

SERUM DIOXIN CONCENTRATIONS AND TIME TO PREGNANCY

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Abstract

On July 10, 1976, as a result of a chemical explosion, residents of Seveso, Italy, experienced the highest levels of TCDD in a human population. Twenty years later, we initiated the Seveso Women's Health Study (SWHS), a retrospective cohort study of the reproductive health of the women. We examined the association between TCDD exposure and fertility as measured by time to pregnancy (TTP). The SWHS cohort comprises 981 women who were 0 to 40 years in 1976, resided in the most contaminated areas, and had adequate archived sera collected soon after the explosion. Individual serum TCDD exposure was measured by high-resolution mass spectrometry. We examined the relation of serum TCDD with TTP using a discrete-time analogue of the Cox proportional hazards model. Of 981 women, 472 attempted pregnancy post-explosion, and 278 had a planned or non-contracepted pregnancy resulting in a live birth. A 10-fold increase in serum TCDD was associated with a 25% increase in TTP (adjusted-fecundability Odds Ratio = 0.75, 95%CI: 0.60, 0.95), and suggests TCDD exposure may be associated with reduced fertility in the Seveso cohort.

Introduction

Exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a widespread environmental contaminant, has been associated with reduced fertility in multiple animal species at doses below toxic levels.¹ To date, no epidemiologic studies have examined the association of TCDD exposure with infertility in women. On July 10, 1976, as a result of a chemical explosion, residents of Seveso, Italy, experienced the highest levels of TCDD in a human population.² Twenty years later, we initiated the Seveso Women's Health Study (SWHS), a retrospective cohort study of the reproductive health of the women. We have previously reported that individual serum TCDD levels were associated with an increased risk for earlier menarche among women less than five years old at the time of the explosion^{3,4} and an increase in menstrual cycle length among women who were premenarcheal at exposure.⁵ We also observed a non-monotonic dose-related association of TCDD with earlier onset of natural menopause,⁶ but found no association between TCDD levels and ovarian function⁷ or with spontaneous abortion.⁸ In the present study, we examine the relationship of TCDD levels measured in sera collected near the explosion and fertility as measured by time to pregnancy (TTP).

Materials and Methods

To be eligible for SWHS, women were newborn to 40 years old at the time of the explosion, had resided in the most highly contaminated area at the time of the explosion (Zones A or B), and had adequate volumes of stored sera collected soon after the explosion (see Eskenazi et al.⁹ for details). Women were interviewed between March 1996 and July 1998. Of the 981 participants, 745 reported a pregnancy, and 472 attempted pregnancy after the explosion. For the main analysis, we included only women who delivered a live birth that was not the result of contraceptive failure (N = 278).

Details of the study are presented elsewhere.⁹ Briefly, participation included signed informed consent, structured personal interview, blood draw, and for most, a gynecologic examination and ultrasound. Medical records were requested for all gynecologic procedures/surgeries. Interviews were conducted in private by trained nurse-interviewers blind to zone of residence and serum TCDD levels. Detailed information was collected about the first post-explosion pregnancy. TTP was determined from the question, "How many months did it take to become pregnant? In other words, for how many months had you been having sexual intercourse without doing

anything to prevent pregnancy?" A calendar and pregnancy wheel were used to assist participants in recollection. The Institutional Review Boards of participating institutions approved the study.

TCDD was measured in archived sera by high-resolution gas chromatography/ high-resolution mass spectrometry methods.¹⁰ Values are reported on a lipid-weight basis in parts per trillion (ppt).¹¹ Details of serum sample selection are presented elsewhere.⁹ For non-detectable values (n=58), a serum TCDD level of one-half the limit of detection was assigned.¹²

Serum TCDD was analyzed both as a continuous variable (\log_{10} TCDD) and as a categorical variable. The cut-point for the lowest group was set at ≤ 20 ppt, the average TCDD level in serum pools collected from unexposed Italian women in 1976.¹³ The three remaining categories were defined by calculating tertiles of exposure > 20 ppt in the 278 women (20.1-44.4, 44.5-100.0, > 100 ppt).

We examined the relation of TCDD levels to TTP, parameterized as the monthly probability of conception within the first 12 months of trying. To analyze the association between serum TCDD and TTP, we estimated fecundability odds ratios (fOR) using Cox proportional hazards models adapted for discrete time data. A fOR less than 1.0 indicates reduced fecundability or longer TTP. Covariates were included in Cox models if they changed the coefficient for \log_{10} TCDD by $\geq 10\%$ or were independently associated with TTP ($p < 0.10$). Final covariates included maternal age, maternal smoking in the year before conception, parity, menstrual cycle irregularity, oral contraceptive use in the year before attempt, paternal age near the time of conception, and history of reproductive and endocrine conditions including pelvic infection, thyroid or urogenital problems.

Results and Discussion

The median lipid-adjusted serum TCDD level for the 275 women was 50 ppt. The median TTP was 2 months and 17% reported taking ≥ 12 months to conceive. For every ten-fold increase in serum TCDD, we observed a 25% increase in TTP (adjusted-fecundability odds ratio = 0.75; 95% confidence interval (CI) 0.60, 0.95) and about a doubling in odds of infertility (adjusted odds ratio = 1.9; 95% CI 1.14, 3.22). These results suggest TCDD exposure may be associated with reduced fertility in the Seveso cohort and may have important implications for fertility in industrialized areas.

Acknowledgments

We gratefully acknowledge Dr. Stefania Casalini for coordinating data collection at Hospital of Desio, and Dr. Donald Patterson and Wayman Turner (CDC) for serum TCDD measurements. We would especially like to thank the women of Seveso, Italy who participated in this study. This study was supported by Grant Numbers R01 ES07171 and F06 TW02075-01 from the National Institutes of Health, R82471 from the U.S. Environmental Protection Agency, EA-M1977 from the Endometriosis Association, 2P30-ESO01896-17 from the National Institute of Environmental Health Sciences, and #2896 from Regione Lombardia and Fondazione Lombardia Ambiente, Milan, Italy.

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