PERGAMON

Chemosphere 40 (2000) 1247–1253

CHEMOSPHERE

Seveso Women's Health Study: a study of the effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on reproductive health

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Abstract

Although reproductive effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) exposure have been reported in numerous investigations of animals, studies of this association in humans are limited. In 1976, an explosion in Seveso, Italy exposed the surrounding population to among the highest levels of TCDD recorded in humans. The relatively pure exposure to TCDD and the ability to quantify individual level TCDD exposure from sera collected in 1976 for the Seveso cohort affords a unique opportunity to evaluate the potential dose-response relationship between TCDD exposure and a spectrum of reproductive endpoints. The Seveso Women's Health Study (SWHS) is the first comprehensive study of the reproductive health of a human population exposed to TCDD. The primary objectives of the study are to investigate the relationship of TCDD and the following endpoints: (1) endometriosis; (2) menstrual cycle characteristics; (3) age at menarche; (4) birth outcomes of pregnancies conceived after 1976; (5) time to conception and clinical infertility; and (6) age at menopause. Included in the SWHS cohort are women who were 0–40 yr old in 1976, who have adequate stored sera collected between 1976 and 1980, and who resided in Zones A or B at the time of the accident. All women were interviewed extensively about their reproductive and pregnancy history and had a blood draw. For an eligible subset of women, a pelvic exam and transvaginal ultrasound were conducted and a menstrual diary was completed. More than 95% of the women were located 20 yr after the accident and roughly 80% of the cohort agreed to participate. Data collection was completed in July 1998, serum TCDD analysis of samples for analysis of endometriosis as a nested case-control study was completed in October 1998, and statistical analysis of these data should be completed in early 1999. Serum samples are now being analyzed in order to relate TCDD levels with the remaining reproductive outcomes.

1. Introduction

The compound, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), is a pervasive by-product of industrial activities, including waste incineration. There is substantial animal evidence suggesting exposure to TCDD has

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0045-6535/00/$ - see front matter
PII: S0045-6535(99)00376-8

developmental and reproductive effects. Birth outcomes associated with maternal TCDD exposure in animal studies include increased fetal mortality (Nau et al., 1986; Roman et al., 1995; Allen et al., 1979; McNulty, 1984; Bjerke and Peterson, 1994), increased fetal resorptions (Allen et al., 1979; Bjerke and Peterson, 1994), decreased litter size (Murray et al., 1979), and reduced body weight of offspring (Roman et al., 1995; Bjerke and Peterson, 1994; Murray et al., 1979; Courtney, 1976). Effects of TCDD exposure on sexual maturation, fertility and fecundity, and estrus have also been noted including delayed onset of puberty and early onset of menopause (Gray and Ostby, 1995; Thiel et al., 1994), reduced ovulation rates and alterations in menstruation (Li et al., 1995a,b; Barsotti et al., 1979), decreased estradiol and progesterone levels (Barsotti et al., 1979; Peterson et al., 1993), and reduced fertility and fecundity (Allen et al., 1979; Murray et al., 1979; Gray and Ostby, 1995; Barsotti et al., 1979; Umbreit et al., 1987). A recent animal study has stimulated much interest in the outcome, endometriosis. Rier et al. (1993) reported a dose-response increased incidence of endometriosis in adult rhesus monkeys exposed to TCDD in feed. Using standard criteria developed by the American Fertility Society, Rier et al. (1993) also found a dose-relationship with severity of the disease. Cummings et al. (1996) showed TCDD could promote the growth of surgically-induced endometriosis in rats and mice. The results of Rier et al. (1993) have recently been confirmed by Yang and Foster (1998).

What is endometriosis and why is there concern about the relationship of this disease with TCDD? Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity (Olive and Schwartz, 1993). It is often (but not always) associated with infertility, dysmenorrhea, dyspareunia, and/or pelvic pain (Olive and Schwartz, 1993). The estimated prevalence of endometriosis is about 10% in women of reproductive age (Wheeler, 1989). It is associated with significant costs for hospitalization and work days lost (Kjerulff et al., 1996; Boling et al., 1988). The average age at diagnosis is 25–29 yr (Olive and Haney, 1986) and the average time to diagnosis in the US is 11.7 yr (Hadfield et al., 1996). A definitive diagnosis for endometriosis can only be obtained via laparoscopy or laparotomy. This poses a problem when conducting a population-based epidemiologic investigation.

To date, four studies have been conducted in humans to determine if there is a relationship between endometriosis and exposure to endocrine disruptor chemicals, such as TCDD or polychlorinated biphenyls (PCBs) (Gerhard and Runnebaum, 1992; Mayani et al., 1997; Boyd et al., 1995; Lebel et al., 1998). All of the studies were hospital-based case-control studies of small sample size and conducted in populations with background-level exposures. Not surprisingly, the results of these studies, presented in Table 1, are inconclusive, with small (Gerhard and Runnebaum, 1992; Mayani et al., 1997) to no increases (Boyd et al., 1995; Lebel et al., 1998) in risk with exposure. We decided to investigate the relationship of TCDD exposure and endometriosis in a population likely to have been exposed. The largest population of heavily exposed women where the population could readily be enumerated was in Seveso, Italy.

In 1976, a chemical plant explosion in Seveso, Italy exposed the residents of the surrounding community to the highest exposure to TCDD known in humans (Mocarelli and Pocchiari, 1988). Materials from an aerosol cloud of sodium hydroxide, sodium trichlorophenate and TCDD were deposited over a 2.8 km^2 area (Mocarelli and Pocchiari, 1988). Initially, the contaminated area was divided into three major Zones (A, B, R) based on the concentration of TCDD in surface soils. Zone A, the most heavily contaminated area, sustained an immediate 25% animal mortality rate; however, residents of Zone A ($n = 736$) were not evacuated until 15 days after the accident. The residents of Zone B ($n = 4737$), the area of next greatest contamination, were not evacuated but were warned about the risk of consumption of locally-grown food products. Zone R had

Table 1
Four epidemiologic studies which have examined the relationship of endocrine disruptors and endometriosis

Authors	Study design	Size	Exposure	Results
Gerhard and Runnebaum (1992), Germany	Laparoscopy case-control	28 cases 441 controls	PCBs Chlorinated pesticides	Cases had significantly higher concentrations of PCBs (138,153,180)
Boyd et al. (1995), Pennsylvania	Laparoscopy case-control	15 cases 15 controls	Dioxins Furans PCBs	No relationship
Mayani et al. (1997), Israel	Laparoscopy case-control	44 cases 35 controls	Dioxin	Positive for TCDD: Cases 18% Controls 3%
Lebel et al. (1998), Quebec	Laparoscopy case-control	86 cases 70 controls	PCBs Chlorinated pesticides	No relationship

31,800 residents who were neither evacuated nor warned (Mocarelli et al., 1992). As evidence of the significant level of TCDD exposure, 193 cases of chloracne were reported among residents of the area, with the most severe cases (types III and IV) being diagnosed among Zone A residents (Assenato et al., 1989).

Initial reproductive studies in Seveso used Zone of residence as a proxy measure of exposure and reported the following: no change in birthweight or duration of pregnancy between 1975 and 1981 (Mocarelli et al., 1991); increased rate of spontaneous abortions from 1976 to 1978 (Fara and Del Corno, 1985); no increase in birth defects from 1977 to 1982 (Mastroiacovo et al., 1988); increased frequency of aberrant cells in cytogenetic analysis of aborted fetuses (Tenchini et al., 1983); and unusual ultrastructural appearance of placental morphology after induced abortion in 1976 (Remotti et al., 1981). Preliminary serum TCDD data, however, suggest Zone may not be a good proxy measure of individual exposure (Needham et al., 1997). For example, for 296 males and females, all living within Zone A, TCDD measurements in sera collected in 1976 ranged from not detectable (<10 ppt) to 56,000 ppt. In the first reproductive study in Seveso that used serum TCDD to measure exposure, a significant excess of female births (sex ratio = 0.54) was found in Zone A from 1977 to 1984 (Mocarelli et al., 1996). Preliminary results suggest high serum TCDD levels in both parents is associated with an excess of female births.

The Seveso cohort represents the largest population of enumerated TCDD-exposed women and among the highest exposure known in humans (Needham et al., 1991). The relatively pure exposure to TCDD (Mocarelli et al., 1990) and the ability to quantify individual level TCDD exposure from sera collected in 1976 for the Seveso cohort affords a unique opportunity to evaluate the potential dose-response relationship between TCDD exposure and a spectrum of reproductive endpoints.

2. Material and methods

The Seveso Women's Health Study (SWHS) is the first comprehensive epidemiologic study of the reproductive health of a female population exposed to TCDD. The primary objectives of the SWHS are to investigate the relationship of TCDD and the following reproductive endpoints: (1) endometriosis; (2) menstrual cycle characteristics; (3) age at menarche; (4) birth outcomes including rate of spontaneous abortion and birthweight of pregnancies conceived after 1976; (5) time to conception and clinical infertility; and (6) age at menopause. Included in the SWHS cohort are women who were 0–30 yr old (Phase I) or 31–40 yr old (Phase II) in 1976, who have adequate stored sera collected between 1976 and 1980, and who resided in the most heavily exposed areas, Zones A ($n = 234$) or B ($n = 1{,}039$) at the time of the accident in 1976. Only women who participated in Phase I are included in the investigation of endometriosis discussed below.

The current address and telephone number of the women and name, address and telephone number of their primary care physicians were located from city records or by contacting relatives. Addresses and telephone numbers were found for 99% of the women and 95% were successfully contacted. Letters were sent to the physicians and the women to inform them of the study. Women were then telephoned to schedule the interview and blood draw.

Informed consent was obtained followed by venipuncture, breakfast, and a structured 1-1/2 hour personal interview. Each woman was interviewed by a highly trained nurse–interviewer who was blind to TCDD level and residence of the woman. Information collected during the interview included sociodemographic information, personal habits, work history, detailed gynecologic and other medical history, detailed pregnancy history including time to conception of first pregnancy after the accident, menstrual cycle history and exposure to TCDD. All women in Phase I and women who were still menstruating in Phase II were scheduled for a gynecologic examination and transvaginal ultrasound. They were also asked to complete three months of a daily menstrual diary. We requested permission for medical records for any previous gynecologic ultrasound, procedure, or disease diagnosis or adverse pregnancy outcome.

The woman underwent a gynecologic examination and a transvaginal ultrasound by a gynecologist who was blind to exposure status and residence of the woman. The ultrasound was recorded on videotape, and photographs were taken of ovaries or any pathology noted. For each woman, the gynecologist completed a data form for the ultrasound and exam, which summarized the findings, and then assigned a probability of endometriosis to the women according to the criteria outlined in Table 2.

The only gold standard available for the diagnosis of endometriosis is laparoscopy. Since it is unethical to perform surgery on asymptomatic women, criteria were developed for assigning a probability of disease based on less invasive tools: gynecologic exam, transvaginal ultrasound, history, symptomatology, and past medical records. Only one other population-based cohort study has been conducted and it used similar criteria (Houston et al., 1987).

If any abnormality was noted on ultrasound, the woman was offered a repeat ultrasound. Laparoscopy was offered at the time of examination to women with either positive ultrasound, present severe symptomatology for dysmenorrhea, pelvic pain, or dyspareunia, or unexplained infertility in women less than 40 yr defined

Table 2
Criteria for probability of endometriosis

			Surgery	US	PE	Symptomatology	
						Past	Present
Cases	Definite		+				
	Highly Probable			+			
	Probable	A			+	+	
		B			+		+
		A–B			+	+	+
	Possible	C			+		
Uncertain	Possible	A				+	
		B					+
		A–B				+	+
Controls	Unlikely			−	−	−	−
	Negative		−				

+: Surgery, US, PE was conducted and results were consistent with disease.
−: Surgery, US, PE was conducted and results were consistent with no disease.

as $\geqslant 12$ months of trying to become pregnant. The criteria for offering laparoscopy were established based on the current standard of medical care. All laparoscopies were recorded on videotape and if possible, lesions were excised and sent for histologic evaluation. Of 34 women offered laparoscopy, 9 were completed and 25 refused.

The criteria for assigning the probability of endometriosis are outlined in Table 2. *Definite* disease is assigned to women who have a laparoscopy-, laparotomy- or hysterectomy-confirmed diagnosis of endometriosis. *Highly Probable* disease is assigned to women who have a positive ultrasound with cysts with characteristics specific to endometriosis. *Probable* disease is assigned to women who have a negative ultrasound, but a positive exam and positive symptomatology (A: past symptomatology; B: present; A–B: past and present). Positive exam findings include painful nodules, uterosacral ligament scarring, pain at the pouch of Douglas, Douglas nodularity, vaginal lesions/endometriotic lesions, painful/fixed adnexal masses, or fixed uterus. Positive symptomatology includes moderate or severe pain on the verbal rating scale or a visual rating of $\geqslant 5$ cm on a 10 cm line (where 0 is no pain) for dysmenorrhea, pelvic pain, or dyspareunia. *Possible* disease is assigned to women who have both a negative ultrasound and a negative exam, but positive symptomatology (A: past symptomatology; B: present; A–B: past and present). Category C of *Possible* disease is assigned to women who have a positive exam, but a negative ultrasound and no symptomatology. *Unlikely* disease is assigned to women who have a negative ultrasound, negative exam, and negative symptomatology. *Negative* disease is assigned to women who have undergone laparoscopy or abdominal hysterectomy, but no endometriosis was found.

For each woman examined, a consultant gynecologist also reviewed the gynecologic exam and ultrasound forms, videotape, and photographs, and independently assigned a probability of disease to the woman based on the criteria in Table 2.

Given the cost of analyzing small volumes of serum for TCDD, we chose to maximize study power by conducting a nested case-control study of endometriosis. For the purpose of this study, we defined a "case" as those who fulfilled criteria for *Definite*, *Highly Probable*, *Probable* or *Possible C*. Those who we considered "uncertain" for endometriosis are those who fulfilled criteria for *Possible A*, *B* or *A–B*. Those who we considered to be not diseased or "controls" were those who fulfilled criteria for *Unlikely* or *Negative*. Individual level TCDD exposure was measured in sera for 100% sample of endometriosis "cases" and a 100% sample of controls. To increase the ability to estimate risk, sera were analyzed for a 50% sample of "uncertain". Archived sera were located and sent to the Centers for Disease Control (CDC) for TCDD analysis using high-resolution gas chromatography/high-resolution mass spectrometry methods previously described (Patterson et al., 1987).

Throughout the diagnostic process, those responsible for diagnosis (P.V., D.O., B.E.) were blind to the women's exposure (Zone of residence or serum TCDD level), and all others were blind to the women's disease status. The interviewers and the women were never informed of the specific study hypothesis.

3. Results

Recruitment of the women began in March 1996 and both phases were completed in July 1998. Of the 953

Table 3
Distribution of women by their probability of having endometriosis

Cases ($n = 82$)	Definite		14	
	Highly Probable		5	
	Probable	A	12	12.6%
		B	21	
		A–B	11	
	Possible	C	19	
Uncertain ($n = 260$)	Possible	A	141	
		B	87	
		A–B	32	
Controls ($n = 307$)	Unlikely		268	
	Negative		39	
	Excluded[a]		2	
	Total		651	

[a] Women diagnosed with Turners Syndrome.

women in Phase I (0–30 in 1976), 12 (1.2%) could not be contacted and 16 (1.6%) were ill or dead. Of the 925 eligible women, 751 (81%) completed the interview and blood draw, 5 (<1%) completed blood draw only, and 169 (18%) refused to participate. Of the 320 women in Phase II (31–40 in 1976), 5 (1.6%) could not be contacted and 17 (5%) were ill or dead. Of the 296 eligible women, 230 (78%) completed the interview and blood draw, 1 (<1%) completed blood draw only, and 65 (22%) refused to participate.

Of the 751 women who were interviewed in Phase I, 651 (87%) completed the gynecologic examination/ultrasound and 100 (13%) refused. For the nested case-control study analysis, the 651 women from Phase I who completed the examination are included and a breakdown of the probability of disease for these women is presented in Table 3. Including women who are *Definite*, *Highly Probable*, *Probable*, or *Possible C* for disease in the case group yields an estimated prevalence of disease of about 13%.

TCDD measurements in sera have been completed for all women in the case and control groups and for 50% of the women in the uncertain group. Statistical analyses are ongoing to determine if there is a relationship between TCDD level and endometriosis. For the final case control study, women who did not undergo a pelvic examination will be excluded ($n = 50$) from the analysis. Serum TCDD analyses are currently being conducted for Phase II women. Phases I and II women will be included in the study of TCDD levels and other reproductive outcomes such as age at menarche, menstrual cycle characteristics, birth outcomes of pregnancies conceived after 1976, time to conception and clinical infertility, and age at menopause.

4. Discussion

In conclusion, there is substantial animal evidence suggesting that TCDD has developmental and reproductive effects. Previous human studies either include small numbers of women, background levels of exposure or no measure of individual exposure. The SWHS is the first comprehensive reproductive health study of a female TCDD-exposed cohort. Exposure has been assessed by TCDD in serum collected soon after the explosion, between 1976 and 1980. Data collection is complete and analysis of endometriosis as a nested case-control study is underway.

Acknowledgements

Supported by Grant Numbers R82471 from the US Environmental Protection Agency, R01 ES07171 and 2P30-ES01896 from the National Institute of Environmental Health Services, EA-M1977 from the Endometriosis Association, and by grant number 2896/96 from Regione Lombardia and Fondazione Lombardia Ambiente, Milan, Italy.

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