime exposure)
- History of lead poisoning as a child (represents maternal exposure)

IMPACT OF LEAD EXPOSURE ON FERTILITY AND REPRODUCTIVE SYSTEM INTEGRITY

Maternal Exposure

Epidemiologic and experimental evidence suggest that lead is a potent reproductive toxicant, but relatively little is know about the biological mechanisms of effect. Lead may exert some of its reproductive effects through decreases in both maternal and paternal fertility and fecundity. For the purposes of this review, the focus will be on maternal exposures.

Reproductive System Integrity

Tang and Zhu (2003) conducted a retrospective analysis of occupationally-exposed women (N=57) and controls (N=62)(mean age 32, range 23-45 years) for a variety of reproductive factors including: menses, sexual libido, spontaneous abortion and delivery outcomes. Average lead exposure period was 7.4 years (range, 1-17 years). The incidence of prolonged (p=0.004) and abnormal (p=0.09) menstruations, polymenorrhea (p=0.004), and hypermenorrhea (p=0.03) was higher in the lead exposed group than in controls. Spontaneous abortion was reported by 6 exposed female workers and not in the control group (p = 0.01). The authors conclude that occupational lead exposure of female workers could lead to the impairment of the functions of reproductive system, however poor working conditions and workload could not be ruled out as responsible for the reproductive functional disorders in the subjects under study.

Selevan et al. (2003) conducted a cross-sectional analysis of blood lead and pubertal development in girls (females age 8-18 years) using data from the third National Health and Nutrition Examination Survey (NHANES III). Puberty was measured on the basis of the age at menarche and Tanner stage for pubic-hair and breast development. Blood lead concentrations of 3 µg/dl were associated with significant delays in breast and pubic-hair development suggesting that environmental lead exposure may alter growth and reproduction through endocrine disruption.

Time-to-Pregnancy

A retrospective time-to-pregnancy (TTP) study was conducted among women being biologically monitored for exposure to lead who were participants in a previous study on spontaneous abortion. They were classified into exposure categories on the basis of questionnaire information, and individual blood lead (BPb) measurements. The adjusted incidence density ratios (IDR) of clinically recognized pregnancies were 0.93 (95% CI 0.56-1.57) for very low (BPb < 0.5 mmol/L), 0.84 (95% CI 0.48-1.45) for low (BPb 0.5-0.9 mmol/L), and 0.80 (95% CI 0.42-1.54) for higher (BPb >= 1.0 mmol/L) exposure compared with no exposure, in the discrete proportional hazards analysis. Exposure to inorganic lead was not associated with fecundability at current, low-exposure levels. The suggestive finding among the eight most heavily exposed women (BPb 1.4-2.4 mmol/L, IDR 0.53; 95% CI 0.19-1.52) should be confirmed or refuted in a larger study (Sallmen et al. 1995).

Participants in a study of environmental lead exposure and reproductive health in Mexico City were followed to assess the relationship between the time required to become pregnant and lead exposure (Guerra-Tamayo, et al. 2003). Of the 142 women, 42 got pregnant: 34 before the first year of follow-up, and 8 at a later date. Survival analysis was performed and no differences were detected in blood lead levels (mean=9.3 μg/dl) and TTP in the first year. However, in women with blood lead levels above 10.0 μg/dl, the likelihood of not achieving pregnancy was five times higher (95% CI 0.05-0.56) after one year of follow-up compared to women with blood lead levels below 10.0 μg/dl.

Paternal Exposure

Inorganic lead may impair male fecundity and fertility through its action on the germinal epithelium, the endocrine system or both, but information on the potential impacts in exposed populations is limited. Reduced male fecundity, which is correlated with exposure to lead, may not necessarily result in reduced fertility. Several European countries are currently involved in studies to determine the impact on time-to-pregnancy and semen quality in lead-exposed populations (reference needed). The individual studies related to male fertility are beyod the scope of this review. Sallmen 2001 (Review paper) for discussion.

Summary of the Evidence: Fertility and Reproductive System Integrity

Although the evidence is limited it suggests that blood lead levels grater than 10 μg/dl may be associated with increase time to pregnancy.

IMPACT OF LEAD EXPOSURE ON MATERNAL HEALTH DURING PREGNANCY

There is some evidence that maternal physiologic parameters in pregnancy can be modulated by low levels of lead exposure (Takser, et al., 2005; Tellez-Rojo, et al., 2004; Tabacova, et al. 1994). However, the definitive relationship between lead exposure and maternal health outcomes in pregnancy is unclear. Lead has been linked to hypertension in non-pregnant adults. Hypertension is one of the most common complications of pregnancy. Lead may exert its effects through damage to the kidneys and/or vascular system. Therefore, the relationship between lead and maternal blood pressure is the most well-studied of the maternal health outcomes during pregnancy.

The most widely used classification of high blood pressure in pregnancy is that of The National High Blood Pressure Education Program Working Group, ("Working Group" 2000*). This classification distinguishes between hypertension arising during the pregnancy after 20 weeks (gestational hypertension, formerly known as gestational hypertension), and pre-existing hypertension (chronic hypertension). Hypertension in pregnancy is defined as a systolic blood pressure of 140 mmHg or higher or diastolic pressure of 90 mm Hg or higher that occurs after 20 weeks gestation in a woman with previously normal blood pressure. Preeclampsia, a pregnancy-specific disorder associated with increased maternal and perinatal morbidity and mortality, is defined as: (1) systolic blood pressure >=140 mmHg and/or diastolic blood pressure >=90 mmHg beginning after the 20th week of gestation and (2) proteinuria >=300 mg per 24 hours. Clinically, it is important to differentiate between non-proteinuric hypertension and hypertension

plus proteinuria (preeclampsia), as adverse clinical outcomes are more closely related to the latter.   Severe hypertension (usually defined as a systolic BP of $\geq$ 180 or diastolic BP of $\geq$ 110 mmHg, even in the absence of proteinuria, has been associated with adverse maternal and perinatal outcomes.

  *Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000;183:S1-S22

Gestational Hypertension

In an early study, Rabinowitz, et al. (1987) conducted a cross-sectional analysis of 3,851 women delivering at a Boston hospital from 1979-1981. Prevalence of hypertension, systolic blood pressure (SBP), and diastolic blood pressure (DBP) increased significantly across quartiles of umbilical cord blood lead. Pearson correlation coefficients (p-value) were: SBP=0.081 (0.0001) and DBP= 0.051 (0.0001). There was no association with preeclampsia observed.

In another cross-sectional analysis of third trimester primigravid women in Malta (N=143), investigators compared normotensive women to those with gestational hypertension, defined as two successive BP measurements 4 hours apart of >=140/90 (Magri, et al. 2003). Pearson correlation coefficients (p-value) controlling for age and body mass index (BMI) were: SBP=0.236 (0.025) and DBP= 0.221 (0.036). Cases had significantly higher blood lead levels when compared to normotensive controls (correcting for age and BMI).

Factor-Litvak, et al. (1993) found an increased risk of proteinuria measured by urine dipstick in a nested case-control study of a cohort of over 1500 women enrolled in Yugoslavia. Results relating to maternal blood pressure are not published in the peer-reviewed literature (Pamela Factor-Litvak, 1992 doctoral dissertation and published abstract unavailable).

In Eastern Poland, one study compared women living in villages with high soil lead concentrations to women in areas with elevated levels and found hypertension was more common (15 vs. 22%) and of higher magnitude (mean blood pressure 140 vs. 129 mmHg) in the study group than in the control women (Laudanski et al., 1991).

The prevalence of gestational hypertension has been shown to be increased even at blood lead levels lower than 5 μg/dl. Sowers et al. (2002) studied a cohort of 705 women aged 12-34 years who presented for prenatal care at one of three clinics in NJ with average blood lead in pregnancy equal to 1.2 μg/dl (SD=0.03). They found maternal blood lead significantly associated with pregnancy induced-hypertension (p=0.03) adjusting for age, calcium intake, and race/ethnicity. Blood lead levels increased in a linear fashion over time among women with gestational hypertension, whereas in normotensive women, blood lead levels fit a quadratic function over time.

Rothenberg, et al. (2002) reported on results of a prospective cohort study of 1,006 women age 16-44 enrolled during their third trimester of prenatal care in South Central Los Angeles. This study was unique in that it included measures of tibia and calcaneus bone lead, representative of chronic exposures, in addition to maternal blood lead levels. A previous report from this group (Rothenberg, et al. 1999) among 1,627 women found that blood lead was a statistically-significant predictor of maternal blood pressure only among immigrants in the study (GM blood lead=2.3 μg/dl) and not among non-immigrants (GM blood lead=1.9 μg/dl).

Hu & Hernandez-Avila (2002), in an editorial accompanying the Rotherberg et al. (2002) paper, suggest that bone lead may be a better biological marker of dose for studying such

outcomes, such as maternal blood pressure during pregnancy, which may be the result of long-term chronic exposures to lead.

Bogden, et al. (1995) studied the potential interactive effects of dietary calcium and lead exposure on maternal blood pressure and birth outcomes in pregnant rats. The results suggested that dietary calcium-lead interactions may not influence blood pressure until the third trimester and also suggested that lead exposure may contribute to gestational hypertension if the maternal diet is low in calcium.

A study was conducted among 110 non-occupationally-exposed women, ranging from 30-41 weeks gestation, in Tehran, Iran to assess the relationship between blood lead levels and gestational hypertension (Vigeh, et al. 2004). Fifty-five subjects were hypertensive and the other 55 subjects were age- and gravidity-matched normotensive controls. Blood lead levels, collected within 24 hr after delivery, were significantly higher among cases (range = 2.2-12.6 μg/dl) in comparison to controls (range = 1.9-10.6 μg/dl)(p=???). There were no significant differences in blood lead concentrations among hypertensive subjects with proteinuria (n = 30) and those without proteinuria (n = 25). **Need to get this paper**

 "Transient complications of pregnancy (anemia, toxemia, proteinuria, arterial hypertension and hyperemesis) were studied in pregnant women from the general population reporting to local hospitals. Comparison of blood lead levels (PbB) was made between women with normal pregnancies and those with complications. Significantly higher PbB were found in women with pregnancy complications as compared to those with normal pregnancies." (Kaul, et al. 2002) **Need to get this paper**

Preeclampsia

In a small study, Dawson, et al. (1999) measured lead in the amniotic fluid of women undergoing amniocentesis between 33 and 40 weeks of pregnancy. The authors compared amniotic fluid lead in normal (N=101) and preeclamptic (N=29) pregnancies and found significant differences in lead levels between the two groups (p<0.001). The results of this study should be interpreted with caution since there are no standardized protocols or quality control criteria for measuring lead in amniotic fluid. In addition, selection bias and confounding cannot be ruled out in this study due to the high-risk nature of pregnancies undergoing amniocentesis. In another small study (N=44) conducted in a high-risk pregnancy clinic, Dawson, et al. (2000) observed significant differences between normotensive and preeclamptic pregnancies with respect to red blood cell lead content. They found maternal blood pressure to be directly proportional to RBC lead content. Again, the selection criteria and study population in this small, high-risk population are not well-defined, so selection bias and confounding cannot be ruled out.

Vigeh, et al. (2005) surveyed 433 postpartum volunteers (85% of women delivering at two hospitals) in Tehran, Iran and 396 met inclusion criteria for the study. Umbilical cord blood samples collected in metal-free tubes at delivery and maternal whole blood samples were collected within 24 hours of delivery. Samples were frozen and later analyzed for lead concentration. Thirty-one subjects (7.8%) were diagnosed with preeclampsia and concentrations of umbilical cord lead (p<0.05) and umbilical cord to maternal blood lead ratios (p<0.01) were significantly higher compared to non-preeclamptic control subjects. In a multivariate logistic

regression analysis, the odds ratio for umbilical cord lead was 12.96 (95% CI 1.570-107.025, p=0.017).

Other Related Studies of Lead and Blood Pressure (Non-pregnancy)

Hertz-Picciotto and Croft (1993) reviewed the epidemiologic literature on lead and blood pressure in general populations and occupational cohorts. They found that, overall, the evidence was suggestive of a small dose-response through the range of blood lead levels up to 30-40 μg/dl, however, most of the studies were conducted in males. Nomiyama, et al. (2002) conducted a cross-sectional survey of women factory workers in Beijing, China who were either lead-exposed (mean blood lead=55.42, range 22-99 μg/dl) or unexposed (mean blood lead=6.42, range 4-11 μg/dl) at work. Among the 193 women, blood lead was the strongest (and statistically significant) predictor of both systolic and diastolic blood pressure. Using nationally-representative data from the National Health and Nutrition Examination Study (NHANES-III) Nash, et al. (2003) found blood lead level to be positively associated with both systolic and diastolic blood pressures and risk of both systolic and diastolic hypertension among women aged 40 to 59 years. The relationships between blood lead and hypertension were most pronounced in postmenopausal women. In a case-control study, Korrick et al. (1999) found that patella lead (but not tibia or blood lead) was associated an increased risk of hypertension in middle-aged women supporting the evidence that low-level, chronic exposures to lead may be an important risk factor for hypertension in non-occupationally exposed women.

Summary of the Evidence: Maternal Health Outcomes

Severe gestational hypertension (define) and pre-ecclampsia have been clearly associated with adverse maternal and peri-natal outcomes. Lead exposure has been associated with increased risk of gestational hypertension but the magnitude of the effect, the exposure level at which risk begins to increase, and whether risk is most associated with acute or cumulative exposure, remain uncertain. It is unclear whether lead-induced increases in blood pressure during pregnancy leads to severe hypertension, preeclampsia, or eclampsia. However, even mild gestational hypertension can be expected to lead to increased maternal and fetal surveillance, medical interventions, and additional health care costs.

IMPACT OF LEAD EXPOSURE ON PREGNANCY OUTCOMES

Early Fetal Loss (Spontaneous Abortion) and Stillbirth

One way lead may exert its effects on the developing fetus is by precipitating early fetal loss. Data linking lead and adverse pregnancy outcomes dates back to 1860 when Paul published a report on a case series of 25 women with a history of occupational exposures (or whose husbands had occupational exposures to lead). Among the five women who had previous pregnancies, there were 36 subsequent pregnancies with 83% of those ending in spontaneous abortion or stillbirth. Legge (1901) published data from a report of factory inspectors in England showing that of the 212 pregnancies (among 77 women employed in the lead industry), 52% ended in spontaneous abortion or stillbirth. More recently, Nordstrom et al. (1978) reported on the increased frequency of spontaneous abortions from occupational and environmental risks in and around a smelter in northern Sweden. Hu (1991) provides interesting data on the

pregnancies of women who had experienced lead poisoning as children and were later identified from hospital records and interviewed regarding their pregnancy histories. The hypothesis, as proposed by Silbergeld (1991), was that previously-accumulated maternal bone lead burdens would be mobilized during pregnancy and that concurrent exposures alone were not sufficient when studying lead toxicity in states of increased bone mobilization, such as pregnancy. In a matched case-control study, the proportion of pregnancies ending in spontaneous abortion or stillbirth was 22% (11/51) among cases with matched controls, 29% (8/28) among cases with no matches, and 13% among the controls (6/48).

Hertz-Picciotto (2000) reviewed seven studies of lead and spontaneous abortion in populations with low-to-moderate levels of exposure and found that the studies suffered from a variety of methodologic issues, including: small sample sizes, problems with definition or ascertainment of outcome and exposure assessment, and lack of control for confounding. Another study that was conducted to address the limitations of previous studies, and in which Hertz-Picciotto was involved, was also reviewed (Borja-Aburto et al. 1999). All but one (Lindbohm, et al. 1991) of the studies reviewed focused on maternal environmental or occupational exposures to lead. Three studies evaluated women surrounding active smelter sites or industrial pollution (McMichael et al 1986; Murphy et al 1990; Tabacova & Balabaeva, 1993); three studies evaluated occupational exposures (Taskinen et al., 1988; Lindbohm, et al. 1991; Driscoll et al., 1998) and two focused on general environmental exposures (Laudanski et al. 1991; Borja-Aburto et al. 1999).

McMichael et al. (1986) reported on spontaneous abortions within an ongoing prospective cohort study and found no significant differences in blood lead between women who had a miscarriage and those whose pregnancies survived. However, there were only a small number of cases, women from the "non-exposed" community were not included, and timing of lead measurements differed between cases and controls. Murphy et al. (1990) conducted a retrospective assessment among pregnant women with a second pregnancy in a smelting and a control community using ecologic measures of exposure based on self-report of residence in same home since first pregnancy. No significant differences were found in BLLs of women with spontaneous abortion versus women with surviving pregnancies in the exposed community. Retrospective assessment of pregnancy history and exposure, based on soil lead concentrations, was used by Laudanski et al. (1991). The "exposed" group had a lower risk of spontaneous abortion, but there was no adjustment for confounding in this study. In addition, the "unexposed" group had a higher proportion of employment in agriculture which may have lead to substantial exposure misclassification. Taskinen et al. (1988) used a nested case-control design focusing on maternal exposures (Lindbohn, et al,, 1991 conducted a similar study in the same population focusing on paternal exposures). They linked registry data in Finland to questionnaire and biological monitoring data and found no significant associations between blood lead level and spontaneous abortion. However, there was evidence of a dose-response gradient (not statistically significant) although few women had high exposures and some were not monitored for lead. A study conducted in several smelting and petrochemical communities in Bulgaria reports significantly higher levels of blood lead in women with complicated pregnancies; however, the endpoints of these pregnancies are not explicitly defined (Tabacova & Balabaeva, 1993). The only U.S. study involved the retrospective ascertainment by self-report on mailed questionnaires to women employed by the U.S. Forest Service who work may have involved the use of lead-based paints for marking trees (Driscoll et al., 1998). This study employed multivariate adjustment for potential confounders and used generalized estimating

equations to adjust for repeated measures (multiple pregnancies) among subjects. Although the study found increased risks of abortion related to lead paint use, there are several other potentially-hazardous chemical solvents in these paints which would lead to uncontrolled confounding in this study. Given the methodological limitations, these studies provide little evidence of the link between low-to-moderate levels of maternal lead exposure and increased risk of spontaneous abortion.

However, one study of spontaneous abortion addresses some of the limitations of previous studies and provides evidence that increases in blood lead may pose an increased risk even at low levels of environmental exposures. In a prospective study in Mexico City (Borja-Aburto et al. 1999), 668 women in their first trimester of medically-confirmed pregnancy were enrolled and followed biweekly. This study, which is the only study specifically designed to identify spontaneous abortions by HCG, used a nested case-control design with incidence density matching on gestational age at entry into the cohort. This provided for comparable opportunity between the cases and their matched controls to experience the outcome (spontaneous abortion). A dose-response relationship between blood lead and risk of spontaneous abortion was observed (p for trend=0.03): odds ratios for spontaneous abortion comparing 5-9, 10-14, and > or =15 microg/dL with the referent category of <5 microg/dL of blood lead were 2.3, 5.4, and 12.2, respectively. For every 5 µg/dL increase in blood lead, the odds ratio for spontaneous abortion was 1.8 (95% CI 1.1-3.1).

Spontaneous Abortion (Paternal Exposure)

Using data from national databases, Lindbohm et al. (1991a) studied paternal occupational exposures and risk of spontaneous abortions in 99,186 pregnancies in Finland. In 10% of the pregnancies, the husband was exposed to one or more of the mutagens, and the rate of spontaneous abortion was unaffected (OR = 1.0), however, rates of spontaneous abortion were higher among wives of rubber products workers than among unexposed men. A case-control study was then conducted to determine if occupational exposure of men to inorganic lead was related to spontaneous abortion in their wives (Lindbohm, et al. 1991b). The results did not show a statistically significant relationship between spontaneous abortion and paternal lead exposure (PbB greater than or equal to 1.5 mmol/l {31.25 µg/dl}) among all the study subjects, however, a significant increase was observed in the risk of those women whose husbands had been monitored during or close to the time of spermatogenesis. The association between lead exposure and spontaneous abortion was also modified by maternal age and paternal alcohol use.

Preterm Delivery/Gestational Age and Birth Weight

Andrews et al. (1994) reviewed the epidemiologic literature on prenatal lead exposure in relation to gestational age and birth weight. The twenty-five studies included in that review (Rajegowda, 1972; Gershanik, 1974; Fahim, 1976; Clark, 1977; Wibberley, 1977; Bogden, 1978; Buchet, 1978; Nordstrom, 1979; Huel, 1981; Angell & Lavery, 1982; Moore, 1982; Needleman, 1984; Ernhart 1986; Graziano, 1986; McMichael, 1986; Dietrich, 1987; Ward, 1987; Moore, 1988; Bornschein, 1988; Cooney, 1989; Wang, 1989; Baghurst, 1991; Bellinger, 1991, Factor-Litvak, 1991; Satin, 1991) will not all be reviewed in detail here. It is important to note that these studies differed with respect to study design, geographic location, sample size, and degree of control for confounding. However, based on these twenty-five studies, the authors concluded that prenatal lead exposure appears to increase the risk of preterm delivery and reduced birth

weight. The association between prenatal lead and gestational age, a possible confounder of the lead-birthweight relationship, was unclear. Lead did not appear to be related to premature rupture of the membranes. Studies conducted after the Andrews, et al. review are discussed below.

Preterm Delivery/Gestational Age

Fagher et al. (1993) evaluated the effect of lead in blood, myometrium, and placenta among 30 Swedish and Polish women on preterm delivery (<37 weeks gestation) and noted no significant differences in lead levels between subjects who delivered preterm or at full term. However, among women with preterm delivery (N=17) there was a significant correlation between concentrations of lead in maternal peripheral venous blood and pregnancy week at delivery (r=0.6, p<0.01). Falcon, et al. (2003) studied placental lead in relation to premature rupture of membranes (PROM) and preterm birth among 89 mother-infant pairs in Spain. They found a negative correlation between placental lead and gestational age (r= -0.324, p=0.002). Below 120 ng/g (ppb) of lead, only 8.8% of deliveries had an adverse outcome (1 premature birth, 4 PROM), while at higher levels 40.6% experienced abnormal pregnancy outcomes (9 premature births, 4 PROM)(p=0.0001).

West, et al. (1994) observed inverse correlations of maternal blood lead with gestational age (r= -0.29, p=0.004) and Ponderal Index (r= -0.29, p=0.004), but no association with birth weight (r= -0.03, NS). A case-cohort study was conducted to determine the risk of preterm birth in relation to umbilical cord lead levels among women in Mexico City (Torres-Sanchez, et al. 1999). After adjusting for other known risk factors for preterm birth, the frequency of preterm birth was almost three times higher among women with umbilical cord lead >=5.1 µg/dl in comparison to women with cord blood lead <5.1 µg/dl. This effect was only observed among primiparous women that could suggest that mobilization of cumulative maternal lifetime bone lead stores may be more important in the first pregnancy than during subsequent ones.

Birth Weight

A cross-sectional study of 50 consecutive deliveries from six different locations in Russian and Norwegian arctic and sub-arctic areas and birth outcomes was conducted by Odland, et al. (1999). In a multivariate linear regression model, maternal blood lead was a negative predictor of birth weight (p<0.05) and child's body mass index (BMIC) (p<0.05), with or without adjustment for gestational age. Further analyses revealed several significant relationships between lead biomarkers: cord and maternal blood lead (p < 0.001); placental and maternal blood lead (p < 0.001); placental and cord-blood lead (p < 0.001). Placental lead was also a negative predictor of birth weight (p<0.05) and child's body mass index (BMIC) (p<0.05)(Odland 2004). In a another small study, blood lead levels (mean 9.91; range 2.28-36.35 µg/dL) were measured in 73 pregnant women at the time of delivery in Pakistan and no association with gestational age, birth weight, recumbent length, or head circumference was observed (Rahman, et al. 2003).

In an analysis of maternal blood and bone lead as determinants of infant birth weight, it was found that increased lead in tibia (cortical) bone was associated with a significant decrease in birth weight (González-Cossío et al., 1997). Birth weight decreased 73 grams for each 10 microgram increase in lead per gram of bone mineral (p=0.03). The decline in birth weight was nonlinear and accelerated at the highest levels of bone lead. Patella lead was also inversely related to birth weight, but this association was not significant (-27 grams per 10 µg/g increase in bone lead, p=0.1).

"Transient complications of pregnancy (anemia, toxemia, proteinuria, arterial hypertension and hyperemesis) were studied in pregnant women from the general population reporting to local hospitals. Comparison of blood lead levels (PbB) was made between women with normal pregnancies and those with complications. Significantly higher PbB were found in women with pregnancy complications as compared to those with normal pregnancies. Increments in the PbB levels were accompanied by statistically significant decrements in neonate birthweights. Complications of pregnancy may be induced by higher PbB and may also compound the adverse effects of decrements of neonate birthweights." (Kaul, et al. 2002) **Need to get this paper**

Birth Length/Head Circumference

Rothenberg et al. (1999) examined the association between maternal lead during pregnancy and infant head circumference at age 6 months. They found that head circumference at 6 months of age, but not at birth or later ages, was inversely related to maternal lead at 36 weeks gestation (p=0.0004) and that maternal lead at delivery was inversely related to head circumference at 18 months of age. They suggested that this provides evidence for lead effects on critical periods of development and "latency" of the manifestation of the effect. The authors also suggest that lead exposure may interfere with the timing or magnitude of episodic growth

Hernandez-Avila et al. (2002) evaluated the effects of maternal bone lead on infant anthropometry at birth and observed an increased risk of lower-than-normal-birth-length score with increasing tibia lead levels (OR=1.03 95%CI 1.01, 1.06). When comparing women in the highest quintile of tibia lead to those in the rest of the sample, there was a 79% increase in risk of having a lower birth length score (OR=1.79 95%CI 1.01, 3.22). This effect was independent of umbilical cord or maternal blood lead levels and remained significant after control for birth weight. Maternal patella lead was associated with lower head circumference score (OR=1.02 95%CI 1.01, 1.04). When comparing women in the highest quintile of patella lead to those in the rest of the sample, there was more than a two-fold increase in risk of lower head circumference score (OR=2.13 95%CI 1.14, 3.97). Since bone lead is a measure of cumulative exposure, bone lead measurements obtained at one-month postpartum were supposed to be representative of maternal bone lead during pregnancy.

Congenital Malformations

Needleman et al. (1984) obtained umbilical cord blood lead levels from 5,183 consecutive deliveries of at least 20 weeks' gestation at a Boston hospital and evaluated the association with congenital anomalies. A dose-response relationship was observed for lead and minor congenital anomalies (**Need to get paper** - insert results here).

An ecological study of environmental lead exposure and neural tube defects was carried out in Lancashire, England (Bound et al. 1997) using cases obtained through a prospective survey of major congenital malformations between 1957 and 1981. Mothers living in wards (districts) with a higher proportion of houses with greater than 10 μg/L (ppb) lead in water had a greater risk of having a baby with a neural tube defect (difference in deviance=8.08, p=0.004). When this was controlled for "deprivation" score (an index of socioeconomic status for the district) the effect was attenuated but remained marginally significant (difference in deviance=3.09, p=0.079). These effects can be expressed such that a relative risk of a neural tube defect (compared with a normal birth) increases by about 25% for each 10% increase in the number of houses with tap water levels >10 μg/L. The results of this study should be interpreted

with caution due to the lack of individual level exposure data and information on potential confounders.

Jackson et al (2004) investigated the association between parental lead exposure and total anomalous pulmonary venous return (TAPVR) which is a congenital malformation of the cardiovascular system. They conducted a case-control study and found that paternal exposure during the six months prior to conception was associated with an increased odds of the outcome (OR=1.83 95% CI 1.00-3.42) and maternal exposure during the three months prior to conception through the 1st trimester of pregnancy was also associated with an increased odds of the outcome (OR=1.57 95%CI 0.64-3.47).

Porter et al. (2004) reported on a case study of a 31-year old, primiparous women who had sustained a gunshot wound 15 years earlier and had a retained bullet lodged in her lumbar spine. The fetus showed multiple abnormalities on routine ultrasound at 21 weeks gestation (maternal blood lead level=31 μg/dl) and was born with a number of birth defects involving the heart, lungs, and brain. The infant's blood lead level was 36 μg/dl at age 4 months and the maternal blood lead levels rose to 75-85 μg/dl by 4-5 months postpartum.

Several studies investigated whether paternal occupational lead exposure was associated with congenital malformations (Sallmen et al. 1992; Kristensen et al. 1993; Alexander et al. (1996). Irgens et al. (1998) examined both maternal and paternal occupational lead exposure and reproductive outcome for all births in Norway between 1970-1973. Infants born to mothers with prenatal occupational exposure had an increased risk of neural tube defects (RR=2.87 95% CI 1.05-6.38) and low birth weight (RR=1.34 95% CI 1.12-1.60).

Summary of the Evidence: Pregnancy Outcomes

Lead has been shown to be associated with spontaneous abortion and still birth at levels of exposure associated with clinical lead poisoning. The relationship between lower level exposures and pregnancy loss is less certain. A recent well designed study demonstrated a clear association between lead exposure at levels as low as 5 – 9 μg/dl and spontaneous abortion using elevation in HCG to define pregnancy.

Prenatal lead exposure appears to increase the risk of reduced birth weight. The association between prenatal lead and gestational age, a possible confounder of the lead-birthweight relationship, is unclear. Studies that accounted for gestational age suggest that the mechanism may be due to decreased fetal growth and may primarily reflect the impact of chronic as opposed to acute maternal exposure. There is limited and inconsistent evidence on the effect of lead exposure on HC, birth length, and congenital malformations. Lead may be related to preterm birth, but does not appear to be related to premature rupture of the membranes. The available data is inadequate to establish the presence or absence of an association between maternal lead exposure and major congenital anomalies in the fetus.

IMPACT OF LEAD EXPOSURE ON INFANT GROWTH AND NEURODEVELOPMENT

Infant Growth

In a companion study among the same cohort, investigators determined that maternal bone lead levels were also negatively associated with infant attained weight at one month of age and to postnatal weight gain from birth to one month (Sanin et al., 2001). The findings on lead biomarkers in relation to velocity of infant growth also showed that maternal bone lead predicted

decreased rate of weight gain between birth and one month of age (Peterson, et al. *In preparation,* 2005).

Shukla, et al. (1989) investigated the effects of prenatal (maternal) and postnatal lead exposure on infant growth and found that linear growth rates were negatively related to infant postnatal blood lead, however, this relationship was observed only among those infants whose mothers had prenatal lead levels above the median value (7.7 µg/dl) for the cohort. Infants who experienced a blood lead increase of 10 µg/dl between 3 and 15 months of age, born to a mother with prenatal blood lead concentration greater than 7.7 µg/dl, were about 2 cm shorter at 15 months of age (p=0.01).

Greene and Ernhart (1991) evaluated the effects of prenatal and postnatal lead exposure on infant weight, stature (length), and head circumference at various developmental stages. This study was designed to study fetal alcohol syndrome and not specifically to examine the effects of prenatal lead exposure. They used an average value of maternal blood lead and umbilical cord lead at delivery to represent prenatal exposure. Prenatal lead (estimates represent changes for each µg/dl increase in prenatal lead) was negatively associated with birth weight (B= -0.69), birth length (B= -4.88) and head circumference (B= -0.03). Although none of these associations were statistically significant, the study may have been underpowered to detect differences of the magnitude reported. They observed a marginally significant (p=0.06) positive effect of prenatal lead on the rate of standardized growth (1.85% of one SD per year to each additional µg/dl lead) which could be consistent with an adverse effect of prenatal lead on birthweight if the later growth represents "catch-up" growth from a lead-suppressed weight at birth.

Lead and Neurodevelopment

Lead has been recognized as a potent neurotoxin for centuries (Lin-Fu, 1985). Neurotoxic effects of lead have been observed during episodes of acute poisoning in both children and adults. Byers and Lord (1943) reported poorer school performance, decreased attention, restlessness and distractibility among children previously treated for lead poisoning. During the past twenty years there have been significant advances in the understanding of the absorption, distribution, retention, and toxic effects of lead (NRC, 1993 – check for newer reference). It is unclear whether prenatal or postnatal lead exposure is more detrimental to neurodevelopment. A number of chemicals, including lead, have been shown, in experimental models as well as in humans, to cause morphological changes in the developing nervous system (Costa et al., 2004). Little is known about the direct contribution of endogenous exposures to the toxic effects of lead but given the incomplete blood-brain barrier in their developing nervous systems, children may be more susceptible to insults during the prenatal and early postnatal periods (Rodier, 1995; Bearer, 1995; Weiss and Landrigan, 2000). In addition, there is a need to better elucidate whether the effects from postnatal exposure to lead are a continuum of the effects from *in utero* exposure (Goyer. 1996).

Lead and Brain Development

Evidence is growing from animal research indicating that the central nervous system is the most vulnerable of all body systems to developmental chemical injury (Rodier, 2004), with vulnerabilities that pertain to processes critical to neurodevelopment, such as the establishment of neuron numbers; migration of neurons; establishment of synaptic connections,

neurotransmitter activity, receptor numbers; and deposition of myelin. Neurons are formed even before the neural tube closes. Most cerebral neurons form during the second trimester of gestation and migrate to their adult location well before birth (Goldstein, 1990). Neuronal connections, however, are sparse at birth when compared to adulthood. During the first 24 months of life, a progressive increase in synaptic density and cerebral metabolic rate occur with measures exceeding twice those of the normal adult by age three years.   Proliferation of synaptic connections (synaptogenesis) during the developmental period is critical for the formation of basic circuitry of the nervous system (Rodier, 1995). Synaptic "pruning" during early child development establishes the final number of necessary neurons.   Lead is known to interfere with the process of synaptogenesis (Goldstein, 1992). The fluid environment of the nervous system is maintained under strict control by the blood-brain barrier which is created by the endothelial cells and their tight junctions (Goldstein, 1990). The development of this barrier function is a gradual process beginning *in utero* and continuing through the first year of life (Goldstein, 1990). Exposure to lead may actually change the microenvironment of the brain thus disrupting the blood-brain barrier. Lead appears to be preferentially accumulated by endothelial cells in the brain, however it is the interaction between the endothelial cells and astrocytes that is suspected to influence the toxic action of lead (Goldstein, 1990).

Lead and Biochemical Alterations

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 functions pharmacologically by interfering with synaptic mechanisms of neurotransmitter release. Lead can substitute for calcium (Ca^{2+}) and zinc (Zn^{2+}) as a second messenger in ion-dependent events at synapse. Lead is also responsible for the observed impairment of various neurotransmitter systems (e.g. cholinergic, dopaminergic, noradrenergic, GABergic) and activation of protein kinase C (a structural component of blood-brain barrier). Peripheral neuropathy, segmental demyelination and possibly axonal degeneration (Schwann cell degeneration), and slowing of nerve conduction with predominant involvement of motor neurons have been associated with lead exposure (Feldman, 1999). Animal research suggests that chronic exposure to lead by neuronal cells leads to cellular loss in the absence of gross pathological changes.

Experimental Evidence for Neurodevelopmental Effects of Lead

Much of the knowledge about lead neurotoxicity is based on animal studies and a substantial amount of has focused on neurochemical changes in animals. Specifically, research has focused on NMDA receptors, dopaminergic receptors, neurotransmitter release, and disruptions in the blood- brain barrier (Goldstein, 1990; Bressler and Goldstein, 1991; Cory-Slechta, 1995). Work by numerous investigators has demonstrated that lead disrupts neurotransmitter release and calcium dependent neurotransmission (Guilarte et al., 1994; Cory-Slechta, 1997). The effect of lead on dopamine systems is consistent with an impaired regulation of dopamine synthesis and lead may act as a dopamine agonist (Cory-Slechta, 1995). Some investigators have hypothesized that these disturbances in neurotransmitter release cause disruptions in the normal organization of synaptic connections (Bressler and Goldstein, 1991). By interacting with calcium dependent enzymes, lead will stimulate spontaneous neurotransmitter release (Goldstein, 1993). Lead will also inhibit neuronal calcium ion channels thereby inhibiting depolarization-evoked neurotransmitter release (Minnema et al., 1988). 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). Lead-exposed animals exhibit impairment on a wide variety of tasks designed to assess learning and memory. Animal experiments have uncovered similar deficits as those observed in lead-exposed children: increased distractibility, decreased attention span, impulsive behaviors, and robust deficits in learned skills (Rice, 1993). Lead research using animal models has revealed lead-induced impairment at increasingly lower doses on a wide range of neurobehavioral tasks (Rice, 1996).

Epidemiologic Evidence for Neurodevelopmental Effects of Lead

In an early study, Bellinger et al. (1987) showed that umbilical cord blood lead levels exceeding 10 µg/dL were associated with delays in early cognitive development through 24 months of age. These delays were largely overcome if postnatal exposures to lead were low in the preschool years, but appeared to be more persistent among children whose postnatal blood lead levels remained greater than 10 µg/dL (Bellinger et al., 1990). Although a few investigators did not find similar findings (McMichael et al., 1988; Cooney et al., 1989), the findings of other prospective lead studies were consistent with Bellinger et al. (Dietrich et al., 1987; Ernhart et al., 1987; Wasserman et al., 1997). Dietrich et al. (1987) reported that lead-related reductions in birthweight and gestation may be partially responsible for neurobehavioral deficits observed in early infancy. Results from Dietrich et al. (1991) have been interpreted to suggest that *in utero* lead exposure results in more persistent deficits in behavior than does postnatal exposure. In a recent example, among children living near a lead smelter in Kosovo, IQ scores at age 8 were inversely associated with a composite index of prenatal lead exposure (average of mothers' blood lead levels at mid-pregnancy and at delivery), an association independent of changes in postnatal blood lead levels (Wasserman et al., 2000).

In Mexico City, Gomaa et al. (2002) found that umbilical cord blood lead (mean of 6.7 µg/dL, range 1.2 to 21.6) and maternal bone lead levels were each independently associated with covariate-adjusted scores at 2 years of age on the Mental Development Index (MDI) score of the Bayley Scales of Infant Development with no evidence of a threshold effect when cord blood lead levels were less than 10 µg/dL. Infants of mothers from the highest quartile of bone lead had lower scores, after adjusting for umbilical cord blood lead, maternal IQ, gestational age, gender and birth weight (*p*=0.07). Infants of mothers with patella lead levels in the lowest quartile had a mean MDI score that was 5.4, 7.2, and 6.5 points higher than the mean scores of children in the second, third, and fourth quartiles, respectively. This study provides evidence that maternal bone lead levels have toxic *in utero* effects and that mobilized bone lead stores pose a significant threat to fetal development in a way that is not adequately reflected by measuring blood lead levels. The findings of this study suggest that cord blood and bone lead levels provide complementary rather than redundant information about fetal lead exposure.

Shen et al. (1998) classified 133 infants in Shanghai into two groups based on umbilical cord blood lead levels, which ranged from 1.6 to 17.5 µg/dL: <30th percentile or >70th percentile. The geometric mean level in the entire sample of 348 was 9.2 µg/dL. At 3, 6, and 12 months of age, the infants in the high exposure group had significantly lower covariate-adjusted scores on the Mental Development Index of the Bayley Scales, with the differences ranging from 3.4 to 6.3 points. Both of these studies therefore extend the findings of the earlier prospective studies.

Tang et al. (1999) studied a group of 244 infants who had been exposed to low levels of lead in utero (mean umbilical cord blood lead level: 3.9 µg/dL, 5th-95th percentile: 2.5-7.5). At 9-months of age, infants were administered the Brunet-Lezine Scales, which yield a global score

as well as scores on posture, coordination, language, and sociability. To explore potential neurochemical mechanisms of lead toxicity, two monoamine metabolites were measured in cord plasma, homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA). Only the sociability score was significantly associated, in an inverse direction, with cord blood lead level. The association remained statistically significant if 5-HIAA concentration was controlled by means of partial correlation, but it did not if HVA concentration was controlled. The investigators speculated that HVA, and thus the dopaminergic system rather than the serotonergic system, mediated the association between lead and sociability.

Emory et al. (2003) administered the Fagan Test of Infant Intelligence, a recognition memory paradigm, to 79 of the infants at age 7 months. As with the neonatal assessments, the investigators chose to include only a subset of the infants in the analyses they reported. They created a 2 X 2 contingency table to which 24 of the 79 infants contributed data (Fagan Test low risk: >85th percentile; Fagan Test high risk: <15th percentile; high prenatal lead: 4th quartile; low prenatal lead (1st, 2nd, and 3rd quartiles) as measured by maternal blood lead levels (when?). The chi square statistic was statistically significant, although the difference between the mean blood lead levels of the high- and low-performing infants on the Fagan Test was very small (0.44 versus 0.94 µg/dL).

Rothenberg et al. (1989) showed that third trimester increases in maternal blood lead levels were associated with decreased ability of Mexican newborns to self-quiet and be consoled during the first 30 days of life. They also found that low-level prenatal and perinatal lead exposure altered brainstem auditory evoked responses suggesting that brain structures involved in spatial localization of sound may be compromised by prenatal lead exposure (Rothenberg et al., 1994; 2000). In a cohort of disadvantaged urban children, multivariate analyses revealed no statistically significant relationship of either prenatal or early preschool blood lead with measures of language development (Ernhart and Greene 1990). However, this study was originally designed to study fetal alcohol syndrome and not designed to look at the association between prenatal lead exposure and child development.

Prenatal Lead Exposure and Behavioral Outcomes

Bellinger et al. (1994) studied the association between early lead exposure and later behavior problems in a cohort of children born during a 12-month period at one hospital. Umbilical cord blood lead (mean = 6.8 micrograms/dl, SD = 3.1) was not associated with the overall prevalence or nature of problem behaviors. Significant associations were observed between lead in shed deciduous teeth (mean = 3.4 micrograms/g, SD = 2.4) and increases in both internalizing and externalizing behavior scores in school-age children as measured by ratings on the Teacher Report Form of the Child Behavior Profile.

Emory et al. (1999) evaluated the association between blood lead levels, measured at 6 to 7 months of gestation and at delivery, and scores on the Neonatal Behavior Assessment Scale (NBAS), administered at 1 to 2 days of age, in 103 African-American neonates. The findings were weak and equivocal. No associations were found when conventional methods of clustering NBAS items were applied. In secondary analyses involving only 40 of the children, the investigators compared the scores of neonates in the lowest ($\leq$1 µg/dL; mean 0.86) and highest blood lead quartiles ($\geq$2.5 µg/dL; mean 4.0) on individual NBAS items that were considered, on the basis of previous studies, most likely to be related to lead exposure: attention, motor function, and social interaction. Applying 1-tailed tests of significance without adjustment for potential

confounding, the investigators reported group differences, favoring the lowest quartile group, on 4 of the 9 items evaluated. Trends in the same direction were found for the other items.

In the Cincinnati prospective study cohort, the frequencies of self-reported delinquent and anti-social behaviors were significantly associated with both prenatal and early postnatal blood lead levels (Dietrich et al., 2001). Among 195 inner-city 15-17 year olds in Cincinnati, maternal blood lead level in the first trimester, which ranged from 1 to approximately 30 µg/dL, was inversely related to children's scores on tests of attention and visuoconstruction (Ris et al., 2004) and to the frequency of self-reported delinquent behaviors (Dietrich et al., 2001).

In these preliminary analyses of 252 children in Mexico City (LaMadrid et al., in preparation), maternal bone lead concentration predicted poorer scores on behavior at 24 months of age, measured by scores on the Behavior Rating Scale of the Bayley Scales of Infant Development (BSID-II), as they pertain to adaptation (p= 0.05); attention to tasks (p=0.22); frenetic movement (p=0.02), hyperactivity (p=0.02), tremulousness (p=0.02), and soothability when upset (p=0.06).

Threshold Levels and Persistence of Effects

There is apparently no threshold for lead effect suggesting that any exposure may be harmful to the central nervous system (Schwartz et al., 1988; Schwartz, 1993). Recent evidence suggests that *postnatal* blood lead levels less than 10 µg/dL are associated with enduring adverse neurodevelopment (Lanphear et al., 2000; Canfield et al., 2003; Bellinger and Needleman, 2003; Chiodo et al., 2004). Using data from the Third National Health and Nutrition Examination Survey (NHANES III), Lanphear and colleagues (2000) reported 0.7-, 1-, 0.1-, 0.5- point decrements in mean arithmetic, reading, nonverbal reasoning, and short-term memory scores, respectively, among 4,853 children ages 6-16 years.

When estimated in a nonlinear model of 172 children, IQ scores at five years of age declined by 7.4 points as lifetime average blood lead concentrations increased from 1 to 10 microg per deciliter (Canfield et al. 2003). In the subsample of 101 children whose maximal lead concentrations remained below 10 µg/dl, the change in IQ associated with a given change in lead concentration was greater when compared to children whose lead concentrations surpassed 10 µg/dl. Bellinger and Needleman (2003) reanalyzed data from a prospective cohort study, focusing on 48 children whose blood lead levels never exceeded 10 µg/dl and found that IQ at 120 months was inversely related to the lead level at 24 months (p=0.03). Nonlinear models suggested that the inverse association persisted at blood lead levels below 5 µg/dl and the blood lead coefficient (−1.56) was greater than that derived from analyses including children with peak levels above 10 µg/dl (−0.58). Both studies suggest that the inverse slope between lead and cognition might be greater at lower blood lead levels than at higher blood lead levels. In a sample of 246 African American, inner-city children assessed at 7.5 years of age, neurobehavioral deficits in relation to low levels of lead (<10 µg/dl) were reported in the areas of: intelligence, reaction time, visual-motor integration, fine motor skills, attention, including executive function, off-task behaviors, and teacher-reported withdrawn behaviors (Chiodo et al., 2004). Lanphear et al. (2005) examined data collected from 1,333 children who participated in seven international population-based longitudinal cohort studies, followed from birth or infancy until 5-10 years of age with full-scale IQ score as the primary outcome measure. The lead-associated intellectual deficit, for a given increase in blood lead, among children with a maximal blood lead level < 7.5 µg/dL was significantly greater than that observed for those with a maximal blood lead level > or = 7.5 µg/dL (p = 0.015).

It remains unclear whether or not these effects are reversible. One study compared amount decline in BLL with cognitive performance and found that deficits associated with early childhood exposure to lead appear to be only partially reversible (Tong et al., 1998; Burns et al., 1999). The effectiveness of chelating agents in reversing or modifying the adverse neurobehavioral effects of lead is also unlikely. Although chelating agents have been shown to decrease blood lead levels, treatment with succimer lowered blood lead levels but did not improve scores on tests of cognition, behavior, or neuropsychological function in children with blood lead levels below 45 µg/dL (Rogan et al., 2001). At 36 months of follow-up, the mean IQ score of children given succimer was one point lower than that of children given placebo and the behavior of children given succimer was slightly worse as rated by a parent. However, the children given succimer scored slightly better, though not statistically significant, on the developmental neuropsychological assessment. When assessed after school entry at age 7 years, chelation therapy was not associated with neurodevelopmental benefits in these children (Dietrich et al., 2004).

Other Related Studies

Hu (1991) reported that women with a history of lead poisoning during childhood were three times as likely to report having a child with a learning disability when compared to women with no history of lead poisoning (matched by age and neighborhood). In addition, these women suffered lasting residual cognitive deficits 50 years after lead poisoning during childhood when compared with their matched controls (White et al., 1993).

Twin pairs age 6-15 years, discordant on blood lead levels (difference > 20 µg/dL), were tested for neuropsychological performance. High-lead twins exhibited reduced proficiency on reversal learning tasks (Evans et al., 1994) suggesting that social environment alone does not explain lead's effects on the central nervous system.

Opler, et al. (2004) investigated prenatal lead exposure and schizophrenia in a cohort of live births collected prospectively from 1959-1967 in Alameda County, California as part of the Kaiser-Prenatal Determinants of Schizophrenia Study. The study used delta-aminolevulinic acid (δ-ALA), measured in 2nd trimester maternal serum samples, as an indirect biologic marker of lead exposure. The adjusted odds ratio for schizophrenia spectrum disorder associated with higher δ-ALA was 2.43 (95% CI 0.99-5.96) suggesting that effects of prenatal lead exposure may extend into later life.

Summary of the Evidence: Infant Growth and Neurodevelopment

The findings of recent cohort studies suggest that even with maternal blood lead levels below 10 µg/dl, prenatal exposure to lead is inversely related to neurobehavioral development with an effect that is independent to that of postnatal exposure. These results are consistent with earlier studies in terms of the effect sizes, however, additional research and replication of these findings is needed to clarify their importance. While the lead-associated differences in test score are small when viewed as a potential change in an individual child's score, they acquire substantially greater importance when viewed as a shift in the mean score within a population (Bellinger, 2004). The mechanism(s) by which low-level lead exposure, whether incurred prenatally or postnatally, might adversely affect neurobehavioral development remains uncertain, although many hypotheses have been proposed (Lidsky and Schneider, 2003).