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

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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. (Fertil Steril® 2016;106:864–70. ©2016 by American Society for Reproductive Medicine.)

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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 United States, 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 owing 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 (8), in addition to 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, some studies on exposure to BPA and reproductive outcomes have confirmed these endocrine-disrupting activities. For example, doses below the present lowest observed adverse effect level (LOAEL; $<$50 mg/kg) for BPA were 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, doses below the present LOAEL for BPA were related to decreased testosterone levels in rats (15, 23, 27, 28) and mice (29). Only a few animal studies did not conclude that BPA was a testicular toxicant (30–33). There are differences across studies related to methodologic aspects such as dose, exposure route, timing, and outcomes measured. For example, three animal studies that found significant results

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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 ($<15 \times 10^6$ per mL) and vitality (<58%), more than four times the risk of having low sperm count ($<39 \times 10^6$ 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