2013

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Recommended Citation

Robledo, C., Peck, J. D., Stoner, J. A., Carabin, H., Cowan, L., Koch, H. M., & Goodman, J. R. (2013). Is bisphenol-A exposure during pregnancy associated with blood glucose levels or diagnosis of gestational diabetes?. Journal of toxicology and environmental health. Part A, 76(14), 865–873. https://doi.org/10.1080/15287394.2013.824395

HHS Public Access

Author manuscript

J Toxicol Environ Health A. Author manuscript; available in PMC 2014 January 01.

Published in final edited form as:

J Toxicol Environ Health A. 2013 ; 76(14): 865–873. doi:10.1080/15287394.2013.824395.

Is bisphenol-A exposure during pregnancy associated with blood glucose levels or diagnosis of gestational diabetes?

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Abstract

Recent epidemiological studies indicate bisphenol-A (BPA), an estrogenic chemical used in production of epoxy, polycarbonate and plastic may increase risk of insulin resistance and type 2 diabetes. Exposure to BPA during pregnancy may contribute to development of gestational diabetes mellitus (GDM), a precursor to type 2 diabetes in women. This pilot study examined the association between BPA exposure, fasting blood glucose levels (FBG) and GDM diagnosis during pregnancy. Banked urine samples from 22 cases of GDM and 72 controls were analyzed for total (free BPA + conjugates) urinary BPA concentrations (μg/L). FBG levels (mg/dl) were obtained from 1 h 50 g glucose tolerance tests (GTT) that women underwent for routine GDM screening (mean gestational age=26.6 weeks sd=3.8). Those with an initial screening value ≥135 mg/dl underwent 3-hr 100 g oral GTT. GDM diagnoses were made when the initial screening value was ≥ 200 mg/dl or when values at ≥ 2 time points exceeded 3-hr oral GTT thresholds. Among controls, median FBG levels (mg/dL) did not differ across exposure tertiles, defined according to the distribution of total specific-gravity adjusted urinary BPA concentrations. Logistic regression models controlling for race/ethnicity did not provide evidence of association between BPA exposure and case status across increasing tertiles of BPA exposure (number of GDM cases/controls in tertile 1: 13/24, tertile 2: 6/24 tertile 3: 3/24).. Findings do not support a

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Conflict of interest

The authors declare no conflict of interest.

relationship between total urinary BPA concentrations and altered glucose metabolism during pregnancy. However, due to study limitations findings need to be interpreted with caution.

Keywords

bisphenol-A; gestational diabetes; glucose; pregnancy

Introduction

Several epidemiological studies have linked diabetes mellitus and exposure to endocrine active compounds such as dioxin (Cranmer et al., 2000), polychlorinated biphenyls (Longnecker et al., 2001; Vasiliu et al., 2006; Wang et al., 2008), phthalates (Lind et al., 2012; Stahlhut et al., 2007; Svensson et al., 2011) and most recently bisphenol-A (BPA) (Lang et al., 2008). Human exposure to bisphenol-A (BPA), an estrogenic chemical used in the production of epoxy resins and polycarbonate plastics is widespread (Kang et al., 2006; Kasper-Sonnenberg et al., 2012; Shin et al., 2010). Initially thought to be a weak environmental estrogen, evidence now indicates that low dose exposures to BPA may elicit cellular responses with effects in various types of tissues that are just as efficacious and potent as estradiol (Welsons et al., 2003, 2006; Wozniak et al., 2006). Estradiol concentrations outside the normal range have been shown to disrupt glucose homeostasis and perhaps contribute to the risk of developing type 2 diabetes mellitus (Barros et al., 2006; Ding et al., 2007; Godsland, 1996; Godsland, 2005; Livingstone and Collison, 2002; Nadal et al., 2008). By mimicking estradiol, BPA was also found to adversely alter glucose homeostasis by targeting estrogen receptors henceforth disrupting pancreatic beta cell function (Alonso-Magdalena et al., 2005; 2006; 2010a; 2010b; Mauvais-Jarvis, 2011; Ropero et al., 2008). Animal studies using mice demonstrated that a single low level exposure to BPA (10 μg/kg) administered subcutaneously (sc) increased plasma insulin, and prolonged exposure elevated pancreatic beta cell insulin content provoking postprandial hyperinsulinemia and insulin resistance (Alonso-Magdalena et al., 2006; Ropero et al., 2008). A recent study in pregnant mice, administered BPA sc on days 9–16 of gestation demonstrated an association between BPA exposure, glucose intolerance and increased plasma insulin during pregnancy and 4 months postpartum. (Alonso-Magdalena et al., 2010b). It was therefore hypothesized that exposure to BPA during pregnancy may contribute to development of GDM by mimicking the actions of estradiol and disrupting glucose homeostasis. This pilot study used banked urine specimens from an existing (parent) case-control study of GDM to assess the association between total urinary BPA levels during pregnancy, blood glucose levels and diagnosis of GDM.

Methods

Participants in the parent case-control study were recruited from the University of Oklahoma Medical Center Women's and High Risk Pregnancy clinics located in Oklahoma City, Oklahoma between August 2009 and May 2010. The study and subsequent analyses were approved by the University of Oklahoma Health Sciences Center (OUHSC)'s Institutional Review Board. Clinical lab reports were reviewed to identify all pregnant women screened

at OUHSC Women's Clinic for GDM. Patients who were referred to the OUHSC High Risk Pregnancy Clinic for the diagnosis of GDM (n=65) were recruited during their first post-diagnostic visit. Controls (n=244) were selected concurrently from eligible obstetrical patients in the OUHSC Women's Clinic who screened negative for GDM. Women were eligible to participate in the parent study if (1) they resided in one of 9 counties predominately served by the clinics (Oklahoma, Kingfisher, Logan, Lincoln, Pottawatomie, Cleveland, Canadian, McClain and Grady counties), (2) were 18 years of age or older, (3) had no pre-existing diagnosis of Type 1 or 2 diabetes mellitus, and (4) spoke English or Spanish. The sample size for this pilot study was limited by the amount of seed grant funds available to support the cost of lab analyses. Thus, a sub-sample of 22 cases and 72 controls was selected from subjects who consented to the banking of their specimens for future research and who self-reported their race as Hispanic, Non-Hispanic White or Non-Hispanic Black. The characteristics of the cases and controls in the sub-sample did not differ significantly from cases and controls in the parent study with respect to age, race/ethnicity, income and obesity.

Urine specimens were collected at enrollment in sterile polypropylene containers and stored in sterile 2 ml polypropylene cryovials at −20°C. Specimens were shipped in dry ice to the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance - Institute of the Ruhr-Universität Bochum (IPA), Bochum, Germany. Total (free BPA + conjugates) and free urinary BPA concentrations were determined using a high performance liquid chromatography – mass spectrometry method (on line SPE HPLC – MS/MS) with isotope dilution described previously (Koch et al., 2012). The limit of quantification (LOQ) for both total and free BPA was 0.1μg/L. Levels reported below the limit of detect (LOQ) (n=5), were imputed by dividing the LOQ by the square root of two (Hornung and Reed, 1990). A random subsample of specimens (n=34) underwent LC-LC/MS-MS without enzymatic hydrolysis to measure free BPA concentrations. Quantification of free BPA in the subsample did not indicate BPA contamination or sample degradation in the pre-analytical phase or during sample collection and storage. Specimens were adjusted for urinary dilution using creatinine concentrations (μg/g) reported by the analytical lab (Lauwerys and Hoet, 2001) and specific gravity (μg/L) measured at the time of collection using a calibrated hand-held refractometer. Total urinary BPA concentrations among women without GDM (control group) were used to categorize BPA exposure into tertiles (e.g., specific-gravity (SG) adjusted BPA: ≤0.66 μg/L, >0.66 to <1.44 μg/L and ≥ 1.44 μg/L). Exposure tertiles were created for unadjusted, creatinine and SG-corrected total urinary BPA concentrations. The associations between BPA exposure and GDM were also explored using total urinary BPA concentrations that were categorized into low levels (less than the median, specific-gravity adjusted BPA: <1.36 microgram/L) or high levels (greater than or equal to the median specific-gravity adjusted BPA: ≥1.36 microgram/L). Results from models are presented where BPA exposure was modeled using tertiles because findings did not vary using other exposure cutoffs.

Blood glucose levels for all participants were obtained from a 1 hr 50 g oral glucose challenge test (OGTT) routinely administered to screen pregnant women for GDM. Those with an initial screening value of 135–199 mg/dl underwent a 3 hr 100 g OGTT for diagnosis of GDM. A clinical diagnosis of GDM was made when the initial screening value

was ≥ 200 mg/dl or when the 3 hr 100 OGTT values at ≥ 2 time points exceeded recommended thresholds (Carpenter and Coustan, 1982; Metzger and Coustan (Eds) 1998). Blood glucose levels obtained from the 1 hr 50 g OGTT were used to assess the relationship between blood glucose levels and BPA exposure.

A questionnaire administered at the time of enrollment collected information on covariates of interest including demographic factors such as age, race/ethnicity, educational level, and annual household income, parity, previous diagnosis of GDM and family history of type 2 diabetes mellitus. Prior to urine collection, participants were also asked to report the number of hr since last meal and the number of canned goods or beverages consumed in the previous 24 hr. The interviewer also recorded the time of urine collection. Pre-pregnancy body mass index (BMI) (kg/m^2) was calculated using self-reported height and weight. Gestational age at enrollment (weeks) was calculated by subtracting the self-reported date of the last menstrual period from the date of enrollment and dividing the number of days by 7. To evaluate maternal smoking as a confounder, urinary cotinine concentrations ≤ 15 ng/ml were used to define an active smoker (Benowitz et al., 2009a, 2009b).

All statistical analyses were conducted using SAS version 9.1.3 and performed for unadjusted (μg/L), creatinine (μg/g) and SG corrected (μg/L) total urinary BPA concentrations. Results of analyses by BPA standardization technique were generally similar and therefore only results for SG-corrected BPA concentrations are presented, unless otherwise noted. Geometric mean concentrations, 95% confidence intervals and distribution percentiles of total BPA urinary concentrations were calculated for GDM cases and controls. Categorical patient characteristics including BPA exposure were summarized and compared separately for GDM cases and controls using the Chi-square test of independence. Mann-Whitney tests were used to compare 1) continuous patient characteristics by case status and 2) median BPA urinary concentrations between categories of demographic characteristics.

Logistic regression was used to model the odds of higher levels of total urinary BPA among GDM cases compared to controls (using lowest tertile as the reference group), while controlling for covariates of interest. Confounding of the association between BPA exposure and GDM diagnoses was assessed for all covariates. A logistic regression model was created for GDM diagnosis with each BPA exposure variable and a given potential confounder. Due to the small number of GDM cases confounding for each covariate was assessed separately. Confounding was assessed by evaluating the change (>20%) in the crude and the adjusted odds ratios when controlling for the covariate in the model (Miettinen, 1976). Race/ethnicity (Hispanic, non-Hispanic) was the only factor that met the criteria for confounding in these analyses and this factor was controlled for in the final models. There were no active smokers among GDM cases. Thus, analyses were also repeated after restricting cases (n=22) and controls (n=51) to women who were not active smokers. Parameter estimates did not differ when compared to those obtained when including all women regardless of smoking status; therefore results from the complete data are reported here.

Analyses examining the association between total urinary BPA concentrations and blood glucose levels were restricted to controls (n=72). Blood glucose levels were log transformed to normalize the distribution of the residuals. Multiple linear regression was used to model

log blood glucose levels by tertiles of total urinary BPA concentrations controlling for potential confounders. Confounding was assessed using the methods previously described. However, to determine whether changes in log blood glucose due to adjustment were clinically relevant, parameter estimates from crude and adjusted models were back transformed and then compared to assess the absolute and relative increase in blood glucose levels for BPA exposure tertiles. No covariates met the criteria for confounding in the linear regression models.

Results

Demographic characteristics were found to differ by GDM case status (Table 1). Cases of GDM tended to be older, have higher BMI, and were more frequently overweight or obese than controls. There was an important discrepancy in the ethnic distribution with about two-thirds of the cases being Hispanic compared to one-quarter of controls. An examination of lifestyle factors and reported medical history also revealed differences between GDM cases and controls. No GDM cases were categorized as being active smokers; thus, smoking among controls was more prevalent. The majority of GDM cases and controls reported having at least one family member with type 2 diabetes mellitus. Median gestational age at the time of GDM screening and at time of study enrollment did not differ significantly by case status.

The total BPA urinary concentrations of GDM cases and controls were low. Table 2 lists the geometric means, 95% confidence intervals and distribution percentiles by GDM case status for total urinary BPA concentrations adjusted and unadjusted for urinary dilution. Specific gravity-corrected geometric mean (GM) total BPA concentrations among cases (GM=0.8 ng/L, 95% CI: 0.5, 1.1) were numerically lower than among controls (GM=1.67 ng/L, 95% CI: 1.01, 2.32). Among GDM cases, SG-corrected total urinary BPA concentrations (ng/L) did not significantly differ across characteristics examined (Table 3). Among the control group, median urinary BPA concentrations differed between categories of BMI, education and ethnicity. No significant associations were observed between BPA exposure categories and GDM diagnosis (Table 4). In addition, when considering control participants, linear regression models did not identify a significant relationship between mean log blood glucose levels and BPA exposure categories (data not shown).

Discussion

This study is the first to explore associations between BPA exposure during pregnancy, blood glucose levels and physician diagnosis of GDM. This study was not able to demonstrate an association between total urinary BPA concentrations and blood glucose levels, or diagnosis of GDM in a low income and racially diverse pregnant population. These findings are in accordance with a review showing no adverse affects on human health at biologically relevant doses of BPA exposure (Willhite et al., 2008) and a study in mother-child pairs showing that less than 16% of circulating levels was free of active BPA (Kasper-Sonnenberg et al., 2012). A recent cross-sectional study of US adult men and women (n=1455) using data obtained from the 2003–2004 National Health and Nutrition Examination Survey (NHANES) found associations between BPA exposure, fasting blood

glucose levels and self-reported diagnosis of diabetes mellitus (DM). After controlling for age, gender, race/ethnicity, education, income, BMI, waist circumference and urinary creatinine, the odds of self-reported DM diagnosis (type 1 and type 2) was 1.39 (95% CI, 1.21–1.60) fold higher with a 1 standard deviation elevation in total urinary BPA concentration. This study reported that log transformed fasting glucose levels rose with a 1-SD increase in BPA urinary concentration, when adjusted for age, race/ethnicity and urinary creatinine (β=0.02, 95% CI, 0.00, 0.03) (Lang et al., 2008).

These contradictory results are most likely attributed to differences in study populations and sample size. Our study was conducted in pregnant women and the outcome of interest was GDM, not type 1 or type 2 diabetes mellitus. Unlike the previous study where self-reported diabetes may be more susceptible to misclassification error, participants in this study underwent screening for GDM and further testing was used to confirm GDM diagnosis. Further, the association between low levels of BPA and diagnosis of GDM was examined using categories of BPA exposure based on distribution percentiles. In this study, total urinary BPA concentrations among pregnant women were observed to be at least two-fold lower than those reported in pregnant women in the US (Braun et al., 2011; Harley et al., 2013), Netherlands (Ye et al., 2008) and Spain (Casas et al., 2011). Although results were robust to different exposure cut points, our small sample size limited statistical power to detect modest associations and may have also hindered our ability to comprehensively explore and control for confounders. Despite the differences in characteristics observed between GDM cases and controls, only race/ethnicity was found to be a confounder when examining the association between BPA and GDM diagnosis. Therefore, results need to be interpreted cautiously.

Exposure assessment may not have occurred at the etiologically relevant time window for GDM. Therefore, misclassification of exposure may account for the null associations observed between total BPA concentrations and GDM. BPA exposure was based on a single spot urine sample collected at the time of GDM screening during the second trimester of pregnancy. Several studies documenting within-person variability of total BPA urinary concentrations reveal that a single sample may be an inadequate assessment of BPA exposure and may lead to misclassification of exposure (Mahalingaiah et al., 2008; Stahlhut et al., 2009). BPA is quickly metabolized in the body and therefore, total urinary BPA concentrations may reflect at most exposure to BPA in the last 24 hr (Stahlhut et al., 2009). A study conducted among men and women undergoing infertility evaluation and treatment measured specific gravity-adjusted BPA in at least 3 urine samples from each participant, with a mean of 172 days between the first and last collection days (Mahalingaiah et al., 2008). The detected sensitivity and specificity of a single urine sample in predicting whether a subject was in the highest tertile of BPA exposure was moderate (0.64 and 0.76). A more recent study of BPA variability in pregnant women (n=389) obtained three spot urine samples at mean gestational ages (±SD) of 16±2, 26±2 and 39±1.8 weeks (Braun et al., 2011). The study found low reproducibility of BPA measurements using unadjusted (intra class correlation coefficient (ICC) = 0.25) and creatinine-corrected total urinary BPA concentrations (ICC=0.10). The findings also indicated that unadjusted and creatinine-corrected concentrations varied by time of day, decreasing from early morning through midmorning and increasing again in the afternoon (Braun et al., 2011). It was possible to

collect information regarding factors that might account for differences in BPA exposure among GDM cases and controls. Prior to spot urine collection, GDM cases and controls were not found to differ in the number of hr since last meal, the number of canned goods or beverages consumed in the previous 24 hr or time of urine specimen collection.

Conclusions

In this small pilot study it was not possible to demonstrate an association between BPA exposure and development of GDM. Larger studies are needed to assess whether environmental contaminants such as BPA play a role in the etiology of GDM. Exposure assessment in future studies would be improved by using repeated specimen collection to measure BPA during etiologically relevant windows for GDM and other outcomes of interest. Such investigations are warranted to identify environmental exposures that may impact the health of vulnerable populations, including pregnant women and their offspring.

Acknowledgments

This research was also supported in part by the Oklahoma Tobacco Research Center and the Intramural Research Program of the NIH, Eunice Kennedy Shriver National Institute of Child Health & Human Development.

Funding Sources

Grant funds for lab analyses were provided by Grant No. T42OH008421 from the National Institute for Occupational and Environmental Health (NIOSH)/Centers for Disease Control and Prevention to the Southwest Center for Occupational and Environmental Health (SWCOEH), a NIOSH Education and Research Center.

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Table 1

Distribution of demographic and clinical characteristics of cases of gestational diabetes mellitus (GDM) and their controls in Oklahoma

	Cases (n=22)	Controls (n=72)	p-value
Age (years)	**n (%)**	**n (%)**	
≥25	17 (77)	34 (47)	0.010[c]
Median (Range)	29.0 (19, 35)	24.0 (18, 42)	0.009[e]
Body Mass Index (kg/m^2)			
≥25	18 (82)	33 (46)	0.003 [c]
Median (Range)	29.5 (21.6, 58.9)	24.5 (16.8, 44.6)	0.004[e]
Race/Ethnicity			
Hispanic	14 (64)	20 (28)	0.002 [c]
Income			
<$10,000 per year	7 (32)	40 (56)	0.051 [c]
Education			
<High School	16 (73)	21 (29)	0.0003 [c]
Active Smoker			
Yes	0 (0)	15 (21)	0.003[d]
Family History of Type 2 DM[a]			
Yes	18 (82)	38 (53)	0.053[d]
Previous GDM Diagnosis[b]			
Yes	8 (42)	1 (2)	<0.0001[d]
Parity			
Nulliparous	4 (18)	22 (31)	0.256 [c]
Gestational Age (weeks)	**Median (Range)**	**Median (Range)**	
at GDM Screen	25.9 (9.7, 32.9)	26.6 (22.3, 34.43)	0.08[e]
at Enrollment	29.5 (16.9, 34.7)	30.6 (26.0, 38.1)	0.16[e]
Blood Glucose Levels (mg/l)			
	163.5 (137, 269)	109.0 (69, 197)	<0.0001[e]

[a] Analysis omitted two controls with unknown family history of type 2 diabetes mellitus

[b] Analysis omitted cases (n=4) and controls (n=22) pregnant for the first time

[c] Chi-Square Test of Independence p-value

[d] Fisher's Exact p-value for Chi-Square Test of Independence

[e] Mann Whitney test p-value

Table 2

Geometric means (GM), 95% confidence intervals and distribution percentiles for total urinary bisphenol-A (BPA) concentrations by gestational diabetes mellitus (GDM) case status

GDM	BPA Exposure	n	GM	GM 95% CI	P10	P25	P50	P75	P90	P95
Cases	BPA (μg/L)	22	0.52	0.35–0.78	0.20	0.34	0.57	0.97	1.25	1.81
	SG[a] corrected BPA (ng/L)		0.80	0.50–1.10	0.29	0.52	0.90	1.80	2.75	5.48
	BPA (μg/g creatinine)		0.60	0.45–0.79	0.27	0.44	0.55	0.76	1.28	1.29
Controls	BPA (μg/L)	72	0.83	0.64–1.08	0.22	0.41	0.87	1.78	3.08	4.75
	SG[a] corrected BPA (ng/L)		1.67	1.01–2.32	0.32	0.43	0.54	0.84	1.72	2.19
	BPA (μg/g creatinine)		0.88	0.71–1.09	0.29	0.53	0.92	1.49	2.56	3.93

[a]SG is Specific-Gravity

Table 3

Median total specific-gravity adjusted urinary bisphenol-A (BPA) concentrations (ng/L) by case status and selected population characteristics

	Cases			Controls		
	n	(ng/L)	p-value[a]	n	(ng/L)	p-value[a]
Body Mass Index						
< 25 kg/m^2	4	0.57	0.71	39	**0.72**	0.04
≥ 25 kg/m^2	18	0.54		33	**1.23**	
Age						
<25 years	5	0.52	0.88	38	0.86	0.63
≥ 25 years	17	0.56		34	1.06	
Race/Ethnicity						
Hispanic	14	0.49	0.28	20	**0.62**	0.04
Non-Hispanic	8	0.79		52	**1.18**	
Education						
< High School	16	0.52	0.49	21	**0.54**	0.03
≥ High School	6	0.66		51	**1.17**	
Income (per year)						
< $10,000	7	0.78	0.11	40	0.92	0.78
≥ $10,000	15	0.48		32	0.91	
Active Smoker						
No	22	0.53	--	57	0.88	0.55
Yes	0	--		15	1.11	

[a]Comparisons between groups defined by demographic variables among cases and controls made using the Mann Whitney test

Table 4

Odds ratios and 95% confidence interval for association between specific-gravity adjusted bisphenol-A (BPA) exposure variables and diagnosis of gestational diabetes mellitus (GDM)[a]

	Cases (n=22)	Controls (n=72)	OR (95% CI)
BPA Tertile Model			
Tertile 1 (reference)	13	24	--
Tertile 2	6	24	0.58 (0.18, 1.19)
Tertile 3	3	24	0.37 (0.09, 1.60)

[a]Models adjusted for race/ethnicity