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Bisphenol A and Human Reproductive Health

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Summary

Bisphenol A (BPA) is a high production volume chemical with adverse endocrine and reproductive health effects in toxicological studies. Despite widespread general population exposure to BPA, knowledge of its potential impacts upon reproduction and pregnancy in humans is limited. This paper reviews the current epidemiological literature on fertility and adverse pregnancy outcomes associated with BPA exposure. It also provides relevant resources for health care providers who are in a unique position to provide guidance in reducing exposure to this endocrine disrupting chemical.

Keywords

BPA; fertility; pregnancy; reproductive health; human; epidemiology; preterm birth; birth weight

Introduction

Bisphenol A (BPA) is one of the highest volume chemicals in use today [101]. Most commonly utilized in production of epoxy resins and polycarbonate polymers, the global market is projected to exceed 6.3 million metric tons by 2015 [101]. Downstream applications include, but are not limited to, a variety of consumer products such as food can linings, water bottles, dental sealants, thermal receipts, medical equipment, flooring, reusable food and drink containers, and water supply pipes. BPA monomers can be released from these products when they are exposed to high heat, alkaline and/or acidic conditions [1-5]. Due to their widespread usage and potential leaching from consumer products, the primary exposure route in humans is thought to occur via dietary ingestion [6, 7].

Given the production levels and application of BPA in a variety of products, it is not surprising that data has indicated widespread human exposure to BPA [8-12]. Specific to the United States, it was reported that over 90% of individuals from both the 2003-2004 and 2009-2010 National Health and Nutrition Examination Surveys (NHANES) had detectable concentrations of BPA in their urine [13, 14]. Of particular concern, due to the susceptibility of the fetus, are findings that detectable concentrations of BPA have been measured in follicular fluid, amniotic fluid, placental tissue, and cord serum [6, 15-17, 102].

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BPA exists as unconjugated or conjugated forms in humans. The unconjugated form, representing ~1-12% of the total BPA in the body, is considered the active form [102]. The unconjugated form of BPA undergoes a rapid glucuronide metabolism in the liver, which has been hypothesized to reduce the biological activity of BPA and leads to rapid elimination in the urine [15]. It is important to note that conjugated BPA can also deconjugate through β-glucuronidase, which is present at high concentrations in placental tissue. Plasma and urine concentrations of unconjugated BPA are very low in the general population, making detection of this biologically active fraction extremely difficult [18, 19]. As essentially all absorbed BPA excreted in urine exists as glucuronide and sulfur conjugates, analysis of total urinary BPA has generally been used as a biomarker of exposure to BPA in biomonitoring studies [20,21]. In pregnancy, it has been hypothesized that the fetus is limited in its ability to conjugate BPA, and since β-glucuronidase is highly active in human placental tissues, it is plausible to speculate that the fetus may have exposure to higher amounts of unconjugated BPA [22].

Initially considered to be a weak environmental estrogen, BPA more recently has been shown to stimulate biological responses at very low concentrations and has been demonstrated to be as potent as estradiol (E_2) in some of its effects [23-26]. Additionally, there is evidence that BPA can also alter thyroid signaling, bind to the glucocorticoid receptor, and is an antiandrogen [27-30]. These studies and others have provided evidence that BPA can be considered an endocrine disrupting chemical (EDC). While there is a vast literature of experimental animal and mechanistic studies, the purpose of this review is to summarize the current epidemiological literature regarding fertility and pregnancy risks associated with BPA exposure.

Fertility

Infertility is defined as the inability to become pregnant after 12 months of regular unprotected sexual intercourse [31]. It has been estimated that 7-15% of the U.S. population is infertile [32]. Roughly less than half of all conceptions advance beyond 20 weeks of gestation, and studies have shown that up to 70% of the lost pregnancies are a result of implantation failure, which are never clinically recognized as pregnancies [33, 34]. The role of environmental toxicants, including BPA, in male and female infertility remains largely understudied.

Male Fertility

A number of toxicological studies have shown that animals exposed to BPA show a range of hormonal responses and altered sperm parameters indicative of adverse male reproductive outcomes [35-40]. To the authors knowledge, only five epidemiological studies have explored the relationship between molecular markers and/or downstream clinical outcomes of reproductive function in men and BPA exposure. Takeuchi and Tsutsumi found significant positive correlations between ELISA measured serum BPA concentrations and total and free testosterone levels in small population of 11 men [41]. In a slightly larger study that assessed creatinine adjusted urinary BPA concentrations and hormone levels in 42 epoxy resin workers and 42 unexposed workers, a borderline significant (p-value=0.07) inverse association was found with BPA and FSH [42]. In another occupationally exposed study, workers with higher urinary BPA concentration reported more frequent reports of sexual dysfunction, such as reduced sex drive or erectile difficulty [43]. In a cross-sectional analysis of 167 men attending a U.S. fertility clinic, Meeker et al. found that urinary BPA concentrations were positively associated with FSH, and inversely associated with inhibin B and the ratio of estradiol to testosterone [44]. In a follow up analysis, Meeker et al. additionally found that urinary BPA concentrations, measured on the same day as a semen sample, were associated with suggestive declines in semen quality parameters and with

increased sperm DNA damage [45]. Mendiola, et al. found suggestive inverse (non-significant) associations between urinary BPA concentrations and various semen parameters including seminal volume, total sperm count, total motile count and percent motile sperm in 375 men with proven fertility from a multicity cross-sectional study in the U.S.[46]. In addition, these researchers found a significant inverse relationship between BPA and the free androgen index (total T × 100/SHBG) which appeared to be driven by a positive association between BPA and sex hormone binding globulin (SHBG) [47]. Though there is some evidence of altered semen quality and hormone levels in males in relation to urinary BPA concentrations, results have not been consistently significant and are drawn from cross-sectional designs. Therefore, there is a need for additional longitudinal studies with repeat biomarker measures of exposures and sufficient statistical power to better understand the potential associations of BPA exposure with male fertility and reproductive function.

Female Fertility

I*n vitro* and animal toxicological studies have consistently reported a potential for decreased female fertility resulting from BPA exposure due to disruption in oocyte maturation, decreased ovarian E_2 synthesis, and early pregnancy loss [48-51]. To our knowledge there have been three human epidemiological studies examining the relationship between BPA exposure and fertility and ovarian function in women, resulting in seven total publications. Takeuchi et al. found significant positive correlations between ELISA measured serum BPA concentrations and total and free testosterone, androstenedione, and DHEAS levels in a population of N=26 normal women and N=47 women with either hyperprolactinemia, hypothalamic amenorrhea, or PCOS. [52]. In three recent reports from a prospective cohort of couple seeking infertility evaluations and treatment in Boston, increased urinary BPA metabolite concentrations were associated with significantly lower serum peak E2, oocyte yield, MII oocyte counts, and number of normally fertilized oocytes [53, 54]. In addition, increased odds of implantation failure were observed in a dose response association with urinary BPA in 137 women from this cohort who underwent a total of180 IVF cycles [55]. Reduced peak E_2 and a non-significant decrease in oocyte yield were also reported with increased unconjugated serum BPA in another smaller IVF (n=31) cohort at the University of San Francisco [56-58]. Consistent findings from both these cohorts of reduced peak E_2 and oocyte yield suggest that BPA may alter reproductive function in women undergoing IVF and warrants further examination among larger study populations. Additionally, the observation of an association between BPA exposure and increased odds of implantation failure by Ehrlich et al. provide intriguing evidence of adverse effects, which, if replicated, may provide a plausible explanation for BPA effects on female infertility.

Adverse Pregnancy Outcomes

Epidemiological evidence for the association of BPA exposure with adverse pregnancy outcomes, such as preeclampsia, early pregnancy loss, and gestational diabetes is lacking to date. There has been one small case-control study (n=45) of recurrent miscarriage in relation to BPA exposure among women with a history of ≥3 consecutive 1st trimester miscarriages who had higher serum BPA levels than controls [59]. However, the study had a number of limitations, such as failure to control for confounding factors, lack of temporality of the BPA serum measures, failure to address influential points, and use of an ELISA method not standardized for human sera, which need to be considered when interpreting these findings [59, 60]. Several *in-vitro* and *in-vivo* studies provide mechanistic evidence to indicate that BPA exposure can disrupt cell survival, differentiation, and increase spontaneous abortions in mice [51, 61-65]. Cross-sectional epidemiological evidence in non-pregnant adult populations suggest a relationship between BPA exposure and both diabetes [66] and hypertension [67], but these associations have yet to be explored in the context of pregnancy. Thus, there is a clear need for epidemiological studies assessing BPA exposure

and adverse pregnancy outcome including gestational diabetes, preeclampsia/eclampsia, and pregnancy loss.

Adverse Birth Outcomes

Low birth weight (LBW) and preterm birth (PTB) are the leading causes of infant mortality and precursors to future morbidity, and both have increased significantly in the United States since 1990 [68]. Current epidemiological evidence for the association of BPA exposure with these adverse birth outcomes and fetal growth parameters is extremely limited. Of six epidemiological studies, only two were designed to assess the risk of delivering a LBW or PTB infant with increasing BPA exposure. Similar to many of the previously described epidemiological studies, all of the studies explored associations of birth outcomes with BPA exposure at a single time point in pregnancy which failed to address variability of exposure throughout pregnancy. Also, inconsistencies in the approaches used to measure biomarkers of BPA exposure between studies made comparisons difficult.

Preterm Birth/Gestational Length

In a small nested case control study (N=60) of preterm birth in Mexico City, researchers found that the adjusted odds ratio of delivering less than 37 weeks in relation to specific gravity adjusted third trimester BPA concentration was 2.5 (95%CI 1.1, 6.0) [69]. When assessing gestational age as a continuous variable, Cantonwine et al. found urinary BPA concentrations were associated with a significant decrease in gestational length. Conversely, in a small study of 40 pregnant women living in Southeastern Michigan, there were no differences in gestational length between women with plasma BPA concentrations > 5 and ≤ 5 ng/mL [70]. Finally, Wolff et al. found no association between urinary BPA exposure during the third trimester and gestational length among 367 infants living in New York City [71]. Due to the lack of studies specifically designed to assess the odds of delivering a PTB infant in relation to BPA exposure, future studies are needed and should account for temporal variability in BPA exposure across pregnancy and the heterogeneous etiologies of preterm birth to enhance study precision.

Infant Growth Parameters

One study that assessed risk of low birth weight and small for gestational age infants found maternal plasma BPA concentrations measured at delivery were associated with increased odds of delivering either a low birth weight infant (OR 3.5; 95% CI 1.1, 4.4) or an infant small for gestational age (OR 1.9; 95% CI 1.4, 2.6) [72]. Recently, Snijder et al. found that higher concentrations of urinary BPA, measured at three time points throughout pregnancy, was associated with lower fetal weight and head circumference assessed by ultrasound [73]. Philippat et al. reported an inverse U-shaped association between birth weight and urinary BPA concentrations, but found a positive association with head circumference in 191 pregnant French women [74]. In an occupationally exposed population, 50 infants born to mothers who worked for manufacturers of BPA and epoxy resins had significantly lower birth weights when compared with offspring from women without BPA exposure in the workplace [75]. Lee et al. (2008) also reported preliminary findings at a conference showing that first trimester maternal urinary BPA levels in 125 women were negatively associated with fetal head circumference and abdominal circumference in the third trimester of pregnancy [76]. By contrast, Wolff et al. found no significant associations between urinary BPA concentrations measured in the 3rd trimester and any fetal growth parameters in 367 pregnant women living in New York City [71]. In summary, there is limited evidence that maternal BPA exposure adversely effects birth weight. The contradictory findings among the existing epidemiological studies may reflect methodological and timing differences related to exposure assessment, or differences in study designs or populations.

Inconsistences have also be found in animal studies with regards to prenatal BPA exposure and birth weight. [77-82]. It is clear that further evidence is needed before it could be concluded that BPA exposure during pregnancy does or does not adversely influence fetal growth parameters.

Conclusions

While there is a growing body of literature suggesting adverse relationships with fertility and birth outcomes in relation to BPA exposure, human studies remain extremely limited and highlights the need for more epidemiological research. The often contradictory findings for the effects of BPA on fertility, adverse pregnancy and birth outcomes may reflect analytical differences, study populations, and methodological issues related to exposure assessment or study design. The majority of the epidemiological studies reviewed here relied upon a single time point measure of BPA which failed to address the temporal relationship between toxicant exposure and pregnancy outcomes. In recent study by Braun et al., a weak intraclass correlation coefficient of 0.11 for BPA was reported using three repeated urine samples during pregnancy [83]. This study illustrates the enhanced need for multiple serial urinary BPA measurements during pregnancy in order to obtain accurate estimates of exposure over time for an individual. In addition, the accuracy of analytical results may be compromised by sample collection, processing and storage protocols used (great care must be taken to prevent external BPA contamination when measuring free BPA) and by measurement techniques utilized (especially at very low concentrations). For example, some of these epidemiological studies relied upon enzyme-linked immunosorbent assay methodology for exposure determinations of BPA concentrations in plasma or serum. This data may be of questionable value due to lack of specificity of the antibody and effects of the biologic matrix that could result in overestimated BPA concentrations [102].

Even though currently available epidemiological evidence for adverse reproductive outcomes is limited and inconsistent, exposure to BPA occurs among virtually all pregnant women and toxicological evidence suggests that low level exposure to BPA may poise relevant adverse health impacts during pregnancy. For those health care professionals and patients who wish to reduce BPA exposure given our current epidemiological understanding, many “BPA free” consumer goods are becoming more commonly available and replacing foods that come in plastic packages and cans with fresh alternatives may reduce exposure by more than 50% [84]. Plastics with recycling codes #3 and #7 may contain BPA and patients could be counseled to reduce or avoid using these products. Hospitals may also help prevent exposures among vulnerable populations (such as in neonatal intensive care units) through their purchasing practices to limit usage of BPA containing devices and supplies [85]. Several general resources are available which will help provide additional information on BPA including: National Institutes of Environmental Health Sciences (http://www.niehs.nih.gov.proxy.lib.umich.edu/news/sya/syabpa/), U.S Food and Drug Administration (http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm297954.htm), and the network of university-based Pediatric Environmental Health Specialty Units (http://www.aoec.org/PEHSU/index.html). While not specific to pregnant women or those trying to become pregnant, these resources offer a vast array of relevant information for patients and clinicians. Finally, clinicians are encouraged to consult with physicians or other professionals trained in environmental and occupational health, as needed, to address specific exposures or potential environment related health conditions. A resource for clinician referrals is found on the Pediatric Environmental Health Specialty Units website (http://www.aoec.org/pehsu.htm).

Expert Commentary

Exposure to endocrine disrupting chemicals (EDCs), such as BPA, is widespread in our society, but our understanding of their potential impacts upon reproduction and pregnancy in humans is lacking. Given the unique susceptibility of the fetus, additional epidemiological studies are needed to understand the relationship between BPA, a high production volume EDC, and potential impacts upon fertility, adverse pregnancy events (such as early fetal loss), and adverse birth outcomes. These studies need to utilize the best available methodology for analytical determinations and incorporate designs that allow for an enhanced understanding of exposure throughout pregnancy. Even with the lack of epidemiological evidence, due to widespread usage and existing mechanistic and toxicological data, there is sufficient reason to warrant use of the precautionary principle for the protection of the fetus. It is also important to note that BPA is only one of many endocrine disruptors that pregnant women are exposed to daily. As we continue to assess potential adverse effects of BPA in humans, the possibility of cumulative effects of BPA with other prevalent endocrine disrupting compounds should not be overlooked. Working in concert with those trained in environmental and occupational health, obstetricians and other health professionals can communicate with patients various ways to reduce their toxicant burdens in hopes of improving the health of fetuses and pregnant women.

Five-year view

Although the understanding of the relationship between EDCs, including BPA, fertility and adverse pregnancy events/outcomes is increasing, there is still a great need for appropriately designed epidemiological studies to help bridge our understanding between the mechanistic impacts of BPA and clinically relevant outcomes. Beyond the sources of information mentioned in this review, there are currently several new epidemiological cohorts designed to investigate the association of BPA with, among other health outcomes, semen quality, time to pregnancy, preterm delivery, and gestational diabetes. Over the next 5 years, results from these studies should help to provide critical information to assist regulators and clinicians in understanding the pregnancy risks associated with everyday exposure to this EDC.

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Key Issues

- Due to production levels and application of BPA in a variety of products, exposure to this endocrine disrupting chemical occurs among virtually everyone (including pregnant women).
- There is suggestive evidence of an association between BPA exposure and altered reproductive hormone and semen quality in men, indicative of adverse male reproductive function, but there is need for additional studies to verify.
- Maternal exposure to BPA is associated with reduced peak E_2, oocyte yield, and increased odds of implantation failure among women undergoing IVF. This suggests that BPA may alter reproductive function in women.
- With the potential to impact fertility in men and women, health care providers should counsel patients on methods to reduce exposure to BPA for those seeking infertility treatment.
- Epidemiological evidence for the association of BPA exposure with adverse pregnancy outcomes, such as preeclampsia, early pregnancy loss, and gestational diabetes is lacking.
- Maternal exposure to BPA may be associated with reduced gestational length and increased risk of delivering an infant prematurely, warranting future epidemiological studies.
- Even with only limited epidemiological evidence, due to widespread usage and existing mechanistic and toxicological data, there is sufficient reason to warrant reduction of BPA exposure during pregnancy for the protection of the fetus.