Bisphenol A and ovarian steroidogenesis

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Bisphenol A is widely used as a component in polycarbonate plastics for food and beverage packaging, epoxy linings for canned foods, and dental sealants, among other applications. Experimental literature demonstrates BPA's affinity for estrogen receptors and downstream effects on estrogen-responsive genes. Additional data suggest that BPA reduces endogenous estrogen synthesis, likely by antagonizing ovarian enzyme activities involved in sex-steroid hormone synthesis. More specifically, evidence indicates BPA-mediated disruption of STAR, CYP450scc, and HSD-3β in theca cells and CYP450 aromatase activity in granulosa cells. Yet the results of the few human studies reported to date are equivocal. It also remains in question the extent to which BPA penetrates developing ovarian follicles. Uncertainty as to the relevance of experimental BPA doses and administration routes for common human exposure levels limits extrapolation of experimental results. To more definitively address the potential risk of BPA on human ovarian steroidogenesis, additional experimental studies using biologically active BPA doses likely to reflect those within the ovarian follicle will be necessary, as will additional prospective investigations in human populations with the use of standardized assay methodology. (Fertil Steril® 2016;106:857–63. ©2016 by American Society for Reproductive Medicine.)
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Bisphenol A (BPA) is a high-volume-production plastic monomer used widely for manufacturing polycarbonate plastics, polyvinyl chloride, dental sealants, epoxy linings for canned food goods, and for myriad additional commercial applications (1). First synthesized in the late 19th century (2), BPA was briefly considered for use as a pharmaceutical estrogen in the 1930s (3), yet it did not enter commercial production until the 1950s and began to be synthesized in large volumes in the 1970s (2). Global BPA production reached 12 billion pounds in 2011 and was growing at ~5% per year (1). The ester bond linking BPA monomers into the polymers used for packaging and containers is vulnerable to hydrolysis, fostering migration into foods and beverages and allowing gastrointestinal exposure (4); dermal exposures result from contact with thermal receipts, paper money, and paper products (5, 6). Substantial experimental evidence implicates BPA as an estrogenic endocrine disruptor in vitro (7) and in vivo (8). BPA is a weak ligand for the classic estrogen receptors alpha (ERα) and beta (ERβ) (9) with reported binding affinities that are 1,000–10,000× lower than endogenous E_2 (10). It is a potent ligand for the orphan estrogen-related receptor gamma (ERRγ) (11) and for the nonclassic membrane-bound G-coupled protein receptor (12). It is also an antiandrogen and a human pregnane X receptor (hPXR) agonist, activates ER-mediated nongenomic pathways, can activate ion channels, and induces proinflammatory cytokines and chemokines (13). Given the diverse mechanisms of action of BPA and the importance of ovarian steroidogenesis in reproductive health, numerous reviews have addressed the possible connection between BPA and reproductive performance (e.g., Gore et al., 2015 [13]), although few with a focus specifically on human ovarian steroidogenesis (14–16). The finding of BPA in the ovarian antral follicle suggests a possible effect of this endocrine-disrupting chemical (EDC) on ovarian sex-steroid hormone synthesis, with the potential for downstream effects on reproduction. Herein, we summarize the current state of the literature regarding BPA's impact on ovarian steroidogenesis as a putative mechanism to account for adverse reproductive effects in humans. We first discuss exposures and metabolism of BPA, challenges in measuring BPA, the biochemistry of ovarian steroidogenesis, and then a summary of experimental and epidemiologic studies evaluating BPA and effects on ovarian steroidogenesis, followed by speculation of clinical impacts and suggestions for future research directions.

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EXPOSURES AND METABOLISM OF BPA

Inadvertent consumption through ingestion of contaminated food and beverages associated with use in food packaging applications is the primary route of BPA exposure for general populations (17, 18). BPA is rapidly metabolized (10, 19) and inactivated (20) via glucuronide and sulfate conjugation, with subsequent excretion (21). BPA also induces hepatic CYP3A4 via binding to the hPXR (22). Endogenous estrogens are oxidized by hepatic cytochrome P450 enzymes (23) and then similarly sulfated or glucuronidated during metabolism (24). Induction or inhibition of these and related pathways (25) might alter estrogen bioavailability (26). For example, Kim et al. reported higher levels of biologically active oxidative estrogen metabolites (2-hydroxyestrogen and 4-hydroxyestrogen) among women with high (8.4 μg/g of creatinine) compared with low (0.7 μg/g of creatinine) geometric mean urine BPA (27). However, no associations were found for ratios of urine sex-steroid hormone metabolites and BPA in a case-control study of precocious puberty (28). Despite BPA's very short, ~4 hours, in vivo half-life, the widespread and ongoing nature of exposure in developed countries may introduce a state of "pseudopersistence" and a biologically meaningful internal dose (29).

CHALLENGES IN MEASURING BPA

Discrepancies between pharmacokinetic models and the results of epidemiologic studies have led to a significant controversy surrounding possible reproductive health risks associated with long-term low-level BPA exposure (30, 31). Rapid inactivation of ingested BPA may account for the null results reported in a large human study by Minguez-Alcaron et al. (32), despite associations previously reported from smaller studies and experimental results implicating BPA as a disruptor of estrogen synthesis. However, different approaches for extracting and measuring BPA in human biospecimens may in part account for discrepant results, because sensitivities, specificities, and reliabilities of analytic methods vary across laboratories (33). Potential exogenous contamination by BPA present in biospecimen collection and laboratory consumables and reagents, and possible in situ deconjugation of glucuronidated or sulfated BPA, present additional challenges for the accurate assessment of BPA exposure in human populations (34). Standardization of BPA assay methodology is warranted.

BPA IN HUMAN OVARIAN FOLLICULAR FLUID

In the context of what appears to be nearly ubiquitous and continual exposure among women in the U.S. (35) and elsewhere (4), as well as widespread distribution throughout the environment (36), the endocrine-disruptive effects of BPA have galvanized clinical and public health concerns for possible effects on women's fertility (13,37–39). The U.S. Environmental Protection Agency promulgates a reference dose of 50 μg/kg/d BPA, with presumably no adverse health effects over a lifetime below that amount. In a seminal study, Ikezuki et al. reported BPA levels of 1–2 ng/mL in 36 human follicular fluid aspirates as determined by an ELISA approach (40). However, no BPA was detected in a more recent study by Krotz et al. of ovarian follicular fluid extracted from five women (41) and determined with the use of a more specific high-performance liquid chromatography approach coupled to tandem mass spectrometry (LC-MS/MS). Still, determination of BPA in follicular fluid may be vulnerable to contamination from laboratory consumables, as mentioned above, leading to false positives, so urine analysis of conjugated BPA has been recommended (34).

OVARIAN STEROIDOGENESIS

Fundamental to ovarian function is the production and secretion of estrogen. As the primary source of E_2, granulosa cells within the ovarian follicle are subject to complex regulation by a number of molecules. During folliculogenesis when primordial follicles develop into preovulatory follicles, granulosa cells proliferate and undergo differentiation to produce E_2. As summarized briefly in Figure 1, antral follicle steroidogenesis is defined by the two-cell, two-gonadotropin hypothesis in which theca cells outside of the follicle produce androgens that are transported into the developing antral follicles with subsequent conversion into estrogens via aromatase (CYP450arom; CYP19A1) activity (42). As the precursor to steroidogenesis, cholesterol can either enter the theca cell primarily via lipoprotein-receptor mediated endocytosis or be produced de novo within the theca cells. Within the theca cell, steroid acute regulator (STAR) protein governs cholesterol transport from the outer mitochondrial membrane into the mitochondrial matrix, providing the substrate for initiation of steroidogenesis (43).

Cholesterol is the substrate for P450 cholesterol side-chain cleavage enzyme (CYP450scc; CYP11A1), which catalyzes the conversion to pregnenolone. Pregnenolone is then converted to a precursor androgen, DHEA, via an intermediate steroid, 17-hydroxypregnenolone, that involves the enzyme 17α-hydroxylase-17,20-desmolase (CYP45017α; CYP17A1). DHEA is then converted to androstenedione via the enzyme 3β-hydroxysteroid dehydrogenase (HSD3β). Although an alternative delta-4 pathway exists in which pregnenolone is converted to progesterone via HSD3β initially and then metabolized to androstenedione via CYP45017α and 17β-hydroxysteroid dehydrogenase (HSD17β), the majority of androstenedione is converted from pregnenolone via the delta-5 pathway with DHEA as the intermediate steroid. Recent evidence would also suggest an alternate backdoor pathway that leads to dihydrotestosterone production within the theca cell via conversion of 17-hydroxyprogesterone to 17OH-dihydroxyprogesterone, followed by conversion to 17OH-allopregnanolone, androsterone, androstanediol, and finally dihydrotestosterone (44). The final androgenic steroid produced in the theca cell is T, which uses androstenedione as the substrate and the enzyme HSD17β. Androstenedione and T are androgen end-products of theca cell steroidogenesis and migrate across the basal lamina of the follicle to gain access to granulosa cells within the developing antrum.

Follicle-stimulating hormone is the primary signaling molecule responsible for increasing expression of CYP450arom enzyme in granulosa cells. Higher CYP450arom