Published in final edited form as:
Environ Res. 2007 October ; 105(2): 247–255.

Risk of Spontaneous Abortion among Women Exposed to Polybrominated Biphenyls

Chanley M. Small, PhD[a,*], **Keely Cheslack-Postava, MSPH**[b], **Metrecia Terrell, MSPH**[a], **Heidi Michels Blanck, PhD**[c], **Paige Tolbert, PhD**[a,d], **Carol Rubin, DVM, MPH**[e], **Alden Henderson, PhD**[e], and **Michele Marcus, PhD**[b,d]

a *Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA*

b *Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD USA*

c *Division of Nutrition & Physical Activity, Centers for Disease Control and Prevention, Atlanta, GA, USA*

d *Department of Environmental Health Sciences, Rollins School of Public Health, Emory University, Atlanta, GA, USA*

e *Health Studies Branch, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA*

Abstract

Accidental contamination of livestock in Michigan in 1973 with polybrominated biphenyls (PBBs) led to the establishment of a registry of exposed individuals in 1976. At the time of enrollment, serum was collected and analyzed for PBBs and polychlorinated biphenyls, PCBs. In 1997, women aged 18 years or older and active in the registry were invited to participate in a telephone interview about their health. Using generalized estimating equations to account for correlated outcomes within the same woman, we assessed the risk of spontaneous abortion among 529 women with 1344 potentially exposed pregnancies. PBB and PCB exposure were not associated with risk of spontaneous abortion after adjusting for maternal age at conception, age at menarche, and prior infertility. Compared to pregnancies with PBB exposure below the limit of detection, those with levels above 2.9 ppb had a non-significant reduced odds of spontaneous abortion (adjusted OR=0.73; 95% CI= 0.47-1.13). Compared to pregnancies with PCB exposure below the limit of detection, those with levels above 6.5 ppb had little difference in risk (adjusted OR=0.91; 95% CI= 0.59-1.41). Maternal age at conception above 34 years was significantly associated with elevated risk of spontaneous abortion (OR=2.46; 95% CI= 1.10-5.49). The effect of prior infertility was of borderline significance (OR=1.52; 95% CI= 0.98-2.38). Older age at menarche was associated with decreased risk of spontaneous abortion (adjusted OR=0.58; 95% CI: 0.38-0.89, comparing menarche at 12-13 with menarche <12). Our results do not support an association between exposure to PBBs or PCBs and risk of spontaneous abortion.

*Corresponding Author: Chanley M Small, Ph.D. Department of Epidemiology Emory University 1518 Clifton Rd. Atlanta GA 30322 Phone: 404-727-1268, Fax: 404-727-8737 csmall@sph.emory.edu

Protocol Approval: As stated in the Methods section, the Institutional Review Board at Emory University, Atlanta, GA, the Centers for Disease Control and Prevention, Atlanta, GA, and the Michigan Department of Community Health reviewed and approved the protocols used in this study. The participants gave informed consent.

Keywords

Spontaneous Abortion; Miscarriage; Pregnancy; Polybrominated Biphenyls; Polychlorinated Biphenyls

1. Introduction

In 1973, the inadvertent substitution of a livestock feed supplement (NutriMaster) with fire retardant (FireMaster) led to widespread contamination of meat and dairy products in Michigan with polybrominated biphenyls (PBBs). Exposed cattle experienced reproductive abnormalities (Jackson et al., 1974). Public concern over possible adverse health outcomes in humans prompted the Michigan Department of Public Health to initiate a registry of exposed residents in 1976. Details of the incident and cohort are described elsewhere (Carter, 1976; Fries, 1985).

PBBs are a member of a structurally similar family of polyhalogenated aromatic hydrocarbon chemicals, including polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), which have been shown to cause endocrine disruption in humans and wildlife (Tolbert, 2000). Although the production of PBBs and PCBs has ceased, concern over their health effects remains because they persist in the environment, are fat soluble, bioaccumulate in the food chain, and have a long half-life in the body. Furthermore, similar persistent organic chemicals continue to be produced and used worldwide.

PBBs have been associated with decreased litter size and increased risk of spontaneous abortion, stillbirth, or fetal resorption in mice, rats, rhesus monkeys, mink and cattle experimentally exposed to PBBs (Jackson et al., 1974; Beaudoin, 1977; Moorhead et al., 1977; Allen et al., 1978; Aulerich et al., 1979; Welsch et al., 1985; Schanbacher et al., 1987). PCBs have been associated with decreased litter size, spontaneous abortion or fetal resorption in minks, rhesus monkeys, rats, guinea pig, and rabbits (Aulerich et al., 1973; Linder et al., 1974; Barsotti et al., 1976; Altman et al., 1979; Bleavins et al., 1980; Brunstrom et al., 1982; Brezner et al., 1984; Aulerich et al., 1985; Arnold et al., 1990; Arnold et al., 1993; Seiler et al., 1994; Arnold et al., 1995). In humans, PBB exposure was not associated with fetal mortality after 20 weeks gestation (Humble et al., 1984). PCB exposure has been associated with human spontaneous abortions or stillbirths in some (Bercovici et al., 1983; Leoni et al., 1989; Gerhard et al., 1998; Yu et al., 2000), but not all studies (Dar et al., 1992; Mendola et al., 1995; Yang et al., 2000; Sugiura-Ogasawara et al., 2003; Axmon et al., 2004).

The present study is the first, to our knowledge, to evaluate the association between PBB exposure and pregnancy loss prior to 20 weeks gestation. Because Michigan residents are exposed to PCBs through the environment (e.g. diet including fish), the association between PCB exposure and spontaneous abortion was also examined.

2. Methods

2.1 Study Population

Beginning in 1976, the Michigan Department of Public Health enrolled over 4000 Michigan residents who lived on or consumed food from contaminated farms into a long-term registry. In 1997, women aged 18 years or older, and active in the registry were invited to participate in a telephone interview about their health. Of 1530 eligible women, 88 (6%) could not be located, 9 (0.6%) were deceased, and 8 (0.5%) were too ill to participate. Of the remaining 1425 women, 1185 (83%) agreed to participate, of whom 1045 (88%) had serum PBB levels measured at enrollment into the registry. For the present analysis, we included women with a history of at least one pregnancy who had potential dietary exposure to PBB. One hundred forty-eight nulligravid women and 10 women with potential *in utero* PBB exposure were excluded. PBB exposure at the time of pregnancy was estimated using a decay model described below in “Exposure Assessment.” We were unable to estimate PBB exposure for 44 pregnancies in which women did not report a date of pregnancy end or in women whose adult body mass index (BMI=kg/m^2) at registry enrollment was not available (both of which were required to estimate PBB exposure at the time of the pregnancy). The remaining 880 women reported 2612 live singleton or twin births, 389 spontaneous abortions, 58 elective abortions, 23 ectopic pregnancies, 21 stillbirths, 2 molar pregnancies and 26 pregnancies in progress at the time of interview. Our analyses include the 861 women reporting one or more live births or spontaneous abortions. The Institutional Review Board at Emory University, Atlanta, GA, the Centers for Disease Control and Prevention, Atlanta, GA, and the Michigan Department of Community Health approved the protocols, and the participants gave informed consent.

2.2 Exposure Assessment

Initial serum PBB and PCB levels were measured at enrollment in the registry using gas chromatography with electron-capture detection (Burse et al., 1980; Kuwahara et al., 1980; Needham et al., 1981). Before being measured for PBB, the denatured serum sample went through an ether-ethyl or hexane-ether extraction and then through either a Florisil or Florisil and silica gel column. The size of the chromatography peak was compared to a control sample containing a known quantity of FireMaster-FF1 ®. The limit of detection for PBB in the serum was 1 part per billion (ppb=μg/L). PBB quantitation was based on the main congener, 2,2',4,4', 5,5'-hexa-bromobiphenyl, which made up 61% of the fire retardant mixture (Hass et al., 1978). The reliability of this method was assessed by running repeat measurements on samples with known quantities of PBB. The coefficients of variation, a measure of variability standardized by the mean, ranged from 7.1% to 14.0%. The recovery ranged from 80 to 90% (Needham et al., 1981).

PCB was measured with a modified Webb-McCall packed column gas chromatography technique as described elsewhere (Needham et al., 1981). The standard used was Aroclor 1254. The coefficients of variation ranged from 12 to 30%, and the average recovery was 82% (Burse et al., 1980; Needham et al., 1981). The limit of detection for PCB was 5 ppb. The PBB and PCB measures were not adjusted for serum lipid levels.

For each pregnancy, we estimated maternal PBB level at the time of conception by applying a decay model to the maternal serum PBB at enrollment. Briefly, the decay model included BMI at initial PBB measurement, parity, age, smoking, and breastfeeding. The details of the model are described elsewhere (Blanck et al., 2000). Predicted and measured PBB levels were highly correlated (R=0.92) (Blanck et al., 2000). The conception date for each pregnancy was estimated by subtracting the estimated gestational age from the date of birth or end of pregnancy. When gestational age was missing, it was estimated as 40 weeks for live birth (n = 35) and 8 weeks for SA (n = 22). These were the median values reported for each outcome. When the pregnancy end date was missing, it was estimated as the temporal midpoint between dates for the prior and next pregnancies, if available (n = 23). Due to its ongoing presence in dietary sources, serum PCB measured at the time of enrollment was used as an estimate of PCB exposure at the time of conception. Estimated serum PBB at the time of conception and measured PCB levels at enrollment were not correlated (Spearman correlation= 0.07).

2.3 Pregnancy Outcome and Covariate Assessment

For each pregnancy, women reported the pregnancy outcome, its duration (gestational age), and date of delivery or pregnancy end. A reported miscarriage or stillbirth before 20 weeks gestation was defined as a spontaneous abortion. Miscarriages without a reported gestational age were considered spontaneous abortions. We excluded stillbirths occurring after 20 weeks gestation, stillbirths without a reported gestational age, ectopic and molar pregnancies, and pregnancies ending in elective abortion.

Medical records were requested from the physicians of women reporting spontaneous abortions. A spontaneous abortion was verified if any of the following were found in the medical records: date of pregnancy confirmation or positive human chorionic gonadotropin test, date of last menstrual period, or date of pregnancy loss, determined, for example, by report of products of conception or dilation and curettage. Medical records were obtained for 74 (38%) spontaneous abortions. Of those obtained, 92% verified the spontaneous abortion, 5% indicated a spontaneous abortion was suspected by the doctor, and 3% did not confirm a pregnancy. Medical records were not obtained for 122 spontaneous abortions because the woman did not see a physician (6%), the woman did not authorize the release of her medical record for that pregnancy (33%), or we were unable to obtain a medical record from the physician (61%).

During the telephone interview, women reported the number of months of unprotected intercourse it took to become pregnant, and whether they consumed alcohol during the first trimester or smoked during the year prior to each pregnancy. In addition, we obtained information on demographics (age, income, and BMI), health care access (insurance coverage and frequency of visits to a health care provider), and reproductive history (age at menarche, gravidity, and history of infertility, uterine fibroids, endometriosis or pelvic inflammatory disease). For each disease reported, women were asked about their age at first diagnosis. We compared the woman's age at diagnosis to her age at conception and created time-dependent covariates for infertility, uterine fibroids, endometriosis, pelvic inflammatory disease, and thyroid disease diagnosis prior to each pregnancy.

2.4 Statistical Analysis

In our primary analysis, we examined the effect of PBB exposure on the risk of spontaneous abortion including only pregnancies occurring after the contamination incident (after July 1, 1973), with the exposure of each pregnancy estimated by the decay model, as described above. In a secondary approach, all pregnancies ending in live birth or spontaneous abortion were included, regardless of conception date. Pregnancies that occurred before the contamination incident (prior to July 1, 1973) were categorized as unexposed. Pregnancies that occurred after July 1, 1973 were assigned the exposure estimated by the decay model. In both approaches, PBB and PCB exposure at the time of conception was categorized into three groups with the lowest group defined by the limit of detection (LOD). In order to have an equal number of spontaneous abortions among the upper two exposure categories, we defined these groups based on the median exposure level among the spontaneous abortions with detectable levels. The categories for PBB were: <1 ppb, 1 – 2.9 ppb, and >2.9 ppb. The categories for PCB were: <5 ppb, 5-6.5 ppb, >6.5 ppb and missing. Six percent of the participants did not have PCB exposure measured. Because PBB exposure at the time of conception was estimated by a decay model, likely containing some additional error, we also ran the models described above using serum PBB measured at the time of enrollment as the exposure variable.

We examined the unadjusted association between potential risk factors and spontaneous abortion using a Chi-squared test, and calculated an odds ratio (OR) and 95% confidence intervals (CI) using logistic regression. In the adjusted analysis, we modeled the odds of spontaneous abortion using generalized estimating equations (GEEs), which accounts for the lack of independence between pregnancies from the same woman. As a comparison, we modeled the odds of spontaneous abortion for each woman's first pregnancy using logistic regression.

Covariates that were associated with spontaneous abortion in either our unadjusted analyses or previous studies were evaluated as potential confounders. Characteristics specific to each pregnancy (time-dependent) considered as potential confounders were: maternal age at conception (<20, 20-29, 30-34, ≥35), number of prior pregnancies (0, 1, 2, ≥3), maternal smoking in the year prior to pregnancy (yes, no), history of spontaneous abortion prior to July 1, 1973 (yes, no), infertility (yes, no), self-reported physician diagnosis of thyroid problem (yes, no) or self-reported physician diagnosis of pelvic inflammatory disease (yes, no). Characteristics specific to each woman (time-independent) considered as potential confounders were: annual household income (<$35,000 or ≥35,000), visiting a healthcare provider at least once a year (yes, no), and age at menarche (≤11 years, 12-13 years, ≥14 years). In addition, we evaluated whether the association between PBB and spontaneous abortion differed depending on the age at exposure (before or after menarche) by including an interaction term in our model as well as using a stratified approach. Because we did not have BMI at the time of each pregnancy, it was not included as a covariate. A backwards elimination strategy was used to obtain a reduced model. Effect modifiers with *p* values greater than 0.05 were removed from the model. Covariates that were significantly associated with spontaneous abortion ($p \leq 0.05$) or that altered the effect estimates for PBB or PCB by more than 10% were retained in the reduced model. For each model, odds ratios and 95% confidence intervals were calculated. SAS Version 9.0 was used for all analyses.

2. Results

The characteristics of women with conceptions after 1973 (n=529) varied from the study population (n=861) primarily because of differences in the age distribution and secular trends in childbearing and education. This population subset was younger, with higher annual income and education, lower gravidity and was more likely to be exposed before menarche (Table 1). Among women with conceptions after 1973, the mean age at interview ± standard deviation (SD) was 39 ± 8 years. Sixty-two percent of women reported an income greater than or equal to $35,000, and 59% had completed at least some college education. Forty-three percent of women were exposed to PBB before their menarche. Seventeen percent of women had PBB levels below the limit of detection (<1 ppb) and 42% had PCB below the limit of detection (<5 pbb) at enrollment into the registry.

These 529 women experienced a total of 1344 pregnancies ending in live birth (n=1148) or spontaneous abortion (n=196). Table 2 shows the characteristics of individual pregnancies stratified by pregnancy outcome (live birth or spontaneous abortion). The unadjusted odds ratio was significantly elevated in pregnancies conceived among women aged 35 y or above (OR = 2.99; 95%CI: 1.46-6.12), those with three or more prior pregnancies (OR = 2.55, 95% CI: 1.65-3.94), and those with a history of spontaneous abortion (OR = 2.44, 95% CI: 1.76-3.39), infertility (OR=1.73, 95% CI: 1.22-2.46), thyroid problem (OR = 1.79; 95% CI: 1.05-3.06), or pelvic inflammatory disease (OR = 2.29; 95% CI: 1.00-5.24). These associations remained significant after controlling for maternal age (data not shown). The association with parity was attenuated (OR=1.67, 95% CI: 1.0-2.8) after controlling for history of spontaneous abortion. Neither PBB nor PCB appeared related to risk of spontaneous abortion in the unadjusted analyses.

In the GEE models, PBB and PCB concentrations were not associated with risk of spontaneous abortion after adjusting for maternal age at conception, age at menarche, and prior infertility (Table 3). Compared to pregnancies with PBB exposures below the LOD, those with levels above 2.9 ppb had a non-significant reduced odds of spontaneous abortion (adjusted OR=0.73; 95% CI= 0.47-1.13). Compared to pregnancies with PCB exposures below LOD, those with levels above 6.5 ppb had little difference in risk (adjusted OR=0.91; 95% CI= 0.59-1.41). Maternal age at conception above 34 years remained significant in the adjusted GEE model

(OR=2.46; 95% CI= 1.10-5.49), while the effect of prior infertility was slightly attenuated (OR=1.52; 95% CI= 0.98-2.38). Older age at menarche was associated with decreased risk of spontaneous abortion (adjusted OR=0.58; 95% CI: 0.38-0.89 for 12 to 13 year olds compared to those younger). However, age at menarche did not confound the association between PBB and spontaneous abortion, and the interaction of PBB with age at exposure (before or after menarche) was not significant (data not shown). Smoking did not confound either the association with PBB or PCB.

Models using serum PBB levels measured at enrollment in the cohort, and those including pregnancies prior to 1973 resulted in similar estimates to those shown in Table 3 (data not shown). Modeling only medically verified spontaneous abortions resulted in a significantly reduced risk of PBB on spontaneous abortion (OR= 0.36, 0.16-0.81, comparing >2.9 ppb with those < LOD). However, only 68 (35%) spontaneous abortions were included in this analysis. As expected, the mean gestational age of medically verified spontaneous abortions was longer (9.7 weeks vs. 7.9 weeks, t-test for difference p value=0.002). When PBB exposure was categorized with the highest exposure group defined by the highest decile of exposure from the decay model (>8.8 ppb), pregnancies in this group had a reduced odds of spontaneous abortion that approached statistical significant (OR 0.48, 0.23-1.00).

For a subset of pregnancies (n=433), we were able to examine the association between several individual PCB congeners (PCB118, PCB138, PCB153, PCB170, PCB180) and spontaneous abortion. No significant associations with spontaneous abortions were found for any individual congeners (data not shown).

4. Discussion

The findings from our primary analysis do not support an association between PBB or PCB exposure and spontaneous abortion. Factors significantly associated with an increased risk of spontaneous abortion in our adjusted analysis were: conceiving at age 35 or greater, experiencing menarche before age 12, and a history of infertility (borderline significance). Maternal age is a well known risk factor for spontaneous abortion (Risch et al., 1988; Coste et al., 1991; Cramer et al., 2000; Nybo Andersen et al., 2000). Some (Liestol, 1980; Casagrande et al., 1982; Martin et al., 1983; Wyshak, 1983; Bracken et al., 1985; Parazzini et al., 1991) but not all studies (Mayaux et al., 1983; Sandler et al., 1984; Dominguez et al., 1991) support an association between early age at menarche and spontaneous abortion. Possibly, similar underlying endocrinologic characteristics explain both early menarche and spontaneous abortion. Alternatively, early menarche may result in earlier sexual activity, higher likelihood of pelvic inflammatory disease and higher risk of spontaneous abortion. Our study is in agreement with other studies showing an association between higher rates of miscarriage among women with a history of fertility problems (Hakim et al., 1995). Controlling for prior spontaneous abortions did not account for the effect of prior infertility in our study. Our PCB findings are in agreement with other studies that did not find an association between PCB exposure and fetal loss (Dar et al., 1992; Mendola et al., 1995; Yang et al., 2000; Sugiura-Ogasawara et al., 2003; Axmon et al., 2004).

While not significant in our primary analysis, the decreased likelihood of spontaneous abortion among the higher PBB exposed pregnancies was unexpected. This decrease persisted and became more pronounced in various sensitivity analyses, including modeling only medically verified spontaneous abortions, only spontaneous abortions with gestational age less than or equal to 12 weeks, or categorizing “high” PBB exposure based on the highest 10%. The suggestion that PBB exposure is associated with a reduced odds of spontaneous abortion is not supported by animal data (Jackson et al., 1974; Beaudoin, 1977; Moorhead et al., 1977; Allen et al., 1978; Welsch et al., 1985; Schanbacher et al., 1987) and is most likely due to chance.

Alternatively, the observed lower risk may result from an increase in fetal loss before the time of detection (Selevan et al., 1987) or confounding by unrecognized risk factors. Furthermore, we relied heavily on self-reported data which is subject to recall bias that could have differentially affected earlier pregnancies (Wilcox et al., 1984). Due to secular changes in pregnancy diagnosis and longer recall, spontaneous abortions occurring closer to 1973, which would tend to have higher PBB exposure levels, may have been under-reported as compared to later miscarriages and all live births. This would have produced a negative bias on the estimate of effect, which may explain observed reduced odds ratio. However, when we controlled for the decade of the pregnancy, our findings were similar.

The etiology of spontaneous abortions may differ depending on gestational age (Bulletti et al., 1996). Grouping all cases together may mask an effect occurring only in either early or late miscarriages. When we restricted our analysis to miscarriages occurring up to 8 or 12 weeks in gestational age, our findings were similar indicating a non-significant decrease in risk among the most highly exposed.

Breastfed girls exposed to high PBB levels *in utero* reached menarche earlier than unexposed girls (Blanck et al., 2000). It is unknown whether childhood PBB exposure has a similar association. If so, age at menarche could be a mediator between PBB exposure and spontaneous abortion risk, and thus its inclusion in the model would have precluded estimation of the full effect of PBB exposure. Modeling risk of spontaneous abortion separately for women exposed to PBB before and after menarche, and omitting control for age at menarche in the pre-pubertal exposure group, resulted in similar findings.

Our primary exposure variable, although based on a serum measurement, was estimated by a decay model to the point of conception and subject to misclassification due to error in this model. Refitting the final model classifying exposure status according to initial PBB level results in an attenuated OR (0.88, 95% CI: 0.56-1.38, comparing those with highest exposure to those below the LOD).

There were differences between women with pregnancies after 1973 and those with pregnancies before 1973 due to secular trends in childbearing and education. However, the selection of only women with pregnancies after 1973 for our primary analysis did not appear to bias our findings. The results were similar when all women were included in the analysis, and pregnancies before 1973 were considered unexposed.

We did not have pregnancy-specific information for sociodemographic variables whose values may change over time. Although this probably resulted in substantial misclassification for these variables, they have not been found previously to be strong predictors of spontaneous abortion risk (Bulletti et al., 1996). We were unable to examine the effects of BMI because women provided information on current BMI in the 1997-98 interviews and not at the time of each pregnancy.

A strength of this study was the utilization of biological measurements of exposure rather than proxy measures such as food consumption levels. The availability of a serum decay model (Blanck et al., 2000) allowed the estimation of exposure levels specific to the time of each pregnancy. The existence of this well-established cohort with high participation rates (83%) minimized the possibility of selection bias.

While this study supports an association between risk of spontaneous abortion and both maternal age at conception and age at menarche, it does not support an association with exposure to either PCB or PBB. As many as 30% of pregnancies end in miscarriage (Wilcox et al., 1988; Stewart, 2004) and of these 30- 50% are idiopathic (Bulletti et al., 1996). Continued investigation of environmental exposures is valuable to our understanding of the causes of spontaneous abortion and could lead to knowledge that would reduce the risk of spontaneous abortion for individual women.

Acknowledgements

Funding for this research was provided by US EPA. (R 825300), NIEHS (RO1 ES08341 and R01 ES012014), and by CDC cooperative agreement U37/CCU500392. We thank Dr. Lorraine Cameron and the staffs of the Michigan Department of Community Health and the Michigan Public Health Institute for their assistance in carrying out the Michigan Female Health Study.

List of Abbreviations

BMI, body mass index
CI, confidence interval
kg, kilogram
MDCH, Michigan Department of Community Health
m^2, meters-squared
LOD, limit of detection
OR, odds ratio
pbb, parts per billion
PBB, polybrominated biphenyl
PCB, polychlorinated biphenyl
PHAH, polyhalogenated aromatic hydrocarbon

References

Allen JR, Lambrecht LK, et al. Effects of polybrominated biphenyls in nonhuman primates. JAVMA 1978;173:1485–1489.

Altman NH, New AE, et al. A spontaneous outbreak of polychlorinated biphenyl (PCB) toxicity in rhesus monkeys (Macaca mulatta): clinical observations. Lab. Anim. Sci 1979;29:661–665. [PubMed: 117226]

Arnold DL, Bryce F, et al. Toxicological consequences of Aroclor 1254 ingestion by female rhesus (Macaca mulatta) monkeys. Part 1B. Prebreeding phase: clinical and analytical laboratory findings. Food & Chemical Toxicology 1993;31:811–824. [PubMed: 8258410]

Arnold DL, Bryce F, et al. Toxicological consequences of aroclor 1254 ingestion by female rhesus (Macaca mulatta) monkeys. Part 2. Reproduction and infant findings.[see comment]. Food Chem. Toxicol 1995;33:457–474. [PubMed: 7797173]

Arnold DL, Mes J, et al. A pilot study on the effects of Aroclor 1254 ingestion by rhesus and cynomolgus monkeys as a model for human ingestion of PCBs. Food Chem. Toxicol 1990;28:847–857. [PubMed: 2125970]

Aulerich RJ, Bursian SJ, et al. Toxicological manifestations of 2,4,5,2′,4′,5′-, 2,3,6,2′,3′,6′-, and 3,4,5,3′, 4′,5′-hexachlorobiphenyl and Aroclor 1254 in mink. J. Toxicol. Environ. Health 1985;15:63–79. [PubMed: 3920403]

Aulerich RJ, Ringer RK. Toxic effects of dietary polybrominated biphenyls on mink. Archives of Environmental Contamination & Toxicology 1979;8:487–498. [PubMed: 226005]

Aulerich RJ, Ringer RK, et al. Reproductive failure and mortality in mink fed on Great Lakes fish. Journal of Reproduction & Fertility - Supplement 1973;19:365–376. [PubMed: 4206410]

Axmon A, Rylander L, et al. Polychlorinated biphenyls in serum and time to pregnancy. Environ. Res 2004;96:186–195. [PubMed: 15325879]

Barsotti DA, Marlar RJ, et al. Reproductive dysfunction in rhesus monkeys exposed to low levels of polychlorinated biphenyls (Aoroclor 1248). Food Cosmet. Toxicol 1976;14:99–103. [PubMed: 817997]

Beaudoin AR. Teratogenicity of polybrominated biphenyls in rats. Environ. Res 1977;14:81–86. [PubMed: 196845]

Bercovici B, Wassermann M, et al. Serum levels of polychlorinated biphenyls and some organochlorine insecticides in women with recent and former missed abortions. Environ. Res 1983;30:169–174. [PubMed: 6403348]

Blanck HM, Marcus M, et al. Determinants of polybrominated biphenyl decay among women in the michigan pbb cohort. Environ. Health Perspect 2000;108:147–152. [PubMed: 10656855]

Blanck HM, Marcus M, et al. Age at menarche and Tanner Stage in girls exposed in utero and postnatally to polybrominated biphenyl. Epidemiology 2000;11:1–7.

Bleavins MR, Aulerich RJ, et al. Polychlorinated biphenyls (Aroclors 1016 and 1242): effects on survival and reproduction in mink and ferrets. Archives of Environmental Contamination & Toxicology 1980;9:627–635. [PubMed: 6776911]

Bracken M, Bryce-Buchanan C, et al. Menarcheal age and habitual miscarriage: evidence for an association. Ann. Hum. Biol 1985;12:525–531. [PubMed: 4091507]

Brezner E, Terkel J, et al. The effect of Aroclor 1254 (PCB) on the physiology of reproduction in the female rat--I. Comparative Biochemistry & Physiology C, Comparative Pharmacology & Toxicology 1984;77:65–70.

Brunstrom B, Kihlstrom I, et al. Studies of foetal death and foetal weight in guinea pigs fed polychlorinated biphenyls (PCB). Acta Pharmacol. Toxicol. (Copenh) 1982;50:100–103. [PubMed: 6803516]

Bulletti C, Flamigni C, et al. Reproductive failure due to spontaneous abortion and recurrent miscarriage. Hum. Reprod. Update 1996;2:118–136. [PubMed: 9079408]

Burse VW, Needham LL, et al. Interlaboratory comparison for results of analyses for polybrominated biphenyls in human serum. J. Anal. Toxicol 1980;4:22–26. [PubMed: 6098783]

Carter LJ. Michigan's PBB Incident: Chemical Mix-Up Leads to Disaster. Science 1976;192:240–243. [PubMed: 17831151]

Casagrande JT, Pike MC, et al. Re: “Menarcheal age and spontaneous abortion: a causal connection?”. Am. J. Epidemiol 1982;115

Coste J, Job-Spira N, et al. Risk factors for spontaneous abortion: a case-control study in France. Hum. Reprod 1991;6:1332–1337. [PubMed: 1752937]

Cramer DW, Wise LA. The epidemiology of recurrent pregnancy loss. Seminars in Reproductive Medicine 2000;18:331–339. [PubMed: 11355791]

Dar E, Kanarek MS, et al. Fish consumption and reproductive outcomes in Green Bay, Wisconsin. Environ. Res 1992;59:189–201. [PubMed: 1425509]

Dominguez V, Calle E, et al. Adjusting risk factors in spontaneous abortion by multiple logistic regression. Eur. J. Epidemiol 1991;7:171–174. [PubMed: 2044715]

Fries GF. The PBB episode in Michigan: an overall appraisal. Critical Reviews in Toxicology 1985;16:105–156. [PubMed: 3002722]

Gerhard I, Daniel V, et al. Chlorinated hydrocarbons in women with repeated miscarriages. Environ. Health Perspect 1998;106:675–681. [PubMed: 9755145]

Hakim RB, Gray RH, et al. Infertility and early pregnancy loss. Am. J. Obstet. Gynecol 1995;172:1510–1517. [PubMed: 7755065]

Hass JR, McConnell EE, et al. Chemical and toxicologic evaluation of firemaster BP-6. Journal of Agricultural & Food Chemistry 1978;26:94–99. [PubMed: 202620]

Humble CG, Speizer FE. Polybrominated biphenyls and fetal mortality in Michigan. AJPH 1984;74:1130–1132.

Jackson TF, Halbert FL. A toxic syndrome associated with the feeding of polybrominated biphenyl-contaminated protein concentrate to dairy cattle. Journal of the American Veterinary Medical Association 1974;165:437–439. [PubMed: 4425399]

Kuwahara SS, Calera F, et al. Distribution of polybrominated biphenyls (PBB) among fractions derived from contaminated human plasma. Transfusion 1980;20:229–234. [PubMed: 6245485]

Leoni V, Fabiani L, et al. PCB and other organochlorine compounds in blood of women with or without miscarriage: a hypothesis of correlation. Ecotoxicol. Environ. Saf 1989;17:1–11. [PubMed: 2496968]

Liestol K. Menarcheal age and spontaneous abortion: a causal connection? Am. J. Epidemiol 1980;111:753–758. [PubMed: 7386450]

Linder RE, Gaines TB, et al. The effect of polychlorinated biphenyls on rat reproduction. Food Cosmet. Toxicol 1974;12:63–77. [PubMed: 4218577]

Martin EJ, Brinton LA, et al. Menarcheal Age and Miscarriage. Am. J. Epidemiol 1983;117:634–636. [PubMed: 6846320]

Mayaux MJ, Spira A, et al. Re: “Menarcheal age and spontaneous abortion: a causal connection?”. Am. J. Epidemiol 1983;117:377–378. [PubMed: 6829567]

Mendola P, Buck GM, et al. Consumption of PCB-contaminated sport fish and risk of spontaneous fetal death. Environ. Health Perspect 1995;103:498–502. [PubMed: 7656880]

Moorhead PD, Willett LB, et al. Pathology of experimentally induced polybrominated biphenyl toxicosis in pregnant heifers. J. Am. Vet. Med. Assoc 1977;130:307–313. [PubMed: 188792]

Needham LL, Burse VW, et al. Temperature-programmed gas chromatographic determination of polychlorinated and polybrominated biphenyls in serum. J. Assoc. Off. Anal. Chem 1981;64:1131–1137. [PubMed: 6270054]

Nybo Andersen AM, Wohlfahrt J, et al. Maternal age and fetal loss: population based register linkage study.[see comment]. BMJ 2000;320:1708–1712. [PubMed: 10864550]

Parazzini F, Bocciolone L, et al. Risk factors for spontaneous abortion. Int. J. Epidemiol 1991;20:157–161. [PubMed: 2066215]

Risch HA, Weiss NS, et al. Risk factors for spontaneous abortion and its recurrence.[see comment]. Am. J. Epidemiol 1988;128:420–430. [PubMed: 3273482]

Sandler DP, Wilcox AJ, et al. Age at menarche and subsequent reproductive events. Am. J. Epidemiol 1984;119:765–774. [PubMed: 6720673]

Schanbacher FL, Willett LB, et al. Serum isocitrate dehydrogenase during polybrominated biphenyl toxicosis in dairy cattle. J. Anim. Sci 1987;64:467–473. [PubMed: 3030994]

Seiler P, Fischer B, et al. Effects of persistent chlorinated hydrocarbons on fertility and embryonic development in the rabbit. Hum. Reprod 1994;9:1920–1926. [PubMed: 7531205]

Selevan SG, Lemasters GK. The dose-response fallacy in human reproductive studies of toxic exposures. J. Occup. Med 1987;29:451–454. [PubMed: 3598737]

Stewart, F. Pregnancy Testing and Management of Early Pregnancy. In: Hatcher, RA.; Trussell, J.; Stewart, F., et al., editors. Contraceptive Technology. Ardent Media, Inc.; New York: 2004. p. 646

Sugiura-Ogasawara M, Ozaki Y, et al. PCBs, hexachlorobenzene and DDE are not associated with recurrent miscarriage. Am. J. Reprod. Immunol 2003;50:485–489. [PubMed: 14750556]

Tolbert, PE. Potential Endocrine Disruptors in the Workplace. In: Harris, RL., editor. Patty's Industrial Hygiene. John Wiley & Sons, Inc.; New York: 2000.

Welsch F, Morgan KT. Placental transfer and developmental toxicity of 2,2′,4,4′,5,5′-hexabromobiphenyl in B6C3F1 mice. Toxicol. Appl. Pharmacol 1985;81:431–442. [PubMed: 3001974]

Wilcox AJ, Horney LF. Accuracy of spontaneous abortion recall. Am. J. Epidemiol 1984;120:727–733. [PubMed: 6541871]

Wilcox AJ, Weinberg CR, et al. Incidence of early loss of pregnancy. N. Engl. J. Med 1988;319:189–194. [PubMed: 3393170]

Wyshak G. Age at menarche and unsuccessful pregnancy outcomes. Ann. Hum. Biol 1983;10:69–73. [PubMed: 6838157]

Yang J, Buck G, et al. Consumption of PCB-contaminated fish from Lake Ontario and risk of pregnancy loss--a follow-up study. Society for pediatric and perinatal epidemiologic research. 2000

Yu ML, Guo YL, et al. Menstruation and reproduction in women with polychlorinated biphenyl (PCB) poisoning: long-term follow-up interviews of the women from the Taiwan Yucheng cohort. Int. J. Epidemiol 2000;29:672–677. [PubMed: 10922344]

Table 1

Characteristics of women with pregnancies ending in spontaneous abortion or live birth (n=861)

	All Women N=861	Women with Pregnancies after July 1, 1973 N=529
	N (%)	N (%)
Age at interview (years)		
24-35	193 (22%)	193 (37%)
36-45	226 (26%)	226 (43%)
46-55	147 (17%)	95 (18%)
≥56	295 (34%)	15 (3%)
BMI at interview (kg/m^2)		
<20	40 (5%)	30 (6%)
20-25	309 (36%)	214 (41%)
>25	509 (59%)	282 (54%)
Income		
< $35,000/year	350 (41%)	174 (33%)
≥ $35,000/year	432 (50%)	327 (62 %)
Not reported	79 (9 %)	28 (5%)
At least some college education		
No	434 (51%)	215 (41%)
Yes	425 (49%)	314 (59%)
Health insurance		
No	57 (7%)	44 (8%)
Yes	803 (93%)	485 (92%)
At least 1 health care visit /year		
No	101 (12%)	78 (15%)
Yes	755 (88%)	450 (85%)
Ever smoker		
No	600 (70%)	356 (67%)
Yes	261 (30%)	173 (33%)
Gravidity		
1	51 (6%)	40 (8%)
2	222 (26%)	167 (32%)
3	203 (24%)	144 (27%)
4	164 (19%)	88 (17%)
≥5	221 (25%)	90 (16%)
History of spontaneous abortion		
No	608 (71%)	376 (71%)
Yes	253 (29%)	153 (29%)
History of spontaneous abortion prior to July, 1973		
No	734 (85%)	502 (95%)
Yes	127 (15%)	27 (5%)
Age at menarche		
≤ 11	171 (20%)	94 (18%)
12- 13	477 (56%)	312 (59%)
≥ 14	207 (24%)	121 (23%)
PBB exposure before menarche		
No	630 (74%)	302 (57%)
Yes	225 (26%)	225 (43%)
Age at PBB exposure in 1973 (years)		
≤ 10	184 (21%)	184 (35%)
11 – 20	226 (26%)	226 (43%)
21 – 30	147 (17%)	101 (19%)
≥ 31	304 (35%)	18 (3%)
Serum PBB at enrollment (ppb) [a]		
<1	172 (20%)	90 (17%)
1- 3	414 (48%)	212 (40%)
> 3	275 (32%)	227 (43%)
Serum PCB[c] level at enrollment (ppb) [a]		
<5	278 (32%)	220 (42%)
5 – 6.5	239 (28%)	140 (26%)
>6.5	297 (35%)	136 (26%)
Not measured	47 (6%)	33 (6%)

Abbreviations: BMI, body mass index; PBB, polybrominated biphenyls; PCB polychlorinated biphenyls; pbb, parts per billion.

[a]PBB and PCB cut-points are based on the limit of detection and the median value of those above the level of detection (among women with pregnancies after July 1, 1973).

TABLE 2

Characteristics of 1344 pregnancies occurring after July 1, 1973 that ended in spontaneous abortion or live birth.

	Livebirth (n=1148)	SA (n=196)	Chi Square *p* value	Unadjusted OR
Pregnancies	**N (%)**	**N (%)**		
Maternal age at conception (years)				
< 20	122 (11%)	19 (10%)	0.001	Ref
20 – 29	801 (70%)	123 (63%)		0.99 (0.59-1.66)
30 - 34	182 (16%)	34 (17%)		1.20 (0.65-2.20)
≥ 35	43 (4%)	20 (10%)		2.99 (1.46-6.12)
Maternal PBB at conception (ppb) [a]				
<1	625 (54%)	116 (59%)	0.21	Ref
1 – 2.9	221 (19%)	40 (20%)		0.98 (0.66-1.44)
> 2.9	302 (26%)	40 (20%)		0.71 (0.49-1.05)
PCB exposure (ppb) [a]				
<5	481 (42%)	85 (43%)	0.45	Ref
5-6.5	291 (25%)	54 (28%)		1.05 (0.73-1.52)
>6.5	303 (26%)	50 (26%)		0.93 (0.64-1.36)
Not measured	73 (6%)	7 (4%)		0.54 (0.24-1.22)
Time to pregnancy				
< 12 months	819 (87%)	133 (86%)	0.75	Ref
≥ 12 months	125 (13%)	22 (14%)		1.08 (0.67-1.77)
Prior spontaneous abortion [b]				
No	935 (81%)	126 (64%)	<0.0001	Ref
Yes	213 (19%)	70(36%)		2.44 (1.76-3.39)
Number of prior pregnancies [b]				
0	336 (29%)	38 (19%)	0.0001	Ref
1	356 (31%)	52 (27%)		1.29 (0.83-2.01)
2	231 (20%)	41 (21%)		1.57 (0.98-2.52)
≥ 3	225 (20%)	65 (33%)		2.55 (1.65-3.94)
History of infertility [b]				
No	950 (83%)	144 (73%)	0.002	Ref
Yes	198 (17%)	52 (27%)		1.73 (1.22-2.46)
Thyroid problem[b]				
No	1046 (86%)	171 (14%)	0.03	Ref
Yes	63 (77%)	19 (23%)		1.79 (1.05-3.06)
Uterine fibroid[b]				
No	1126 (98%)	192 (98%)	0.84	Ref
Yes	21(2%)	4 (2%)		1.12 (0.38-3.29)
Endometriosis[b]				
No	1099 (96%)	187 (95%)	0.84	Ref
Yes	49 (4%)	9 (5%)		1.08 (0.52-2.23)
PID prior to pregnancy [b]				
No	1123 (98%)	187 (96%)	0.05	Ref
Yes	21 (2%)	8 (4%)		2.29 (1.00-5.24)
Maternal smoking during year prior to pregnancy				
No	905 (79%)	146 (74%)	0.15	Ref
Yes	240 (21%)	50 (26%)		1.29 (0.91-1.84)
First trimester maternal alcohol consumption				
No	998 (87%)	165 (86%)	0.68	Ref
Yes	143 (13%)	26 (14%)		1.10 (0.70-1.72)

Abbreviations: OR, odds ratio, PBB, polybrominated biphenyls; PCB polychlorinated biphenyls; pbb, parts per billion, PID, pelvic inflammatory disease.

[a]PBB and PCB cut-points are based on the limit of detection and the median exposure of spontaneous abortions above the level of detection.

[b]Prior to the index pregnancy

Table 3

Unadjusted and adjusted probability of spontaneous abortion among pregnancies occurring after July 1, 1973.

	Unadjusted GEE[a] n=1344		Adjusted GEE [a] n=1344		Adjusted Logistic [b] n=529	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
PBB *(ppb)*[c]						
< 1	Ref		Ref		Ref	
1–2.9	1.07	0.69-1.66	1.05	0.67-1.63	0.51	0.24-1.11
> 2.9	0.69	0.45-1.07	0.73	0.47-1.13	0.67	0.33-1.33
PCB *(ppb)*						
≤ 5	Ref		Ref		Ref	
> 5 – 6.5	1.06	0.68-1.64	0.97	0.62-1.52	1.14	0.57-2.26
> 6.5	0.88	0.57-1.36	0.91	0.59-1.41	1.15	0.56-2.36
Not measured	0.50	0.20-1.27	0.48	0.19-1.26	0.76	0.21-2.78
Maternal age at conception (years)						
< 20	Ref		Ref		Ref	
20 – 29	0.96	0.56-1.64	0.94	0.55-1.61	0.60	0.30-1.21
30 - 34	1.13	0.62-2.06	1.07	0.57-2.01	1.22	0.45-3.31
≥ 35	2.76	1.22-6.27	2.46	1.10-5.49	2.11	0.70-6.36
Age at Menarche						
≤ 11	Ref		Ref		Ref	
12- 13	0.52	0.34-0.80	0.58	0.38-0.89	0.30	0.16-0.57
≥ 14	0.53	0.32-0.87	0.55	0.34-0.91	0.37	0.17-0.81
Prior Infertility[d]						
No	Ref		Ref		Ref	
Yes	1.68	1.11-2.54	1.52	0.98-2.38	1.74	0.92-3.30

Abbreviations: GEE, generalized estimating equation, OR, odds ratio; CI, confidence interval; PBB, polybrominated biphenyls; PCB polychlorinated biphenyls; pbb, parts per billion.

[a] Generalized estimating equations were used to account for the dependency between pregnancies of the same woman. Adjusts for all covariates in table.

[b] The adjusted Logistic Model includes only the first pregnancy after July 1, 1973 for each woman and controls for all of the covariates listed in the table.

[c] PBB at the time of conception as determined by the decay model.

[d] Prior to index pregnancy