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Conjugated Bisphenol A (BPA) in maternal serum in relation to miscarriage risk

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Abstract

Objective—To examine the relationship between maternal serum Bisphenol-A (BPA) concentration at the time of the missed period and miscarriage risk.

Design—Retrospective cohort of prospectively collected serum samples.

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Setting—Academic fertility center.

Patients—Women presenting for early pregnancy monitoring with singleton pregnancies.

Intervention—Stored serum samples from 4-5 weeks gestation were analyzed for conjugated serum BPA concentrations.

Main Outcomes—Live birth, miscarriage, and chromosome content of miscarriage.

Results—Of the 115 included subjects, there were 47 live births and 68 clinical miscarriages (46 aneuploid and 22 euploid). Median conjugated BPA concentrations were higher in women with miscarriages than those with live births (0.101 vs 0.075 ng/ml). Women with the highest quartile of conjugated BPA had an increased relative risk of miscarriage (1.83, 95% CI 1.14-2.96) compared to women in the lowest quartile. We found a similar increase risk for both euploid and aneuploid miscarriages.

Conclusions—Maternal conjugated BPA was associated with higher risk of aneuploid and euploid miscarriage in this cohort. The impact of reducing individual exposures on future pregnancy outcomes deserves further study.

Keywords

Bisphenol A; miscarriage; endocrine disruptor; pregnancy; aneuploidy

INTRODUCTION

Bisphenol A [BPA; 2,2-bis(4-hydroxyphenyl) propane] is a high volume (>10 billion pounds per year) industrial chemical and building block for polycarbonate plastic and epoxy resins (1). Dayto-day exposure is common in humans because BPA is found ubiquitously in household items including the lining of metal food and drink cans, computers, thermal receipt paper, plastic food and beverage containers, medical devices, and dental sealants. The common assumption is that the primary exposure of humans is through the diet, as BPA can leach from plastics and the lining of cans containing food and water, although the lack of information concerning the products that contain BPA limits the utility of current exposure models. The 2003-2004 National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention (CDC) found detectable levels of BPA in 93% of urine samples (n=2517) from people six years and older, demonstrating that exposure is ubiquitous (2).

BPA belongs to an important group of chemicals called endocrine disrupting chemicals (EDCs) that can potentially interfere with the production, release, transport, metabolism, binding, action, or clearance of endogenous hormones involved in human conception and development often at extremely low doses (3). There is growing concern of a potential relationship between BPA and negative effects on human health given animal data showing effects in rodents at ranges well within the current levels of human exposure in developed countries (4). Evidence suggests that prenatal BPA in humans exposure may be linked to preterm delivery, low birth weight and reduced head circumference (5-7)]. Human exposure to BPA leading to adult disease has been the subject of several review papers (8-10) and an

association with reproductive disorders such at endometriosis, infertility, PCOS and thyroid disease has been seen.

Despite this growing concern, there are limited data regarding the reproductive health effects associated with BPA. In mice, low-dose in vivo BPA exposure during the final stages of ooctye growth has been shown to increase meiotic errors in mature oocytes and synaptic errors in fetal oocytes when exposures occur prenatally (11, 12). Further evidence of a prenatal effect has been described, where exposure to BPA during pregnancy can disturb rhesus monkey fetal oocyte development and increase the rate of aneuploid embryos in the offspring (13, 14). The only published study to date to investigate BPA and miscarriage in humans suggests that exposure to BPA is associated with recurrent human miscarriage (15). However, the Sugiura-Ogasawara et al. study has not been replicated, and the sample size was small (n=45). Furthermore, karyotypes were not known for miscarriages and therefore the study was unable to investigate a correlation of BPA with aneuploidy in human conceptions (15).

This study aims to assess whether maternal BPA levels during early pregnancy are associated with risk of first trimester miscarriage. We hypothesized that elevated maternal serum BPA levels during conception or early pregnancy would be associated with an increased risk of miscarriage. Because animal research has suggested that BPA exposure induces meiotic aneuploidy in oocytes, we examined the chromosome status of all miscarriages included to ascertain more information regarding the risk of aneuploidy in human conceptions.

MATERIALS AND METHODS

Study design

This cohort study of 115 subjects included 68 first-trimester spontaneous miscarriages and 47 live births from women with stored frozen serum samples who sought treatment for infertility or recurrent pregnancy loss (RPL) at Stanford Fertility and Reproductive Medicine Clinic from September 2005 until January 2009. Patients were selected from a database of patients who consented to have their serum stored for research if they had either a confirmed live birth or clinical miscarriage with chromosome analysis. Blood samples were drawn during the course of routine clinical care.

Institutional Approval

This study was approved by the Stanford Institutional Review Board. Written informed consent was obtained from each woman to have their medical information and excess serum used for future research analysis.

Study Population

Subjects were identified from the Stanford Fertility and Reproductive Medicine Clinic research database if they had a clinical intrauterine pregnancy confirmed by serum HCG and ultrasound with a known pregnancy outcome and stored serum samples. Miscarriage was defined as a loss of a clinical pregnancy after gestational sac was confirmed on ultrasound.

Miscarriages were only included in this analysis if karyotype of the products of conception was performed. Live births were confirmed by review of electronic medical records. Biochemical pregnancies, molar pregnancies, and pregnancies of unknown location were excluded. Retrospective review of medical records was performed to gather demographic and clinical information on all subjects.

Subjects were eligible if they had conceived spontaneously or with treatment (including controlled ovarian stimulation and intrauterine insemination, controlled ovarian stimulation alone, or fresh cycle in vitro fertilization) and if they had at least one serum sample collected at diagnosis of pregnancy and frozen for future analysis. This blood sample was collected on or near the expected menses at an approximate gestational age of 4 weeks. For the majority of subjects (86%), a second blood sample collected 2-15 days after initial diagnosis of pregnancy was also available for analysis.

Because our goal was to study sporadic and unexplained miscarriage, women with a known etiology for miscarriage were excluded, including an abnormal parental karyotype, uterine anomaly, uncontrolled diabetes, autoimmune disorder, or thrombophilia. Gestational carriers, women who conceived using donor eggs or embryos, and women undergoing in vitro fertilization with pre-implantation genetic screening or frozen embryos were also excluded from the study.

Initial review of the Stanford Fertility and Reproductive Medicine Clinic research database identified a total of 360 index pregnancies with stored serum samples and known outcomes between September 2005 and January 2009. A total of 156 of these identified pregnancies met initial inclusion/exclusion criteria. Forty-one of these pregnancies were later excluded for the following reasons: serum samples had inadequate volume for analysis or were no longer in storage (n=37), twin miscarriage (n=2), unable to confirm reported fetal karyotype (n=1), and a second pregnancy from a woman already included in the study (n=1). No more than one pregnancy per patient was included in this study. This analysis includes 46 aneuploid miscarriages, 22 euploid miscarriages, and 47 live births, for a total of 115 subjects. Of the 22 euploid miscarriages, there were 11 normal 46, xx miscarriages and 11 normal 46,xy miscarriages. The pregnancy losses were analyzed for chromosome errors using standard cytogenetics using the GTW banding method.

Conjugated Bisphenol-A serum measurement

Blood samples were collected and processed according to standard procedures. Serum samples were stored in 5-mL, bisphenol-A-free polystyrene tubes at -20C. Serum samples were de-identified and assigned a random number prior to shipping overnight on dry ice to the University of Missouri-Columbia for serum BPA analysis, where they were again stored at -20C. For analysis, the technician was blinded to the outcome of pregnancy associated with the sample as well as which samples belonged to the same woman.

For determination of serum conjugated BPA concentrations, samples were extracted twice with methyl tert-butyl ether. The ether extract was dried under nitrogen and reconstituted in 50:50 methanol:water. After extraction of unconjugated BPA, for analysis of unextracted conjugated BPA, samples were incubated overnight at 37oC in 100 mM ammonium acetate

buffer (pH 5.0) containing 100 units -glucuronidase (Type H-1, Sigma-Aldrich, St. Louis, MO; this enzyme preparation also contains sulfatase activity). The samples were then spiked with an internal standard (C13-BPA, Cambridge Isotope Laboratories Inc., Andover, MA; purity 99%) and extracted twice with methyl tert-butyl ether. The extracts were dried under nitrogen and reconstituted in 50:50 methanol:water for analysis. All solvents (methanol, methyl tert-butyl ether) and water were HPLC grade, and were obtained from Fisher Scientific (Waltham, MA).

After deconjugation, serum BPA was quantified by liquid chromatography with tandem mass spectrometry (LCMS/MS) using a Thermo TSQ Quantum Access Max (Thermo Fisher Scientific, Waltham, MA) connected to an integrated Thermo-Accela LC system; analytes were detected using electrospray ionization with negative polarity, and conditions (tube lens setting, collision energy) were optimized for each analyte using the instrument software. Separations were performed on a 100x4.6 mm 3 micron Hyperclone HPLC column (Phenomenex, Torrance, CA), at a flow rate of 350 ul/minute. Samples were run isocratically in 60% methanol. Thermo LCQuan software was used to autotune, acquire, and process the LC/ MS data. BPA and C13-BPA were detected using selected reaction monitoring for m/z 227>212 and m/z 239>224 respectively, and quantitation was made against a standard curve of BPA (Sigma-Aldrich, St. Louis MO; purity > 99%) at concentrations ranging from 1-200 ng/ml. The limit of quantitation (LOQ) for BPA was 0.1 ng/ml based on extraction of a 1.5 serum sample (sample volumes assayed ranged from 1.15 – 2.70 ml). Values that ran lower than the LOQ were estimated by extrapolation from the standard curve. Extrapolation was used to determine the concentration in 76 of the 215 samples (35%).

Statistical analysis

BPA levels are reported as the average of the two samples obtained from the same patient. If only one sample was available for a subject, this value was used for analysis. Spearman's coefficient was used to assess the correlation between sample 1 and sample 2 within the same subject. Data for mean, standard deviation, and median (interquartile range) were calculated. Fisher's Exact test, Student's t-test, and Mann-Whitney U test were used to determine if age, BMI, FSH level, prior pregnancy history, conception method, smoking status, or BPA levels were associated with miscarriage.

The pooled group distribution was calculated and used to define four quartile-based categories of conjugated BPA serum level. Logistic regression was used to calculate relative risks and 95% confidence intervals for risk of all miscarriages, and risk of specific karyotype (aneuploid versus euploid miscarriage), controlling for significant variables from the univariate analysis, using the lowest quartile of conjugated BPA exposure as the reference group. Statistical analyses were performed using SPSS 21.0. A p-value <0.05 was considered statistically significant.

RESULTS

Demographics

The demographic characteristics of subjects with miscarriages and live births are provided in Table 1. The two groups were similar in terms of age, BMI, FSH level, smoking status, and whether or not there had been a prior successful pregnancy. A significantly higher proportion of miscarriage patients had a history of prior miscarriage than participants with live births (51.5% vs 25.5%; p=0.025). Method of conception was also significantly different in the miscarriage cases compared to women with live births (p=0.010). There were 68 miscarriages and 47 live births included in this study. Among the miscarriages, there were 46 aneuploid miscarriages and 22 euploid miscarriages (11 euploid female and 11 euploid male miscarriages).

Conjugated Serum Bisphenol-A Levels

Percentiles (including median and IQR) and overall range for conjugated BPA levels in the miscarriage and live birth groups are reported in Table 2. The median of BPA level was significantly higher in subjects with miscarriages compared to the subjects continuing to live births (p=0.014). Of the 215 samples used, 27 were previously thawed. There were no statistically significant differences in BPA levels from previously thawed serum samples and never thawed serum samples (0.2578 ng/ml vs 0.2911 ng/ml, p = 0.859); hence all samples were included in the analysis (data not shown). Of the 215 samples assayed for conjugated BPA 3% had no BPA detected and 33% were below the LOQ and had the value estimated by extrapolation from the standard curve. BPA levels between the baseline sample 1 and subsequent sample 2 in subjects were not significantly correlated (Spearman's Coefficient=0.02; p=0.827).

Logistic Regression—The logistic regression model assessing the relationship between serum conjugated BPA level (pooled population quartiles) early in pregnancy and risk of subsequent miscarriage versus live birth is presented below in Table 3. Relative risks were calculated for each serum BPA level quartile with the first quartile used as the reference category. The relative risks are presented for all miscarriages as well as sub-divided between aneuploid or euploid miscarriage. A significant positive association between serum conjugated BPA level quartile and miscarriage was observed. The highest quartile of serum conjugated BPA level was a significant independent predictor of all miscarriages compared to live births. Subjects whose average serum BPA level was in the fourth quartile were 1.83 times more likely to have a miscarriage than those subjects with serum BPA level was in the first quartile. The highest quartile of serum BPA level was also significantly associated with increased risk of both aneuploid and euploid miscarriage, with relative risks of 1.97 and 3.33, respectively. Additionally, the data suggests a dose-response relationship, as there was a trend towards increasing risk of miscarriage for each quartile of serum BPA level analyzed. When significant variables from the univariate analysis were included in the regression model, conception method was the only additional significant predictor of miscarriage, with IUI and IVF being protective relative to NC/TIC; RR (95% CI) = 0.107 (0.027, 0.423) and RR (95% CI) = 0.213 (0.060, 0.764), respectively. Smoking status was not significantly associated with miscarriage in the univariate analysis and hence was not

included in the final regression model (p=0.56). For past/current smoker, the RR (95%CI) = 0.78 (0.43, 1.41).

DISCUSSION

Our findings suggest a significant correlation with maternal serum conjugated BPA level and first trimester miscarriage. The patients with conjugated BPA levels in the highest quartile had an overall 83% increased risk of miscarriage compared to women in the lowest quartile. This association was demonstrated for both aneuploid and euploid miscarriages, with a relative risk of for aneuploid miscarriages and euploid miscarriages of 1.97 and 3.33, respectively. A trend toward increasing risk of miscarriage with increasing conjugated serum BPA level quartile was noted across both subtypes of miscarriage. This is the largest study in the literature to measure BPA levels during early human pregnancy. Women with live births and miscarriages were similar in terms of BMI, age, and ovarian reserve testing, reducing the potential impact of these confounders.

This analysis focuses on the relationship between serum conjugated BPA and pregnancy outcome rather than unconjugated BPA, as there is disagreement concerning the degree to which contamination of serum samples may occur due to leaching of unconjugated BPA from equipment used in blood collection or handling after collection (3, 16). Glucuronidation of BPA in the liver is the primary conjugation pathway, and the serum levels of BPA-glucuronide are related to exposure to BPA in humans, monkeys and rodents (17). Conjugated BPA levels thus cannot be impacted by contamination during or after collection of blood.

This study was designed to identify if serum conjugated BPA levels obtained early in pregnancy correlate with miscarriage risk. One of the strengths of this study is the consistent timing of the blood sampling among patients. All samples were drawn during early pregnancy shortly after implantation. Because BPA exposure has been shown to interfere with meiotic progression in mice (12,18) as well as altered progesterone receptor expression in the endometrium in non-human primates (19-20), we hypothesize that peri-conception levels are critical in determining oocyte and endometrial competence for a given menstrual cycle and therefore the most relevant when studying miscarriage as a primary outcome(12, 18-20). Additionally, known chromosome status of the miscarriages allows us to differentiate between aneuploidy and euploid miscarriage to further explore the mechanism of action of BPA in miscarriage. It is interesting that conjugated BPA levels were associated with increased risk of both euploid and aneuploid miscarriages, suggesting that BPA may be acting on both pre-implantation and post-implantation development. An additional strength of this study is the analysis represents “real life” BPA exposures, not experimental conditions.

Several prior studies also suggest that peri-conception BPA concentration in maternal serum may have a negative impact on gamete quality and implantation. Animal studies have demonstrated the link between preconception BPA exposure and oocyte aneuploidy (7). Human studies have shown that increased serum and urinary BPA concentrations in women undergoing in vitro fertilization are associated with reduced fertilization and blastocyst

development (21-23). Additionally, Ehrlich et al. demonstrated that urinary BPA levels are associated with reduced implantation during IVF (21, 23). Furthermore, additional evidence suggests a reduction in estradiol response to gonadotropin stimulation associated with increased BPA exposure (24, 25). Through dysregulation of the estrogen receptors, BPA may also impact endometrial receptivity, progesterone receptor expression, or follicular environment (12, 20, 22). Sugiura-Ogasawara M measured BPA using an enzyme-linked immunoassay (ELISA) in women with recurrent miscarriage and non-pregnant control women (15). While an association was found between higher BPA levels in the recurrent miscarriage cohort, the small sample size and method of BPA assessment limited the conclusiveness of the study (15).

The current understanding of BPA metabolism is that the chemical has a short half-life post-exposure. Because patients were not instructed to fast prior to blood sampling, the lack of correlation between samples from the same patient is not unexpected and is likely due to variable clearance and types of exposures during the study period. Given that the blood samples collected occurred at the time of pregnancy assessment rather than during the ovulatory LH surge when meiosis completion occurs, it is hypothesized that the association between conjugated BPA and aneuploidy miscarriages may reflect intermittent or recurring exposure to BPA during the window of vulnerability. The finding that euploid losses were also increased could either suggest a non-chromosomal effect on the oocyte or a potential post-implantation effect of BPA exposure. There is evidence that BPA binds to human placental estrogen-related receptor (ERR), and thus it has been hypothesized that a direct endometrial or placental effect may exist (26, 27). Further studies on the mechanism for the association between BPA and euploid pregnancy loss are needed.

There are several limitations to our study. By examining only conjugated BPA in the female partner we are ignoring the possible interactions with other EDCs, which may not only be additive but potentially compounded by BPA. Male exposure to BPA and other EDCs may also influence embryo quality and miscarriage risk (28, 29) and should be examined in future studies. Although it is possible that men and women living in the same environment may have similar levels, we did not examine this in our current study. Although, our serum samples were typically drawn within 2-5 days of each other, the BPA concentrations did not correlate well between samples. This finding indicates that BPA levels can vary significantly within an individual, confirming prior findings of a low correlation between BPA levels in urine collected from women at different times in pregnancy (30). Day-to-day exposures need to be examined to identify the ingestions or exposures associated with this variability. The levels seen in this study may or may not correlate with preconception or later first trimester levels, limiting our ability to discern the potential critical window of exposure. We acknowledge that the BPA measurements obtained were not necessary obtained during the window of vulnerability, especially if non-disjunction events occurred in response to BPA exposure.

In summary, our study adds to the growing literature that low levels of exposure to EDC may negatively impact human reproduction. Further studies examining the effect of BPA on human embryo competency and pregnancy outcomes are critically needed. If additional studies validate that human exposure to BPA is associated with aneuploidy in human

conceptions, this would represent a potentially modifiable risk factor for aneuploidy. Current recommendations to reduce individual exposure include; minimizing ingestion of canned foods, reducing contact with register receipts and avoiding heating food in plastic containers. The effect of lifestyle modification aimed at lowering BPA exposure deserves further study but has been shown to impact systemic BPA concentrations(31, 32). In the meantime, couples suffering from infertility or recurrent miscarriages would be best advised to reduce BPA exposures because it has the potential to adversely affect fetal development. (4)

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CAPSULE

Conjugated Bisphenol A at the time of the missed period was associated with miscarriage risk in an infertile population. There was a similar increased risk for both euploid and aneuploid miscarriage.

Table 1

Demographic characteristics of study subjects

Variable	Miscarriage *(n=68)*	Live Birth *(n=47)*	P-value
Age (years)	36.5 (4.3)	35.9 (4.4)	0.449
BMI (kg/m^2)	22.3 [20.4, 25.8]	23.3 [21.1, 25.3]	0.422
FSH Level[a]	7.6 [6.3, 9.4]	7.3 [5.8, 9.7]	0.927
Prior pregnancies			
0	21 (30.9%)	20 (42.6%)	0.237
≥1	47 (69.1%)	27 (57.4%)	
Prior miscarriages			
0	33 (48.5%)	35 (74.5%)	0.025
1	18 (26.5%)	8 (17.0%)	
2	7 (10.3%)	3 (6.4%)	
≥3	10 (14.7%)	1 (2.1%)	
Prior live births			
0	46 (67.6%)	30 (63.8%)	0.693
≥1	22 (32.4%)	17 (36.2%)	
Conception method			
NC	21 (30.9%)	4 (8.5%)	0.010[b]
IUI	16 (23.5%)	19 (40.4%)	
IVF	31 (45.6%)	24 (51.1%)	
Smoking status			
Never smoked	63 (94.0%)	45 (97.8%)	0.566
Past smoker	1 (1.5%)	0 (0%)	
Smoker	3 (4.5%)	1 (2.2%)	

Values reported as mean (SD), median [IQR], or n (%). P-values were calculated using Fisher's Exact test, Students t-test, and Mann Whitney U test. NC=natural conception without hormonal treatment; IUI=intrauterine insemination; IVF=in vitro fertilization (fresh cycle)

[a] Highest measured FSH level prior to index pregnancy

[b] Statistically significant

Table 2

Comparison of conjugated Bisphenol-A serum levels between miscarriages and live births

Percentiles[a]	**Miscarriage** ***(n=68) Bisphenol A (ng/mL)***	**Live Birth** ***(n=47) Bisphenol A (ng/mL)***	**P-Value**
25th Percentile	0.0725	0.0592	
50th Percentile	0.1005	0.0753	0.014[b]
75th Percentile	0.2179	0.1237	
Range	0.0419 - 4.7900	0.0020 - 1.4390	

All values are reported as ng/mL.

[a] Percentiles were calculated utilizing the average serum concentration of sample 1 and sample 2 for each subject

[b] p-value listed in table represents comparison of 50th percentile value using Student's t-test

Table 3

Relative risks for miscarriage associated with conjugated Bisphenol A level by quartile

Quartile	Serum BPA Level (ng/mL)	All Miscarriages (n=68)		Aneuploid (n=46)		Euploid (n=22)	
		RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
1st quartile	<0.0636[a]	1.00	Reference	1.00	Reference	1.00	Reference
2nd quartile	0.0636 - <0.0874	1.30	(0.74 – 2.25)	1.18	(0.57 – 2.45)	2.11	(0.61 – 7.24)
3rd quartile	0.0874 - <0.1651	1.58	(0.95 – 2.63)	1.63	(0.86 – 3.09)	2.50	(0.74 – 8.47)
4th quartile	>0.1651	1.83[b]	(1.14 – 2.96)	1.97[b]	(1.08 – 3.59)	3.33[b]	(1.04 – 10.71)

Abbreviations: CI, confidence interval; OR, odds ratio. All relative risks were calculated by logistic regression with the 1st quartile defined as the reference category. Quartiles were defined by pooled study population analysis.

[a] Reference category

[b] Statistically significant at p<0.05 value