Bisphenol A (BPA) is a ubiquitous environmental toxicant with endocrine-disrupting properties and is suspected to affect human reproduction. The objective of this review was to summarize the potential effects of male exposure to BPA on markers of testicular function and couple reproductive outcomes. Five epidemiologic studies on BPA and reproductive hormones all found significant associations with at least one reproductive hormone; however, no consistent relationships were observed across studies. Six epidemiologic studies evaluated the relation between BPA and semen parameters, and although the majority reported negative associations with various parameters, there were few consistent trends across studies. Finally, three epidemiologic studies examined BPA and couple reproductive outcomes, and only one found an association. Overall, the evidence supporting an association between BPA exposure and adverse male reproductive health outcomes in humans 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 urinary concentrations (occupationally vs. non-occupationally exposed), misclassification of BPA exposure (e.g., using one urine sample to characterize exposure vs. multiple samples), sample sizes, study design (e.g., cross-sectional vs. prospective), and residual confounding (e.g., due to diet and lifestyle factors). It is also possible that some of the statistically significant findings were due to chance alone. Clearly, further studies are needed to further clarify the role of this ubiquitous endocrine-disrupting chemical on male reproductive health.

Key Words: Bisphenol A, semen quality, male reproductive, hormones, epidemiology

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used parenteral BPA as the exposure route (13, 24, 27), which bypasses the first-pass hepatic metabolism (inactivation), whereas the remainder of the animal studies used oral (enteral) administration (12, 14–23, 25, 26, 28–33).

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 urinary BPA concentrations and markers of couple fecundity and fertility such as time to pregnancy and live birth (Table 1). Therefore, the objective of the present review was to review the epidemiologic literature on the potential effects of exposure to BPA as measured in urine on semen quality, reproductive hormones, and fecundity. A handful of studies have explored these relationships with the use of other biologic matrices (e.g., blood and seminal plasma) to measure BPA exposure (46–50). However, it has been shown that urine is the optimal matrix for measuring nonpersistent, semivolatile, hydrophilic environmental chemicals such as BPA, and therefore those earlier studies are not considered further (51).

**BPA AND SEMEN QUALITY**

Only six studies have explored the relationship between urinary BPA concentrations and semen parameters, and two of these studies also examined the association with sperm DNA damage (Table 1). In the only prospective study to date, Li et al. explored the association of urinary BPA concentrations on semen parameters among 218 factory workers from four regions in China (39). Their 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), who had much higher urinary creatinine-adjusted BPA concentrations (median 38.7 [interquartile range (IQR) 6.3–354.3] μg/gCr) compared with factory workers who did not have BPA occupational exposure (median 1.4 [0–17.9] μg/gCr). However, when models were restricted to nonoccupationally exposed factory workers (n = 88), who had lower urinary creatinine-adjusted BPA concentrations, the only significant association was with diminished sperm concentrations. That study also found that on average, men who had detectable urinary BPA levels had more than three times the risk of having reduced sperm concentration (<15 × 10⁶ per mL) and vitality (<58%), more than four times the risk of having low sperm count (<39 × 10⁶ per ejaculate), and more than two times 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 that population of Chinese workers (39).

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 (42). However, there were no associations of BPA with other sperm parameters. Of note, this population had low background urinary BPA concentrations (median unadjusted urinary BPA concentration 3.3 ng/mL [5th–95th percentiles 0.6–14.9 ng/mL]) (42). The associations of BPA with semen parameters have also been assessed in several studies of men who, along with their partners, were trying to conceive (36, 38, 41, 45). Knez et al. investigated the relationship between urinary BPA concentrations and semen quality in 149 male partners of couples seeking infertility treatment at the Department of Reproductive Medicine and Gynecologic Endocrinology in Maribor, Slovenia (2011–2012) (41). They found that increased urinary BPA concentrations (geometric mean [GM] 1.6 [5th–95th percentiles 0.3–6.7] ng/mL) were associated with lower sperm count, sperm concentration, and sperm vitality. Meeker et al. explored the association of urinary BPA concentrations with semen parameters and DNA damage in 190 male partners in subfertile couples seeking treatment from the Vincent Andrology Laboratory at Massachusetts General Hospital (MGH) in Boston, Massachusetts (2000–2004) (36). 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 a lower percentage of progressively motile sperm. Although 89% of samples in this population of subfertile men had detectable BPA concentrations, overall these men had relatively low urinary BPA concentrations (unadjusted GM 1.6 [IQR 0.8–2.3] ng/mL). In the two other studies that included men from couples trying to conceive unassisted, BPA was not associated with semen parameters despite having urinary BPA concentrations similar to the previous study of subfertile men (38, 45). For instance, Mendiola et al. investigated the relationship 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, California; Minneapolis, Minnesota; Columbia, Missouri; and Iowa City, Iowa) who conceived without medical assistance from 1999 to 2005 (38). Urinary BPA concentrations (GM 1.5 [IQR 0.8–3.0] ng/mL) were not associated with any of the examined semen parameters in this study. Similarly, Goldstone et al. 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 that followed couples attempting pregnancy in Michigan and Texas (45). Urinary BPA concentrations (unadjusted GM 0.6 ng/mL [5th–95th percentiles 0.5–0.6] ng/mL) were not associated with semen parameters among these men. Unexpectedly, higher urinary BPA concentrations were associated with lower sperm DNA fragmentation.

**BPA AND REPRODUCTIVE HORMONES**

The epidemiologic literature investigating the endocrine-disrupting effects of BPA on male reproductive hormones also is limited and presents heterogeneous results (Table 1). To date, one study has explored this association among men occupationally exposed to BPA (34), two studied the
<table>
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<tr>
<th>Author and year</th>
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<td>Hanaoka et al. 2002</td>
<td>(34)</td>
<td>Cross-sectional</td>
<td>42 occupationally exposed and 42 occupationally nonexposed men</td>
<td>Reproductive hormones</td>
<td>Median (range): Exp 1.1 (0–11.2) Nonexp 0.5 (0–11.0)</td>
<td>Associated with lower FSH in occupationally exposed men. No differences in LH and fT.</td>
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<tr>
<td>Galloway et al. 2010</td>
<td>(35)</td>
<td>Cross-sectional</td>
<td>307 men from general population</td>
<td>Reproductive hormones</td>
<td>GM 4.0 (5th–95th 3.8–4.3)</td>
<td>No associations with E2, SHBG, and fT. Associated with higher T.</td>
</tr>
<tr>
<td>Meeker et al. 2010</td>
<td>(36)</td>
<td>Cross-sectional</td>
<td>190 men attending a fertility clinic</td>
<td>Semen parameters and DNA damage (measured as % of damage in comet tail in a subset of 132 men)</td>
<td>GM 1.4 (IQR 0.8–2.5)</td>
<td>Associated with lower sperm concentration, normal morphology and motility. No association with total sperm count. Associated with higher sperm DNA damage.</td>
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<td>Meeker et al. 2010</td>
<td>(37)</td>
<td>Prospective cohort</td>
<td>167 men attending a fertility clinic</td>
<td>Reproductive hormones</td>
<td>GM 1.3 (IQR 0.7–2.4)</td>
<td>Associated with lower inhibin B and LH and higher FSH. No relationship with T, SHBG, E2, fT, T3, T4, and TSH.</td>
</tr>
<tr>
<td>Mendiola et al. 2010</td>
<td>(38)</td>
<td>Cross-sectional cohort</td>
<td>315 fertile men from prenatal clinics (302 for semen analysis)</td>
<td>Semen parameters and reproductive hormones</td>
<td>GM 1.5 (IQR 0.8–3.0)</td>
<td>Associated with lower FAI and FAI/LH and higher SHBG. No association with semen parameters, FSH, LH, T, inhibin B, and fT.</td>
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<tr>
<td>Li et al. 2011</td>
<td>(39)</td>
<td>Prospective cohort</td>
<td>218 occupationally exposed and nonexposed men</td>
<td>Semen parameters</td>
<td>Median (IQR)b: Exp 38.7 (6.3–354) Nonexp 1.4 (0–17.9)</td>
<td>Associated with lower sperm concentration, total count, normal motility and vitality in all men. Associated with lower sperm concentration, normal motility and vitality in occupationally exposed men. No association with ejaculate volume and morphology.</td>
</tr>
<tr>
<td>Buck-Louis et al. 2014</td>
<td>(40)</td>
<td>Prospective cohort</td>
<td>439 male partners of couples trying to become pregnant</td>
<td>Fecundability measured as time to pregnancy</td>
<td>GM 0.5 (5th–95th 0.4–0.6)</td>
<td>No association with time to pregnancy. Associated with lower total sperm count, concentration, and motility. No association with other semen quality parameters.</td>
</tr>
<tr>
<td>Knez et al. 2014</td>
<td>(41)</td>
<td>Prospective cohort</td>
<td>149 male partners of couples undergoing IVF treatments</td>
<td>Semen parameters</td>
<td>GM 1.6 (5th–95th 0.3–6.7)</td>
<td>Associated with lower sperm concentration, total count, concentration, and motility. No association with other semen quality parameters.</td>
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<tr>
<td>Lassen et al. 2014</td>
<td>(42)</td>
<td>Cross-sectional</td>
<td>308 young men from general population</td>
<td>Semen parameters and reproductive hormones</td>
<td>Median 3.3 (5th–95th 0.6–14.9)</td>
<td>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.</td>
</tr>
<tr>
<td>Bae et al. 2015</td>
<td>(43)</td>
<td>Prospective cohort</td>
<td>220 singleton live births of couples trying to become pregnant</td>
<td>SSR defined as the ratio of male to female births</td>
<td>Not reported</td>
<td>Associated with more female births.</td>
</tr>
<tr>
<td>Dodge et al. 2015</td>
<td>(44)</td>
<td>Prospective cohort</td>
<td>218 male partners of couples attending a fertility clinic</td>
<td>Fertilization rate, embryo quality, and implantation in IVF cycles. Live birth rates in IUI and IVF cycles.</td>
<td>GM 1.6 (IQR 0.8–2.8)</td>
<td>No association with IUI or IVF outcomes.</td>
</tr>
<tr>
<td>Goldstone et al. 2015</td>
<td>(45)</td>
<td>Prospective cohort</td>
<td>418 male partners of couples trying to become pregnant</td>
<td>Semen parameters, DNA damage and fragmentation</td>
<td>GM 0.6 (5th–95th 0.5–0.6)</td>
<td>Associated with lower % sperm DNA fragmentation. No association with semen quality parameters.</td>
</tr>
</tbody>
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Note: Exp — exposed; FAI — free androgen index; fT — free testosterone; GM — geometric mean; IQR — interquartile range; IUI — intrauterine insemination; IVF — in vitro fertilization; Nonexp — nonexposed; SSR — secondary sex ratio; T₃ — triiodothyronine; T₄ — thyroxine.

* GM based on 473 men who provided a semen sample; however, the urine for BPA assessment was collected in 418 men (final study population).
* Creatinine-adjusted BPA concentrations (μg/g).

association among men from the general population (35, 42), and two studies investigated this association among either fertile men or subfertile men from a fertility clinic (37, 38). Hanaka 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 (34). FSH levels were lower in the 42 workers who were BPA exposed compared with 42 workers who were not occupationally exposed; however, LH and free testosterone (fT) levels were not different between groups. Surprisingly, these Japanese workers had low levels of urinary BPA (median BPA concentration 1.1 [range 0–11.2] μg/gCr for BPA-exposed workers and 0.5 [0–11.0] μg/gCr for BPA-nonexposed workers) (34).

Galloway et al. 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 (35). Increasing urinary BPA concentrations were associated with higher serum testosterone concentrations among a population who had a GM BPA concentration of 4.0 (5th–95th percentiles 3.8–4.3) ng/mL. However, the authors did not find an association between BPA and E2, SHBG, or fT (35). 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 urinary BPA concentrations similar to the previous study (median 3.3 ng/mL [5th–95th percentiles 0.6–14.9] ng/mL) (42). 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 et al. evaluated the association of urinary BPA concentrations with reproductive hormones in a cohort of 315 fertile men recruited from prenatal clinics (38). Although the urinary BPA concentrations were lower than the previous two cohorts (GM 1.5 [IQR 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 ratio. 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, urinary BPA concentrations were negatively associated with inhibin B levels and E2:T ratio and positively associated with FSH levels and FSH:inhibin B ratio (37). This group of men also had low urinary BPA concentrations (GM 1.3 ng/mL [IQR 0.7–2.4 ng/mL]) compared with the European cohorts; however, their concentrations were similar to those in the study by Mendiola et al.

**CONCLUSION**

We have reviewed the available epidemiologic literature on the association of male BPA exposure with semen quality, reproductive hormones, and couple reproductive outcomes. Although the epidemiologic literature on this topic is growing, the evidence supporting an association between urinary BPA concentrations and male reproductive health in humans remains limited and inconclusive. Several methodologic differences could explain discrepancies between human studies. First, studies 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, the distribution of urinary BPA concentrations varied across studies. If there is a nonlinear association between BPA exposure and markers of reproductive health then we may not 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 similar urinary concentrations. Third, many studies used only one urine sample as a biomarker of exposure to BPA, which, given its short half-life, may 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 (within-individual variability is known to exist), 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 (e.g., the last 90 days for spermatogenesis). Fifth, all of the human studies measured adult male exposure only and did not assess early life exposure (e.g., prenatal or peripubertal

**BPA AND COUPLE REPRODUCTIVE OUTCOMES**

The association of male urinary BPA concentrations with couple reproductive outcomes was recently assessed in two studies (Table 1). Using the EARTH study, a cohort of subfertile couples undergoing fertility treatment at MGH, Dodge et al. 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 (44). 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 the LIFE study of 501 couples discontinuing contraception with the intention of becoming pregnant. Similarly to the study among fertility clinic patients, Buck-Louis et al. did not find association between paternal urinary BPA concentrations and time to pregnancy (fecundity odds ratio 1.04 [95% confidence interval [CI] 0.91–1.18]) (40). 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 (relative risk [RR] 0.77 [95% CI 0.62–0.95] per 1 SD increase in urinary BPA) (43). In both the EARTH and the LIFE studies, the men had, on average, low urinary BPA concentrations (unadjusted GMS 1.6 [IQR 0.8–2.8 ng/mL] and 0.5 [5th–95th percentiles 0.4–0.6] ng/mL, respectively).
windows) which may be more sensitive to effects of BPA. Sixth, although 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), those studies had limited power to observe small to moderate differences in effect estimates for these outcomes. Finally, residual confounding due to diet and other lifestyle factors correlated with BPA exposure and semen quality is possible, because most studies were unable to account for those potentially important variables. For example, none of the studies included diet as a potential confounder; therefore, it is possible that results do not represent the true relationship between BPA and reproductive outcomes. It is also important to note that we can not exclude the possibility that some of the statistically significant findings were due to chance alone. In conclusion, there is currently insufficient evidence on adult male exposure to BPA, at low to moderate levels, and its association with human reproductive outcomes.

REFERENCES


