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The Correlation of Urine Bisphenol A with Semen Parameters in Men Referred to Infertility Centers: A Cross-Sectional Study

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Abstract

Background: Bisphenol A (BPA) is known as an endocrine disruptor that has harmful effects on general health. It is commonly used in various industrial products. In this study we tried to evaluate the amount of BPA in urine samples of the men referred to an infertility center.

Materials and Methods: The cross-sectional study population consisted of male partners of infertile couples, who were referred to infertility clinic in Mazandaran, a northern state of Iran. Questionnaires included demographic characteristics, medical history, lifestyle factors, physical examinations. A semen sample and a spot urine sample were taken from each participant. In the initial study group of 240 men, 3 groups were excluded, and 122 men remained for the analysis. High-performance liquid chromatography (HPLC) was applied to measure the amount of BPA in the urine samples.

Results: BPA was not detected in about half of the samples (53.3%). Multiple linear regression analysis showed that no significant relationship existed between the urine concentrations of BPA, semen parameters and male reproductive hormones. However, in a comparison with semen parameters in people with detectable urine BPA versus nondetectable ones, an inverse association was noticed with sperm concentration. In other parameters, differences were not significant. Smoking had no effects on sperm parameters, but body mass index (BMI) ≥25 reduced the percentage of normal sperm parameters.

Conclusion: In most participants, urinary BPA was not detected. Probably in this study low environmental exposure to BPA is the cause of lower urine BPA concentrations compared to other industrially developed countries. Therefore, no overall relationship was observed between BPA level and male infertility.

Keywords: Bisphenol A, Male Infertility, Semen Parameters

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Introduction

Endocrine disruptor chemicals (EDCs) are considered as exogenous chemicals, that interfere with hormonal actions (1, 2). Bisphenol A (BPA) is one of the EDCs that is suspected to have great adverse health consequences. BPA is an organic monomer that is widely used as the main and essential ingredient of epoxy resin and polycarbonate plastic. This substance enters the body through dietary and transdermal absorption. Continuous and extensive exposure to BPA, particularly in developed countries, has led to the presence of detectable levels of urine BPA, as certified by biomonitoring studies in humans. Therefore, the possibility of adverse effects of this substance, caused an increase in concerns about human health (3-5). The deferent acknowledge about biological effects of BPA are various. The larger portion of BPA molecule is less biologically active. Glucuronidation causes it to be metabolized into conjugated compounds in the liver, which is less water-soluble and quickly excreted in urine (6). One of the organs likely affected by BPA is the reproductive system. Exposure to BPA may cause poor semen quality (7). Even low dose exposures of this substance cause certain effects on the male reproductive system in animal studies (6).

Evidence shows that BPA affects the onset of meiosis (8, 9). Several recent studies in humans have evaluated BPA exposure and male fertility with inconsistent results. Some studies showed that BPA has negative effect on sperm, so that decrease sperm motility and sperm concentration, and increases abnormal sperm morphology (10-12). In contrast,

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Mendiola et al. (13) showed in 2010 that BPA cannot affect the semen quality. BPA can affect the hypothalamic-pituitary-gonadal axis, which causes hypogonadotropic hypogonadism (14). A study on male rats showed that even low doses of BPA exposure during the perinatal critical period of hypothalamic sexual differentiation caused a delayed onset of puberty (15). Furthermore, ongoing exposure to BPA and similar substances can change the structure of testicular tissue, thus modifying the endocrine glands in the male reproductive system (16). Oxidative stress produced by these chemicals affects the reproductive system and cause a negative effect on the testes and spermatogenesis in male rats (17).

Higher concentrations of BPA and its analogues BPA-B, BPA-F and BPA-S in the early development of male rats may lead to incorrect function of reproductive system (18). However, more studies on human exposure to such chemicals are needed to determine the relevance of these finding to human health. Since BPA is metabolized rapidly and is discarded through urine without evidence of collection in the body (19), we suppose that evaluation of BPA in urine sample prepare a better assessment of exposures than evaluation of these compounds in serum. Also, it has been previously shown that the half-life of BPA in serum or plasma is short and there is a possibility of contamination during sample collection and analysis. Studies that have investigated the role of BPA in male fertility are few and sometimes the outcomes turn out to be different. The present study tends to investigate the amount of urine BPA in infertile men referred to Fatemeh Zahra Infertility Clinic, in Mazandaran/Iran, and evaluate the correlation between urine BPA concentration and semen parameters and reproductive hormones such as testosterone, follicular-stimulating hormone (FSH), luteinizing hormone (LH), Prolactin, thyroid-stimulating hormone (TSH), and dehydroepiandrosterone sulfate (DHEA-S).

Materials and Methods

The cross-sectional study population consisted of male partners from infertile couples with unknown causes of infertility, attending our infertility clinic for diagnosis. The average sperm concentration of the samples from these men were >15 million/ml. These subjects were recruited from June 2020 through October 2020 (simultaneously with Covid-19 pandemic) in north of Iran, Mazandaran. In brief, all participants with no evidence of Covid-19 infection at the time of the interview prior to enrollment, signed a written informed consent form. To collect information, each participant filled a questionnaire that included demographic characteristics, medical history, and lifestyle factors. Also, physical examinations such as height, weight, waist and wrist circumferences of the men were measured. The lifestyle factors, including alcohol intake, smoking cigarette and the use of plastic containers in daily eating, were evaluated. Participants were given containers to collect urine samples at the beginning of the morning before any medical intervention. Also, each semen sample was obtained through masturbation. The obtained urine samples were transferred into special BPA-free containers in less than 1-hour post-collection and stored at -20ºC until analysis.

The tests to evaluate hormones such as FSH, LH, Prolactin, TSH, DHEA-S and testosterone, which would be performed routinely for male patients in this center, were used in this study. Of the 240 men who were originally interviewed for the study, 3 groups were excluded and were the limitations of our study: 1- having a history of a severe type of coronavirus (COVID-19) disease, that led to hospitalization in the last three months, 2- leaving an incomplete questionnaire with missing information, and 3- having a fear of getting coronavirus disease (COVID-19), during an interview. The remaining 122 eligible men were selected for the study and their data were collected for analysis.

Laboratory methods

To evaluated the optical density of LH, FSH and total testosterone, the wavelengths of 450 to 630 nm of an ELISA reader were used. Coefficients of variation of intra- and inter-assay contain 2.3 and 2.8% for LH, 3.9 and 4.5% for FSH and 5.6 and 6.6% for total testosterone, respecticely. Prolactin concentration was assessed by chemiluminescent immunoassays (normal range: 5-35 ng/mL), using a commercial kit (Shenzhen Yahuilong Biotechnology, Shenzhen, China). The thyroid function (normal range: 0.35-4.94 nmol/L) was determined through the evaluation of TSH. Chemiluminescent microparticle immunoassays was used for DHEA-S assessment.

Urinary Bisphenol A measurement

The urine samples that were stored in a freezer at -20°C were sent to a laboratory in the Department of Pharmaceutical Science Research Center of Babol University of Medical Science for analysis. BPA and NP >99% pure and some other chemicals were purchased from local commercial sources. The level of BPA in urine was determined using the method explained in Völkel et al. (20) study with some modification. Briefly, to measure the amount of BPA in the urine, 100 µl of the urine was transferred to a 5-ml vial. Then 100 µl of 0.01 M ammonium acetone buffer with pH=4.5 and 4 ml of a mixture of hexane and diethyl ether in a 70: 30 ratio were added to the vial. Then the mixture was vortexed for 30 seconds, then centrifuged at 12,000 rpm for 10 minutes. The organic layer was separated from the sample and placed in a refrigerator at 5°C to allow the solvent to evaporate Next, 400 µl of the mobile phase solvent was added to the vial and vortexed. The vial containing the sample was transferred to the refrigerator to reach the volume of the solvent and sample to 100 µl, and after reaching the desired volume, 20 microliters of it was injected into the HPLC. Total BPA (conjugated and free) in urine were measured with high-performance liquid chromatography (HPLC). Finally, the amount of urine BPA in the urine was measured using a standard chart.

The limit of detection (LOD) of urine BPA was 0.11 ng/mL that is in agreement with Adoamnei et al. (21).

Semen analysis

Briefly, after 2-5 days of sexual abstinence, participants gathered semen samples via masturbation into polypropylene containers. During the first hour after liquefaction, sperm concentration, motility and morphology was evaluated according to WHO, 2010 guidelines (22).

Statistical analysis

Data were presented as number (%) or mean ± SD. To assess the relationship among predictors the t test, one-way analysis of variance (ANOVA), Kruskal-Wallis test, and U Mann-Whitney test were used as appropriate according to the nature and distribution of the variables. Then, because of the abnormal distribution of urine BPA levels, log10-transforma was considered and a multiple linear regression model for log BPA was applied by all predictors in simple analysis. Regardless, the simple correlation of variables including BMI, smoking and alcohol history as well as location was significant. Based on the literature, some confounders in multiple regression models were determined. In linear regression, statistics is β and 95% confidence interval (CI) is related β. The urine BPA level was categorized to 4 quartiles, first percentile that is known as 25th percentile was below limit of detection, second percentile known as 50th percentile, that was between the 25th percentile to the median, third percentile named 75th percentile that was between 50th and 75th percentile, and finally fourth percentile, which was more than 75th percentile values. All quartiles were compared to the first quartile as a reference with the lowest concentration of BPA. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 20, SPSS Inc., USA) software. P<0.05 was considered as significant.

Ethical considerations

Ethical approval was obtained from the local Ethical Committee of the Iranian National Committee on Health Research Ethics (IR.IAU.SARI.REC.1399.153). All participants filled the informed written consent before participation.

Results

Demographic characteristics of all 122 males participants that were referred to infertility clinics for treatment are shown in Table 1. The compression of semen parameters with demographic variables showed that alcohol consumption and BMI ≥25 reduced the number of progressive motile sperms and changed the sperm morphology (P=0.01), but smoking and location had no effects on sperm parameters (P>0.05, Table 2).

BPA was not detected in about half of the samples (53.3%). In less than half of the samples (46.7%) the total urinary BPA concentrations were measured as a mean and median concentration of 0.9 and 0.04 ng/ml, respectively. First, participants were divided in two groups, including men who had no detectable urinary BPA and a BPA detectable group. A comparison was done between the two groups in terms of semen quality parameters and reproductive according to the type and distribution of the variables. In sperm concentration, there was a significant difference between the two groups P<0.01, while in semen volume, sperm morphology, progressive motile sperm differences were not significant. Then, a comparison was carried out among 4 quartiles of BPA in terms of semen quality parameters, among which no significant difference was observed (Table 3). Multiple linear regression analysis showed that there is no relationship between the urinary BPA and male reproductive hormones that are presented in Table 4. Also, there is no associations between semen quality parameters and urinary BPA concentration in men that are presented in Table 5.

Table 1: Demographic data from study population (n=122)

Characteristic	n (%)
Education	
Primary	75 (61)
High School	14 (11.5)
Higher	33 (27.5)
Location	
Urban	69 (56.6)
Rural	53 (43.4)
Smoking	
No	93 (76.2)
Yes	29 (23.8)
BMI (kg/m^2)	
<25	24 (19.6)
≥25	98 (76.2)
Mean ± SD	27.9 ± 4.7
Min-Max	17-48
Duration of couple's infertility (Y)	
1-2	64 (52.4)
2-3	11 (22)
3-5	24 (19.6)
>5	23 (18.8)
Age (Y)	
Mean ± SD	35.1 ± 23
Min-Max	20-50
Alcohol use	
None	107 (87.7)
<1 drink/week	6 (4.9)
1-3 drinks /week	7 (5.7)
Everyday	2 (1.6)

BMI; Body mass index.

Table 2: The comparison of quality sperm parameters based on certain demographic variables

Variables	Semen volume (mL)[a]	Sperm concentration (million/mL)[b]	Morphologically normal forms (%)[b]	Progressive motile (%)[a]
BMI				
<25	3.15 ± 1.28	60.00 (135.3)	5 (70.1)	48.66 ± 11.61
≥25	2.79 ± 1.14	40.00 (500.2)	4 (42.0)	48.64 ± 18.99
P value	0.17	0.11	0.01	0.62
Smoking user			3.00 (17.1)	
Yes	2.76 ± 1.16	40.00 (90.2)	4.00 (70.0)	49.00 ± 15.66
No	2.90 ± 1.18	50.00 (500.2)		46.43 ± 18.40
P value	0.57	0.07	0.35	0.50
Alchol user				
Yes	2.90 ± 0.96	30.00 (80.8)	4 (17.1)	52.86 ± 7.23
No	2.86 ± 1.20	50.00 (500.2)	4 (70.0)	46.22 ± 18.64
P value	0.91	0.23	0.53	0.01
Location				
Urban	2.83 ± 1.16	40.00 (50.2)	4 (70.0)	46.36 ± 18.24
Rural	2.91 ± 1.19	50.00 (80.5)	4 (8.0)	47.92 ± 17.24
P value	0.63	0.16	0.47	0.72

[a]; Based on Independent t test (mean ± SD), [b]; Based on U Mann-Whitney test t [median (IQR)], and BMI; Body mass index.

Table 3: The comparison of semen index among BPA quartiles

BPA quartiles	Semen volume (mL)[a]	Sperm concentration (million/mL)[b]	Morphologically normal forms (%)[b]	Progressive motile (%)[a]
1st quartile	2.83 ± 1.07	47.50 (2.500)	4 (0.70)	47.45 ± 17.98
2nd quartile	3.30 ± 1.87	55.00 (3.70)	4 (1.17)	41.40 ± 16.72
3rd quartile	2.25 ± 1.04	35.00 (3.70)	4 (2.7)	47.50 ± 12.58
4th quartile	3.32 ± 1.69	54.00 (10.60)	4 (1.24)	47.00 ± 22.42
P value	0.37	0.84	0.89	0.98

[a]; Based on one-way ANOVA (mean ± SD), [b]; Based on Kruskal-Wallis test [median (IQR)], and BPA; Bisphenol A.

Table 4: The comparison of semen index among BPA quartiles

BPA quartiles	T (nmol/L)	LH (IU/L)	FSH (pmol/L)	TSH (nmol/L)	DHEA-S (µg/dl)	PRL (ng/mL)
1st quartile	Reference	Reference	Reference	Reference	Reference	Reference
2nd quartile	1.82 (-1.62, 5.26)	-5.80 (-34.48, 22.83)	-0.14 (-3.49, 3.21)	-0.38 (-1.89, 1.74)	-1.67(-5.40,2.06)	4.74(-1.49,10.98)
P value	0.29	0.68	0.93	0.95	0.37	0.13
3rd quartile	1.01 (-3.98, 6.02)	-6.93 (-48.25, 34.38)	-0.32 (-5.15, 4.50)	-0.7 (-18.11, 13.66)	-0.38 (-5.80,5.04)	-4.35 (13.48,4.76)
P value	0.68	0.73	0.89	0.93	0.88	0.34
4th quartile	0.15 (-4.87, 5.18)	-1.09 (-42.57, 40.39)	0.87 (-3.96, 5.71)	1.24 (-0.55, 3.03)	-2.04(-7.45,3.36)	0.75(-8.46,9.97)
P value	0.15	0.95	0.71	0.55	0.45	0.87
Log BPA	0.54 (-2.18, 3.28)	5.65 (-16.89,28.19)	0.15 (-2.48, 2.79)	0.31 (-0.67, 1.30)	-1.10(-4.05,1.84)	2.11(-2.87,7.09)
P value	0.69	0.61	0.90	0.52	0.45	0.40

Data are presented as median (min-max). BPA; Bisphenol A, T; Testosterone, LH; Luteinizing hormone, FSH; Follicular-stimulating hormone, TSH; Thyroid-stimulating hormone, DHEA-S; Dehydroepiandrosterone sulfate, and PRL; Prplactin.

Table 5: The relationship between urinary BPA and semen parameters in men [considered as model coefficients (95% CI)].

BPA quartiles	Semen volume (mL)	Sperm concentration (million/mL)	Morphologically normal forms (%)	Progressive motile (%)
1st quartile	Reference	Reference	Reference	Reference
2nd quartile	0.38 (-0.56, 1.33)	-1.13 (-51.11, 48.28)	2.11 (-0.71, 4.95)	-2.48 (-16.11, 11.15)
3rd quartile	-0.79 (-2.14, 0.55)	-17.71 (-89.15, 53.72)	-0.33 (-4.51, 3.84)	1.54 (-18.11, 13.66)
4th quartile	0.1 (-0.83, 1.89)	5.4 (-0.66, 77.22)	4.87 (0.91, 8.83)	2.2 (-17.50, 21.90)
Log BPA	-0.41 (-0.71, 0.79)	-7.38 (-46.45, 31.69)	1.87 (-0.44, 4.01)	-4.71 (-15.38, 5.93)
P value (Log BPA)	0.72	0.16	0.88	0.32

Data are presented as median (min-max). Adjusted by BMI, smoking and alcohol history and geographic location. BPA; Bisphenol A, BMI; Body mass index, and CI; Confidence interval

Discussion

In this study, we found that in about half of the participants, urinary BPA was not detected. Sampling was done in Mazandaran province in northern Iran, which has a mild, semi-humid climate and is a non-industrialized area of Iran. Perhaps the simple lifestyle based on traditional agriculture, the non-industrial nature of the region and low environmental exposure to BPA are among the causes of finding lower urine BPA concentrations compared to relatively more developed industrial regions (12, 23). The level of BPA has been reported in several studies.

Li et al. (10) states that the median value in Chinese workers in a factory chosen for likely higher contamination is 38.7 ng/ml, while it is measured to be 0.4-20 ng/ml by Mendiola et al. (13) or 1.81- > 3.27 ng/ml by Pollard et al. (24), in environments, which have not been contaminated. We found that no adverse effects were observed with our detected BPA levels in the fourth quartiles and semen parameters and male reproductive hormones. Nevertheless, when comparing semen parameters in men who had non-detectable urinary BPA to those with detectable BPA levels, a significant inverse association was noticed with sperm concentration, while for other parameters, differences were not significant. Li et al. (10) showed in 215 factory workers that there was a reverse association between BPA concentration and total count, concentration, viability, and motility of sperm cells. However, the difference was not significant when comparing semen volume or sperm morphology. Interestingly, only in a creatinine-adjusted BPA subgroup a significant reduction in sperm concentration was observed. Pollard et al. (24) in a prospective pre-conception cohort study, in which 161 men in ages 18-40 with no known subfertility were participating, defined that high BPA exposure causes abnormal sperm tail morphology. However, the reports by Mendiola et al. (13) and Goldstone et al. (25) showed that there was no significant relationship between urinary BPA and semen parameters in male partners attending infertility clinics. Although both of these studies have been conducted in the US, their subjects were from regions that were not selected for contamination with BPA, but they may still be expected to be higher than a rural Iranian population in terms of PBA exposure. Also, a study conducted in Iran on women undergoing in vitro fertilization (IVF) treatment showed that the levels of BPA in follicular fluid had no negative effects on mature oocytes. However, it had adverse effects on degenerated oocytes and germinal vesicle (GV) (26).

Our study showed that there was no association between the urinary BPA and male reproductive hormones. There are a limited number of studies that have evaluated the endocrine-destroying effects of BPA on reproductive health, especially male hormones, and the results are somewhat inconclusive. For this reason, Mendiola et al. (13) assessed this relationship in 375 fertile men. Their findings were different from two previous cohort studies, as they found that BPA was lower [geometric mean=1.5 (0.8, 3.0) ng/mL], had positive association with sex hormone bonding globulin (SHBG), while presenting an inversed association with free androgen index (FAI) and FAI/LH. Also, in this population, there was no relationship between BPA levels and inhibin B, FSH, LH, free testosterone (fT) or testosterone (T). In the study by Hanaoka et al. (27) on Japanese men who were exposed to BPA with epoxy resin spray, it was shown that there was a relationship between urinary BPA and testosterone levels and plasma gonadotrophic. Although in this study two groups of exposed and un-exposed workers had the same levels of LH and free testosterone, but FSH levels in the 42 un-exposed workers were more than the occupationally exposed ones. BPA concentration in the exposed group was lower than that in BPA un-exposed group (median 1.06; not detected to 11.2 μmol/mol creatinine) and (median 0.5; not detected to 11.0 μmol/mol creatinine) respectively. Galloway et al. (28) showed that a higher level of urinary BPA causes a higher level of serum testosterone. But the same relationship was not seen between BPA, estradiol and (SHBG).

In the present study we showed that normal sperm morphology was reduced in men with BMI ≥25. There are contradictory results on the relationship between BMI ≥25 and sperm parameters among various studies. In a study by Jurewicz et al. (29), increased BMI causes semen volume reduction. Fejes et al. (30), on the other hand, showed that significant association was found between semen parameters and waist and hip circumferences. Chromatin-intact, normal-motile sperm, total sperm count and sperm motility per ejaculation were fewer in men with BMI ≥25 (31, 32). Whereas data from 31 meta-analysis studies revealed that increased BMI had no negative effects on semen parameters (33). We showed that alcohol users and smokers had lower semen values than reported in other studies. This study showed that sperm motility was lower, but not significantly, in people who drank alcohol. The existing data on alcohol and semen quality are sparse and sometimes contradictory in some studies. Data from Marinelli et al. (34) and Povey et al. (35). showed that moderate alcohol drinking has a definite protective effect on sperm parameters, may be caused by antioxidant effects of some alcoholic beverages. Also, authors in this study found that there was no evidence showing that cigarette smoking had reverse effects on sperm quality. while Sharma et al showed the opposite result in his study. They demonstrated that generally, semen parameters could be affected by cigarette smoking negatively (36). They emphasized that World Health Organization (WHO) laboratory procedure for the evaluation of semen parameter had a least effect on the value of effect size in their study, that supporting the adverse effects of cigarette smoking on conventional semen parameters.

Our study had some limitations: first; sample collection was the main limitation in our experiment because of the COVID-19 pandemic situation. Secondly; we did not examine urinary creatinine for daily assessment with

BPA, although urine dilution would have a better result with creatinine assessment. Thirdly; Due to the short half-life of urinary BPA, about 6 hours (37) it would have been better to collect 24-hour urine sample.

Conclusion

According to our findings, in about half of the participants, urinary BPA was not detected. Probably the low environmental exposure to BPA in this population lead to this less than detection levels. So, no adverse effects were observed between BPA levels in four urinary BPA quartiles and semen quality and male reproductive hormones.

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Authors' Contributions

M.M.R.A., H.S.; Participated in study design, data collection and visited the patients. M.G.T.; Designed and performed the experiments, analyzed data and wrote the first draft of the manuscript. L.M., A.A.; Contributed to designing the experiments and analyzed data. F.H., N.M.G., P.M.; Helped in sampling and filling out the questionnaires. All authors read and approved the final manuscript.

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