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The Evidence that Lead Increases the Risk for Spontaneous Abortion

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Background *Reports from a period spanning more than a century, and covering occupationally exposed women in several countries, support an increase in pregnancy loss from high maternal lead exposures. Nevertheless, most studies conducted among populations with low/moderate exposures have provided little evidence of an association with pregnancy loss, or in particular, spontaneous abortions.*
Methods *A critique of these low/moderate level studies reveals small sample sizes, problems in definition or ascertainment of outcome, lack of control for confounding, and/or deficiencies in the exposure assessment. For estimating exposure, either an ecologic measure was used, or individual biologic specimens were taken but attention was not paid to the timing of measurement of lead levels in these samples. A prospective study that overcame most of the deficiencies of previous studies enrolled pregnant women in Mexico City with low-to-moderate-level lead exposures, collected blood specimens during their first trimester, and ascertained spontaneous abortions by week 20. A key design element of this study was the use of incidence-density-matched controls in order to achieve comparable opportunity for the outcome and comparable timing of exposure measurements. The latter is especially important because blood lead levels are altered by pregnancy.*
Results *In the prospective Mexico City Study, a striking dose–response relation between blood lead and risk of spontaneous abortion was found: the odds ratio for spontaneous abortion was 1.8 (95% confidence interval = 1.1–3.1) for every 5 μg/dL increase in blood lead.*
Conclusions *Low-to-moderate lead exposures may increase the risk for spontaneous abortion at exposures comparable to U.S. general population levels during the 1970s and to many populations worldwide today; these are far lower than exposures encountered in some occupations. Further research is needed to confirm the association, to delineate the role of maternal vs. paternal exposures, and to assess increases in menstrual variability as an explanation for this finding.* Am. J. Ind. Med. 38:300–309, 2000. © *2000 Wiley-Liss, Inc.*

KEY WORDS: reproductive toxicity; lead poisoning; blood lead; spontaneous abortion; pregnancy outcome

INTRODUCTION

Although neurodevelopmental effects from prenatal and early childhood exposures have been observed at relatively low levels of lead [Needleman et al., 1979; Dietrich et al., 1987; Schwartz, 1994; Baghurst et al., 1995] effects on pregnancy itself and on other reproductive events have not been extensively studied. This gap in our understanding is somewhat surprising, as the observations of adverse pregnancy outcomes, similar to those regarding childhood neurologic deficits, date back to the 19th century. This paper (a) describes historical and recent evidence on pregnancy loss in relation to high-level lead exposures, and then (b) reviews and critiques the literature at moderate/low level exposures.

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For clarity, two definitions are in order. First, low/moderate level exposure to lead is defined as falling in the range of approximately 0–30 μg/dL. While the upper end of this range is high for children, occupationally exposed populations frequently have much higher levels. Second, spontaneous abortion is here defined to mean a pregnancy loss occurring before the 20th week of gestation, but past the stage of unrecognized, subclinical loss. In other words, these are recognized losses which are too early to be characterized as stillbirths. While we have used 20 weeks as the cutpoint in the study described below, other definitions have been used. For instance, among the historical papers, a spontaneous abortion was defined to be expulsion of the fetus in months 2–6 [Paul, 1860] or by 6 ½ months of pregnancy [data of Arlidge, in Legge, 1901]. Although many papers did not provide a definition, currently, the overwhelming majority of fetal losses by the 6th month actually occur in the first 12 weeks. Where authors have combined all reported losses, the resulting measures of the effect of lead on viability of the pregnancy or fetus are less specific, but no less valid.

HIGH-LEVEL LEAD EXPOSURE AND SPONTANEOUS ABORTIONS

Much of the evidence regarding high-level lead exposure and reproductive toxicity comes from the literature on industrial exposures in Europe during the 19th Century, and was summarized in considerable detail by Alice Hamilton [e.g., Hamilton, 1929; Hamilton and Hardy, 1974]. Perhaps the first data documenting adverse effects on pregnancy were published by Paul in 1860, in France. His report details the pregnancies of 25 women who had either worked in the lead industry, or whose husbands had. The women are divided into six series according to their specific exposure histories. Among five women who had had at least one successful pregnancy and no miscarriages or stillbirths prior to entering the lead industry, subsequent pregnancies numbered 36, of which 26 (72%) spontaneously aborted between months 2 and 6, with three other stillbirths, of which one was premature and the other two delivered at term. Only a small part of this difference could be due to the women being older after entry into the lead industry, as most entered while still quite young and the difference is enormous. Among women who had never experienced lead poisoning but whose husbands were exposed, there were eleven miscarriages in 32 pregnancies (34%), and an additional stillbirth. While Paul does not provide a control series (indeed, he laments the lack of such data), he does provide comparison data from Paris on stillbirths (those occurring after 6 ½ months). From his series of exposed women, 9 out of 59, or 15.3% of exposed pregnancies which survived to 6 ½ months ended in stillbirth, whereas 2,796 out of 40,493 Parisian pregnancies, representing 6.9%, ended either in a stillbirth or in a livebirth that died before a certificate was completed, for a relative risk of 2.2.

As a comparison for the risk of spontaneous abortion, data before the industrial revolution are found in Graunt's summary from the Bills of Mortality (Death Certificates) of England in the late 1500s and early 1600s. Graunt [1662] reports a ratio of about 1:20 miscarriages to christenings (the Church carried out the birth registration), or about 5%, slightly lower than the proportion of pregnancies that today are known to end in recognized spontaneous abortion in the US: 7–15% [Hertz-Picciotto and Samuels, 1988]. However, once the Industrial Revolution began, the rate in the general population may have been higher: Legge [1901] cites a ratio of miscarriages-to-pregnancies for wage-earners of 1:7 based on a series of 2,000 cases; Oliver [1911], reporting early in the 20th century states that 17% of pregnancies ended in spontaneous abortion among the general population, and also cites data indicating that prior to employment in the lead industry, a group of 239 women had a ratio of 1:14.

Legge [1901] published case series data from an 1897 annual report of factory inspectors in England showing that among 212 pregnancies to 77 women employed in the lead industry, 52% ended in spontaneous abortion or stillbirth. He also reports figures provided by the Certifying Surgeon of the district of Stoke, a Mr. Arlidge. These data, concerning 239 women working in lead processes in the china and earthenware industry, demonstrated that the risk of miscarriage or stillbirth during or after such employment was 1.7 times higher than before. See Table I for details.

Sir Francis Oliver, in 1911, delivered a lecture entitled "Lead Poisoning and the Race" to the Eugenics Education Society of London. It is, perhaps, of historical note that during the period following Darwin's publication "*Origin of the Species*," the ideological framework for the advocacy of a cleaner and healthier workplace was the goal of improving the "race," a concept that is understood today to have clear overtones of racism. Oliver recounts his decades of work towards protecting women from occupational exposures to lead. He describes a reported cluster of stillbirths in one town in Yorkshire, which was ultimately traced to lead having contaminated the drinking water, and which ceased when the exposure was removed. He also reports findings from his investigation in Hungary of what he considered the worst conditions he had seen anywhere. In villages devoted to the cottage industry of pottery manufacture, houses were characterized by extremely high levels of lead-contaminated dust. In these villages, he observed widespread childlessness, as well as convulsions and severe growth stunting of the few offspring who survived.

Oliver cites Dr. Reid's "*Report of the Departmental Committee on the Dangers attendant on the Use of Lead...*" and shows adverse pregnancy events in different occupations. Unfortunately the data are presented per 100 women

TABLE I. Data from 19th and Early 20th Century on Occupational Exposures to Lead and Viability of the Fetus and Infant

Country, time period (source of data/reference)	Woman's exposure	No. of miscarriages + stillbirths/ 100 women[a]	No. of miscarriages + stillbirths/ 100 pregnancies	No. of infant deaths/ 1000 births
France, mid-1800s [Paul, 1860]	Prior to employment in lead factory	0.0[b] (5 women)	0.0 (9 preg)	0
	During or after employment in lead factory	650.0[b] (5 women[c])	72.2 (36 preg)	800 (10 births)
	Paternal exposure	157.1 (7 women)	34.4 (32 preg)	400 (20 births)
	Entire case series	492.0 (25 women)	59.3 (123 preg)	400 (50 births)
England, late 1800s [Data compiled by Patterson and Deane, reported in Legge, 1901]	Employed in lead factory	144.2 (77 women)	52.4 (212 preg)	
England, late 1800s [Data compiled by Arlidge, reported in Legge, 1901]	Prior to employment in china & earthenware factory	40.6[b] (239 women)	9.2 (487 preg)	
	During or after employment in china & earthenware factory	68.5[b] (239 women[c])	15.5 (566 preg)	
England, late 1800s–early 1900s [Data compiled by Reid, reported in Oliver, 1911]	Housework	43.2 (not reported[d])		150
	Mill work, no lead exposure	47.6		214
	Lead work before marriage	86.0		157
	Lead work only after marriage	133.5		271
	Husband Pb work	48.0		189
Italy, early 1900s in Milan [Torelli, 1930]	General population		4.0–4.5	150
	Women in lead (primarily printing) industry		24	320
	Husband in lead (primarily printing) industry		14	
Italy, early 1900s, Sardinia [Data compiled by Frongia, reported in Torelli, 1930]	Women working in lead mines	110.4 (297 women)	22.1 (1483 preg)	469 (1155 births)
	Husband working in lead mines	122.2 (45 women)	27.6 (199 preg)	

[a]Women who conceived at least once.

[b]Where data were available on the same women before and during employment in lead industries, I have calculated a standardized count per 100 women for each period as follows: since the number of pregnancy losses is a function of the number of pregnancies, the inverse of the proportion of lifetime pregnancies that occurred during the given time period was used as a multiplier to obtain the expected average number of pregnancy losses per woman.

[c]Same women as preceding line.

[d]If the number of women or pregnancies or births is omitted, it was not reported in the original publication.

rather than per 100 pregnancies, but if we assume the pregnancy rates are similar across the occupations (in this period prior to the availability of modern contraceptive methods), then these data demonstrate an approximate two-fold increased risk of total pregnancy loss (spontaneous abortions and stillbirths combined) for women who were employed in the lead industry prior to marriage only, and a three-fold increase for those employed after marriage. Two reference groups showing similar risks consisted of those women working only at home or in mills without lead exposure. Unlike the data from Paul, those whose husbands worked in the industry did not experience an elevated risk.

Oliver also investigated whether the mechanism of reproductive toxicity involved a direct effect on the embryo/fetus. He experimentally coated chicken eggs with lead nitrate and others with a strong solution of lime. The lead-coated eggs never produced a live chick, and in these shells, the embryos were "always found to have reached a fair stage of development." In experiments with rabbits, he found aborted fetuses whose internal organs were contaminated with lead. His conclusion was that the frequency of stillbirths among women lead workers was due to direct transmission of lead to the developing fetus. Other researchers observed lead in human stillbirths.

A few decades later, Torelli [1930] provided statistics on pregnancies in Milan, where the printing industry was a source of lead exposure. He reported the risk of spontaneous abortion to be 4.5% in the general population, 14% in wives of men employed in the printing industry, and 24% in women who themselves were so employed; these data yield relative risks of 3.1 and 5.3. Thus, unlike in Reid's data, but similar to Paul's findings, there appeared to be an effect from paternal exposure. Infant mortality more than doubled among exposed women as compared with the rate in all of Italy: 320 vs. 150 per 1,000 livebirths.

Finally, Hu [1991] provides interesting data from Boston, Massachussetts on the pregnancies of women who themselves experienced lead poisoning during their childhood in the years 1930–1944. The rationale for this study lies in the fact that lead is stored in bone tissue for decades, and the possibility, supported by several studies, that demineralization of the skeleton takes place during certain physiologic states such as pregnancy [Silbergeld et al., 1988; Rothenberg et al., 1994; Hertz-Picciotto et al., 2000] and menopause [Symanski and Hertz-Picciotto, 1995]. The cases of childhood plumbism were identified from hospital records, traced in the 1980s, and interviewed regarding their pregnancy histories. Matched control subjects were identified and interviewed for 14 females of 22. The proportion of pregnancies ending in spontaneous abortion or stillbirth was 22% (11/51) among cases with matched controls, 29% (8/28) among the cases with no matches, and 13% (6/48) among controls. The matched-pairs odds ratio was 1.6, with a 95% confidence interval of (0.6–4.0) reflecting the small size of the study. Additionally, the risk for learning disabilities was elevated among the surviving offspring of women with a history of childhood lead poisoning. No elevated risk of spontaneous abortion was seen for pregnancies fathered by lead-poisoned men. However, the reliability of male reports regarding the pregnancy histories of their partners is not high [Selevan, 1980].

As a whole, this literature provides consistent evidence in the form of both case series and epidemiologic studies, that the risk of spontaneous abortion is increased by maternal exposure to high levels of lead. The data on male exposures and spontaneous abortions is more sparse and less consistent.

LOW-LEVEL LEAD EXPOSURE AND SPONTANEOUS ABORTIONS

Few studies have addressed the risk of spontaneous abortion at lower levels of exposure. Studies conducted in seven different countries are summarized in Table II, along with their strengths and weaknesses. On the whole, most of these reports provide essentially no evidence that lead exposures in the low-to-moderate range are associated with an increased risk of spontaneous abortion. A study from Finland provides suggestive evidence of a dose-related effect from paternal exposures, and two studies provide support for an association, one from occupational and the other from environmental exposures.

In the first of these recent studies, McMichael et al. [1986] examined pregnancies of women living in a smelter community and a comparison community in Australia; however, spontaneous abortions were not the primary outcome of interest. Only nine pregnant women were enrolled from the non-smelter community by week 14, hence this group was not used for analyses of this outcome. Thus, the authors compared cases who spontaneously aborted with pregnancies that survived within the exposed town. Since the gestational age distribution for blood lead measurements is heavily weighted after 14 weeks, it is probable that on average, the blood specimens from surviving pregnancies were drawn later in pregnancy than those who spontaneously aborted. Several reports now demonstrate that blood lead levels change throughout pregnancy [Rothenberg et al., 1994; Hertz-Picciotto et al., 2000], indicating the need for cases and surviving pregnancies to have blood drawn at comparable gestational ages. Of further concern is the small number of cases ($n = 22$), of which not all had a blood lead measurement, resulting in very low statistical power.

A second study, conducted in Yugoslavia, similarly concerns two communities, one with and one without a smelter. Murphy et al. [1990] enrolled women during pregnancy, but this analysis is based on interview information regarding the outcome of each woman's first pregnancy, among those who had had at least one previous pregnancy and had been living at the same address since their first pregnancy. Over 300 women from each town contributed to this analysis, and the two groups were comparable with respect to their age, education, and mean number of previous pregnancies. Small differences in the percent smokers or alcohol consumers were observed and women from the unexposed town had lived fewer years in the current address. Exposed women experienced a risk of 16.4% for spontaneous abortions, compared with 14.0% for unexposed women, yielding an adjusted odds ratio of 1.1. Although blood or ambient air lead levels were not known for the time periods when these women had their first pregnancies, at the time of the interviews, women from the smelter community had a three-fold higher blood lead level than those in the comparison community. This study is, overall, one of the strongest on this topic. Nevertheless, some concerns remain. The contrast between the two towns may or may not have been as great in the first pregnancies, since a minimal duration of residence prior to their first pregnancy was not required. (For instance, the mean number of years at the current address was 7 for unexposed women, despite 30% having lived at the same address since birth—suggesting a substantial percent lived at their current

TABLE II. Studies of Low-To-Moderate-Level Lead Exposures in Relation to Spontaneous Abortion

Authors and date; Location	Design	Strengths	Limitations	Results
McMichael et al. [1986]; Australia	Clinic-based cohort study; PbB of cases compared with PbB of surviving pregnancies within a lead-smelting community	Individual measurements of exposure. Prospective enrollment of pregnant women	Small number of cases. Women from non-smelting community were excluded. Different timing of PbB measurement for cases vs. surviving pregnancies	PbB in cases not significantly higher than in controls. Mean PbB: Cases = 11.3 μg/dL Controls = 10.8 μg/dL
Murphy et al. [1990]; Yugoslavia	Retrospective interview among pregnant women: Intercommunity comparison of outcomes of first pregnancy among multigravid women currently pregnant in a smelting community and an unexposed one	Adequate sample size. Strong contrast between two towns in terms of blood lead differences. Control for many confounders	Ecologic measure of exposure based on residence in same home since first pregnancy. Communities may have differed on past residential mobility. Retrospective self-report with potential for misreporting outcome. Included only women with a 2nd pregnancy	Exposed community had nonsignificantly higher risk of spont. ab: Exposed = 16.4% Unexposed = 14.0%, adjusted OR = 1.1 (0.9, 1.4)*
Laudanski et al. [1991]; Poland	Retrospective interviews: Intercommunity comparison of pregnancy histories, using soil lead to define exposed areas	Full reproductive histories, with many women beyond reproductive age	Blood lead values differed minimally between exposed and unexposed areas. Unexposed area had a much higher proportion employed in agriculture; no adjustment for confounding	Exposed had lower risk of spont ab. Percent with at least one prior spont. ab: Exposed = 11.0% Unexposed = 19.5%
Taskinen [1988]; Finland	Questionnaires of women with miscarriages or livebirths in hospital registry. Maternal job histories linked to registry of occupational PbB measurements. Matched on maternal age	Questionnaires to supplement biological monitoring data. Multivariate adjustment. Strong exposure contrasts	Few women with high exposures. Most were not themselves monitored	No signif. assoc. Adjusted ORs (vs. referents with no exposure): PbB < 0.5 μmol/L, OR = 0.9 PbB 0.5–0.9 μmol/L, OR = 0.7 PbB > 0.9 μmol/L, OR = 0.8
Lindbohm et al. [1991]; Finland	Questionnaires of women with miscarriages or livebirths in hospital registry and of husbands. Paternal job histories linked to registry of occupational PbB measurements. Matched on maternal age	Questionnaires to both fathers and mothers used to supplement biological monitoring data. Clear ascertainment of exposures during period of spermatogenesis. Multivariate adjustment for numerous potential workplace and lifestyle confounders	Paternal exposures inferred through extrapolation or interpolation for most cases. Only 61% of cases from Finnish Registry both responded and recalled the pregnancy of interest, and among these, 22% were excluded because of inadequate data to classify lead exposure	No significant. assoc. Adjusted ORs, with 0.0 to 0.9 μmol/L as referents: PbB 1.5–1.8 μmol/L, OR = 1.3 PbB > 1.9 μmol/L, OR = 1.6 Signif assoc when restricted to men monitored within a year of spermatogenesis: PbB > 1.5 μmol/L, OR = 3.8 (1.2, 12.0)*

(*Continued*)

TABLE II. (*Continued*)

Authors and date; Location	Design	Strengths	Limitations	Results
Tabacova and Balabaeva [1993]; Bulgaria	Cohort of pregnancies from lead smelting areas and areas near a petrochemical plant	Individual biological measures, including blood lead, total blood glutathione and percent oxidized, lipid peroxides in blood, as well as metabolites of solvents	Process for selection of subjects not described. Outcome was not well defined: n = 24 "threatened spontaneous abortion" but actual abortions not analyzed per se	PbB in cases significantly higher than in controls. Mean PbB: Cases = 7.1 μg/dL Controls = 5.2 μg/dL
Driscoll [1998]; United States	Retrospective questionnaires of a cohort of women employed by U.S. Forest Service. Exposures investigated included use of lead-containing paints for marking trees to be clear-cut	Outcomes ascertained by self-report on mail questionnaire. Multivariate adjustment for potential confounders. Generalized estimating equations used to adjust for non-independence of multiple pregnancies per woman	Response rate of usable questionnaires was 59%. Paints with lead also contained solvents potentially related to spontaneous abortion, hence possible confounding	Three types of paint with lead pigments: 1: OR = 4.3 (2.0, 9.3)* 2: OR = 2.0 (1.2, 3.3) 3: OR = 1.8 (1.2, 2.6)
Borja-Aburto et al. [1999]; Mexico	Clinic and physician-based cohort of women with general environmental exposures, seeking prenatal care or pregnancy test	Individual blood lead measure obtained prospectively, prior to the time of spontaneous abortion for cases, and at comparable gestational ages for referents. Matching on public/private clinic, calendar time (± 2 weeks) and gestational age at entry (± 2 weeks). Multivariate adjustment for confounders	Small number of cases. Incomplete ascertainment of outcomes of pregnancies (16% lost to follow-up)	PbB in cases significantly higher than in controls. Mean PbB: Cases = 12.0 μg/dL Controls = 10.1 μg/dL Dose–response: for every 5 μg/dL increase in PbB, RR = 1.8 (1.1, 3.1)*

*Numbers in parentheses represent the 95% confidence interval.

address for a very short time. Perhaps some of these women had lived in the smelter town only 25 miles away.) Additionally, self-reports may entail inaccurate reporting of induced abortions as spontaneous. Also, if pregnancy losses occurred at a higher rate among residents near smelters, those families experiencing reproductive failure may have been more likely to leave the smelter community, leaving only the more fecund families from the exposed town to participate in a study limited to survivors who achieve another pregnancy. Similarly, if lead is related to subfecundity, as some recent research suggests [Sallmén et al., 2000], use of a cohort of women with a second pregnancy could have introduced bias.

The third study followed a similar design, examining women in Poland from villages with either high or low lead content in soil [Laudanski et al., 1991]. Again, exposure was based on residence, not individual measurements. Women from a wide age range (20 to over 80 years) reported their pregnancy histories. Those from villages with high lead soil content (n = 136) had a lower risk of spontaneous abortion than those from the uncontaminated areas (n = 264). Based on the published report, I calculated the odds ratio to be 0.49 with a 95% confidence interval of (0.26–0.91). However, unlike the Yugoslavian study, the blood lead values in women from the two areas did not differ, i.e., there was no real contrast between the two areas in terms of body burdens. Furthermore, the analysis did not control for any confounders, despite the fact that there were more women in the low-lead areas who were employed in agriculture (70 vs. 55%). This difference suggests the possibility of negative confounding (confounding that reduces the association, and can even reverse it) from farm exposures.

Two studies [Taskinen, 1988; Lindbohm et al., 1991, 1992] were conducted in Finland using a nested case–control design, with the first focused on maternal exposure, and the second on paternal exposure during the 80-day period prior to conception, i.e., during the estimated time of

spermatogenesis. The authors linked two registries, one recording all births and estimated to cover 80–90% of recognized spontaneous abortions, and the other based on monitoring of workplaces with potential lead exposure. By law, if any worker has a PbB >2 μmol/L ($\sim$41 μg/dL), then all workers doing similar tasks should be monitored periodically. The authors used mail questionnaires to collect extensive occupational, medical, lifestyle, and reproductive information. This information was then linked to the monitoring data to estimate the level of exposure to the mother during pregnancy or to the father during spermatogenesis. In the study of maternal exposures [Taskinen, 1988], which appeared to have 84 cases and 243 controls, over 50% reported being in an industry where their job tasks were monitored during the relevant time period. The adjusted ORs were all below unity, with wide confidence intervals. Too few women were themselves monitored during pregnancy or in the year preceding it, for meaningful analyses of this subgroup. For the study of paternal exposure, which involved 213 cases and 300 referents, interpolation and extrapolation were used to estimate the relevant exposures for the time period of interest [Lindbohm et al., 1991]. After multivariate adjustment, the study found odds ratios of 1.3 and 1.6 in the second-to-highest (1.5–1.8 μmol/L or 31 to $\sim$38 μg/dL) and highest (≥ 1.9 μmol/L or ≥ 39 μg/dL) blood lead level categories, respectively, as compared with the lowest, but the confidence intervals were wide. An analysis restricted to those men monitored within ± 1 year of spermatogenesis yielded a multivariate adjusted OR of 3.8 (1.2–12.0) comparing those above 30 μg/dL with those below 20 μg/dL.

The sixth study, conducted in several communities in Bulgaria, enrolled women prospectively during their pregnancies [Tabacova and Balabaeva, 1993]. About 175 of the women resided in metal-smelting areas and 130 in a region with a petrochemical plant and associated pollution. Although the authors report significantly higher levels of blood lead and increased excretion of the metabolites of organic solvents in women with complicated pregnancies, they do not provide clear definitions for their health endpoints, in particular, for ''threatened spontaneous abortion.'' It is unclear whether any of these pregnancies resulted in an actual spontaneous abortion.

A survey of women employed by the U.S. Forest Service assessed job exposures and reproductive outcomes [Driscoll, 1998]. A mail questionnaire was sent to over 10,000 women aged 18–52 who were full-time employees with at least 1 year of service. The questionnaire collected information on job duties and reproductive histories for a 10-year period. Questions inquired about use of herbicides, pesticides, and specific paints, as well as potential confounders including smoking, alcohol, hobbies, home pesticide applications, etc. A 59% response rate was achieved. The initial analysis showed foresters to have a greater proportion of pregnancies ending in miscarriage (18%) than the non-foresters (14%), with an adjusted OR of 1.4 (95% CI = 1.1–1.9). When analyses were conducted for specific work exposures, use of several paints with pigments containing 4–60% lead by weight was associated with increased risk of spontaneous abortion. The ORs for use of three particular paints during the 6 months prior to the pregnancy, after adjustment for age, smoking, alcohol and strenuous work activity, ranged from 1.8 to 4.3, with lower confidence bounds 1.2 or greater. These paints also contained solvents, which in some studies have been associated with spontaneous abortion. The primary weaknesses in this study were the low response rate with consequent possible selection bias, and the inability to separate lead from solvent exposure.

Mention should also be made of an abstract describing a 22% risk of reported spontaneous abortions among housewives in a ceramic-producing district of Italy, vs. 13.3% among housewives in the unexposed area [Vivoli et al., 1998]. An even higher risk was found among those employed in the ceramic industry; no full report of this study is available.

Finally, a study of spontaneous abortion was conducted in Mexico City, where average population lead levels have been documented as greater than 10 μg/dL [Farias et al., 1996; Borja-Aburto et al., 1999]. A cohort of 668 women with medically confirmed pregnancies still in their first trimester was enrolled through both public and private prenatal care clinics. At enrollment, the women were asked to donate a blood sample and interviewed about lifestyle, demographic, occupational, medical, and reproductive factors. Spontaneous abortions were ascertained by contacting the women biweekly. The blood samples were used for measurement of lead and of antibodies to several infectious agents associated with adverse pregnancy outcomes. Cost efficiency was achieved by conducting a nested case–control study, so that not all specimens collected had to be analyzed. To achieve comparable opportunity for experiencing the outcome, controls were matched to cases on the gestational age at entry into the cohort. This type of incidence density matching permits the equivalent of a survival analysis, which is necessary for studies of spontaneous abortions in clinic-based cohorts [Hertz-Picciotto et al., 1989]. Figure 1 depicts a case followed through time in the upper line and an eligible control in the second line. The third line represents a noncase who would not be eligible to serve as a control for the case shown, due to later entry into prenatal care (a noncase entering too early would also have been ineligible). In light of changes in blood lead over the course of pregnancy documented in other studies [e.g., Rothenberg et al., 1994; Hertz-Picciotto et al., 2000], this matching also prevented bias due to noncomparable times for the measurement of the exposure. Other matching factors

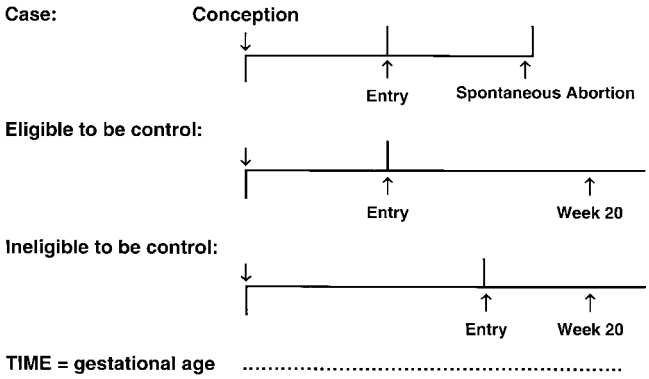

FIGURE 1. Incidence-Density Matched Study Design. For each case, the control was matched within 2 weeks for gestational age at entry. Those who entered more than two weeks later or earlier were not eligible to serve as a control for that case.

included maternal age, calendar time of entry, and public vs. private clinic.

Cases (n = 35) were found to have significantly higher blood lead levels than their matched controls [Borja-Aburto et al., 1999]. Medians and interquartile ranges were 11.7 μg/dL (6.5–16.0 μg/dL) for cases and 8.7 μg/dL (6.2–14.0 μg/dL) for controls. A dose–response relationship was observed, in categories of 5 to < 10, 10 to < 15, and 15+ μg/dL compared with the reference category of 0 to < 5 μg/dL: the ORs based on the matched sets were, respectively, 2.3, 5.4, and 12.2 (test for trend $P = 0.03$). In a conditional multiple logistic regression analysis, a large array of factors was made available for inclusion (spermicide use, active and passive smoking, alcohol, coffee, age, education, income, physical activity, hair dye use, video display terminal exposure, and medical conditions), but none was significant when blood lead was in the model. The adjusted OR was 1.13 for each μg/dL of PbB. Translating this finding into a more meaningful increment, for a 5 μg/dL increase in blood lead, the estimated OR for a spontaneous abortion is 1.8 with a 95% confidence interval of (1.1–3.1).

The strengths of this study are its prospective design; confirmation of all pregnancies; the use of individual rather than ecologic measurements of exposure; careful matching of the timing of exposure measurement and of the opportunity for the outcome to be observed; the large number of potential confounders assessed; efficient control for secular trends in lead exposure and for seasonal trends through matching on calendar time; efficient adjustment for socioeconomic variability through matching on clinic type; and the clear dose-response observed. Limitations are the loss to follow-up of 16% of the cohort and the small number of cases. The small number of cases reduced the precision of our estimates; the loss to follow-up could have resulted in upward bias, if women with higher lead levels among those lost to follow-up were less likely to abort than those who were successfully followed, or if the untraced women with lower blood lead levels were more likely to abort. (Converse scenarios would have yielded a downward bias.)

Women with menstrual irregularities, as compared with those who reported regular menstrual periods, were also more likely to have a spontaneous abortion (relative risk = 1.6 among those who had not been using oral contraceptives as their most recent of birth control). If lead increases the risk for menstrual irregularities, then there could be some bias in the Mexico City study's estimates of the effect of lead, since the apparent gestational age, which is measured by time since the last menstrual period, might be an overestimate. The overestimation of gestational age occurs if the woman has a longer than average follicular phase, as often occurs among women with menstrual irregularity. On the other hand, menstrual irregularity could be a marker for hormonal deficiencies, possibly resulting from lead exposure, and might therefore be an indication for an intermediate variable on the causal pathway leading to increased risk of pregnancy failure. Further research should address these issues.

DISCUSSION

Of the largely null reports specifically addressing low or moderate level lead exposure, one did not provide data on actual spontaneous abortions, and another involved an ecologic comparison of areas which had similar blood lead levels and made no adjustment for confounders. A third was not designed to evaluate spontaneous abortion, had few events, and measured exposure at different time points for cases as compared with controls. A fourth study had few exposed women, but a companion paper observed a nonsignificant dose–response in relation to paternal exposure during spermatogenesis, and when analysis was restricted to men monitored within ± 1 year of spermatogenesis, a significantly elevated risk was seen for those at the highest exposure levels. Finally, one study had a sufficient size cohort and controlled for confounding; however, there are concerns about the validity of the self-reported spontaneous abortions, the timing of the exposure assessment, and possible bias from residential mobility and the use of a survivor cohort of pregnant women. In short, the lack of evidence for an association between low-to-moderate-level lead exposure and the risk of spontaneous abortion could be due to the deficiencies of these studies.

In two studies with clear positive associations for maternal exposures, one may have suffered from selection bias and/or confounding from solvent exposures. The other overcame most of the deficiencies of previous studies. Pregnant women were enrolled prospectively and the individual-level biologic measures of exposure collected with attention to comparable timing for cases and non-cases was a major strength, and may have made up for the small

number of cases; additionally, the matched design and analysis increased precision.

The design of the Mexico City study of spontaneous abortions addresses the deficiencies apparent in previous studies of this outcome. While the findings remain to be confirmed in further research, the results suggest that increased blood lead, even in the low-to-moderate-range, could have reproductive consequences. However, just as in the literature on high-exposure effects, the potential roles of paternal vs. maternal influences remain unclear. For example, the blood lead of the woman could be elevated if her husband's occupation involved exposures to lead dust brought home on his clothing. Another scenario is a shared source of exposure (e.g., contamination of food from lead-glazed cookware) that could have altered sperm in the preconceptional period, potentially rendering the woman's blood lead measurement simply a surrogate of the harmful paternal exposure. A third alternative would involve lead in seminal fluid as a source of maternal and fetal exposure during pregnancy. Thus, although the study utilized a biological measurement in maternal tissues, paternal exposures could have played a significant role. Issues surrounding male-mediated reproductive toxicity for lead have been reviewed thoroughly [Apostoli et al., 1998].

The mechanism for inducing pregnancy loss is also not clear. Besides preconceptional chromosomal damage to the sperm or a direct teratogenic effect on the fetus, interference with the maternal/fetal hormonal environment is possible, as endocrine-disrupting activity has been observed in rodent, primate, and human studies. Vascular effects on the placenta are also plausible, given the literature on lead and hypertension [Hertz-Picciotto and Croft, 1993]; developmental toxicity to the fetus is also possible. Further epidemiologic studies should be supplemented and complemented by directed mechanistic research.

CONCLUSIONS

Although lead appears to play a role in excess fetal loss among those with high exposures, most studies of the risk from low-to-moderate-level exposures have provided little evidence for such reproductive toxicity. These studies, however, are far from definitive, due to numerous methodologic deficiencies. In a carefully designed prospective study of pregnant women in Mexico City, an association was observed between the risk of spontaneous abortion and the individual level of blood lead measured prospectively, prior to the pregnancy loss in cases and at a comparable gestational age for surviving (control) pregnancies. Based on these results, it appears that lead exposures in the range of 10–25 μg/dL could have adverse effects on pregnancy. These exposure levels are becoming less common in Western countries but are still frequently observed environmentally in some countries and in occupational settings throughout the world. Before this association can be deemed causal, it needs confirmation in other studies. If causal, the role of maternal vs. paternal contributions to these pregnancy losses will need to be explored.

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