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Reproductive Outcomes Among Women Exposed to a Brominated Flame Retardant In Utero

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Abstract

The authors studied 194 women exposed to polybrominated biphenyls (PBB) in utero when their mothers consumed products accidentally contaminated in Michigan in 1973. Generalized estimating equations were used to examine the effect of in utero PBB exposure on adult pregnancy-related outcomes. Compared to those with the lowest exposure (≤1 ppb), those with mid-range (>1–3.16 ppb) and high (≥3.17 ppb) PBB exposure had increased odds of spontaneous abortion with wide confidence intervals (odds ratio [OR] = 2.75, 95% confidence interval [CI] = 0.64–11.79, OR = 4.08, 95% CI = 0.94–17.70; respectively; *p* for trend = .05). Exposure during infancy to PBB-contaminated breast milk further increased this risk. Time to pregnancy and infertility were not associated with in utero exposure to PBB. Future studies should examine the suggested relationship between spontaneous abortion and other brominated flame retardants.

Keywords

brominated flame; retardant; fertility; PBB; polybrominated flame retardant; spontaneous abortion

Brominated flame retardants (BFRs) are used in electronics, furniture, textiles, and other products to prevent injury and property damage. Human exposure occurs when BFRs leach from products and are inhaled as dust or consumed with food.[1–3] Despite widespread exposure, [4] information regarding possible health effects among humans is limited.

Polybrominated biphenyls (PBBs), a class of halogenated BFRs, were manufactured in the early 1970s in the United States and added to plastic products to decrease flammability. Although PBB production ceased in 1979 in the United States, concern remains for their long-term health effects given their stability and accumulation in the environment and adipose tissue of humans and animals.[5,6] Furthermore, production of structurally related organohalogen flame retardants continues.[7,8]

Increased spontaneous abortions have been associated with concurrent exposure to PBBs in animals,[9–12] but not humans.[13,14] The effect of in utero exposure may differ from adult exposure on reproductive outcomes because the initiation of follicular development occurs in utero. Furthermore, the concentration of exposure relative to body weight is larger for a fetus compared to an adult. Evidence for second-generation reproductive effects is found from related compounds in animal models,[15–17] and in utero diethylstilbestrol (DES) exposure has been associated with spontaneous abortions in women.[18]

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This study reports reproductive outcomes, including spontaneous abortion, among women exposed to PBB in utero as the result of an industrial accident in 1973. We previously demonstrated placental transfer of PBB[19] and found evidence of a transgenerational effect of PBB exposure on girls' puberty within this cohort.[20]

METHODS

Study population

In 1973, PBB entered the food chain when bags of Firemaster, a brominated flame retardant, were inadvertently included with a shipment of NutriMaster, a nutritional cattle feed supplement. Michigan residents were exposed to PBB through the consumption of animal products such as meat, eggs, and dairy products.[21–23] Beginning in 1976, the Michigan Department of Community Health (MDCH) enrolled ~4,000 individuals with a range of exposure levels into a cohort study for long-term health monitoring. This cohort of exposed individuals and their offspring have been followed through the present.

The study population includes second-generation female cohort members. We defined generations based on the route of PBB exposure. First-generation cohort members were exposed to PBB through the consumption of contaminated food, between the time when contaminated feed was delivered to Michigan farms (~May 1973), and the time at which the farms were quarantined (~May 1974). Infants born after July 1, 1973, were potentially exposed in utero and are considered the "second generation."

The primary source of information for the present study was 2 telephone interviews of female cohort members, including questions on reproductive and general health. These interviews took place in 1997–1998 and 2003–2006. Of 1,342 participants, 247 had potential in utero PBB exposure (born after July 1, 1973). We excluded 6 women with unknown PBB levels and 47 women conceived after July 1, 1973, but before May 10, 1974, because they may not have been exposed to PBB for their entire gestation. The final sample size was 194 women.

The Institutional Review Board at Emory University in Atlanta, Georgia, the Centers for Disease Control and Prevention in Atlanta, Georgia, and the Michigan Department of Community Health in Lansing, Michigan, approved the study. Participants gave informed consent.

Outcome assessment

Seventy-three gravid women reported a total of 142 pregnancies. For each pregnancy, women reported time to pregnancy, pregnancy complications, whether or not they smoked or consumed alcohol during pregnancy, and pregnancy outcomes.

Time to Pregnancy—For each pregnancy in which a woman was not taking measures to prevent the pregnancy, she reported the number of months it took to conceive the pregnancy. Of the 142 pregnancies, women reported that they were not taking measures to prevent 111 of these pregnancies. One was missing a response for time to pregnancy. Thus, 110 pregnancies from 61 women were included in the time to pregnancy analysis.

Pregnancy Complications—During the 2003 interview, participants reported whether they had developed high blood pressure/preeclampsia/toxemia, diabetes/high blood sugar, infection of the reproductive tract, or any other pregnancy-related complications (specified with an open-ended response) during each pregnancy. The 1997 interview did not ask women to report pregnancy complications. Of the 142 pregnancies, 24 pregnancies were

missing information on pregnancy complications because they were reported in the 1997 interview (n = 14) or they were current pregnancies (n = 10). We limited our analysis to hypertension because of the sparse numbers in other complication categories.

Pregnancy Outcome—The 73 gravid women reported 142 pregnancy outcomes, including single live birth, multiple live births, spontaneous abortion, elective abortion, stillbirth, other (such as an ectopic or molar pregnancy), or "currently pregnant" at the time of the interview. We obtained outcomes for the current pregnancies from birth certificates, medical records, and in 1 case, a follow-up telephone interview. In the analyses of spontaneous abortion, outcomes other than live birth or spontaneous abortion (n = 8) were excluded resulting in a sample size of 134. Medical records were available for 30% (7 out of 23) of the spontaneous abortions, and all confirmed the self-reported spontaneous abortions.

Infertility—Women reported whether they had ever had unprotected intercourse for a year or more without conceiving. The analysis of infertility was limited to married women participating in the 2003 interview (n = 74) because of the young ages of the second-generation participants of the 1997 interview (maximum age = 22) and their unknown marital status.

Exposure assessment

Serum PBB levels were measured at the time of enrollment in the cohort using gas chromatography with electron-capture detection.[24,25] PBB quantification was based on the main congener, PBB-153 or 2,2′,4,4′,5,5′-hexabromobiphenyl, which made up 61% of the fire-retardant mixture.[26] The coefficients of variation for PBB ranged from 7.1% to 14.0%, and recovery ranged from 80% to 90%.[25] The limit of detection (LOD) for serum PBB was 1 part per billion (ppb). Samples were collected from nonfasting participants, and serum lipid levels were not available.

We used 2 surrogate measures for in utero PBB exposure. First, we used the participant's mother's (the first-generation) enrollment serum PBB concentration. Second, we estimated PBB exposure at the time of the participant's conception by applying a decay model to her mother's enrollment serum PBB concentration. Briefly, this model included body mass index (BMI) at initial PBB measurement, parity, age, smoking status, and breastfeeding history. The decay model was validated using a subset of women who had multiple samples taken over time. The correlation between the predicted and observed concentrations was r = .93.[27] The estimated date of conception was calculated by subtracting the gestational age (reported in the mother's interview) from the date of birth.

Being breastfed during infancy is an additional route of PBB exposure during the perinatal period. We assessed the interaction between in utero PBB exposure and exposure through breast milk among the subgroup (86% of study participants) for whom we have this information from telephone interviews.

Statistical analyses

The participants' estimated in utero PBB exposure was categorized into 3 groups based on the limit of detection (LOD) and themedian exposure of those above the LOD(≤1, 1.1–3.16, ≥ 3.17 ppb). Other characteristics of study participants were categorized as follows: age at interview (18–20, 21–23, 24–27, and 28–31 years), BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), and gravidity (1, 2, 3+). We compared the percentage of women in each demographic category among all participants (n = 194), among the subgroup of gravid women (n = 73) who were used in the pregnancy-related analyses, as well as among the

married participants of the 2003 interview (n = 74) who were used in the analysis of infertility.

We examined the unadjusted association between in utero PBB exposure and the reproductive outcomes, including time to pregnancy (continuous and dichotomized at 12 months), hypertension during pregnancy, pregnancy outcome (spontaneous abortion versus live birth), and infertility with chisquare tests and a Cochran-Armitage test of trend.

Time to Pregnancy—For adjusted analyses, we dichotomized time to pregnancy (≤12 vs > 12 months), and used generalized estimating equations (GEEs) to model the odds of a long waiting time to pregnancy with an exchangeable correlation structure to control for the lack of independence among the pregnancies from an individual woman. As a comparison, we limited our analysis to the first pregnancy for each woman (n = 73) and examined time to pregnancy continuously using survival analysis. We calculated odds ratios comparing those with a mid-range (>1–3.16 ppb) or high (≥3.17 ppb) PBB exposure to those with little or no PBB exposure (≤1 ppb) and calculated 95% confidence intervals.

Pregnancy Hypertension and Spontaneous Abortion—We modeled the odds of pregnancy-induced hypertension and, separately, the odds of spontaneous abortion using generalized estimating equations (GEEs), with an exchangeable correlation structure, and calculated odds ratios and 95% confidence intervals.

Infertility—We used logistic regression to model the odds of infertility (reporting a history of 12 months or more of unprotected intercourse without becoming pregnant) among all married participants and calculated odds ratios and 95% confidence intervals.

Within each model, we considered the following as a priori potential confounders: maternal age at pregnancy, tobacco use (ever and around the time of conception), alcohol consumption during the first trimester, endometriosis, and pelvic inflammatory disease. None of these covariates altered the effect estimates of any outcomes by more than 10%, so we present results unadjusted for confounders. We also considered effect modification by whether or not the participant was breastfed. The data analysis used SAS software, Version 9.2 (Cary, NC).

RESULTS

The average age of the female participants was 23.3 years (range: 18–31 years). Gravid participants (N = 73) tended to be older than the entire group and were more likely to have smoked and had higher BMI (Table 1). Among married women who participated in the 2003 interview (N = 74), 22 women (30%) reported having unprotected intercourse for 12 months or more without conceiving (Table 1).

Characteristics of the 142 pregnancies (from 73 women) are shown in Table 2. Twenty-three pregnancies ended in spontaneous abortion (16%). One stillbirth was reported by a participant whose PBB level was below the LOD. In 14% of the pregnancies (n=20), the mother experienced pregnancy-induced hypertension. Participants reported smoking around the time of conception for 35% of the pregnancies and drinking alcohol in the first trimester for 11% of pregnancies.

Among the most highly exposed women (PBB levels ≥3.17 ppb), 26% of pregnancies ended in spontaneous abortion compared to only 9% among those least exposed (≤1 ppb) (Cochran-Armitage test for trend p = .04; Table 3). Pregnancy-induced hypertension was lowest among those most exposed, but this difference did not reach statistical significance in

unadjusted analyses, and there was no dose response. No associations with PBB exposure were seen for time to pregnancy or infertility. The results were similar when we examined maternal serum PBB concentration at enrollment.

In analyses adjusting for multiple pregnancies from a single woman (Table 4), we found a significant dose response relationship between a woman's maternal enrollment PBB exposure and her risk of spontaneous abortion ($p = .05$). Compared to those with the lowest exposure (≤1 ppb), those with PBB levels in the mid range (> 1–3.16 ppb) and the highest range (≥3.17 ppb) had increased odds of spontaneous abortion with wide confidence intervals (odds ratio [OR] = 4.08, 95% confidence interval [CI] = 0.94–17.70; OR = 2.75, 95% CI = 0.64–11.79, respectively). This dose-response relationship was attenuated when looking at a woman's estimated PBB level at conception ($p = .16$). When we examined effect modification by breastfeeding, the data were sparse, resulting in unstable effect estimates. Eight of 23 women (35%) who were exposed to ≥3.17 ppb PBB in utero and who were breastfed during infancy reported spontaneous abortions. This risk was higher than among women with the lowest in utero exposure who were not breastfed (OR = 3.59, 95% CI = 0.29–43.80).

In adjusted analyses, pregnancies to women in the highest category of PBB exposure was associated with a decreased risk of pregnancy-induced hypertension (OR = 0.22, 95% CI = 0.05–1.05). However, no increased risk was found for mid-range in utero PBB exposure (OR = 1.18, 95% CI = 0.41–3.35) compared to those in the referent group. To further investigate this relationship, we divided in utero PBB exposure into quartiles, and no dose response was evident. Compared to the lowest exposure group, the ORs for the 2nd, 3rd, and 4th quartiles were 0.73, 3.96, and 0.32, respectively.

Of the 110 pregnancies with reported time to pregnancy, the majority of pregnancies (67%) were conceived within 3 months of unprotected intercourse. No association was seen between in utero PBB exposure and time to pregnancy of greater than 12 months (Table 4). Furthermore, no association was seen with time to pregnancy as a continuous variable or with self-reported infertility (ever having unprotected intercourse for 12 months or more without becoming pregnant).

COMMENT

The results suggest a dose-response relationship between in utero PBB exposure and the risk of spontaneous abortion in adulthood. Exposure during infancy to PBB-contaminated breast milk may increase this risk further. Time to pregnancy and infertility were not associated with in utero exposure to PBB.

The spontaneous abortion results are supported by animal studies showing second-generation effects among similar compounds, including suppressed egg laying among kestrels[15] and increased fetal resorption in rats.[16] Although we might expect increased rates of spontaneous abortion to be reflected in increased times to pregnancy, this was not apparent in our sample. However, we were limited by retrospective self-report of both spontaneous abortions and time to pregnancy.

Exploratory analyses were performed to examine the relationship between the increased risk of spontaneous abortion found here and prior results suggesting earlier puberty among girls with high in utero exposure.[20] There was some suggestion of an interaction with menarche, but the sample size was too small for formal analyses. Among women in the highest exposure group, those reporting a spontaneous abortion had mean age at menarche of 11.4 years compared to a mean age at menarche of 12.3 among women reporting live births.

Among those least exposed no difference in age at menarche is seen (means: 12.1 vs 12.0 years). Additional studies are needed to further explore this possible interaction.

Pregnancy-induced hypertension appeared higher than expected[28] in this population, which likely indicates a mixing of chronic hypertension with pregnancy-induced hypertension. Because of the lack of dose response, the association between PBBs and decreased risk of hypertension is likely due to chance. Although not statistically significant, smoking during pregnancy was associated with a decreased risk of hypertension as has been shown in the literature.[29] However, smoking did not confound the association between PBBs and hypertension.

In utero exposures may affect adulthood reproductive capabilities by interfering with follicular or uterine development during embryogenesis. Primordial follicles form during fetal development and supply the ovarian cycle throughout life. These early events in folliculogenesis are regulated by estrogens, progesterone, and androgens. Estrogen-deprived embryos of rats, mice, and baboons have shown decreased number of primordial follicles.[30]

Although the exact mechanism of PBB action is unknown, the Firemaster mixture has demonstrated estrogenic and antiestrogenic activity in vitro[31–34] and animal models show effects on hormonal activity, including accelerating steroid sex hormone metabolism,[35] attenuating the normal physiologic responses to estrogen,[34,36] lengthening estrous cycles, [37] and decreased serum progesterone concentrations.[38,39] Thus, it is plausible that PBBs may alter the hormonal milieu of the developing fetus and its pool of primordial follicles.

Our study was limited by the young age of second-generation participants, which led to small sample sizes and wide confidence intervals. This made it particularly difficult to evaluate the combined effect of exposure to PBBs in utero and through breastfeeding. Both spontaneous abortion and time to pregnancy were self-reported retrospectively. Thus, the time to pregnancy analysis was conditional on a woman becoming pregnant and we were not able to control for the frequency and timing of intercourse. The young age of our study population (18 to 31 years) is the likely reason that we did not detect a maternal age affect on spontaneous abortion.

Detecting an increase in spontaneous abortions with an environmental exposure is complicated by the timing of the spontaneous abortion. Early losses often go unnoticed by women. By measuring the human chorionic gonadotropin (hCG) concentration in daily urine samples of study participants, Wilcox and his colleagues[40] found that 22% of pregnancies detected by the researchers were lost prior to being clinically recognized (by a home pregnancy test or a diagnosis by a physician). Because the present study used self-reported data, it is likely that spontaneous abortions were underreported (16% of pregnancy outcomes). Thus, it is noteworthy that 35% of pregnancies in the highest exposure category (participant's in utero PBB level≥3.17 ppb and breastfed during infancy) ended in self-reported spontaneous abortions.

To our knowledge, this is the first study to provide information on reproductive outcomes among women with in utero PBB exposure. Although the production of PBBs ceased in 1979, the long-term follow-up of this cohort offers an unusual opportunity to study the transgenerational effects of a brominated flame retardant. Furthermore, the use of a biological marker of PBB exposure and a decay model allowed a more accurate estimate of the in utero PBB exposure. This study suggests an association between in utero PBB exposure and an increased risk of spontaneous abortion during adulthood. The transgenerational effect of brominated flame retardants on reproductive outcomes should be replicated in other populations.

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Table 1

Characteristics of Second-Generation Women Interviewed in 1997–1998 and/or 2003–2006

	All participants (*N* = 194)		Gravid participants[b] (*N* = 73)		Married participants of the 2003 interview[c] (*N* = 74)	
	n	%[a]	*n*	%[a]	*n*	%[a]
Participant's estimated in utero PBB exposure[d]						
≤1 ppb	62	32.0	19	26.0	25	33.8
>1–3.16 ppb	66	34.0	27	37.0	26	35.1
≥3.17 ppb	66	34.0	27	37.0	23	31.1
Participant's maternal enrollment PBB level						
≤1 ppb	73	37.6	26	35.6	32	43.2
>1–3.16 ppb	55	28.4	21	28.8	19	25.7
≥3.17 ppb	66	34.0	26	35.6	23	31.1
Participant was breastfed[e]						
Yes	91	46.9	32	43.8	30	40.5
No	76	39.2	32	43.8	31	41.9
Missing	27	13.9	9	12.3	13	17.6
Interviewed between						
1997–1998 only	28	14.4	8	11.0	—	
2003–2006 only	108	55.7	29	39.7	35	47.3
Both interviews	58	29.9	36	49.3	39	52.7
Age at interview (years)						
18–20	44	22.7	8	11.0	2	2.7
21–23	59	33.0	18	24.7	18	24.3
24–27	56	28.9	26	35.6	31	41.9
28–31	30	15.5	21	28.8	23	31.1
Ever smoked						
Yes	68	35.1	38	52.1	30	40.5
No	126	64.9	35	47.9	44	59.5
BMI at interview (kg/m^2)						
<18.5	8	4.1	1	1.4	1	1.4

	All participants (*N* = 194)		Gravid participants[b] (*N* = 73)		Married participants of the 2003 interview[c] (*N* = 74)	
	n	%[a]	*n*	%[a]	*n*	%[a]
18.5–24.9	98	50.5	30	41.1	32	43.2
25.0–29.9	50	25.8	25	34.3	25	33.8
≥30.0	37	19.1	17	23.3	16	21.6
Missing	1	0.5	—		—	
Health insurance status (at interview						
Yes	157	80.9	65	89.0	65	87.8
No	36	18.6	7	9.6	9	12.2
Missing	1	0.5	1	1.4	—	
Frequency of health care visits						
< Once per year	51	26.3	10	13.7	10	13.5
≥Once a year	141	72.7	62	84.9	63	84.1
Missing	2	1.0	1	1.4	1	1.4
Had unprotected intercourse for ≥12 months without conceiving						
Yes	—		—		22	29.7
No	—		—		52	70.3
Total number of pregnancies						
0	119	61.3	—		21	28.4
1	34	17.5	32	43.8	18	24.3
2	24	12.4	24	32.9	20	27.0
3+	17	9.8	17	23.29	15	20.3

[a] Percentages may not sum to 100 due to rounding.

[b] Gravid women were included in analysis of spontaneous abortion, time to pregnancy, pregnancy complications, and birth defects. The number of pregnancies differs between all participants and the gravid participants because 2 gravid women did not report these outcomes.

[c] Married participants of the 2003 interview were included in the analysis of infertility.

[d] The participant's estimated in utero exposure was determined based on a decay model applied to her mother's (first-generation) enrollment PBB level.

[e] Breast feeding was another potential route of exposure for the participants in the study.

Table 2

Pregnancy Characteristics of 73 Gravid Second-Generation Women Interviewed in 1997–1998 and/or 2003–2006

	Pregnancies (*N* = 142)	
	n	**%**[a]
Maternal age at conception of pregnancy		
13–19	45	31.7
20–24	69	48.6
25–28	28	19.7
Pregnancy outcomes		
Single live birth	110	77.5
Multiple live birth	1	0.7
Spontaneous abortion	23	16.2
Elective abortion	7	4.9
Stillbirth	1	0.7
Missing	—	
Pregnancy complications		
Hypertension	20	14.1
Gestational diabetes	2	1.4
Infection	4	2.8
Anemia	2	1.4
Edema	1	0.7
Uterine bleeding	2	1.4
Preterm labor	1	0.7
Kidney stones	1	0.7
Missing[b]	24	16.9
Smoked around the time of conception		
Yes	50	35.2
No	92	64.8
First trimester alcohol consumption		
Yes	16	11.3
No	124	87.3
Missing	2	1.4

[a] Percentages may not sum to 100 due to rounding.

[b] Participants of the 1997 interview (*N* = 14) and those currently pregnant at the time of interview (*N* = 10) were not asked about pregnancy complications.

Table 3

Unadjusted Association Between Reproductive Outcomes and the Estimated Maternal In Utero PBB Exposure

		Estimated in utero PBB exposure (ppb)							
		≤1		>1–3.16		≥3.17			
	N	*n*	%	*n*	%	*n*	%	χ^2 *p* value	Trend *p* value[b]
Pregnancy outcome									
Live birth	111	32	91.4	45	84.9	34	73.9	.10	.04
Spontaneous abortion	23	3	8.6	8	15.1	12	26.1		
Hypertension in pregnancy									
No	98	27	79.4	36	76.6	35	94.6	.07	.09
Yes	20	7	20.6	11	23.4	2	5.4		
Time to pregnancy									
≤12 months	103	28	90.3	37	92.5	38	97.4	.49[a]	.22
>12 months	7	3	9.7	3	7.5	1	2.6		
Infertility[c]									
No	52	17	68.0	19	73.1	16	69.6	.92	.90
Yes	22	8	32.0	7	26.9	7	30.4		

[a] Fisher's exact test *p* value.

[b] Cochran-Armitage test of trend.

[c] Participants were asked whether they had ever gone for 12 months or more without conceiving.

Table 4

Association Between In Utero PBB Exposure and Reproductive Outcomes Adjusting for Multiple Pregnancies Within a Woman

		Estimated PBB level at conception (ppb)					Enrollment PBB level (ppb)				
		≤1>1–3.16		≥3.17			≤1>1–3.16		≥3.17		
		OR	95% CI	OR	95% CI	*p* value	OR	95% CI	OR	95% CI	*p* value
Spontaneous abortion[a]	Ref	1.52	0.35–6.58	2.82	0.64–12.35	.16	Ref	2.75	0.64–11.79	4.08	0.94–17.70	.05
Hypertension in pregnancy[a]	Ref	1.18	0.41–3.35	0.22	0.05–1.05	.04	Ref	1.38	0.48–3.96	0.24	0.05–1.10	.06
Time to pregnancy >12 months[a]	Ref	0.65	0.1–4.14	0.29	0.03–3.0	.27	Ref	1.14	0.18–7.37	0.39	0.04–4.03	.55
Infertility[b]	Ref	0.78	0.23–2.62	0.93	0.27–3.16	.90	Ref	0.79	0.22–2.79	0.96	0.30–3.07	.92

[a] Generalized estimating equations accounted for the nonindependence of multiple pregnancies per woman.

[b] Logistic regression was used to model infertility.