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EXPOSURE TO LEAD AND MALE FERTILITY

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Abstract. Lead is a reproductive toxicant. Exposure to inorganic lead is detrimental to human semen quality. The studies of the risk of spontaneous abortion and congenital malformation have shown contradictory findings. The aim of the following review is to summarise the epidemiological evidence of the effects of inorganic lead on male fertility. The focus is on epidemiological studies of time-to-pregnancy and related fertility measures. Blood lead measurements were applied to exposure assessment in all the studies.
The results of the studies on fertility rates are consistent in showing an association between lead and reduced fertility. Also, there seems to be a tendency towards stronger association at older age with increasing duration of exposure. The independent roles of exposure duration and effect modification by age may have been difficult to distinguish. There is a paucity of studies on time taken to conceive. The studies conducted only weakly suggest that male exposure to lead is associated with delayed conception. The findings of time-to-pregnancy and fertility rate studies contradict. The possible reasons for this discrepancy is discussed briefly.
There are a number of mechanisms by which exposure to lead may reduce male fertility. On the basis of animal studies, alterations in sperm chromatin stability or epigenetic effects may be the most probable mechanisms involved at low exposure level.

Key words:
Lead exposure, Pregnancy delay, Infertility, Human studies

INTRODUCTION

There is evidence that heavy exposure to inorganic lead is detrimental to semen quality [1]. A decrease in various parameters of semen quality and a possible modest effect on the endocrine profile has been observed at PbB concentrations $\geq$40 μg/dl. The adverse effects of lead on sperm seem to be at least partially reversible [2]. In this prospective study, average PbB decreased from 40 to 20 μg/dl during the observation period. Concomitantly, improvements were seen in the proportion of motile cells, and in penetration. Historical data connects both female and male heavy exposure to inorganic lead with infertility and adverse pregnancy outcome [3]. However, the current epidemiological evidence on male-mediated developmental toxicity is contradictory and inconclusive. In some studies, paternal exposure to lead has been linked with an increased risk of spontaneous abortion or congenital malformation [4,5].

The aim of the following review is to summarize the knowledge on the effects of inorganic lead on male fertility. The review is restricted to those epidemiological studies in which time-to-pregnancy and closely related fertility measures, such as subfecundity, fertility rates or infertility, has been the outcome of interest. Blood lead measurements were applied to exposure assessment in all the studies. Throughout the paper, fertility is viewed as the ability to produce live offspring.

There are four studies of the effects of paternal lead exposure and delayed conception (Table 1A) [6–9]. Data of the

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Table 1. Summary of studies of the relationship between paternal exposure to inorganic lead and fertility

Study population (reference)	Source of fertility (F) and exposure (E) data	Response rate (%)	Exposure, blood lead (PbB)	Number of subjects, pregnancies, person years (births/100 pyrs)	Fertility and (effect) measures	Occurrence ratio	95% CI	Controlled potential confounders
A. Studies of time-to-pregnancy or delayed conception:								
Workers monitored for lead exposure vs. no occupational lead exposure [9]	F: questionnaire E: PbB and questionnaire	93	<20 μg/dl 20–40 μg/dl 40 μg/dl exposed, level unknown controls	42 84 95 77 473	TTP > 1 yr(%)	4.5 8.7 4.0 11.7 5.0	1)	No adjustment
Battery workers, copper foundry w., wire-drawing w. vs. unexposed control [7]	F: questionnaire E: PbB and questionnaire	84	<20 μg/dl 20–34 μg/dl 35–49 μg/dl ≥50 μg/dl	46 132 69 18	TTP (FOR)	1.15 1.09 1.11 1.34	0.84–1.58 0.88–1.34 0.85–1.45 0.82–2.18	Age, oral contraceptive use
Workers monitored for exposure to lead vs.PbB <10 μg/dl [8]	F: questionnaire E: PbB, questionnaire	72	10–20 μg/dl 21–30 μg/dl 31–40 μg/dl >40 μg/dl	203 79 21 23	Time-to-pregnancy (FDR)	0.92 0.89 0.58 0.83	0.73–1.16 0.66–1.20 0.58–0.96 0.50–1.32	Age, personal habits of spouses, menstrual cycle parameters, pregnancy history, contraception, solvent exposure
B. Cohort studies on birth rates and infertility:								
Lead battery workers vs. US white population [15]	F: interview (W) E: PbB, company records	69	Pre-employment, <25 μg/dl 25–40 μg/dl 41–60 μg/dl >60 μg/dl	71 77 260 50	Birth rate, (SFR)	1.03 0.73 0.84 0.68	0.81–1.30 0.58–0.91 0.74–0.95 0.51–0.90	Age, parity, calendar time
Lead battery workers vs. non-exposed workers [12]	F: annual interview E: PbB air measurements	N. A. (100%?)	<40 μg/dl 40–60 μg/dl >60 μg/dl	261 pyrs (16.1) 389 pyrs (13.6) 135 pyrs (19.3)	Infertility 2) (OR)	0.94 1.20 0.79	0.70–1.26 0.91–1.59 0.55–1.13	Age, nationality, education parity, smoking, alcohol, heat
Lead battery workers vs. workers with PbB <20 μg/dl [13]	F: questionnire E: PbB	100	mean: 46.3 μg/dl (range: 24.0–75.0 μg/dl) duration of exposure: <10,7 yrs ≥ 10.7 yrs	74 37 37	Probability of a live birth within 1 yr (OR)	0.65 0.72 0.48	0.43–0.98 0.46–1.31 0.22–1.07	Age, birth cohort, parity, occurrence of a recent live birth
Lead exposed workers in the New York State Heavy Metal Registry vs. bus drivers [14]	F: birth certificates E: PbB	100	≥20 μg/dl Elevated PbB of >5 yrs 20–34 μg/dl 35–49 μg/dl ≥50 μg/dl Duration of exposure: >5 yrs 1–5 yrs <1 yr	4256 2147 1665 444 413 959 1144	Birth rate (SFR) Ratio of fertile (OR) Ratio of fertile (OR)	0.88 0.43 0.9 0.9 1.1 0.3 1.0 1.0	0.81–0.95 0.31–0.59 0.7–1.0 0.8–1.0 0.8–1.5 0.2–0.5 0.9–1.3 0.8–1.2	Age, race, education, residence
Lead battery workers vs. before or after exposure [11]	F: population register E: PbB, pension fund, population register	100	Mean: 35.9 μg/dl (SD 15,2 μg/dl) One PbB >20 μg/dl Duration of exposure: 1–12 mths 13–60 mths 60–120 mths >120 mths Level of PbB: 1–20 μg/dl 21–40 μg/dl >40 μg/dl	1349 1137 1151 pyrs 1048 pyrs 800 pyrs 886 pyrs 119 pyrs 553 pyrs 415 pyrs	Birth rate (RR) Birth rate (OR)	1.00 0.87 0.95 1.09 1.15 1.10 0.77 0.92 1.21	0.87–1.13 0.69–1.10 0.76–1.20 0.86–1.38 0.86–1.51 0.81–1.50 0.35–1.67 0.64–1.33 0.83–1.76	Age, parity Age, parity, calendar year, recent birth
Workers monitored for exposure to lead vs. PbB <10 μg/dl [10]	F: hospital register E: PbB	100	10–20 μg/dl 21–30 μg/dl 31–40 μg/dl 41–50 μg/dl >51 μg/dl	1067 625 242 112 65	Infertility 1) (RR)	1.27 1.35 1.37 1.50 1.90	1.08–1.51 1.12–1.63 1.08–1.72 1.08–2.02 1.30–2.59	Age at marriage

W – wife; H – husband; TTP – time-to-pregnancy i.e. number of months or menstrual cycles of unprotected sexual intercourse to achieve a pregnancy; SFR – standardized fertility ratio; OR – odds ratio; RR – relative risk; FDR – fecundability density ratio (identical to hazard ratio); FOR – fecundability odds ratio, where fecundability – probability of a conception during a menstrual cycle; pyrs – person years.

1) Proportion of couples with delayed conception.

2) An occurrence ratio under unity reflects reduced fertility except in the studies [10] and [13] in which the outcome has been infertility defined as non-occurrence of live birth during one observed year [10] or first years of marriage [13], and OR or RR above unity mean increased risk.

Italian study [6] are included in the multicentre study [7], and are therefore not presented. In the Polish study [9], the percentage of couples with delayed conception were similar among the exposed and unexposed subjects. However, no multivariate analyses were performed in that study. In the European multicentre study [6,7], the focus was on the time-to-pregnancy for the youngest child of the worker. The findings of this study did not point to an association between exposure to lead and decreased fertility – rather the opposite seemed to be true. By contrast, the findings of the Finnish study [8] suggest that paternal exposure to lead may be associated with decreased fertility. This conclusion was further strengthened by the observation that infertility was more common among the families of occupationally exposed men (PbB > 10 μg/dl) than in the less exposed controls [10].

Table 1B is a summary of studies focusing on male exposure to lead and infertility. The outcome measure has been the birth rate or the fertility rate in five studies on paternal lead exposure [11–15]. One study [10], was focused on the occurrence of pregnancy during the first years of marriage. The findings of four studies [10,13–15] suggest an association between lead exposure and infertility. PbB levels with positive findings were >25 μg/dl, 24–74 μg/dl, and >10 μg/dl in the three studies [10,13,15]. Two studies found no effect of lead exposure on fertility rates [11,12]. However, the design of the French study [12] has been criticized [13]. In the Danish study [11], a slight effect modification by age was observed (Bonde JP, personal communication). Exposure to lead was associated with reduced fertility among older men but not among younger ones (cut off point at 30 years of age) in a subset of battery workers with at least one PbB >20 μg/dl. A tendency towards stronger association at older age was also observed in the US [9] and Finnish [10] studies (data not shown here). Also, there seems to be a tendency toward decreased fertility with increasing duration of exposure [13,14]. However, the independent roles of duration of exposure and effect modification by age may have been difficult to distinguish.

The findings of time-to-pregnancy and fertility rate studies are contradictory. There is an obvious methodological reason for this discrepancy [16]. Involuntarily childless couples are excluded from retrospective time-to-pregnancy studies. By contrast, also voluntarily childless couples are included in the fertility rate studies. The findings of time-to-pregnancy studies may be selective underestimates whereas the opposite may be true in the studies of fertility rates.

There is a number of mechanisms by which lead may affect male reproductive health. Direct toxic effects on sperm and gonads have been observed in animal tests. Furthermore, lead exposure has been linked with chromosomal aberrations in workers. Both animal experiments and human studies suggest that the sperm chromatin structure is altered already at low exposure. A biological rationale for this finding is that lead and other cations (mercury, copper) may cause a partial replacement of zinc which is essential for sperm head chromatin stabilization. Failure of or delay in sperm chromatin decondensation may lead to decreased fertility or different kinds of DNA damage in the fertilization process [17]. Epigenetic mechanisms, i.e. non-mutational changes in the germ-line DNA that alter gene activity, are also possible [18–20]. Recently, male-mediated effects have been observed in genomic expression in 2-cell embryos fathered by male rats with PbB 15–23 μg/dl [18]. Interestingly, fertility was reduced only at a higher PbB level (27–60 μg/dl). The findings of this study suggest an effect on the regulation of gene transcription or translation rather than direct genetic damage to the male germ cell.

CONCLUSIONS

On the basis of the studies of semen quality, lead is a reproductive toxicant for human males at exposure level of PbB $\geq$40 μg/dl. There is moderate evidence that male fertility is reduced even at a lower exposure level. The results of the studies of fertility rates are consistent in showing an association between lead exposure and reduced fertility. A reservation against stronger evidence is related to the lack of information on a desired family size in studies of fertility rates, and to the paucity of time-to-pregnancy data. In future, childless subjects must be considered in retrospective studies of time-to-pregnancy. Alterations in sperm

chromatin stability or epigenetic effects may be the most probable mechanisms involved at low exposure levels.

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