

PATERNAL CHEMICAL HERBICIDE EXPOSURE AND FETAL LOSS

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Introduction

Evidence for an association between paternal exposure to phenoxy herbicides and fetal death is inconsistent. Most studies are limited by small sample size and insufficient exposure assessment. Studies of fetal loss due to paternal occupational exposure of 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) have reported no association.^{1,3} Studies of Vietnam Veterans thought to be exposed have shown conflicting results. One study attempted to directly assess exposure by measuring serum dioxin levels among Vietnam Veterans⁴ and found suggestion of an increased risk of fetal loss among the veterans exposed to low or background level and no increased risk in the highly exposed group. Human and animal studies indicate that dioxin can alter gonadotrophin and testosterone levels, but at fairly high levels of exposure.⁵

We studied the pregnancy outcomes among wives of men occupationally exposed to dioxin-contaminated chemicals and non-exposed neighborhood referents who participated in a cross-sectional medical study. In the current report, we examine whether paternal exposure to dioxin at the time of conception is associated with fetal loss. Analysis of birth defects and other adverse pregnancy outcomes in this cohort will be the subject of another report.

Methods and Materials

This reproductive health study was executed as part of a cross-sectional medical study conducted by the National Institute for Occupational Safety and Health (NIOSH). The details of the study design have been described previously.⁶ The medical study, conducted in 1987, consisted of workers employed more than 15 years earlier at two plants that produced sodium trichlorophenate (NaTCP) or 2,4,5 trichlorophenoxyacetic ester (2,4,5 T ester), both of which were contaminated with TCDD. Referents with no self-reported occupational exposure to TCDD contaminated substances were selected from the workers neighborhood at the time of the study and matched on age (± 5 years), race, and gender. Information on health status and risk factors was obtained via questionnaire and medical examination which included the drawing of blood for determination of serum dioxin.

For the reproductive health study, a brief questionnaire on reproductive history was administered to the male study subjects, including contact information for current and former wives/partners. In-depth telephone interviews with the wives of the study subjects collected detailed information on reproductive history, medical history, lifestyle factors, and occupational factors.

Each singleton conceptus conceived by a study subject was classified into pregnancy outcomes of interest, such as spontaneous abortion, stillbirth, and live birth. Other outcomes of pregnancy (e.g. tubal pregnancies, induced abortion) were excluded from the analysis. A spontaneous

abortion was defined as a pregnancy which was involuntarily terminated ≤ 20 weeks from the last menstrual period. A stillbirth was defined as an infant born after the 20th week of gestation showing no signs of life.

Serum TCDD levels were used to categorize TCDD exposure level for each pregnancy. The worker's serum dioxin level at the time of each conception was estimated using a mathematical exposure model. The TCDD level at the time of conception was based upon the following factors: serum TCDD level at time of examination, dates of employment in dioxin-related processes, and body mass index (BMI) at the time of examination and at the time of first employment. For workers, all pregnancies conceived prior to employment at the plant were considered unexposed. For referents, all pregnancies were considered unexposed.

Univariate descriptive analyses were followed by a search for medical, exposure, and lifestyle factors that could potentially confound multivariate analyses. Analyses stratified workers and referents by dioxin level at the time of conception to assess an exposure/response relationship. One analysis used the log of TCDD level and a second used categorical TCDD exposure levels (<20 ppt, 20-254 ppt, 255-1119 ppt, >1120 ppt). We selected the <20 ppt category as the lowest category since none of the referent serum samples exceeded this amount. About 20% of the worker pregnancies fell into this category. We assigned worker pregnancies to the other three exposure categories as follows: Pregnancies with ≥ 1120 ppt constituted the upper 20% of the extrapolated serum values and were placed in the highest category; the remaining 60% of the worker pregnancies were split equally into two categories 20-254 ppt and 255-1119 ppt. The confounder assessment was carried out for the two main analyses: log of TCDD value at time of conception, and categories of TCDD at time of conception.

Because individual pregnancies within the same woman cannot be considered independent events, analyses were conducted using a class of generalized estimating equations that takes into account the correlation of pregnancy outcomes for the same woman, adjusting the odds ratios and corresponding standard errors accordingly.⁷

Results and Discussion

Among living current and former wives, we were able to interview 295 (71.8%) of the worker's wives and 274 (74.7%) of the referent wives. There was a total of 1,339 eligible pregnancies, 707 referent pregnancies and 632 worker pregnancies. Among pregnancies conceived by the workers, 300 were conceived prior to employment at the study company and 332 were conceived during or after employment. The two groups were mostly white, with a high school education and a similar age at first pregnancy. The mean lifetime number of pregnancies and mean number of eligible study pregnancies per woman was also similar for workers and referents.

Median paternal TCDD levels at the time of conception was 253.9 ppt for workers whose pregnancies were conceived on or after employment at the plant with a broad range (2.9 to 16,340.0 ppt). For referents, the median paternal serum TCDD level at the time of conception was estimated to be 6.08 ppt with a range of 2.05 to 19.74 ppt. Pregnancies conceived by workers prior to exposure at the plant was assigned the median referent TCDD level of 6.08 ppt.

The overall crude rates of spontaneous abortion were 10.5 percent for worker pregnancies and 13.3 percent for referents. The potential confounders included in the final model were: mother's age at each conception, Hispanic ethnicity and thyroid medication during the first trimester. The

analysis showed no association between paternal TCDD level at the time of conception and spontaneous abortion when TCDD level was modeled as a continuous or categorical variable.

These findings are similar to other studies of paternal TCDD exposure and fetal loss. The Ranch Hand study was the only other paternal study to analyze serum TCDD levels in relation to fetal loss, and it also found no effect.⁴ The current NIOSH study was smaller than that study, but paternal serum TCDD levels were higher (median=253.9 ppt, range 2.9-16,340 and 110 ppt, range <10 - 1,424, respectively).

References

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