Evidence for bisphenol A-induced female infertility: a review (2007–2016)

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We summarized the scientific literature published from 2007 to 2016 on the potential effects of bisphenol A (BPA) on female fertility. We focused on overall fertility outcomes (e.g., ability to become pregnant, number of offspring), organs that are important for female reproduction (i.e., oviduct, uterus, ovary, hypothalamus, and pituitary), and reproductive-related processes (i.e., estrous cyclicity, implantation, and hormonal secretion). The reviewed literature indicates that BPA may be associated with infertility in women. Potential explanations for this association can be generated from experimental studies. Specifically, BPA may alter overall female reproductive capacity by affecting the morphology and function of the oviduct, uterus, ovary, and hypothalamus-pituitary-ovarian axis in animal models. In addition, BPA may disrupt estrous cyclicity and implantation. Nevertheless, further studies are needed to better understand the exact mechanisms of action and to detect potential reproductive toxicity at earlier stages. (Fertil Steril® 2016;106:827–56. ©2016 by American Society for Reproductive Medicine.)

Key Words: Infertility, female, bisphenol A, ovary, uterus, implantation, hypothalamus, pituitary

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Female infertility is generally defined as the inability to get pregnant naturally and to deliver a live healthy newborn. According to the Centers for Disease Control and Prevention (CDC; http://www.cdc.gov/nchs/nsfg/key_statistics/i.htm#infertility), between 2011 and 2013, 6.1% of married women were considered to be infertile in the United States alone. The percentage of infertile women can reach 30% worldwide (1). Infertility in women can be the result of various factors, including physical problems, endocrine problems, lifestyle habits, and environmental factors. Environmental factors, such as exposure to chemicals with endocrine disrupting properties, can mimic or block the endocrine activity of endogenous hormones and thus adversely affect reproduction.

One of the most extensively studied endocrine disrupting chemicals is bisphenol A (BPA). Bisphenol A is incorporated in many daily used products; it is used by the manufacturers of polycarbonate plastics and epoxy resins. Despite the relatively short half-life of BPA (6–24 hours) (2), it was measured in various reproductive tissues (3), including ovarian follicular fluid, placenta, breast milk, and colostrum. Findings from previous publications suggest that BPA is a reproductive toxicant (4–6).

The current review focuses on the scientific evidence for BPA-induced fertility problems in females. We summarized the main findings of epidemiological and experimental studies that examined the potential effects of BPA on female fertility and that were published between 2007 and 2016. We included the morphological and mechanistic findings reported in the reviewed articles. We focused on the reported outcomes of BPA exposure on overall: [1] fertility, [2] reproductive-related processes including the ovarian cycle, and [3] reproductive tissues.

MATERIALS AND METHODS

PubMed (http://www.ncbi.nlm.nih.gov/pubmed) searches for the years 2007–2016 were conducted using the following key words: BPA, bisphenol A, fertility, female, reproduction, ovary, pregnancy, oviduct, ovulation, fertilization, uterus, implantation, hypothalamus, and pituitary. We focused on articles published in 2007–2016 to expand on previous review reports on the same topic (4, 5 ,7–11). In addition, references included in other review articles were examined for relevant information. We included articles that dealt with fertility/infertility outcomes related to overall fertility, implantation, uterine morphology and function, estrous cyclicity, hypothalamus-pituitary, hormone levels (luteinizing

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hormone [LH], follicular stimulating hormone [FSH], and prolactin [PRL]), oviduct, and ovary. We excluded articles about topics that were out of the scope of this review or ones that will be reviewed by other investigators in this special issue (e.g., sexual maturation/behavior, oocyte quality and maturation, ovarian steroidogenesis, pregnancy, miscarriage, endometriosis, polycystic ovarian syndrome [PCOS], and uterine fibroids/leiomyoma).

The BPA studies have used various study designs and included a wide range of doses. Based on the definitions in other studies, we considered a "low dose" of BPA as follows: a dose below the lowest observable adverse effect level of 50 mg/kg/d in animal models (4, 5, 12, 13), 17.2 mg/L for aquatic animals (5, 14), 1×10^{-7} M for cell culture experiments (5, 15), and a dose in the range of typical (not occupational) human exposures for epidemiological studies (5, 16). Most studies described in this review used doses that are within the category of low dose. Throughout the text of this review, we indicated if the doses were considered low or high based on these categories. In the Tables, the specific doses that were used in each study are described in detail. Last, similar to Peretz et al. (4), we defined exposure time during pregnancy as in utero; exposure after birth that ended before weaning as neonatal; and exposure any time after weaning as postnatal or adult exposure.

RESULTS AND DISCUSSION

Overall Fertility

In recent years, several research groups have examined the effects of BPA on overall fertility. Epidemiological studies examined whether BPA levels are higher in infertile women than in fertile women (Table 1). Findings from these studies (19, 26) indicate that infertile women have higher serum BPA levels compared with fertile women. Furthermore, studies (17, 21, 22, 28, 29) conducted in women undergoing IVF treatments show that BPA levels (total or unconjugated BPA) were inversely associated with peak E_2 levels, number of oocytes retrieved, oocyte maturation, fertilization rates, and embryo quality. Thus, increased levels of BPA may decrease the success rate of IVF treatments. Nevertheless, these studies did not take into account potential modifying factors such as co-exposure to other chemicals and the location of sample collection as pointed out by Teeguarden et al. (30, 31). Thus, additional studies are needed to fully understand the associations between BPA exposure and fertility outcomes in women.

Limited information is available on the potential molecular targets of BPA in infertile women. Hanna et al. (24) reported an association between higher serum levels of unconjugated BPA and decreased methylation within the *TSP50* gene promoter in whole blood samples of women undergoing IVF treatments. However, the researchers did not provide any mechanistic explanations of these findings other than to indicate that *TSP50* may be an oncogene based on previous research by other groups (32, 33). Interesting findings reported by Chavarro et al. (20) suggest a potential modifying effect of soy food consumption on the inverse correlations between urinary total BPA concentrations and fertility treatment outcomes. Overall, these studies are suggestive for potential associations between BPA and infertility. However, additional studies are needed to determine a possible cause and effect relationship and the mechanism of action of BPA-mediated effects on fertility in healthy women.

Not all epidemiological studies found an association between BPA exposure and fertility outcomes. Null associations were reported between urinary total BPA concentrations and impaired fecundity or time to pregnancy in generally healthy women (18, 23, 25). In another study (27), null associations between urinary total BPA concentrations and number of oocytes retrieved, embryo quality, and fertilization rates were reported in women undergoing IVF treatments. The differences in the results may be explained by differences in sample characteristics (i.e., generally healthy women without any reported infertility issues vs. women undergoing IVF treatments) and by differences in sample size.

Studies using animal models provide further insights on the effects of BPA exposure on female fertility (Table 2). In mice, Berger et al. (34) reported that low dose BPA exposure of pregnant dams during the preimplantation period significantly reduced the number of litters and litter size compared with controls. Furthermore, in utero low dose BPA exposure after implantation affected the fertility of the females in the subsequent generations (45, 49). Cabaton et al. (35) performed a forced breeding study and found that low dose BPA-exposed females had fewer pregnancies and overall reduced cumulative number of pups compared with controls. Moore-Ambriz et al. (40) examined the effects of BPA exposure in young adult mice on fertilization capacity later in adult life. The fertilization rate of BPA exposed females was reduced compared with controls. Furthermore, impaired fertility was also reported in a study that examined the effects of in utero low dose BPA exposure in three subsequent generations of mice (45, 49). Specifically, F1 females that were gestationally exposed to BPA had reduced fertility, reduced litter size (45), and reduced ability to maintain pregnancy to term (i.e., reduced gestational index) compared with controls (49). Furthermore, F2 females had a reduced gestational index compared with controls (49). In addition, F3 females exhibited reduced fertility and decreased ability to become pregnant compared with controls, indicating a potential transgenerational effect of BPA on female reproduction (49). In chickens, in ovo high dose BPA exposure reduced hatchability (47), whereas in fish, low dose BPA exposure increased the observed hatching rate (41).

In contrast, some experimental studies (36–39, 42, 43 ,46, 48) reported that BPA exposure does not affect fertility outcomes. Specifically, a few studies (36–38,43) indicate that gestational low dose BPA exposure did not alter number of litters or litter size (36–39,42,43,46,48) in mice, rats, and fish. Xi et al. (46) also indicate that gestational BPA exposure at a dose of 50 mg/kg/d (i.e., lowest observable adverse effect level) did not alter litter size in mice. Similarly, Moore-Ambriz et al. (40) reported that low dose BPA exposure did not affect the size of preovulatory follicles, the number of shed oocytes, and zygotes in adult mice that were exposed to BPA at a younger age. One of the reasons for differences between the reported results may be the age of the animals.