Plasticizer Exposure and Reproductive Health: Phthalates and Bisphenol A

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Abstract Phthalates and bisphenol A are among the most popular plasticizers used today, which are ubiquitous environmental chemical pollutants with endocrine disruption. In this chapter, we summarize the basic characteristics of phthalates and bisphenol A and their effects on male and female reproductive health. We focus on the effects of phthalates exposure on testosterone level, anogenital distance, semen quality and hypospadias incidence in the male, as well as on precocious puberty, endometriosis, abnormalities of pregnancy in the female. Moreover, the effects of bisphenol A exposure on male semen quality, reproductive cells, sex hormones and female steroid hormone levels, reproductive organ diseases, and adverse birth outcomes are discussed. Results indicate that exposure to phthalates and bisphenol can adversely affect male and female reproductive health. However, evidence is still controversial. More large-scale prospective cohort studies are needed to verify the effects of plasticizer exposure on reproductive health in humans.

Keywords Plasticizer · Phthalates · Bisphenol A · Reproductive health

1 Introduction

Plasticizers are a category of additives that increase the plasticity or decrease the viscosity of materials. These are the substances which are added in order to alter their physical properties, such as durability, elasticity, and flexibility [1]. Phthalates

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and bisphenol A (BPA) are among the most popular plasticizers used today, which are widely used in consumer and industrial products. Phthalates and BPA are ubiquitous environmental chemical pollutants with endocrine disruption and adversely affect human health through different mechanisms of action [2], especially potential reproductive toxicity for males and females [3, 4]. This chapter examines the basic characteristics of phthalates and BPA and their effects on human reproductive health.

2 Characterization of Phthalates

Phthalates, the diesters of 1,2-benzenedicarboxylic acid (phthalic acid esters), are a class of synthetic chemicals used as plasticizers and softeners widely in consumer and industrial products, mainly polyvinyl chloride (PVC) or vinyl [5]. More than 25 phthalates are used in commercial applications, with each adding unique qualities to the product into which it is incorporated. Ten commonly used phthalates and their metabolites are presented in Table 1. Phthalates can be classified into two categories

Table 1 Phthalates and their metabolites

Parent compounds (acronym)	Major metabolites	Acronym
Dimethyl phthalate (DMP)	Mono-methyl phthalate	MMP
Diethyl phthalate (DEP)	Mono-ethyl phthalate	MEP
Dibutyl phthalate (DBP)	Mono-n-butyl phthalate	MBP
Benzylbutyl phthalate (BzBP)	Mono-benzyl phthalate	MBzP
Dicyclohexyl phthalate (DCHP)	Mono-cyclohexyl phthalate	MCHP
Di-2-ethylhexyl phthalate (DEHP)	Mono-2-ethylhexyl phthalate	MEHP
	Mono-(2-ethyl-5-hydroxyhexyl) phthalate	MEHHP
	Mono-(2-ethyl-5-oxohexyl) phthalate	MEOHP
	Mono-(2-ethyl-5-carboxypentyl) phthalate	MECPP
	Mono-(2-carboxymethyl-hexyl) phthalate	MCMHP
Diisobutyl phthalate (DiBP)	Mono-isobutyl phthalate	MiBP
Diisononyl phthalate (DiNP)	Mono-isononyl phthalate	MiNP
	Mono-(carboxyisooctyl) phthalate	MCiOP
Diisodecyl phthalate (DiDP)	Mono-(carboxynonyl) phthalate	MCNP
	Mono-(carboxyisononyl) phthalate	MCiNP
Di-n-octyl phthalate (DnOP)	Mono-n-octyl phthalate	MnOP
	Mono-(3-carboxypropyl) phthalate	MCPP
	Mono-carboxy-n-heptyl phthalate	MCHpP
	Mono-n-heptyl phthalate	MHpP
	Mono-n-pentyl phthalate	MPeP
	Mono-iso-propyl phthalate	MiPrP

according to their molecular weight and usage. For example, phthalates with high relative molecular weight include those with 9–13 carbon atoms in their chemical backbone, which gives them increased permanency and durability, such as di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DiNP), and benzylbutyl phthalate (BzBP), and they are mainly used in the manufacture of PVC plastics for food packaging, building materials, and medical devices [6, 7]. Phthalates with low relative molecular weight include those with 3–8 carbon atoms in their chemical backbone, such as diethyl phthalate (DEP) and di-n-butyl phthalate (DnBP), and they are commonly used in the manufacture of personal care products (including perfumes, body lotions, cosmetics, shampoos), paints, and adhesives [8, 9]. In the past 5 years, the global phthalates transaction volume has increased by 30%, from $10.39 billion in 2014 to $13.89 billion in 2018, and the production has increased from 5.35 million tons to 6.76 million tons. The increase in phthalates productions and transactions means that more and more phthalates will enter the environment or the human body in various ways.

Human exposure is widespread across the lifespan, and ingestion, inhalation, and dermal contacts are considered the routes of exposure for the general population. When entering into the human body, phthalate diester may first be hydrolyzed to phthalate monoester, oxidized (phase I metabolism) by the catalytic action of cytochrome P450 (CYP) enzyme, and then converted to glucuronide conjugated phthalate (phase II metabolism). Phthalates which have a short biological half-life can be rapidly metabolized to monoester metabolites after exposure and excreted in the urine [10]. As the environmental endocrine disruptor, phthalates can interfere with hormone synthesis, secretion, binding, and metabolism and have antiandrogenic and estrogen-like activities. Phthalates are also a class of harmful substances with teratogenicity, carcinogenicity, mutagenicity, and reproductive toxicity. Evidence from animal experiments and population-based epidemiological studies suggests that exposure to phthalates can affect human reproductive health [11, 12]. Considering the health hazards of phthalate exposure, U.S. Environmental Protection Agency (EPA) has decided to regulate the manufacture, processing, commercial distribution, and/or use of phthalates.

2.1 Phthalate Exposure and Male Reproductive Health

Phthalates have been confirmed to have anti-androgenic activity in animal studies, leading to reduced circulating testosterone and male reproductive tract abnormalities [13]. Male reproductive toxicity is one of the most important toxic effects of phthalates, and phthalate exposure may or may not lead to the “phthalate syndrome” or “testicular dysgenesis syndrome” [14], which is characterized by hypospadias, cryptorchidism, undescended testes, reduced anogenital distance (AGD), decreased sperm count and quality, low testosterone levels, sterility, and testicular cancer [15]. Phthalate exposure during different life stages may cause abnormal levels of hormones in male progeny, lead to decreased sperm quality in adulthood, cause direct

or indirect damage to the structure and function of various testicular cells and has toxic effects on testis and its internal structure, ultrastructure, hormone secretion, semen and sperm quality, and other genitals. The health outcomes of fetal testosterone concentrations, male AGD, semen quality, and hypospadias incidence were discussed in this part.

2.1.1 Phthalate Exposure and Testosterone

Testosterone is the primary male sex hormone. In male humans, testosterone plays a key role in the development of the male reproductive system and is necessary for normal male fertility. And testosterone promotes secondary sexual characteristics such as increased bone density, muscle strength, the growth of body hair at the same time. Low testosterone levels are associated with abnormal sexual differentiation, decreased fertility, and other adverse conditions. There is a mass of evidence that fetal phthalate exposure is associated with decreased testosterone in fetuses of rats. A meta-analysis performed by the National Academy of Sciences of the United States showed that a decrease in fetal testes testosterone after in utero exposure to DEHP in rats. The findings are inconsistent in humans [15]. Main et al. found that mono-n-butyl phthalate (MBP) contamination of human breast milk was negatively correlated with free testosterone ($r = -0.22$, $P = 0.033$) and other phthalate monoesters showed similar but nonsignificant tendencies [16]. Lin et al. detected the phthalate metabolite concentrations of MBP, monobenzyl phthalate (MBzP), monoethylhexyl phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl)phthalate (5OH-MEHP), mono(2-ethyl-5-oxohexyl) phthalate (5oxo-MEHP), monomethyl phthalate (MMP), and monoethyl phthalate (MEP) in maternal urine samples collected in the third trimester and cord sex steroid hormones in 155 pregnant women and their newborns [17]. The results showed that no significant correlation was found between phthalate metabolites for male newborns and each steroid hormone. Overall, since phthalates are detected in different biological samples and the results from different studies are inconsistent; the evidence that phthalate exposure could decrease fetal testis testosterone is considered indeterminate.

2.1.2 Phthalate Exposure and Semen Quality

Male factor infertility leads to approximately 50% of difficulty with conception and a high proportion of cases are unexplained [18]. Sperm quality is an important factor of difficulty in getting pregnant. Studies have shown that the continuous decrease in sperm count and fertility in men over the past decade may be related to the absorption of more and more phthalates [19]. For the outcomes of sperm count and quality, the results from seven studies showed an inverse relationship between decreased semen quality and increased DEHP exposure. The inverse finding above was also supported by the studies that the DEHP exposure increased apoptosis, reactive oxygen species (ROS) generation, and increased sperm aneuploidy, which

may be the potential mechanisms of action [20]. Bloom et al. and Axelsson et al. found that sperm concentration and its motility decreased with increasing exposure to MEOHP and MEHP [21, 22]. Hauser and his colleagues found that urinary levels of MEP and MEHP were associated with DNA damage of sperms [23]. Jurewicz et al. investigated the association of phthalate metabolite levels in urine with semen parameters (sperm concentration, motility, morphology, CASA parameters), sperm aneuploidy, and sperm chromatin structure, and the results demonstrated that urinary phthalate metabolite levels were significantly associated with a decrease in sperm motility (MEHP and MINP), CASA parameters (MBP), testosterone level (MEHP), and an increase in sperm DNA damage (MBP) and sperm aneuploidy (MBzP, MBP, MEHP, and MEP) [24]. Overall, there is robust evidence to confirm the association between increased phthalate exposure and decreased semen quality, specifically sperm concentration.

2.1.3 Effects of Phthalate Exposure on AGD and Hypospadias

AGD is the distance from the midpoint of the anus to the genitalia, the underside of the scrotum or the vagina, which is considered as a significant marker of androgen activity during the male programming window in both humans and animals [25]. The association between phthalate exposure and reduced AGD has been observed in both animals and humans. Of all the studies on phthalate exposure, DEHP exposure is the most studied. The National Academy of Sciences of the United States carried out a systematic review on phthalate exposure and male reproductive tract development in animals from a mass of literature in 2017 and the meta-analyses, meta-regression, and benchmark dose (BMD) estimation were performed in the study. Their research showed that there was consistent evidence for a decrease in AGD in male rats after fetal exposure to DEHP. The BMD analysis showed that the BMD_5 was around 300 mg/kg/day for Sprague Dawley rats, 150 mg/kg/day for Wistar rats, and 250–350 mg/kg/day for mice, suggesting that the Wistar rat was most sensitive to phthalate exposure [26].

As for the effects of phthalate exposure on human reproductive health, prospective cohort studies can provide more convincing evidence. Therefore, here we are only concerned with prospective cohort studies related to phthalate exposure and AGD. In the United States, Swan et al. examined eight phthalate metabolites (DEHP, MEP, MBzP, MBP, MiBP, MCPP, MCNP, and MCOP) in first-trimester maternal urine samples of 753 pregnant women recruited between August 2010 and August 2012 at university-based prenatal clinics in San Francisco, California. Their research presented that the concentrations of DEHP metabolites in first-trimester maternal urine samples were inversely associated with the AGD in male newborns, but not female [27]. Martino-Andrade et al. detected phthalate metabolite concentrations in maternal urine samples collected in three trimesters (the first, second, and third trimesters) in a subset of The Infant Development and the Environment Study mothers ($N = 168$), and the results showed that the concentrations of DEHP metabolites in first-trimester urine samples were inversely related to male AGD [28]. Bustamante-

Montes et al. reported similar findings in Mexico [29]. Radke and his colleagues through the systematic review of human epidemiological evidence showed that there was moderate evidence of an inverse association between AGD and exposure to DEHP and DBP, with mostly consistent results reported among five studies. Evidence for DINP, BBP, DIBP, and DEP was slight [20]. However, Swan et al. showed that MEP, MBP, MBzP, and MiBP were found inversely related to reduced AGD, and no correlation with the AGD was presented in DEHP [30]. In Scandinavia, Jensen et al. found no significant trends toward shorter AGD in boys with higher phthalate exposures, which were measured in the first trimester in this low exposed Danish population [31]. Thus, there is consistent evidence of the shortening of ADG being associated with increased urinary concentrations of phthalate metabolites, especially DEHP.

Hypospadias is a birth defect in boys, resulting in the location of the opening of the penis on the underside instead of at the tip. It is estimated that about 5 boys out of every 1000 born in the United States have hypospadias each year [32]. The overall prevalence of hypospadias was 5.8 boys out of 10,000 male births and presented an increasing trend during 1993–2005 in China [33]. For the relationship between phthalate exposure and hypospadias, Li et al. demonstrated that exposure to DEHP in pregnant rats could cause hypospadias in male rats, and the probability and extent of hypospadias were positively correlated with the exposure dose [34]. However, Jensen et al. conducted a case–control study that was nested within a large biobank of amniotic fluid samples collected in Denmark during 1980–1996 [35]. Their study results showed that there was no significant association between mono(2-ethyl-5-carboxypentyl) phthalate (5cx-MEPP, DEHP metabolite) and hypospadias nor the mono(4-methyl-7-carboxyheptyl) phthalate (7cx-MMeHP, DiNP metabolite) [35]. Chevrier and his colleagues also found that there was no association between hypospadias and urinary concentrations of DEHP metabolites by a nested case-control study [36]. However, these two studies were very small in sample capacity, which limited their power. Overall, evidence from the epidemiological studies that estimate the association between phthalate exposure and hypospadias in male births is limited and inconclusive.

2.2 Phthalate Exposure and Female Reproductive Health

Higher levels of phthalates have been found in women than in men, which revealed an aggregated phthalate exposure in females. General biomonitoring and risk assessment studies in women show that phthalate metabolites can be detected from almost all body fluids in women, such as peripheral blood, urine, saliva, amniotic fluid, follicular fluid, and breast milk [4]. Growing studies have indicated that phthalate exposure is associated with some endocrine-related reproductive outcomes in females during early pregnancy, such as time-to-pregnancy, embryonic loss, pregnancy loss, recurrent pregnancy loss, and thyroid dysregulation. In addition, some related studies have also found that exposure to phthalates is associated

with precocious puberty ovarian function, precocious puberty in girls, endometriosis, and female genital tumors [37].

2.2.1 Phthalate Exposure and Precocious Puberty

Precocious puberty is when a child's body begins changing into that of an adult (puberty) too soon. When puberty begins before the age of 8 in girls, it is considered precocious puberty. Puberty means rapid growth of bones and muscles, changes in body shape and size, and development of the body's ability to reproduce. Precocious puberty signs and symptoms in girls include breast growth and first-time menstruation, pubic or underarm hair, rapid growth, adult body odor, and sometimes acne.

Phthalate exposure has been estimated for the association with precocious puberty in many studies. However, the results are inconsistent. Frederiksen et al. detected 12 primary and secondary metabolites of five phthalate diesters in the urine of 725 healthy girls and 25 girls with precocious puberty by one large prospective cohort study to explore the association between phthalate exposure and precocious puberty. Their research presented that the age at pubarche increased with higher phthalate metabolite quartiles (except for MEP) and no significant association between phthalate exposure and breast development was observed [38]. Hashemipour et al. assessed seven phthalate ester metabolites in plasma in 87 girls with precocious puberty and 63 age- and sex-matched controls and the results showed that DEHP metabolite levels were significantly higher in those with precocious puberty than the levels in controls ($P < 0.05$), but this difference was not significant for other phthalate metabolites. However, phthalates detected in plasma may be contaminated by blood-collecting vessels and the results are more doubtful [39]. Thus, it may be difficult to obtain a definite association between phthalate exposure and precocious puberty, based on existing studies.

2.2.2 Phthalate Exposure and Endometriosis

Endometriosis is an estrogen-dependent disease which is characterized by the growth of endometrial epithelial and stromal cells anywhere in the body outside the uterine cavity [40]. Researchers are interested in the potential relationship between phthalate exposure and endometriosis and the role of estrogens in the pathophysiology of endometriosis. Studies have shown that phthalate exposure can reduce endometrial receptivity and implantation sites. In early pregnancy, adequate progesterone and progesterone receptor (PR), downregulation, and relatively low levels of estradiol are necessary for blastocyst implantation. It has been found that DEHP can up-regulate endometrial estrogen receptor alpha (ERα) and progesterone receptor (PR) levels, thereby reducing endometrial receptivity during implantation from animal experiments [41].

Upson et al. investigated urinary phthalate metabolite concentrations and endometriosis risk based on 92 surgically confirmed cases diagnosed between 1996 and

2001 and 195 population-based controls [42]. They detected eight phthalate metabolites (MEHP, MEHHP, MEOHP, MECPP, MBzP, MEP, MiBP, and MnBP) and observed a strong inverse association between urinary MEHP concentration and endometriosis risk (*OR* = 0.3, 95% *CI*: 0.1–0.7). Their results also suggested increased endometriosis risk with greater urinary concentrations of mono-benzyl phthalate (MBzP) and mono-ethyl phthalate (MEP). The studies of Cobellis et al. and Masuyama et al. also found similar results [43, 44]. Kim et al. reported no significant association between DEHP and endometriosis (*OR* = 1.001, 95%*CI:* 1.000–1.002, *P* = 0.161) and a significant weak association between MEHP and endometriosis (*OR* = 1.020, 95%*CI*: 1.003–1.038, *P* = 0.020) by analyzing 97 cases and 169 controls [45]. Reddy et al. reported similar results in 2006 [46]. The studies mentioned above indicate that phthalate exposure could increase the risk of endometriosis. Nevertheless, many other studies have not found the associations between phthalate exposure and endometriosis among study subjects from different countries [47–49]. Therefore, the available literature till now may not support the association between phthalate exposure and endometriosis, and many more studies should be conducted in the future.

2.2.3 Phthalate Exposure and Abnormalities of Pregnancy

Abnormalities of pregnancy such as embryonic loss, spontaneous abortion, recurrent pregnancy loss, and others constitute the most frequent complication of human pregnancy. Growing evidence has indicated that phthalate exposure is associated with some abnormal reproductive outcomes in females.

Wang et al. reported that compared with the control group, the number of implantation embryos in early pregnancy decreased in the MEHP-treated group, so did the number of embryos and live fetuses in middle and late trimesters [50]. Some studies have also found that DEHP causes a significant increase in the abortion rate in the second trimester. Many epidemiological studies also revealed the association between phthalate exposure and abnormalities of pregnancy. Liao et al. recruited 103 patients diagnosed with recurrent pregnancy loss and 76 controls from the Department of Obstetrics and Gynecology in southern Taiwan between August 2013 and August 2017, and 11 phthalate metabolites were analyzed at the same time. The research illustrated that exposure to phthalates could increase the risk of recurrent pregnancy loss with the *OR* = 2.85, *P* = 0.045 [51]. Gao et al. detected seven urinary phthalate metabolites in morning urine during gestational weeks 5–14 from 3220 pregnant women, who were recruited by a prospective cohort study in China. Their research results showed that there were positive associations of MEP, MEOHP, MEHHP, and ΣHMWP with embryonic loss (during gestational weeks 6–10) and only one association of fetal loss (during gestational weeks 11–27) was observed with MEHHP. The findings indicated that Chinese women exposed to phthalates during early pregnancy increased the risk of clinical pregnancy loss, especially embryonic loss [52]. Jukic and his colleagues presented that urinary concentrations of phthalate metabolites were associated with follicular phase length or

increased the risk of early pregnancy loss, but there was an association between ΣDEHP and reduced risk of early loss [53]. In summary, most studies support the idea that phthalate exposure can lead to abnormal pregnancy such as spontaneous abortion and recurrent pregnancy loss. It is necessary to reduce phthalate exposure among reproductive-aged women as much as possible.

2.2.4 Phthalate Exposure and Other Reproductive Health Effects

Phthalate exposure is also associated with other aspects of reproductive health or has adverse effects. For example, related studies have confirmed that phthalates can cause the increase of luteinizing hormone and testosterone, inhibit the growth of follicles, and induce immature follicular atresia, leading to ovulation disorder and polycystic ovary morphological changes, suggesting that phthalate exposure may be one of the pathogenic factors of polycystic ovary syndrome [54]. Fu and his colleagues demonstrated that significantly positive associations were observed between DEHP metabolites and risk of breast cancer and uterine leiomyoma, especially for MECPP in breast cancer by standard meta-analysis and bioinformatics analysis [55]. Besides, studies on urinary phthalate metabolite concentrations and reproductive outcomes among women undergoing in vitro fertilization showed that urinary concentrations of DEHP metabolites were inversely associated with oocyte yield, clinical pregnancy, and live birth following assisted reproductive technologies [56]. Therefore, much more health effects of phthalate exposure should be explored in the future, and phthalate exposure should be avoided as much as possible among women during reproductive age.

3 Characterization of BPA

BPA is a general material for the synthesis of plastics, which is widely used in the production of epoxy resin, polycarbonate, and other polymer materials. These polymer materials are widely used in toys, thermal paper, food and beverage packaging, dental protective gel, and other daily necessities or medical supplies. BPA molecules in plastics such as polycarbonates and epoxy resins are released by hydrolysis at high temperatures or under acidic conditions [57]. Combined with the widespread use of plastics in daily life, people are increasingly exposed to BPA. Just like phthalates, BPA also has a short biological half-life and can be rapidly metabolized. The Centers for Disease Control and Prevention (CDC) of the United States and the Canadian Health Measures Survey have reported measurable levels of BPA in urine samples in more than 90% of the participants [58, 59].

Recently, BPA has been widely a cause of concern due to its potential endocrine-disrupting effects and reproductive toxicity. The endocrine-disrupting effects interacting with estrogen receptor α/β (ER α/β) [60], estrogen-related receptor γ, androgen receptor (AR), thyroid hormone receptor, or other various physiological

receptors of BPA have been demonstrated by different animal and cell experiments [61]. A mass of epidemiological studies has been performed by researchers all over the world to demonstrate whether BPA has reproductive toxicity. Current results from different animal studies indicate that BPA exposure could decrease sperm production and quality, damage testicular cells, perturb hormone levels, disrupt oocyte quality and maturation, and affect ovary function and uterine morphology [61]. Similar outcomes also have been demonstrated by epidemiological studies [62], and there are also many other health effects caused by BPA. Here, we focus on the effects of BPA exposure on both male and female reproductive health.

3.1 BPA Exposure and Male Reproductive Health

There has been much literature on BPA exposure and male reproductive system. Here we mainly focus on the effects of BPA exposure on male semen quality, reproductive cells, and male sex hormones.

3.1.1 BPA Exposure and Male Sex Hormones

The synthesis of sex hormones is a catalytic reaction of cholesterol as a precursor through a series of steroid hormone synthetases. The main male sex hormones are steroidogenesis including follicle-stimulating hormone (FSH), testosterone (T), estradiol (E2), and luteinizing hormone (LH). BPA can interfere with hormone synthesis.

Till now, there are many epidemiological studies regarding BPA exposure and male sex hormones. Siracusa et al. found the conclusion regarding the relationship between BPA exposure and testosterone in men from a lot of epidemiological studies was inconsistent before 2014, but after that, most studies indicated that BPA exposure could perturb the hormone levels in men [61]. Data from animal experiments suggested that BPA exposure could impair male steroidogenesis in rodents, but the effects varied by species, strain, exposure window, and duration [61]. Some of the results were also demonstrated by some epidemiological studies. For example, Meeker et al. found that increased concentrations of follicle-stimulating hormone and decreased ratios of estradiol to testosterone had associations with high concentrations of BPA in men diagnosed with infertility [63]. However, Mendiola et al. showed significant inverse associations of urinary BPA concentration and free androgen index (FAI) level and the FAI/LH ratio, as well as a significant positive association between BPA and sex hormone-binding globulin [64]. Recently, Liu et al. presented that high BPA exposure was associated with increased prolactin, estradiol, and sex hormone-binding globulin levels in males, potentially contributing to male infertility [65]. Liang et al. proved that men with detectable levels of BPA had a 1.52-fold increased risk (95% *CI*: 1.04–2.21) of having a high LH level

(>75th percentile) compared with men with undetectable levels of BPA, after adjustment for potential confounders [66]. Mustieles et al. found that each natural-log unit increase in urinary BPA concentrations was associated with a 19% increase in geometric mean serum total testosterone levels [67]. Although the results may differ among studies, most of the studies indicate that BPA exposure can disrupt the hormone levels in men.

3.1.2 BPA Exposure and Sperm Quality

Animal experiments show that both prenatal and postnatal BPA exposure decrease sperm quality in mice and rats. Sperm number, sperm apoptosis rate, oxidative stress level, and the alteration of seminiferous tubule morphology are conventional observation markers in previous literature. Recently, genetic markers such as chromosomal abnormalities and meiotic DNA double-strand breaks (DSBs) also have been observed [61]. Compared with the control group, prepubertal male SD rats exposed to BPA presented higher intercellular junction disruptions, sloughing of germ cells, and immature germ cells and cellular debris [68]. In SD rats, BPA exposure at a dose of 50 mg/kg induced higher SOD activity, GSH-Px activity, and MDA level, and BPA exposure at all the other designed doses induced sperm malformation rate and apoptosis in testis [69]. Besides, some researchers found that low-dose BPA exposure induced the accumulation of abnormal chromosomes and meiotic DNA double-strand breaks in the late meiotic stage [70].

Epidemiological data showed that occupationally exposed men from four regions in China and infertility patients recruited from the United States clinics all presented higher urinary BPA levels, which were associated with decreased sperm count and motility. Lassen et al. measured urinary BPA concentrations in 308 young men from the general population and revealed that men in the highest quartile of BPA had significantly lower percentage progressive motile spermatozoa compared with men in the lowest quartile (−6.7%, 95% *CI*: −11.76, −1.63) [71]. Goldstone et al. found that a negative relationship between BPA and DNA fragmentation was the sole significant finding in adjusted linear regression ($\beta = -0.0544$, $P = 0.035$), which suggested less sperm DNA damage. But no evidence that BPA diminishes semen quality was shown in this cohort [72]. Buck Louis et al. found that neither female nor male BPA concentration was associated with time to pregnancy with the OR 0.98(95% CI, 0.86, 1.13) and 1.04 (95% CI, 0.91, 1.18), respectively, by longitudinal investigation of fertility and the environment (LIFE) study [73]. Dodge et al. also showed no significant association between BPA exposure and fertilization or live birth following in vitro fertilization for the first time [74]. Overall, most of the above studies suggest that high exposure to BPA may affect the quality of male sperm, especially decreased sperm motility and forward movement, but no association with other semen quality parameters. However, there is still no strong evidence that BPA exposure can result in infertility.

3.2 BPA Exposure and Female Reproductive Health

The effects of BPA on female reproductive health include ovarian follicle production and quality, female sex steroid hormone levels, ovarian and uterine function and related diseases, abnormal pregnancy outcomes such as time-to-pregnancy, spontaneous abortion, recurrent pregnancy loss endometrium, mammary gland development, and other reproductive tract related diseases. Here, we focus on the impact of BPA on female follicle count, sex steroid hormone levels, and reproductive organ diseases.

3.2.1 BPA Exposure and Ovarian Follicle Number and Quality

Follicle numbers and sex steroid hormone production are required for female fertility.

The effects of BPA exposure on follicular production, maturation, and fertility have been studied by many in vitro and in vivo experiments. BPA reduced ovarian weight and increased the number of multi-oocyte follicles of neonatally exposed lambs, and similar results also were found in macaques [61]. Furthermore, in the in vitro study, Wang et al. showed a decrease in maturation rate when porcine oocytes were exposed to BPA at a dose of 250 μmol/L. [75] Nakano et al. reported that BPA exposure at the dose of 2 μg/mL decreased the maturation rate in ICR mouse oocytes [76]. Besides, results from the Consortium Linking Academic and Regulatory Insights on BPA Toxicity study of the United States showed that BPA exposure at some doses and time points altered follicle numbers and hormone production in female rats [77]. The data mentioned above provide convincing evidence that BPA exposure affects oocyte quality, number, maturation, and induce meiotic arrest of oocytes.

Prospective cohort studies proved that the higher the concentration of BPA in urine, the less the total number of oocytes, mature oocytes, and follicles were normally fertilized, suggesting that BPA can damage the production, maturation and fertilization of oocytes, and reduce the success rate of in vitro fertilization [78, 79].

3.2.2 BPA Exposure and Sex Steroid Hormones

Both epidemiological studies and animal experiments have analyzed associations between BPA exposure and sex steroid hormones such as E2, progesterone(P4), T, and FSH, but the results are not consistent.

The InCHIANTI adult population study showed that BPA exposure was related to changes in estradiol or testosterone levels in women [80]. Lee et al. found urinary BPA levels were associated with higher levels of T, E2, and P4 among individuals with high levels of BPA in Korean girls with precocious puberty. Miao et al. showed that urinary BPA concentrations were positively associated with higher prolactin

(PRL), E2, and P4 levels and a statistically significant inverse association between urinary BPA and FSH in Chinese female workers with occupational BPA exposure [81]. In the United States, BPA was associated with higher total T levels in female adolescents based on the National Health and Nutrition Examination Survey (NHANES) conducted between 2011 and 2012 [82]. Overall, despite the inconsistencies across studies, most of the studies have indicated that BPA levels are associated with alterations of hormone levels in females.

In vivo and in vitro studies confirm that BPA exposure affects sex steroid hormones, including testosterone, progesterone, luteinizing hormone, FHS, and E2. However, its effects vary by animal species, strain, exposure route, and exposure window in vivo, while in vitro studies have indicated that BPA has adverse effects on steroidogenesis [61].

3.2.3 BPA Exposure and Endometriosis

Endometriosis is a gynecological disorder characterized by endometrial glands and stroma that grow outside the uterine cavity. As mentioned above, BPA exposure is associated with E2, indicating that BPA may be involved in the occurrence of estrogen-dependent pathologies. However, the conclusions regarding bisphenol A and endometriosis are not consistent. Cobellis et al. suggested that BPA concentration had an association with the occurrence of endometriosis, but no association between urinary BPA and endometriosis was found by Buck Louis et al. and Itoh et al. [83, 84] Epidemiological studies on BPA and endometriosis are limited and the results are inconsistent, and therefore future studies are needed to elucidate the association between chronic BPA exposure and uterine morphology alterations in the general population.

Polycystic ovary syndrome (PCOS) is a hormonal disorder common among women of reproductive age. Women with PCOS may have infrequent or prolonged menstrual periods or excess male hormone (androgen) levels and can lead to infertility in severe cases. Hu et al. showed that serum BPA may be positively associated with women with PCOS and BPA might be involved in the insulin-resistance and hyperandrogenism of PCOS by a systematic review and meta-analysis [85]. Kandaraki et al. showed higher BPA levels in PCOS women compared to controls and a statistically significant positive association between androgens and BPA, suggesting a potential role of this endocrine disruptor in PCOS pathophysiology [86].

Studies have provided compelling evidence indicating that BPA can adversely affect the uterine both in vivo and in vitro, though the assessment endpoints vary across studies. Signorile et al. and Retha et al. reported that low-dose BPA exposure before pregnancy could induce endometrial polyps and benign or malignant lesions in the uterus of adult mice and effected the Wölffian duct at the same time [87]. Kendziorski and his colleagues found that low-dose BPA exposure of CD-1 mice increased gland nest density, peri-glandular collagen accumulation, and abnormal endometrial epithelial and stromal functions [88].

There are also many other studies on the association between BPA exposure and reproductive organ diseases such as ovarian cancer, breast cancer, and so on. However, most studies are simply correlation analysis, lacking more convincing prospective cohort studies and in-depth mechanisms.

3.2.4 Prenatal Exposure to BPA and Adverse Birth Outcomes

A growing body of evidence from animal studies and humans confirmed that prenatal BPA exposure may be also associated with adverse birth outcomes such as recurrent miscarriage, preterm birth, and decreased birth weight. Lathi RB et al. showed that maternal conjugated BPA exposure was associated with a higher risk of aneuploid and euploid miscarriage [89]. Similar findings were also observed by a study from China [90]. However, a study from *Environmental Health Perspectives* did not show the statistical associations [91]. The relationship between BPA exposure and miscarriage should be confirmed in much more human studies in the future. Researches about BPA exposure and preterm birth or other outcomes also showed similar uncertainties [92]. All in all, the actual impact of BPA exposure on birth outcomes remains unclear untill the present moment.

4 Conclusions

In summary, a large number of studies have been conducted on the effects of phthalate and BPA exposure on male and female reproductive health. In general, both endocrine disruptors have a certain impact on reproductive health, but some results are still controversial. At present, problems in many epidemiological studies are yet to be solved. First, assessments of phthalate and BPA exposure at a single time point cannot represent the true exposure of individuals. Second, most of the studies explore the effects of individual environmental endocrine disruptors on reproductive health, which do not well demonstrate the causality between exposure and outcome. Lastly, the biological samples used to detect exposure to phthalates and BPA are inconsistent, which lead to inability to compare results among different studies. In the future, it is recommended to carry out large-scale prospective epidemiological cohort studies on the effects of BPA exposure on reproductive health and strictly standardize study design and the selection criteria of study subjects.

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