Published in final edited form as:

Paediatr Perinat Epidemiol. 2019 November ; 33(6): 397–404. doi:10.1111/ppe.12578.

Association between peri-conceptual bisphenol A exposure in women and men and time to pregnancy—The HOPE study

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Abstract

Background: Bisphenol A (BPA) is a non-persistent endocrine-disrupting chemical with nearly ubiquitous, involuntary exposure. Previous studies have shown that BPA causes reproductive dysfunction in animal models, but there are limited data regarding the effects of BPA exposure on time to pregnancy (TTP) in humans.

Objective: To evaluate whether peri-conceptual BPA exposure of women and men is associated with couples' TTP.

Methods: A total of 164 heterosexual couples (164 women; 163 men) who have available BPA information as well as time to pregnancy from the Home Observation of Peri-conceptual Exposures (HOPE) Study were included and were followed up to 12 months. Women collected first-morning urine samples starting at the beginning of the fertile window and continued until the onset of menses or 18 days after the estimated day of ovulation (EDO+18 days). The time to pregnancy (TTP) after the enrolment was self-reported and used for the analysis. Discrete-time Cox proportional hazards models were performed to generate fecundability odds ratio (FOR) between BPA and TTP after adjusting for education and age, accounting for right censoring and prior number of cycles trying to conceive.

Results: Among 164 couples, 125 couples became pregnant during the study. There was no association between TTP and peri-conceptual BPA exposure for both men (FOR 1.02, 95% CI 0.72, 1.47) and women (FOR 1.07, 95% CI 0.75, 1.53) after adjusting for education and age.

Conclusions: No association was found between peri-conceptual BPA exposure and fecundability in this preconception cohort of relatively young, healthy pregnancy planners.

Keywords

bisphenol A; endocrine disruptor; fecundability; peri-conception; pregnancy; time to pregnancy

1 | INTRODUCTION

Fecundability, as measured by time to pregnancy (TTP), is used as a sensitive reproductive outcome appropriate for studying the impact of environmental exposures. Decreased fecundability^{1–4} has been associated with life style exposures including tobacco, alcohol, and obesity;^{5,6} occupational exposures including pesticides;⁷ and environmental chemicals in consumer products.⁸ Longer TTP has been associated with adverse pregnancy outcomes including miscarriage, preterm birth, and low birthweight as well as reports of increased adverse outcomes in the neonate and child development.^{9–12} In sum, a growing body of human epidemiologic evidence, as well as experimental animal evidence, indicates that peri-conceptional exposures to environmental chemicals or other exposures may have both short-term and long-term health effects on fecundity, growth, and development.¹³

Most studies of fecundability are limited by their retrospective nature, exclusion of those who never conceived, and lack of prospective peri-conceptional exposure assessment.^{3,14} Although it is possible to implement such study with retrospective study design, prospective studies provide the strongest findings and protection against recall bias in reporting TTP and avoid the selection bias that can occur in retrospective studies.^{1–4,15} Prospective designs can also enable environmental exposure assessment timed with ovulation and conception¹⁶, which may be particularly important for non-persistent exposures.

Bisphenol A (BPA) is a non-persistent endocrine-disrupting chemical (EDC) with nearly ubiquitous, involuntary exposure and is commonly found in polycarbonate plastic, epoxy resins, food can linings, dental sealants, thermal receipt paper, and other commercial products.^{17,18} More than 90% of the population in the United States and Canada shows detectable urinary concentrations of BPA.^{19,20} Previous studies have shown that BPA causes reproductive dysfunction in animal models,²¹ but there are limited data regarding the effects of BPA exposure on TTP in humans. Most studies to date have focused on couples seeking assisted reproductive technology (ART) with their reproductive outcomes and environmental exposures among male, despite women's reproductive function being also susceptible to hormonally active chemicals.²² A few studies have examined the association between peri-conceptional exposure to BPA and time to pregnancy.^{21–23} However, the results were not consistent, perhaps in part because of the daily urine collection at home, which could result in measurement error, and the short metabolic half-life of BPA in the body.

Therefore, we aim to assess the effect of peri-conceptional exposure to BPA for both women and men on couples' TTP using the data from the Home Observation of Peri-conceptional Exposures (HOPE) Study. We hypothesised that higher levels of exposure to BPA in both women and men would decrease fecundability (increase TTP).

2 | METHODS

2.1 | Study population

The study population includes participants (164 couples, 328 participants) from heterosexual couples planning pregnancy within 3 months after enrolment in the Home Observation of Peri-conceptional Exposures (HOPE) Study. Participants were recruited from the greater

Salt Lake City area, Utah, beginning in January 2012. Women were required to be 18–35 years of age, and men were required to be 18–40 years of age. Criteria for exclusion among women included previously diagnosed with infertility, sub-fertility, or a condition that might affect their fertility such as having undergone cervical or infertility treatment, not currently using hormonal contraception in the previous 2 months. The study population has been described in detail previously.²⁴ They were recruited and followed for up to 12 months between 2012 and 2015. After consenting, women completed an online enrolment questionnaire that included questions related to BPA, physical activity, stress and depression, demographics, medical and reproductive history, birthweight, pregnancy intention, and previous knowledge or use of fertility awareness-based methods. The study was approved by the University of Utah Institutional Review Board, and participants signed an informed consent document before participation.

2.2 | Exposure

Women were taught the Peak Day Method, which has been validated as an effective approach to identify timing of ovulation and to estimate the fertile window by women's self-observation of cervical fluid patterns.²⁵ Women collected daily first-morning urine samples starting at beginning of the fertile window and continued until the onset of menses or EDO +18 days. Concentrations of BPA in each urine sample were measured using ultra-high-performance liquid chromatography-tandem mass spectrometry at the Center for Human Toxicology at the University of Utah, which is the typical method for assessing BPA. Method validation included quality control samples at three concentrations in synthetic urine and human urine. Laboratory operating procedures also included validated method parameters of linearity, accuracy, precision, integrity of dilution, selectivity, re-injection reproducibility, recovery/matrix effect, solution stability, and matrix stability in human urine. Method validation also included quality control samples at three concentrations in both synthetic urine and human urine.^{26,27} Men collected daily urine samples starting at the same time but were asked to stop after the estimated day of ovulation (EDO). The timing and collection of samples have been described previously.²⁶ Geometric mean BPA concentration during the last recorded cycle (either the conception cycle or cycle temporally closest to conception) was used for the analysis.

The BPA exposure values were analysed in three different ways: (a) continuous geometric mean BPA concentrations, (b) dichotomous levels with the cut-off determined by the 50th percentile of the BPA levels among the cohort by sex, and (c) tertile levels with the two cut-offs determined by the 33th percentile and 66th percentile of the BPA levels by sex.

2.3 | Outcomes

Women were asked to record the menstrual cycle (based on the Peak day Method) on a daily fertility chart that was turned in to the study staff at the end of every cycle.²⁵ Time to pregnancy was measured as the discrete number of menstrual cycles until the women reported conception with a positive pregnancy test. Women were provided with pregnancy tests and instructed to test for pregnancy at the EDO+18 days. TTP after the enrolment was the outcome for the analysis. Data were censored at the end of the final cycle in the study for

those who had not conceived a pregnancy. TTP was displayed as cumulative proportion conceiving by cycle.

2.4 | Covariate analysis

The covariates considered for the analysis were age (years), income (dollars), smoking, education, race, and body mass index (BMI) (weight in kg/height² in m², measured at enrolment). Additional variables reported to describe the study participants, but not considered to be potential confounders for the analysis were prior pregnancy and frequency of intercourse during the fertile window. The fertile window was defined as the continuous days up to and including the EDO for which the woman recorded any of these types of cervical fluid: (1) slippery, (2) clear, or (3) stretchy.^{28,29} If the days for which the woman defined their cervical fluid as any of the three types preceded seven days before the onset of the next menstrual bleeding, then those days were excluded. The prior number of cycles trying to conceive was also considered as a potential confounder, because of the possibility of behaviour modifications while trying to conceive that might change exposure.

Adding potential confounders one at a time, we removed covariates if their inclusion did not satisfy our a priori change-in-estimate criterion (a coefficient change of >10%). The potential covariates that did not change the association between BPA measure and TTP in the full models were subsequently removed to improve the precision of the estimates. Final models were adjusted for age and education for both men and women.

2.5 | Statistical analysis

Descriptive statistical analyses, including the geometric mean, the median, and the tertiles, were computed to categorise BPA exposure levels. The TTP in relation to the peri-conceptional exposure to BPA was assessed by discrete-time Cox proportional hazards model to estimate the fecundability odds ratios (FORs), accounting for right censoring and adjusting for the number of cycles trying to conceive before study enrolment.

The FORs estimate the odds of becoming pregnant each cycle (across a range of 1–12 cycles for TTP). Diminished fecundability denotes FOR <1 or a longer TTP, whereas FOR >1 denotes a shorter TTP. Initially, the FORs and 95% confidence interval (CI) were estimated for BPA exposure for both men and women, adjusting for potential confounders including age, education, BMI, smoking status, and income.^{30,31} Multivariable models were adjusted for education and age. Separate models were evaluated with women's BPA concentrations, men's BPA concentrations, and couples' mean BPA concentrations as the exposure variable. For the accurate measurement of peri-conceptional BPA exposure, the urine samples after the EDO were dropped for women who became pregnant during the urine collection cycle. Proportional hazards modelling assumptions and linearity between covariates were evaluated by the cumulative sums of martingale residuals and the Kolmogorov-type supremum test and verified with 95% confidence intervals.

Intraclass correlation coefficient (ICC) was calculated to assess between- and within-subject variability of urinary BPA concentrations over the cycles. Cohen's kappa coefficient was also generated to evaluate the agreement of BPA exposure categories within couples. All the analyses were performed in SAS version 9.4.

3 | RESULTS

Total enrolment for the HOPE study was 183 couples. Of those, 164 couples (164 women and 163 men; 1 man did not have available BPA information) that have both available BPA measurements and TTP were included. Each BPA level was calculated from a mean of 17.6 ± 6.1 daily urine samples (range 1–40 days) for women and of 5.3 ± 2.2 daily urine samples (range 1–15 days) for men. Characteristics of the population are presented in Table 1. The study cohort was predominantly white, both Hispanic and non-Hispanic (90.9% women; 87.8% men), and equivalent to college-educated or more than 4 years of college (69.9% women; 57.1% men), with 43.3% of couples reporting prior pregnancy history. The average age of women and men was 27.3 years (± 3.6) and 28.6 years (± 3.8), respectively. The average BMI was 24.8 kg/m^2 (± 5.0) for women, which is considered as normal weight, and 27.0 kg/m^2 (± 5.9) for men, which is considered overweight according to the CDC guideline.³² Women's BPA level ranged from 0.6 to 17.4 ng/mL with the geometric mean of 3.8 ng/mL, while men's BPA ranged from 0.5 to 35.8 ng/mL with the mean of 4.4 ng/mL. During the study, 125 (76%) couples became pregnant. As Table 2 reflects, the key characteristics of the study cohort are dichotomised based on the median BPA level, which was 2.75 ng/mL for women and 2.94 ng/mL for men. The ICC for women was 0.52, which indicates the moderate reproducibility. There was little agreement between women's and men's BPA levels within couples: Cohen's kappa coefficient was 0.25.

Table 3 illustrates the proportion of pregnancies that occurred in each cycle as well as the cumulative proportion of pregnancies in each cycle analysed by time to pregnancy (TTP). The cumulative proportion of becoming pregnant following enrolment was 26.8% at the first cycle (cycle 1), 56.1% (cycle 3), 65.3% (cycle 6), and increased to 73.2% by the end of the study (cycle 12).

In Table 4, the FOR of dichotomised BPA in women in the unadjusted model is 1.02 (95% CI 0.72, 1.46); the FOR of dichotomised BPA in women in the adjusted model is 1.07 (95% CI 0.75, 1.53) after controlling for education and age. The FORs of dichotomised BPA in men were both greater than one in the unadjusted and adjusted model as well, albeit not significantly, 1.02 (95% CI 0.71, 1.45) and 1.02 (95% CI 0.72, 1.47), respectively.

4 | COMMENT

4.1 | Principal findings

The HOPE study is the first prospective study that measured the BPA levels daily for up to two menstrual cycles in both men and women. The association between women's BPA and time to pregnancy did not confirm our hypothesis of decreased fecundability. In both men and women, the FORs for dichotomised BPA levels were >1 whether adjusted or unadjusted, suggesting a shorter time to pregnancy, though the CI includes one. The FORs for tertiles levels of BPA were <1 for women and >1 for men, also the CI including one.

4.2 | Strengths of the study

The HOPE study collected serial, daily urine to support robust BPA exposure assessment, which results in high number of samples per person relative to previous studies.²¹ Most

studies examining association between BPA and health outcomes have three or fewer samples in contrast to our numerous repeat samples. This reduced misclassification of exposure to BPA. We had high compliance with the urine collection protocol and believe that the exposure assessment is highly valid and reliable compared to other previous studies.²⁴ Similar to LIFE study, we assessed BPA in both women and men. Our discrete-time cox proportional hazards modelling provides greater confidence in our findings by accounting for right censoring, prior number of cycles trying to conceive, and several confounders including age and education in relation to BPA and TTP.

4.3 | Limitations of the data

The levels of BPA were analysed from the collection of the urine samples of the observation cycle temporally closest to conception; however, this may not represent the BPA levels across all cycles during the study.

The generalisability of this study is limited by the younger age, the majority of race being white, and especially the small sample size. As with other prospective studies, there may be potential selection bias because the couples that were recruited were trying to conceive at the time of the enrolment of the study. Thus, the study cohort may not represent all women or couples at risk of pregnancy.

Bisphenol A exposure may affect men and women differently.¹⁸ BPA could have affected spermatogenesis and follicular development in earlier process, and it is possible that the time window for BPA measurements could not be accurately relevant. However, this study has measured BPA at a more relevant time compared to previous studies that we collected daily, first-morning urine samples during the fertile window.

4.4 | Interpretation

In the recent Longitudinal Investigation of Fertility and the Environment (LIFE) study, male BPA concentration was positively associated with time to pregnancy, though the CI included one, while women's BPA exposure showed no association with time to pregnancy.²¹ The HOPE study differed from the LIFE study in that we collected daily, first-morning urine specimens for BPA exposure assessment throughout the fertile window for two menstrual cycles, while the LIFE study used a single urine collection at the time of enrolment.²¹ Similar to our study, the Maternal-Infant Research on Environmental Chemicals (MIREC) study, which was a retrospective study that took place in 10 cities across Canada between 2008 and 2011, also found that neither female nor male BPA concentrations were associated with time to pregnancy.²² The North Carolina Early Pregnancy Study (NC EPS) analysed three urine samples from each menstrual cycle including at least one sample from the luteal phase.²³ The NC EPS concluded that the time-to-pregnancy analysis showed no associations of BPA with fecundability. Comparisons of cohort characteristics and findings for HOPE, LIFE, MIREC, and NC EPS are shown Table 5. The median BPA exposure is significantly higher for both men and women in the HOPE study cohort than the previous LIFE and MIREC study cohorts. According to the Fourth National Report on Human Exposure to Environmental Chemicals³³, derived from National Health and Nutrition Examination Survey, the average level of BPA contained in nationally representative sample of urine

during the period of 1999 to 2004 was 2.64 (95% CI: 2.38, 2.94) ng/mL, which is also lower than the BPA levels found among HOPE couples (women: 3.8 ± 2.7 ng/mL; men: 4.4 ± 4.6 ng/mL). Also, the median age for the HOPE cohort is substantially lower than in LIFE, MIREC, and NC EPS. The sample size for HOPE was smaller than LIFE or MIREC, and similar to NC EPS (HOPE: 183 couples; LIFE: 501 couples; MIREC: 2001 women; NC EPS: 221 women). Finally, the number of couples or women who were parous was greater in MIREC than HOPE, and similar between LIFE, HOPE, and NC EPS.

Analysing the association between the BPA and TTP depends on accurate measurement of BPA concentrations and TTP report. We suggest that future studies be designed and analysed with longitudinal measurement of urine samples among couples. Future studies should be done in populations with greater geographic and demographic diversity to provide higher degree of generalisability, in terms of applying the results to a broader range of populations with diverse backgrounds. Exposure to BPA is typically from plastics and packaging which may also be a source of exposure to other endocrine-disrupting chemicals. We recommend that future exposure assessment for endocrine disruptors be designed to capture multiple exposures rather than a single chemical or chemical class.

Based on the findings, we do not recommend any changes in life style in regard to BPA's relationship with time to pregnancy; however, we encourage both men and women to continue healthy peri- conception behaviours.

4.5 | Conclusions

To our knowledge, the HOPE study presents the most robust, prospective BPA exposure assessment thus far for both women and men. Overall, the levels of BPA to which women and men were exposed in HOPE were higher than in prior studies, and we did not find an association between BPA exposure and fecundability in women or men. However, the sample size was smaller, and the age distribution younger than prior studies. Further studies will need to analyse longitudinal assessment of BPA exposure with more variability of age and other demographic characteristics and/or exposures within the study cohort.

ACKNOWLEDGEMENTS

This research was supported by National Institutes of Health, Office of the Director (NIH—1UG3OD023249-01) and by National Institute of Environmental Health Sciences 1R01ES020488-01. We give special thanks to the HOPE participants, staff, and HOPE study group for their valuable contributions to the study.

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Synopsis

Study question

Is there an association between the peri-conceptional BPA exposure and time to pregnancy (TTP) among relatively young, healthy pregnancy planning couples?

What is already known

Previous animal studies have shown that BPA causes reproductive dysfunction, but there is no consensus about the effects of BPA exposure on TTP among couples.

What this study adds

This study constructed robust BPA exposure assessment by collecting daily urine samples from both men and women. Results suggest that there is no association between peri-conceptional BPA exposure and TTP at the levels of exposure we examined in this study.

TABLE 1

Characteristics of women and men

	Women		Men	
	Total (n = 164)	% or mean $\pm$ SD	Total (n = 164)	% or mean $\pm$ SD
Age category ^{a,b}				
<(F:27, M:28)	89	54.3	90	54.9
(F:27, M:28)	75	45.7	74	45.1
Age	164	27.3 $\pm$ 3.6	164	28.6 $\pm$ 3.8
Bisphenol A (ng/mL)	164	3.8 $\pm$ 2.7	163	4.4 $\pm$ 4.6
Bisphenol A (ng/mL)—dichotomised ^{c,d}				
Low	81	49.4	80	49.1
High	83	50.6	83	50.9
Missing	-		1	
Bisphenol A (ng/mL)—tertile ^{e,f}				
Low	55	33.5	54	33.1
Middle	53	32.3	53	32.5
High	56	34.2	56	34.4
Missing	-		1	
Income				
\$0-\$39 000	72	45.0	68	42.5
\$40 000 or greater	88	55.0	92	57.5
Missing	4		4	
Education				
High school-some college (college 1–3 y)	49	30.1	70	42.9
College (4 y, graduate)	114	69.9	93	57.1
Missing	1		1	
Employed				
Employed for wages	113	69.3	110	67.5
Unemployed	50	30.7	53	32.5
Missing	1		1	
Race				

	Women		Men	
	Total (n = 164)	% or mean $\pm$ SD	Total (n = 164)	% or mean $\pm$ SD
White	149	90.9	144	87.8
Non-white/other/multiracial	15	9.2	20	12.2
Household size	164	2.7 $\pm$ 1.0	163	2.7 $\pm$ 1.0
BMI category				
18.4 (underweight)	7	4.3	2	1.2
18.5 < 25 (normal weight)	95	58.0	67	41.1
>25 < 30 (overweight)	37	22.6	56	34.4
30 (obese)	25	15.2	38	23.3
Missing				
BMI	164	24.8 $\pm$ 5.0	163	27.0 $\pm$ 5.9
Pregnancy outcome in study (couples)	Total (n = 164)		% or mean $\pm$ SD	
Yes	125		76.2	
No	39		23.8	
Prior pregnancy (couples)				
Yes	71		43.3	
No	93		56.7	
Intercourse frequency (per day)	161		0.3 $\pm$ 0.2	
Prior number of cycles trying to conceive (couples)	164		2.8 $\pm$ 2.7	

^aAge category for women: n < 27, 27 (median age).

^bAge category for men: n < 28, 28 (median age).

^cDichotomous ranges for women: BPA low (<2.75), BPA high (2.75).

^dDichotomous ranges for men: BPA low (<2.94), BPA high (2.94).

^eTertile ranges for women: BPA low (<2.11), BPA middle (2.11 n < 4.11), BPA high (4.11).

^fTertile ranges for men: BPA low (<2.11), BPA middle (2.11 n < 4.01), BPA high (4.01).

TABLE 2
Demographic and reproductive characteristics in relation to dichotomised BPA levels

	Women				Men			
	Low (<2.75 ng/mL)		High (2.75 ng/mL)		Low (<2.94 ng/mL)		High (2.94 ng/mL)	
	Total (n = 81)	%	Total (n = 83)	%	Total (n = 80)	%	Total (n = 83)	%
Age category ^{a,b}								
<(F:27, M:28)	42	51.9	47	56.6	40	50.0	50	60.2
(F:27, M:28)	39	48.2	36	43.4	40	50.0	33	39.8
Education ^c								
High school-some college (college 1–3 y)	28	34.6	21	25.6	36	45.0	33	40.2
College (>4 y, graduate)	53	65.4	61	74.4	44	55.0	49	59.8
Pregnancy outcome in study								
Pregnant	58	71.6	67	80.7	60	75.0	64	77.1
Not pregnant	23	28.4	16	19.3	20	25.0	19	22.9
Prior pregnancy								
Yes	38	46.9	33	39.8	36	45.0	35	42.2
No	43	53.1	50	60.2	44	55.0	48	57.8

^a Age category for women: n < 27, 27.

^b Age category for men: n < 28, 28.

^c Number of missing observation: 1 woman and 1 man.

TABLE 3

Number of pregnancies, percentages, and cumulative percentages of becoming pregnant per cycle, analysed by time to pregnancy (TTP)

TTP			
Cycles	Total (n = 164)	%	Cumulative %
1	44	26.8	26.8
2	28	17.1	43.9
3	20	12.2	56.1
4	8	4.9	61.0
5	7	4.3	62.3
6	5	3.0	65.3
7	4	2.4	67.7
8	2	1.2	68.9
9	1	0.6	69.5
10	6	3.7	73.2
11	0	0.0	73.2
12	0	0.0	73.2

TABLE 4

Fecundability odds ratios (FOR) associated with peri-conceptional levels of BPA in urine

BPA	Unadjusted ^a			Model 1 ^{a,b}			Model 2 ^{a,c}		
	Women (n = 164)	Men (n = 163)		Women (n = 164)	Men (n = 163)		Women (n = 164)	Men (n = 163)	
	FOR (95% CI)	FOR (95% CI)		FOR (95% CI)	FOR (95% CI)		FOR (95% CI)	FOR (95% CI)	
Continuous ^d	1.02 (0.96, 1.08)	1.00 (0.96, 1.04)		1.02 (0.96, 1.08)	1.00 (0.96, 1.04)		1.02 (0.96, 1.08)	1.00 (0.96, 1.04)	
Dichotomous ^{e,f,i,j}									
Low	1.00 (Reference)	1.00 (Reference)		1.00 (Reference)	1.00 (Reference)		1.00 (Reference)	1.00 (Reference)	
High	1.02 (0.72, 1.46)	1.02 (0.71, 1.45)		1.06 (0.74, 1.50)	1.05 (0.74, 1.49)		1.07 (0.75, 1.53)	1.02 (0.72, 1.47)	
Tertiles ^{g,h,k,l}									
Low	1.00 (Reference)	1.00 (Reference)		1.00 (Reference)	1.00 (Reference)		1.00 (Reference)	1.00 (Reference)	
Middle	0.62 (0.39, 0.97)	1.33 (0.86, 2.04)		0.67 (0.43, 1.06)	1.32 (0.86, 2.04)		0.69 (0.44, 1.08)	1.29 (0.83, 2.00)	
High	0.95 (0.62, 1.43)	1.04 (0.67, 1.61)		0.96 (0.63, 1.45)	1.09 (0.70, 1.70)		0.98 (0.64, 1.49)	1.05 (0.66, 1.67)	

^a All models were adjusted for the cycles trying to conceive prior to study enrolment.^b Model 1: Controlled for education.^c Model 2: Controlled for education and age.^d Total number of participants accounted for continuous BPA: women (N = 164), men (N = 163).^e Total number of participants accounted for dichotomous BPA for women: low (N = 81), high (N = 83).^f Total number of participants accounted for dichotomous BPA for men: low (N = 80), high (N = 83).^g Total number of participants accounted for tertile BPA for women: low (N = 55), middle (N = 53), high (N = 56).^h Total number of participants accounted for tertile BPA for men: low (N = 54), middle (N = 53), high (N = 56).ⁱ Dichotomous ranges for women: BPA low (<2.75 ng/mL), BPA high (≥ 2.75 ng/mL).^j Dichotomous ranges for men: BPA low (<2.94 ng/mL), BPA high (≥ 2.94 ng/mL).^k Tertile ranges for women: BPA low (<2.11 ng/mL), BPA middle (2.11 ng/mL), BPA high (≥ 4.11 ng/mL).^l Tertile ranges for men: BPA low (<2.11 ng/mL), BPA middle (2.11 ng/mL), BPA high (≥ 4.01 ng/mL).

TABLE 5

Comparisons between HOPE^a, LIFE^{21,b}, MIREC^{22,c}, and NC EPS^{23,d} studies

	HOPE ^a		LIFE ^{21,b}		MIREC ^{22,c}		NC EPS ^{23,d}	
	Women	Men	Women	Men	Women	Men	Women	Men
Study design	Prospective study		Prospective study		Retrospective study		Prospective study	
Urine collection	Daily for two menstrual cycles		Once at enrollment		Once during first-trimester visit		Three samples from each menstrual cycle	
Study population	183 (170; BPA available)	183 (169; BPA available)	501 (454; BPA available)	501 (439; BPA available)	2001 (1742; BPA available)		221 (221; BPA available)	
Median Bisphenol A (BPA) Exposure (ng/ml)	3.01	2.94	Pregnant: 0.63 Not pregnant: 0.68	Pregnancy: 0.53 Not pregnant: 0.49	0.80		2.7	
Age	27.3	28.5	30.0	31.8	32.8		29	
Prior birth	42.4%		47.0%	48.0%	71.3%		51.6%	
FOR estimates	1.07 (0.75–1.53)	1.02 (0.72, 1.47)	0.96 (0.83, 1.10)	1.05 (0.92, 1.20)	0.97 (0.83, 1.14)		Not reported	
Impact of increasing BPA on time to pregnancy (TTP)	No association	No association	No association	No association	No association		No association	

^aThe Home Observation of Peri-conceptional Exposures study.

^bThe Longitudinal Investigation of Fertility and the Environment.

^cThe Maternal-Infant Research on Environmental Chemicals.

^dThe North Carolina Early Pregnancy Study.