

Paternal occupational lead exposure and congenital malformations

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Abstract

Study objective—The aim was to investigate whether occupational exposure to lead in fathers is associated with congenital malformation in their children.

Design—The study was a retrospective case-control study, nested within the wives of men biologically monitored for inorganic lead. Information on pregnancy outcome was obtained from medical registers.

Subjects—Cases were defined as wives with malformed child during 1973–82. Three age matched controls were selected for each case from the wives who had given birth during 1973–1983. The final study population was 27 cases and 57 controls.

Measurements and main results—Paternal lead exposure was assessed with blood lead measurements and data obtained from a questionnaire. The response rate was 67% among the cases and 76% among the controls. The odds ratio (OR) of congenital malformation for paternal lead exposure was increased (OR 2.4, 95% confidence interval 0.9–6.5), although not reaching statistical significance. The odds ratios varied from 1.9 to 3.2, when adjusted for one potential confounding variable at a time.

Conclusions—Because of the small numbers and low participation, this study offers limited support for the hypothesis that paternal lead exposure is associated with congenital malformation. Further epidemiological studies on the reproductive hazards of paternal lead exposure are needed.

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Paternal occupational lead exposure was linked with abortions, stillbirths, and postnatal deaths over a hundred years ago.¹ Recent studies suggest that lead impairs the quality of the semen of exposed workers.^{2–5} The results suggest that lead can have a direct toxic effect on sperm and/or an indirect effect through endocrine dysfunction. Rabjerg and Viskum⁵ found in their longitudinal study a simultaneous increase in the number of live sperm, the number of motile sperm, and the penetrating ability of sperm with decreasing exposure at blood lead levels within current workplace standards.

The results of the study of Hakim *et al*⁶ suggest the possibility of a weak association between lead exposure in fathers and strabismus in their offspring. In the spontaneous abortion part of our study we found that there may be an association between paternal exposure to inorganic lead and spontaneous abortion.⁷

The aim of this study was to investigate whether occupational exposure to lead in fathers is associated with congenital malformation in their children. The study population consisted of men biologically monitored for lead exposure. Information on pregnancy outcome was obtained from medical registers.

Methods

IDENTIFICATION OF THE STUDY SUBJECTS

The study population was identified from the following four data sources: the records of men biologically monitored for inorganic lead exposure at the Institute of Occupational Health; the Central Population Register; the Finnish Register of Congenital Malformations; and the nationwide database on pregnancies in Finland.

The biological monitoring of lead in blood has been a service activity of the Institute of Occupational Health since 1968. In Finland all workers should be monitored if the blood lead of any worker at the workplace exceeds 2 µmol/litre. The frequency of monitoring depends on the intensity of lead exposure and varies from one to six times a year.⁸

Data on the lead exposure measurements were collected from the laboratory records of 1973–1983 and completed with personal identification codes. Altogether 56 117 measurements were performed for men in 1973–1983 and the identification codes were obtained in 97% of the measurements. The number of identified men was 19 349.

Information about the wives of the monitored men was obtained from the Central Population Register. The study was restricted to men in their first marriage. The pregnancies of the wives were identified from the nationwide data base on medically diagnosed pregnancies from 1973 to 1983⁹ and the Finnish Register of Congenital Malformations from 1973 to 1982. The registering of malformations is based on compulsory notification of all malformations detected during the first year of life. Studies comparing the registered data with hospital information¹⁰ have revealed a 30% failure rate in reporting and detection. The rate varies by the type of the defect, minor malformations being particularly underreported.

The study was conducted using a case-control design. It was restricted to pregnancies which had started during the marriage. All the 18 to 40 year old wives with a malformed child (subluxations of the hip were excluded) were defined as cases. If the woman had had two or more malformed children, only one pregnancy was randomly selected. Three controls were selected for every case

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from the wives who had given birth (eighth revision of the *International classification of diseases* [ICD]; codes 650–662), but only one pregnancy per woman was included. Only those women who had neither a registered spontaneous abortion (ICD codes 643, 645) nor a registered malformed child during their marriage within the study period were qualified as potential controls. The controls were individually matched with the cases for the wife's age at the time of conception to within a year, the nearest available matching being used. Three controls were found for every case. The maximum age difference between the case mother and her control was 19 days.

ESTIMATION OF EXPOSURE

Separate questionnaires were mailed to the men and their wives to obtain data on their employment, occupation, workplace, and occupational exposure covering the year of conception of the study pregnancy for men and the first trimester of study pregnancy for the women. The men and their wives were asked to describe their work tasks in detail and to indicate potential changes in them, and the months in which the changes occurred during the time period in question.

The study subjects were asked whether their work included any of the most typical lead exposing tasks listed in the questionnaire, for example, soldering or tinning, welding, torch cutting, smelting, spraying, or car repair. They were also asked whether they had handled lead, other metals, or other chemicals, and in what kind of tasks, and whether these substances were present in their work environment. Furthermore, data on work histories, chronic diseases, smoking, and use of alcohol were also sought. The questions about pregnancy history, acute diseases during the first trimester of pregnancy, and use of contraception in the beginning of the pregnancy were asked only of the wives.

The husband's lead exposure was assessed for the estimated time of spermatogenesis, ie, an 80 d period before conception.¹¹ For those holding the same job during the measurement and the spermatogenesis ($n = 55$; 65% of the final study population), lead exposure was defined on the basis of blood lead measurements. If the blood lead analysis was carried out during the spermatogenesis, the result was accepted as such ($n = 12$; 14% of the final study subjects). If the husband was monitored both before and after the spermatogenesis period, a time weighted mean was used ($n = 12$; 14% of the final study subjects).

For those who had been monitored only before or after the study spermatogenesis ($n = 31$; 37% of the final study subjects), lead exposure was estimated from the blood lead result nearest to the spermatogenesis of the individual, by using the fitted time trend correction as described by

Lindbohm *et al.*⁷ This correction did not change the exposure category of any study subject.

The exposure of the men holding a different job at the time of measurement and during the spermatogenesis period ($n = 29$; 35% of the final study population) was classified by one of the investigators into four exposure categories: 0.0–0.9, 1.0–1.4, 1.5–1.8, and ≥ 1.9 $\mu\text{mol/litre}$. The classification was made without knowledge of who was a case and who was a control. The classification was based on the occupation, work description, and lead exposure, as reported in the questionnaire, and on corresponding blood lead measurements. The lowest lead exposure category (0.0–0.9 $\mu\text{mol/litre}$) was used as a reference in the analysis. The classification of all other exposures was based on the answers to the questionnaire.

STATISTICAL ANALYSIS

The odds ratios for exposure were estimated with the logistic regression model for individually matched data based on the conditional likelihood function. The statistical significance for separate variables was evaluated by a comparison of the standardised regression coefficients with a normal distribution.¹²

The potential confounding factors were selected on the basis of a priori knowledge on the risk factors for congenital malformations. Only those variables which showed an odds ratio of > 1.5 in the models of individual variables were included in the final analyses.

A variable controlling missing information was included in the models when necessary. The value of this variable was set at 1 if the modelled confounder of an observation had a missing value. The missing value of the variable in question was replaced by zero (ie, not exposed).

RESPONSE RATE AND THE FINAL STUDY POPULATION

After four mailings the response rate of the cases was 66.7% (34/51) and that of the controls 75.8% (116/153) (table I). All the families confirmed the study pregnancy but seven of the 34 case families did not report the registered malformation.

There were four cases (11.8% of respondents) and 20 (17.2%) controls who had been monitored while in the job held during the spermatogenesis period in question, but the nearest measurement was not within three years of the spermatogenesis. We had no information of the detailed work tasks covering the years outside the year of spermatogenesis. To improve the reliability of the lead exposure assessment, these 24 subjects were excluded from the analysis.

One control who reported a malformed child as the study pregnancy was also excluded from the analysis. Further loss of material was due to the individual matching. All the controls with a missing case and the cases with all controls missing were removed. The final study population consisted of 27 cases and their 57 matched controls.

Results

Ten cases (37%) and 11 controls (19%) were, according to the Finnish reference values, estimated to be occupationally exposed to lead (blood lead ≥ 1.0 $\mu\text{mol/litre}$, table II). None of the controls

Table I Response status of the cases and controls, and the final study population

	Cases	Controls	Total
Total population	51	153	204
Respondents (% of total)	34 (66.7)	116 (75.8)	150 (73.5)
Reliable estimation of exposure ^a (% of respondents)	30 (88.2)	96 (82.8)	126 (84.0)
Final population for matched analysis	27	57	84

^aBlood lead measurement within 36 months from the 80 d period before conception or lead exposure estimated on the basis of the questionnaire

but five of the cases had an estimated blood lead level over 1.5 µmol/litre. The study subjects worked in numerous fields of industry. The most common occupations were: repair of automobiles; electrical, painting, and welding work; and other iron and metal work. The odds ratio of congenital malformation for paternal lead exposure (blood lead ≥ 1.0 µmol/litre) was increased (OR = 2.4, 95% confidence interval 0.9–6.5), though not reaching statistical significance (table III).

Because of the small number of subjects only one potential confounding factor at a time was included in the model in addition to lead exposure. In some of the models, a variable controlling for missing information was present. The odds ratio for paternal lead exposure adjusted for selected potential confounders varied from 1.9 to 3.2 (table III). Paternal exposure to organic solvents in general was not related to congenital malformations, neither was parity. It was also made certain that these two variables did not have any confounding effect.

The distribution of exposed cases by the type of malformation was heterogeneous, and all the five case children of the men in the two highest lead exposure categories (blood lead 1.5–1.8 or ≥ 1.9 µmol/litre) had a different type of malformation (congenital heart disease, oral cleft, clubfoot, polydactyly, and malformation of the adrenal gland).

Maternal use of alcohol during the first trimester of pregnancy was associated with congenital malformation (OR = 4.9, 95% confidence interval 1.5–16.1; univariate analysis). Work related exposures were rare among the wives.

Discussion

The odds ratio of congenital malformation for paternal lead exposure was increased when adjusted for one potential confounding variable at

a time, but reached statistical significance in only one model. The husbands of five cases belonged to the exposure category of blood ≥ 1.5 µmol/litre, whereas no husband of the controls had an estimated lead exposure level over this limit.

CONFOUNDING FACTORS

Simultaneous exposure to potential confounding variables, including organic solvents and other chemicals, was frequent among the study subjects. Different confounders changed the odds ratio for lead exposure in different directions, when included in the model. These changes were probably due to the small size of the study material rather than to real confounding effects.

The year of discharge as a dichotomous variable (1979–1983 *v* 1973–1978) had an obvious (negative) confounding effect. The coverage of the Finnish Register of Congenital Malformations is better in the later part of the study period. Secondly, the level of lead exposure decreased during the study period. Thirdly, the information on malformations covering the year 1983 was not in use at the time of the inquiry (1986), whereas the study pregnancies of the controls could be from that year. In summary, this variable increased the estimate of risk due to lead exposure when included in the model.

RESPONSE BIAS

The possibility of response bias was examined among all those subjects who had been monitored during the spermatogenesis or both before and after it (ie, the estimated spermatogenesis period is between the first and last measurement of the worker, $n = 38$). The crude odds ratio for paternal lead exposure (blood lead ≥ 1.0 µmol/litre) was 4.2 (six cases/six controls) among all responding and non-responding study subjects, and 6.2 (four cases/three controls) in the final study population. This is not suggestive of selective participation.

VALIDITY OF EXPOSURE ASSESSMENT

Lead exposure was assessed for 65% of the study subjects on the basis of individual measurement of blood lead concentration. The assessment is independent of the workers' own reporting and decreases the possibility of recall bias among these study subjects.

The blood lead level of only 14% of the study subjects had been measured during the spermatogenesis. The blood lead concentration indicates rather recent exposure,¹³ and the half life of lead in blood is about 30 days. Problems arise in the use of the blood lead value for exposure assessment if there is a long interval between the measurement date and the spermatogenesis. If the measurement had been made after work tasks with occasional high exposure, the consequence is a false positive finding. The possibility of this error is small in our study, because men who had not been monitored within three years of the spermatogenesis were excluded from the analysis.

The study subjects who had not been monitored in their job of interest were blindly classified into exposure categories on the basis of the questionnaire data. Four (36%) cases and three (16%) controls were classified as occupationally exposed. The possibility of recall bias cannot be excluded in this subpopulation.

Table II Estimated blood lead concentration of men during the 80 d period before conception

Blood lead ($\mu\text{mol/litre}$)	Cases		Controls		Total	
	n	%	n	%	n	%
0.0–0.9	17	63.0	46	80.7	63	75.0
1.0–1.4	5	18.5	11	19.3	16	19.0
1.5–1.8	4	14.8	–	–	4	4.8
$\geq 1.9^a$	1	3.7	–	–	1	1.2
Total	27	100.0	57	100.0	84	100.0

^aHealth based limit for men, as recommended by WHO

Table III Odds ratio of congenital malformation for paternal exposure to inorganic lead; seven logistic regression models

Variable	Exposed		Odds ratio	95% Confidence interval
	Cases	Controls		
Blood lead concentration ≥ 1 µmol/litre	10	11	2.4	0.9– 6.5
Blood lead concentration ≥ 1 µmol/litre Paternal smoking	10 18	11 25	3.2 2.8	1.0–10.2* 0.9– 8.9
Blood lead concentration ≥ 1 µmol/litre Paternal alcohol use (≥ 5 drinks a week)	10 13	11 21	2.2 1.5	0.8– 6.2 0.6– 4.0
Blood lead concentration ≥ 1 µmol/litre Maternal smoking ^a	10 7	11 7	2.2 1.8	0.8– 6.1 0.6– 5.6
Blood lead concentration ≥ 1 µmol/litre Maternal alcohol use ^a	10 13	11 9	1.9 4.5	0.6– 6.1 1.4–15.2†
Blood lead concentration ≥ 1 µmol/litre Maternal febrile illness ^a	10 11	11 11	2.5 2.7	0.9– 7.4 1.0– 7.9
Blood lead concentration ≥ 1 µmol/litre Year of discharge (1979–83)	10 15	11 28	3.1 1.8	1.0–10.0 0.6– 5.7

^aThe model includes a variable controlling for missing information

* $p < 0.05$; † $p < 0.01$

BIOLOGICAL PLAUSIBILITY AND POSSIBLE MECHANISM

Lead is known to be excreted in seminal fluid.^{14 15} There is evidence that lead affects the semen quality of exposed workers. Thus it is biologically plausible that lead may be associated with reproductive hazards.

According to present knowledge, mutations are possible direct mechanisms by which paternal exposure could contribute to birth defects.^{16 17} However, the data on mutagenicity of lead exposure are conflicting.¹⁸⁻²⁰ Thomas and Brogan¹⁹ listed 10 positive and six negative studies on occupational exposure to lead and its relationship to chromosomal aberrations. In the present study none of the malformations among the children of the five most exposed cases was of known chromosomal origin, though congenital heart disease, oral cleft, clubfoot, and polydactyly all have a genetic component in their aetiology.²¹

The results of Wildt *et al*³ suggest that occupational lead exposure decreases sperm chromatin stability and may interfere with the sperm maturation process interacting with zinc. The findings of Johansson and Pellicciari,²² however, indicate that lead increases chromatin stability in mouse sperm. Failure of or a delay in sperm chromatin decondensation may lead to decreased fertility or to different kinds of DNA damage in the fertilisation process.²²⁻²⁴

There are also possible indirect mechanisms. The particular genetic constitution contributed to the fetus by the father could make the fetus more susceptible to environmental factors with which it is later exposed.¹⁶ Also secondary maternal exposure through clothes or by semen is possible.

We did not find a connection between paternal lead exposure with any specific type of malformation. This observation does not contradict the possible association between paternal lead exposure and congenital malformation.

CONCLUSIONS

This study offers limited support for the hypothesis that lead exposure in fathers is associated with congenital malformation of their children. Because of the small number of subjects and low participation rate, no firm conclusions can be drawn. We have studied only whether paternal exposure to inorganic lead during spermatogenesis is associated with congenital malformation. Earlier long term exposure to lead might also have an effect on sperm or germ cells, and thus on the risk of congenital malformation. In addition, secondary maternal exposure by contact with clothes or by semen cannot be excluded.

We regard this study as an addition to the debate on the health effects of lead exposure under current limits.^{5 25 26} It is possible that the current lead levels at workplaces are detrimental to the reproductive health of affected men. Together with the results of our spontaneous abortion study,⁷ the findings of the present study point to the need for further epidemiological studies on the reproductive hazards of paternal lead exposure.

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