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Effects of bisphenol A on male and couple reproductive health: A review

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Abstract

Bisphenol A (BPA) is a ubiquitous environmental toxicant with endocrine-disrupting properties and suspected to affect human reproduction. Yet in humans, the studies exploring the effect of this BPA on male reproductive health including semen quality, reproductive hormones, and couple fecundity and fertility, have produced inconsistent results. The objective of this manuscript was to summarize the effects of male exposure to BPA on markers of testicular function and couple reproductive outcomes. Of the five studies on male BPA exposure and reproductive hormones, all found significant associations with at least one reproductive hormone; however no consistent relations were observed across studies. Similarly, five studies evaluated the relation between BPA and semen quality and while the majority reported negative associations with various parameters, there were few consistent trends across studies. Finally, the three studies which have examined male urinary BPA levels and couple reproductive outcomes did not find associations, with the exception being a link with lower secondary sex ratio (or greater female excess). Overall, while the literature on this topic is growing, the evidence supporting a link between male BPA exposure and male reproductive health remains limited and inconclusive. Reasons for the discrepancies in results could include, but are not limited to, differences in: study populations (e.g. fertile vs. subfertile men), BPA exposure levels (occupationally exposed vs. non-occupationally exposed), study procedures used to collect and measure urinary BPA (e.g. using one urine sample to characterize exposure vs. multiple samples), sample sizes, and study design (e.g. cross-sectional vs. prospective). Based on the available evidence, there is insufficient evidence to conclude that exposure to BPA, at low to moderate levels, has a negative effect on reproductive outcomes in men. Clearly, further studies are needed to further clarify the role of this ubiquitous endocrine disrupting chemical on male reproductive health.

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Introduction

Bisphenol A (BPA) is a high production volume chemical that is widely used in the manufacture of consumer products such as polycarbonate plastics, epoxy resin liners of canned foods, some dental sealants and composites, and thermal receipts (1). Due to its widespread use in consumer products, exposure to BPA is ubiquitous. In the US, more than 90% of urine samples obtained from participants in the 2003–2004 and 2011–2012 National Health and Nutrition Examination Survey (NHANES) had BPA concentrations above the limit of detection (2–4). Exposure to BPA has garnered concern and regulatory attention over the past decade due to its potential endocrine disrupting effects. Specifically, in vitro studies have shown that aglycone (unconjugated) BPA binds to estrogen receptors α and β producing weak estrogenic activity (5, 6). Aglycone BPA also has high affinity for two membrane-bound estrogen receptors, G protein-coupled estrogen receptor 30 (7) and membrane estrogen receptor alpha (mERα) (8), in addition to an orphan nuclear estrogen-related receptor gamma (9, 10). BPA has also been cited for its ability to bind to the androgen receptor, peroxisome proliferator–activated receptor γ, and thyroid hormone receptor in experimental animal studies (11).

In male rodents, the majority of studies on exposure to BPA and reproductive outcomes have confirmed these endocrine-disrupting activities. For example, exposure to low-dose BPA (lowest observed adverse effect level <50 mg/kg) was associated with decreased sperm counts in mice (12, 13) and adult rats (14–16), impaired sperm motility in rats (14, 15, 17) and mice (12), and increased sperm DNA damage in rats (14, 17–23) and mice (12, 24–26). In addition, exposure to low-dose BPA was related to decreased testosterone levels in rats (15, 23, 27, 28) and mice (29). However, a few experimental studies did not conclude that BPA is a testicular toxicant (30–33). These inconsistent results may be due to different methodological aspects such as dose, exposure route, timing, and outcomes. Therefore, further experiments in animals are needed to clarify the role of this endocrine disrupting chemical on male reproductive health.

In humans, there is a growing body of literature exploring the associations between male urinary BPA concentrations and semen quality parameters, DNA damage, and reproductive hormones and a few studies on paternal BPA exposure and markers of couple fecundity and fertility such as time to pregnancy and live birth (Table 1). Therefore, the objective of this manuscript was to review the epidemiologic literature on the effects of male exposure to BPA on semen quality, reproductive hormones and fecundity.

BPA and Semen Quality

Only five studies explored the relationship between urinary BPA concentrations and semen parameters and of these studies, two also examined the association with sperm DNA damage (Table 1). In the only prospective study to date, Li and colleagues explored the association of urinary BPA concentrations on semen parameters among 218 factory workers from four regions in China (34). This study found a negative association between urinary BPA concentrations and sperm concentration, total sperm count, sperm vitality, and sperm motility. Results for sperm concentration, vitality, and motility remained significant when

the study population was restricted to men who were exposed to BPA occupationally (n=130) and had much higher urinary creatinine adjusted BPA concentrations [median (IQR) = 38.7 (6.3, 354.3) μg/gCr] compared with factory workers who did not have BPA occupational exposure [median (IQR) = 1.4 (0, 17.9) μg/gCr]. However, when models were restricted to non-occupationally exposed factory workers (n=88), who had lower urinary creatinine adjusted BPA concentrations, the only significant association was with diminished sperm concentrations. This study also found that on average, men who had detectable urinary BPA levels had more than three times the risk of having a reduced sperm concentration (<15 × 10^6 per mL) and vitality (<58%), more than four times the risk of having a low sperm count (<39 × 10^6 per ejaculate), and more than twice the risk of having low sperm motility (<40%), compared with men who did not have detectable urinary BPA concentrations. Urinary BPA levels were not associated with proportion of morphologically normal sperm in this population of Chinese workers (34).

In a cross-sectional study of 308 young men recruited during a compulsory physical examination for military service in Denmark (2008–2009), urinary BPA concentrations were inversely associated with progressive sperm motility (35). However, there were no associations of BPA with other sperm parameters. Of note, this population had low background urinary BPA concentrations [median (5^{th}–95^{th} percentiles) unadjusted urinary BPA concentration was 3.3 ng/mL (0.6, 14.9 ng/mL)] (35). The associations of BPA with semen parameters and DNA damage has also been assessed in several studies of men who, along with their partners, were trying to conceive (36–38). Meeker and coworkers explored the association of urinary BPA concentrations with semen parameters and DNA damage in 190 male partners of subfertile couples seeking treatment at Massachusetts General Hospital (MGH) in Boston, Massachusetts (2000–2004) (37). They reported that urinary BPA concentrations were negatively associated with sperm concentration, normal morphology, and sperm DNA damage (as measured by the percentage of DNA in comet tail). They also found a suggestive association between higher urinary BPA concentrations and lower percentage progressively motile sperm. While 89% of samples in this population of subfertile men had detectable BPA concentrations, overall these men had relatively low urinary BPA concentrations [unadjusted geomean (GM) (IQR) was 1.6 (0.8, 2.3) ng/mL]. In the two other studies which included men from couples trying to conceive naturally, BPA was not associated with semen parameters despite having similar urinary BPA concentrations to the previous study of subfertile men (36, 38). For instance, Mendiola and colleagues investigated the relation of urinary BPA concentrations and sperm parameters in 315 fertile men from the Study for Future Families (SFF), a multicenter study of couples recruited at prenatal clinics in four U.S. cities (Los Angeles, CA; Minneapolis, MN; Columbia, MO; and Iowa City, IA) who conceived without medical assistance between 1999 and 2005 (38). Urinary BPA concentrations (GM (IQR) was 1.5 (0.8, 3.0) ng/mL) were not associated with any of the examined semen parameters in this study. Similarly, Goldstone and coworkers assessed the association of urinary BPA concentrations with sperm parameters in 418 men included in the Longitudinal Investigation of Fertility and the Environment (LIFE) Study (2005–2009), a cohort study which followed couples attempting pregnancy in Michigan and Texas (36). Urinary BPA concentrations [unadjusted GM (5^{th}, 95^{th}) was 0.6 ng/mL (95% CI 0.5, 0.6 ng/mL)] were not associated with semen parameters

among these men. Unexpectedly, higher urinary BPA concentrations were associated with decreased sperm DNA fragmentation.

BPA and Reproductive Hormones

The epidemiologic literature investigating the endocrine-disrupting effects of BPA on male reproductive hormones is also limited and presents heterogeneous results (Table 1). To date, one study explored this association among men occupationally exposed to BPA (39), two others studied the association among men from the general population (35, 40), and the remaining two studies investigated this association among either fertile men or subfertile men from a fertility clinic (38, 41). Hanaoka *et al.* explored the association of urinary BPA concentrations with plasma gonadotrophic hormones and testosterone levels in male epoxy resin sprayers from Japan who were exposed to BPA diglycidyl ether and mixed organic solvents at work (39). Follicle stimulating hormone (FSH) levels were lower in the 42 workers who were BPA exposed compared with 42 workers who were not occupationally exposed; however luteinizing hormone (LH) and free testosterone (fT) levels were not different between groups. Surprisingly, these Japanese workers had low levels of urinary BPA (median BPA concentration (range) was 1.1 (0, 11.2 μg/g Cr for BPA exposed workers and 0.5 (0, 11.0) μg/g Cr for BPA un-exposed workers) (39).

Galloway and coworkers investigated the association of urinary BPA concentrations with male reproductive hormones among 307 men from the InCHIANTI Study, a population-based study to identify risk factors for mid- and late-life morbidity in randomly selected healthy adults in Tuscany, Italy (40). Increasing urinary BPA concentrations were associated with higher serum testosterone (T) concentrations among a population who had a GM (5^{th}, 95^{th} percentiles) BPA concentration of 4.0 ng/mL (3.8, 4.3). However, the authors did not find an association between BPA and estradiol (E2), sex hormone–binding globulin (SHBG), or fT (40). Urinary BPA concentrations were also positively associated with serum testosterone concentrations in 308 young Danish men from the general population who were military conscripts. Moreover, these men had comparable urinary BPA concentrations to the previous study [median (5^{th}, 95^{th} percentiles) of 3.3 ng/mL (0.6, 14.9) ng/mL] (35). In contrast to the Italian study, however, this study also found that urinary BPA concentrations were positively associated with fT, E2, and LH levels. There was no association between urinary BPA concentrations and FSH, inhibin B, or SHBG in this cohort of young healthy men.

Mendiola and colleagues evaluated the association of urinary BPA concentrations with reproductive hormones in a cohort of 315 fertile men recruited from prenatal clinics (38). While their urinary BPA concentrations were lower than the previous two cohorts (GM (IQR) was 1.5 (0.8, 3.0) ng/mL), they found that urinary BPA concentrations were positively associated with SHBG, and inversely associated with free androgen index (FAI) and FAI/LH. Levels of FSH, LH, T, inhibin B and fT were unrelated to BPA in this population. Finally, in a cross-sectional study of 167 subfertile men from couples seeking treatment at MGH in Boston, urinary BPA concentrations were negatively associated with inhibin B levels and E2:T ratio and positively associated FSH levels and FSH:inhibin B ratio (41). This group of men also had low urinary BPA concentrations [GM (IQR) was 1.3 ng/mL (0.7,

2.4 ng/mL)] compared to the European cohorts; however their concentrations were similar to those in the study by Mendiola and colleagues.

BPA and Couple Reproductive Outcomes

The association of male urinary BPA concentrations with couple reproductive outcomes has recently been assessed in two studies (Table 1). Using the EARTH Study, which is a cohort of subfertile couples undergoing fertility treatment at MGH (Boston), Dodge and collaborators examined the associations of paternal urinary BPA concentrations with fertilization, embryo quality, implantation, and live birth among 218 couples who underwent 195 intrauterine inseminations and 211 *in vitro* fertilization cycles (42). No associations between paternal urinary BPA concentrations and reproductive outcomes following fertility treatment were found. The association of paternal urinary BPA concentrations with couple reproductive outcomes was also investigated in a longitudinal cohort study (LIFE Study) of 501 couples discontinuing contraception with the intention of becoming pregnant. Similar to the findings among the fertility clinic patients, Buck-Louis *et al.* did not find association between paternal urinary BPA concentrations and time to pregnancy (fecundity odds ratio (FOR) was 1.04; 95% CI, 0.91, 1.18) (43). However, in an analysis focused on secondary sex ratio (ratio of male to female births) among couples in the LIFE Study who had a singleton live birth, higher paternal urinary BPA concentrations were significantly associated with fewer male births (RR= 0.77 per 1 SD increase in urinary BPA; 95% CI, 0.62–0.95) (44). In both the EARTH and LIFE Studies, the men had, on average, low urinary BPA concentrations [unadjusted GM (IQR) was 1.6 ng/mL (0.8, 2.8 ng/mL), and (5^{th}, 95^{th} percentiles) was 0.5 ng/mL (0.4, 0.6 ng/mL), respectively].

Conclusions

In this paper, we review the available epidemiologic literature on the association of male BPA exposure with semen quality, reproductive hormones and couple reproductive outcomes. While the literature on this topic is growing, the evidence supporting a link between male BPA exposure and reproductive health remains limited and inconclusive. Several methodological differences could explain some of the discrepancies between studies. First, they included different study populations of men and some, for example, included fertile men who may be less susceptible to the effects of BPA than would subfertile men. Second, urinary BPA concentrations varied across studies. If there is a non-linear association between BPA exposure and markers of reproductive health then we may find consistent results across study populations with markedly different exposure levels. However, it is worth noting that contradictory results were found even among populations with comparable urinary concentrations. Third, many studies only used one urine sample to measure exposure to BPA, despite its short half-life, which could have resulted in substantial measurement error and attenuation of associations. Fourth, the majority of studies relating urinary BPA concentrations to reproductive hormones and semen quality parameters were cross-sectional, which makes causality difficult to determine. Moreover, if exposure to BPA is not constant, the time window of BPA exposure captured in these cross-sectional studies (e.g. the last 24 hours) may not be the biologically relevant exposure window. Finally, while male urinary BPA concentrations were not related to the more clinically relevant outcomes of couple

fecundity (e.g. time to pregnancy or implantation) or fertility (e.g. live birth), these studies had limited power to observe small to moderate effect estimates. In conclusion, there is currently insufficient evidence on male exposure to BPA, at low to moderate levels, and its association with reproductive outcomes.

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Table 1

Male BPA and reproductive outcomes in epidemiological studies.

Reference	Study design	Study population	Measured outcomes	Unadjusted Urinary BPA concentration (ng/mL)	Main findings
Hamaoka *et al.* 2002	Cross-sectional	42 occupational exposed and 42 occupational non-exposed men	Reproductive hormones	Median (range)[b] Exp=1.1 (0, 11.2) Non-exp=0.5 (0, 11.0)	Associated with lower FSH in occupationally exposed men. No differences in LH and fT.
Galloway *et al.* 2010	Cross-sectional	307 men from general population	Reproductive hormones	GM (5^{th}, 95^{th}) 4.0 (3.8, 4.3)	No associations with E2, SHBG and fT. Associated with higher T.
Meeker *et al.* 2010	Cross-sectional	190 men attending a fertility clinic	Semen parameters and DNA damage (measured as % of damage in comet tail in a subset of 132 men)	GM (25^{th}, 75^{th}) 1.4 (0.8, 2.5)	Associated with lower sperm concentration, normal morphology and motility. No association with total sperm count. Associated with higher sperm DNA damage.
Meeker *et al.* 2010	Prospective cohort	167 men attending a fertility clinic	Reproductive hormones	GM (25^{th}, 75^{th}) 1.3 (0.7, 2.4)	Associated with lower Inhibin B and LH and higher FSH. No relationship with T, SHBG, E2, fT, T3, T4, TSH.
Mendiola *et al.* 2010	Cross-sectional cohort	315 fertile men from a prenatal clinics (302 for semen analysis)	Semen parameters and reproductive hormones	GM (25^{th}, 75^{th}) 1.5 (0.8, 3.0)	Associated with lower FAI and FAI/LH and higher SHBG No association with semen parameters, FSH, LH, T, Inhibin B and fT.
Li *et al.* 2011	Prospective cohort	218 occupational exposed and non-exposed men	Semen parameters	Median (25^{th}, 75^{th})[b] Exp=38.7 (6.3, 354) Non-Exp=1.4 (0, 17.9)	Associated with lower sperm concentration, total count, normal motility and vitality in all men. Associated with lower sperm concentration, normal motility and vitality in occupational exposed men. Associated with lower sperm concentration in non-occupational exposed men. No association with ejaculate volume and morphology.
Buck-Louis *et al.* 2014	Prospective cohort	439 male partners of couples trying to become pregnant.	Fecundability (measured as time to pregnancy)	GM (5^{th}, 95^{th}) 0.5 (0.4, 0.6)	No association with time to pregnancy.
Lassen *et al.* 2014	Cross-sectional	308 young men from general population	Semen parameters and reproductive hormones	Median (5^{th}, 95^{th}) 3.3 (0.6, 14.9)	Associated with lower progressive motility. No association with other semen quality parameters. Associated with higher T, LH, E2 and fT No association with FSH, Inhibin B and SHBG.
Bae *et al.* 2015	Prospective cohort	220 singleton live births of couples trying to become pregnant	SSR defined as the ratio of male to female births	Not reported	Associated with more female births.
Dodge *et al.* 2015	Prospective cohort	218 male partners of couples attending a fertility clinic	Fertilization rate, embryo quality and implantation in IVF cycles.	GM (25^{th}, 75^{th}) 1.6 (0.8, 2.8)	No association with IUI or IVF outcomes.

Reference	Study design	Study population	Measured outcomes	Unadjusted Urinary BPA concentration (ng/mL)	Main findings
			Live birth rates in IUI and IVF cycles.		
Goldstone *et al.* 2015	Prospective cohort	418 male partners of couples to become pregnant.	Semen parameters, DNA damage and fragmentation.	GM (5^{th}, 95^{th}) 0.6 (0.5, 0.6)[a]	Associated with lower % sperm DNA fragmentation No association with semen quality parameters.

[a] GM based on 473 men who provided a semen sample, however the urine for BPA assessment was collected in 418 men (final study population).

[b] Creatinine BPA adjusted concentrations (μg/g).

Abbreviations: BPA, bisphenol A; DNA, deoxyribonucleic acid; Exp, exposed; E2, estradiol; FAI, free androgen index; FSH, follicle stimulating hormone; fT, free testosterone; GM, geometric mean; IUI, intrauterine insemination; IVF, *in vitro* fertilization; LH, luteinizing hormone; SHGB, sex-hormone binding globuline; SSR, secondary sex ratio; T, testosterone; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine.