An old culprit but a new story: bisphenol A and "NextGen" bisphenols

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The concept that developmental events shape adult health and disease was sparked by the recognition of a link between maternal undernutrition and coronary disease in adults. From that beginning, a new field—the developmental origins of health and disease—emerged, and attention has focused on the effects of a wide array of developmental perturbations. Exposure to endocrine-disrupting chemicals has been of particular interest, and a ubiquitous environmental contaminant bisphenol A (BPA) has become the endocrine-disrupting chemical poster child. Bisphenol A has been the subject of intense investigation for nearly two decades, and exposure effects have been described in hundreds of experimental, epidemiological, and clinical studies. From the standpoint of reproductive health, the findings are particularly important, as they suggest that the ovary, testis, and reproductive tract in both sexes are targets of BPA action. The findings and the media and regulatory attention garnered by them have generated increasing public concern and resulted in legislative bans on BPA in some countries. The subsequent introduction of BPA-free products, although a masterful marketing strategy, is in reality only the beginning of a new and complex chapter of the BPA story. In this review we attempt to summarize what we have learned about the reproductive effects of BPA, present the reasons why studying the effects of this chemical in humans is no longer sufficient, and outline the challenges that the growing array of next generation bisphenols represents to clinicians, researchers, federal agencies, and the general public. (Fertil Steril® 2016;106:820–6. ©2016 by American Society for Reproductive Medicine.)
Key Words: Bisphenol, reproductive health, epigenetic, testis, ovary, endocrine-disrupting chemicals

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A series of experimental studies at the turn of the century suggested effects on both male and female reproduction as a result of bisphenol A (BPA) exposure (1–7). In the intervening 15 years, intense research effort has been devoted to understanding the levels and routes by which humans are exposed to BPA and the risks imposed by this exposure. Most attention has focused on fetal or neonatal exposure, and subtle changes induced during development have been linked to metabolic, behavioral, and reproductive abnormalities in adults, as well as to increases in reproductive cancers (8). These findings led to growing consumer awareness and concern about this ubiquitous endocrine-disrupting chemical (EDC), resulting in legislative bans on the use of BPA in some types of consumer products (e.g., baby bottles) in several countries including Canada, France, and the United States. As a result, new products have rapidly transformed the marketplace, with the appearance of "BPA-free" plastics, thermal paper, and linings of food and beverage containers. However, although the BPA-free label has proved a valuable marketing strategy, it provides no guarantee of a safer product; in most products, BPA has been replaced by other bisphenols.

We summarize the most recent data on the reproductive effects of BPA exposure in men and women and what we know about human exposure and metabolism. We also summarize emerging research on BPA analogues, the ramifications of the rapid emergence of these structural variants of BPA, and the challenges they present for researchers and clinicians.

THE TESTIS: BPA, TESTICULAR DYSGENESIS, AND RISKS TO SUBSEQUENT GENERATIONS

What is known at present as the Estrogen Hypothesis grew out of observations in men. Analyses of semen samples collected between 1938 and 1991 in the United States and Europe suggested a decline over time in semen volume and sperm number and morphology (9). These changes in gamete production appeared to correlate with increases in the incidence of male reproductive disorders,

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which included undescended testes, urethral malformations, and reproductive tract cancers (9) (reviewed by Skakkebaek et al. [10]). This constellation of male reproductive disorders—known as testicular dysgenesis syndrome (10)—was postulated to result from exposure during development to exogenous estrogens entering our daily lives through foods, consumer products, and pollution (11).

Experimental studies of a number of different environmental estrogens demonstrate that developmental exposure induces changes to the male reproductive tract and testes, providing support for the estrogen hypothesis (reviewed by Sweeney et al. [12] and Skakkebaek [13]). In addition, studies of different EDCs including BPA suggest that the effects of exposure are not limited to the exposed individual, but may affect subsequent generations. The multigenerational and transgenerational inheritance of abnormal phenotypes induced by EDCs has been the subject of several recent reviews (e.g., Xin et al. [14] and Stel et al. [15]). These effects on subsequent generations are thought to result from epigenetic changes but, as discussed later, the link between exposure and altered epigenetic regulation remains unclear and is the subject of intense current investigation.

In the male, effects induced by fetal and early postnatal BPA exposure include changes in sperm and semen quality, hormonal imbalance, and malformations of the reproductive tract (reviewed by Peretz et al. [16]). For example, in rodents, exposure during testis development has been suggested to alter Sertoli cell number (17, 18), Leydig cell function (as evidenced by changes in steroidogenesis [19–21]), and to decrease sperm production (1). Importantly, errors occurring during reproductive tract development prime the male for adult diseases, including cancers of the testis and prostate (22, 23).

Several reports indicate that the deleterious effects of BPA may be transmitted to subsequent, unexposed generations (reviewed in Xin et al. [14]). Because exposure can directly affect the sperm produced, it is easy to understand how phenotypic effects can manifest in the offspring of exposed males. Effects that persist in unexposed generations (i.e., in the grandsons of exposed males) are more difficult to comprehend. This type of transgenerational inheritance not only requires epigenetic changes in the germline of the exposed male, but failure to erase these changes during germline reprogramming in the subsequent generation (see Xin et al. [14] for an excellent recent review). Metabolic, behavioral, and testicular phenotypes resulting from gestational exposure to BPA (24, 25) or to mixtures of plastic chemicals (26) have been reported to be transmitted to unexposed sons and grandsons, suggesting that exposure during specific stages of development may induce transgenerational effects.

Changes that endure across generations are typically thought to result from DNA mutations, but the reproducibility of transgenerational phenotypes induced by BPA and other EDCs implicate alterations to the epigenome rather than genetic mutations. Epigenetic modifications include changes in DNA methylation, histone post-translational modifications, and noncoding RNAs, and the mechanism(s) through which BPA induces transgenerational phenotypes remain unknown. Although several reports suggest that BPA exposure can induce changes in DNA methylation patterns in somatic tissues ([27–29]; reviewed in Xin et al. [14]), and a single study (26) has reported DNA methylation changes in mature sperm two generations after exposure, at present no study has demonstrated the induction of specific germline changes and their persistence across generations.

Because the transmission of disease phenotypes to subsequent generations necessitates passage through the germline, a recent report (30) of permanent changes induced in spermatogonial stem cells is particularly interesting. Specifically, perinatal exposure to BPA or ethinyl E_2 (EE) was reported to induce meiotic perturbations that could be traced back to changes in the spermatogonial stem cells of exposed males (30). Changes induced in spermatogonial stem cells will not only be transmitted to all spermatogenic descendants produced during the lifetime of the male, but can be passed to the next generation through mature sperm. Thus, epigenetic changes to the spermatogonial stem cell itself may be responsible for transmission of disease phenotypes in unexposed descendants. However, we currently have no understanding of the mechanisms that allow epimutations in the germline induced by BPA or other EDCs to escape the genomewide epigenetic reprogramming that occurs during fetal and perinatal development.

THE OVARY: VULNERABILITY AT MULTIPLE STAGES

Experimental data suggest that the ovary is sensitive to BPA exposure during at least three distinct stages of development, and involving multiple processes, including meiotic chromosome dynamics, follicle development and growth, and epigenetic reprogramming (reviewed by Peretz et al. [16]). Data from experimental studies suggest that maternal exposure during midgestation coinciding with the onset of oogenesis in the fetal ovary can alter synapsis and/or recombination between meiotic chromosomes in oocytes from mice, monkeys, and cultured human fetal ovaries (31–33). Importantly, the subtle meiotic changes induced during this fetal stage of oogenesis increase the frequency of chromosomally abnormal eggs and embryos in the adult (31). Exposure at a slightly later stage of development (late gestation in the rhesus monkey and immediately after birth in the mouse) disrupts the formation of ovarian follicles, leading to the generation of multioocyte follicles and unenclosed oocytes (32, 34, 35), altering viable follicle populations in the adult. Given these experimental data, the expectation for adult women exposed in utero would be, as follows: [1] an increase in pregnancy failure and birth defects, if exposure coincides with the onset of meiosis in the fetal ovary, and [2] a decreased ovarian reserve and potential shortening of the reproductive lifespan, if exposure occurs at the time of follicle formation. However, because records of an adult's in utero exposure are currently unattainable, the potential effects of human exposure can only be extrapolated from animal data.

In addition to developmental exposure, experimental data provide compelling evidence that adult exposure can adversely affect later stages of oocyte development, including follicle growth and meiotic maturation. Studies using high and low doses of BPA suggest a nonlinear dose response relationship between BPA exposure and follicle growth.