Bisphenol A as a potential hazardous compound on male reproductive function : A mini-review

Review Article

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ABSTRACT

Background: Male factor infertility contributes for ~50% of the overall cases of infertility. Several causes have been attributed to male factor infertility,which may be pre-testicular, testicular, or post-testicular factors. Exposure to gonadotoxins is nowadays an increasing etiology of male factor infertility,at either the environmental or occupational levels. One of the commonly encountered gonadotoxins is bisphenol A, a xenoestrogen that carries a potential risk on male fertility potential at various levels in several animal species and humans, thus negatively affecting the reproductive capacity (i.e. Spermatogenesis and steroidogenesis) as well as deteriorating sperm quality and functions. Besides that, growing evidence has shown that it may carry a hazardous risk that may lead to other health problems and diseases, such as diabetes, obesity, thyroid dysfunction, cardiovascular diseases, and cancer. Hereby, we focus on the negative effect of bisphenol A exposure on male reproductive function with an up-to-date review of literature.

Key Words: Bisphenol A, endocrine disruptors, male infertility, sperm functions, xenoestrogens.

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INTRODUCTION

Infertility is defined as the inability of sexually active and noncontracepting couples to achieve spontaneous conception within one-year duration. It affects 10–15% of couples around the world and ~50% of infertility cases are attributed to male factors[1]. Male factor infertility may be due to pretesticular (at the level of hypothalamus or pituitary gland), testicular, or post-testicular causes[2]. Among the causes of male factor infertility is the exposure to gonadotoxins,owing to either environmental or occupational biohazards such as heavy metals, chemicals with estrogenic properties (Xenoestrogens), pesticides,and various organic solvents that may negatively affectthe hypothalamo–pituitary–gonadal axis as well as sperm functions and DNA integrity[3].

Bisphenol A (BPA) is one of the endocrine disruptors of the xenoestrogen family that possess a chemical structure similar to estrogens, thus it may interact with estrogen receptors and act as an agonist or antagonist via endocrine receptor (ER)-dependent signaling pathways[4]. It is commonly encountered owing to the wide use in several industries, especially plastics to make them shiny, flexible, and durable. It may enter the human body mainly via several routes such as consuming contaminated food and drinking water, although exposure via environmental (from polluted air and water), domestic (household products and cosmetics), medical (from contaminated equipment and devices), and occupational sources (inhalation, dermal contact, and ingestion during manufacturing processes or industrial use) also occurs[5].

Several studies have reported the potential risk (BPA) exposure and various health hazards in different animal species as well as humans. Health risks owing to BPA exposure may include several endocrine disorders including female and male infertility, precocious puberty, polycystic ovary syndrome (PCOS), hormone-dependent tumors such as breast, ovarian,and prostate cancer and several others, as well as metabolic disorders including diabetes mellitus and thyroid dysfunction[6].

Chemistry of bisphenol A

BPA is an organic synthetic compoundthat belongs to the group of diphenylmethane derivatives with the chemical structure (CH3)2C(C6H4OH)2. It is characterized as colorless crystalline solid particles with an estimated molecular weight of 228.291g/mol and a boiling point of 360.5°C at 760 mmHg. In the 18th century, the Russian chemist Aleksandr P. Diani had synthesized BPA by

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combining phenol with acetone in the presence of an acid catalyst. Later on, scientists discovered that the reaction of BPA with phosgene (carbonyl chloride) produced a clear hard resin known as polycarbonate, which have been widely used in the manufacture of plastics since 1950[10].

Sources of bisphenol A

BPA is a commonly used compound in the industry of plastics, primarily certain polycarbonates and epoxy resins, as well as some polysulfones.In 2008, it was estimated that the total world production of BPA was ~5.2 million tons, and USA was ranked as world's largest producers, contributing with ~22.9% of global production[11]. BPA-based plastic is characterized by being clear and tough and is made into a variety of house-hold utensils, such as plastic water bottles, sports equipment, CDs, and DVDs. Additionally, epoxy resins containing BPA are used to line water pipes, as coatings on the inside of many food and beverage cans, and in making thermal paper as that used in sales receipts. Besides that, it is commonly used in dental materials, particularly in the form of bis-GMA (BPA-glycidyl methacrylate). It was found that this compound could be released from the dental fillings, sealants, or materials used to rebuild the crown of the tooth[12].

Human exposure to bisphenol A

Owing to the widespread use of BPA in the manufacturing of plastics, which is incorporated in our daily uses. Its exposure is considered to be inevitable through various routes such as oral, by inhalation, and transdermal. However, exposure in the general population comes primarily from oral consumption of food and beverages.The latest national survey by the Centers for Disease Control and Prevention found BPA in the urine of more than 90% of the people studied, and among these people, the highest average concentrations were found in children[13]. In addition, BPA has been found in human breast milk; however, several reports have mentioned that infants who are formula-fed have higher daily BPA intake levels than those who are breastfed, because there is more BPA in infant formula than in breast milk, as BPA may be excessively released from baby bottles that are used for formula feeding, especially if the bottles are heated[14].

Recently, scientists have concluded that sources of exposure to BPA other than food may be important. For example, there have been calls for assessments of human exposure from other FDA-regulated products such as drugs and medical devices. Some are concerned about medical devices, such as contact lenses, probes, inhalers, intravenous cannulas, catheters, neonatal incubators or hemodialysis apparatus that could release the chemical into tissues, and in particular, the possible health effects of such exposures in critically ill patients and in whom such products may be used for long periods of time[15,16]. On the contrary, several studies indicated that skin contact with BPA in thermal paper coatings (e.g. the paper used for cash register receipts) may contribute significantly to human exposure[17]. Moreover, some studies have concluded that BPA can be transmitted through the inhalation of dust from laminate flooring, adhesives containing epoxy resins, paints, and household electronic equipment. However, exposure through dust was estimated to be less than 5% of the total exposure to BPA. Exposure resulting from polluted air is less than 0.4ng/kg body weight per day in adults, whereas in infants, it is estimated to be 5.3ng/kg of body weight per day[18].

Health hazards related to bisphenol A exposure

Despite the occupational and environmental exposure to BPA, limited studies have been conducted on health hazards related to exposure. Several reports have shown that chronic exposure to BPA was related to pathogenesis of several disorders.

Bisphenol A and hormone-dependent tumors

Owingto the xenoestrogenic properties of BPA, several studies suggested that prolonged exposure to BPA could predispose to the development of hormone-dependent tumors such as prostate and testicular cancersin males and breast, uterine, and ovarian cancer in females via nuclear estrogen receptor (ER-α and ER-β) as well as trans-membrane G protein-coupled receptor 30 (GPR30) receptor signaling pathway that leads to genetic and epigenetic alterations with subsequent defective gene expression. However, the exact molecular mechanisms by which BPA could lead to the initiation and the progression are still obscure[19,20].

Bisphenol A and metabolic disorders

Obesity and metabolic syndrome are commonly related to each other. A few studies have reported a correlation between BPA exposure and the occurrence of obesity and metabolic syndrome owing to estrogenic effects as well as impaired glucose tolerance and disturbed lipid metabolism[21]. In addition, some studies suggested that chronic BPA exposure was associated with increased cardiovascular metabolic risks especially in children and adolescents[22]. In the same context, a few studies have suggested that BPA could play a role in development of diabetes by various mechanisms, such as disturbed insulin secretion from the pancreas, increased insulin resistance, impaired glucose tolerance, as well as inducing autoimmune response destroying the secretory cells of islets of Langerhans, thus leading to diabetes especially type I diabetes in genetically predisposed children owing to either prenatal maternal exposure or through breast milk feeding; however, scarce data are present to support those findings[23,24]. On the contrary, BPA could lead to thyroid dysfunction; however, the exact etiopathogenesis is still

controversial, including direct effect on thyroid follicular cells, inhibition of T3/T4 synthesis pathways, suppression of thyroid hormone receptor transcription, as well as inducing autoimmune affection of the thyroid follicles[25–27].

Bisphenol A and precocious puberty

Many studies have observed an increasing incidence for the occurrence of earlier onset of puberty and have disclosed an increasing number of children who display precocious puberty. Several theories tried to explain the pathogenesis of precocious puberty among boys and girls; however, none of them are definitive. One of the hypotheses is prenatal and early developmental exposure to endocrinal disruptors, including BPA. Notably, the exact mechanism underlying its activity as a puberty disruptor is not clear;however, it could beowing to its potential estrogenic activity through the positive feedback mechanism that renders the activity of the GnRH pulse generator, with subsequent early release of pituitary gonadotropins (luteinizing hormone and follicle-stimulating hormone)[28].

Bisphenol A and polycystic ovarian disease in females

PCOS is a common endocrinal disorder among women of child-bearing age owingto hyperandrogenism characterized by obesity, hirsutism, acne, menstrual irregularities, infertility, as well as polycystic ovaries by ultrasound PCOS. The exact etiology of PCO is still controversial and complex. Prepubertal exposure to BPA has been proposed to be a cause of PCO owingto its endocrinal disrupting nature. The exact pathogenesis by which BPA can cause this syndrome is still obscure; however, it has been postulated that it may induce the activation of the hypothalamic GnRH pulse generator, leading to a constant increase of plasma luteinizing hormone concentrations, which in turn stimulate the ovarian androgen production and impair proper ovarian follicle development. In addition, BPA has been shown to directly increase ovarian androgen synthesis[29,30].

Effects of bisphenol A on male reproductive function

Effects of inutero exposure to bisphenol A on male reproductive development

Few studies have been conducted to verify the harmful effect of in utero exposure to BPA, and almost all of these studies showed its effect on animal models such as mice. It was found that BPA exposure could have a negative effect on the sexual development of male fetus and may cause a feminizing effect owingto disturbed embryogenesis concerning male internal and external genitalia. Several mechanisms have been postulated trying to verify the feminizing effect of in utero exposure of BPA, including binding to ERs, inhibition of androgen-induced androgen receptor transcriptional activity, and androgen binding to androgen receptor. Recently, some studies suggested an additional mechanism of action of BPA via non-genomic pathway that could be initiated at membrane receptors,including classical ERs and/or GPR30. In the same context, it could prevent AMH action on the Müllerian ducts in the male, leading to the feminization of male fetus. This could be triggered by upregulation of genes required for ovary development (Foxl2 and Wnt4), with simultaneous down-regulation of genes responsible for testis development (Sox9 and Fgf9) in the embryo, therefore increasing incidence of disorders of sexual development[31,32].

Effects of bisphenol A on spermatogenesis and sperm functions

Spermatogenesis is the process of sperm formation starting from the spermatogonial cells up to mature sperm in the seminiferous tubules under the hormonal influence of the hypothalamo–pituitary–testicular axis. BPA could alter spermatogenesis via several mechanisms, including its estrogenic and antiandrogenic properties, alteration of GnRH release from the hypothalamus with subsequent decrease in gonadotropin release, accumulation of ROS, induction of spermatogonial apoptosis, as well as direct toxic effect on spermatogenic cells and Leydig cells. In addition, it was found that BPA could increase expression and production of sex hormone-binding globulin, thus decrease the free bioavailable testosterone with subsequent impairment of spermatogenesis[33–35].

Concerning the effect of BPA on sperm functions, it has been suggested that BPA increases ROS production, increases sperm DNA fragmentation, leads to alteration of sperm motility via disruption of mitochondrial ATP synthesis, leads to interruption of cell membrane integrity via increased lipid peroxidation, as well as leads to induction of apoptosis via activation of caspases(cysteine-aspartic proteases, cysteine aspartases, or cysteine-dependent aspartate-directed proteases)-induced intrinsic and extrinsic pathways[36–38]. However, all of them are still theoretical hypothesis,and further researches should be conducted trying to confirm these postulations. The end result is alteration of sperm parameters as well as impairment of spermatogenesis leading to reduction of fertilization ability, predisposition to infertility, and increased incidence of miscarriages.

Effects of bisphenol A on accessory reproductive organs

Male accessory glands (MAGs) play an important role in seminal fluid secretion, through production of buffers and micronutrients in semen that are essential for sperm motility and vitality to survive in the female reproductive tract as well as promoting the sperm fertilization ability. Very limited research studies have been conducted to assess the harmful effect of BPA on MAGs; besides that, all

of them were conducted on animal models. They showed that BPA had a deleterious effect on MAGs secretory functions as well as reduction of the size of testis, seminal vesicle,and epididymal volumes up to atrophy,which is evident by alterations of histopathology[39–41]. On contrary, it has been found that BPA leads to prostatic enlargement; moreover, malignant changes to the adenocarcinoma could be encountered. These mitogenic effects in the prostatic gland have been confirmed by invitro and invivo studies[42].

CONCLUSION

BPA is a commonly encountered environmental contaminant, resulting mainly from the manufacturing, use, and disposal of plastics and related products. Several reports have mentioned that it could have negative effect on both animals and human subjects on various body systems. Moreover, BPA end products were found to have an endocrinal disrupting property by its xenoestrogenic effect; thus, it could adversely affect male reproductive function. Up till now, all recommendations point at minimizing the use and exposure to BPA and its related products, besides shifting toward less biohazardous compounds in the industry of plastics. In addition, many countries have reinforced laws against the use of BPA owingto its deleterious effects on both animals and humans.

CONFLICTS OF INTEREST

Thre are no conflicts of interest.

REFERENCES

1. WHO. WHO Manual for the Standardized Investigation and Diagnosis of the Infertile Couple. Cambridge: Cambridge University Press; 2000.

2. Jungwirth A, Giwercman A, Tournaye H, Diemer T, Kopa Z, Dohle G, Krausz C; European Association of Urology Working Group on Male Infertility. European Association of Urology guidelines on Male Infertility: the 2012 update. Eur Urol. 2012. 62(2):324-332.

3. GraciaC, SammelM, CoutifarisC, GuzickD, BarnhartK. Environmental exposures and male infertility. Fertil Steril2004; 82:S177.

4. ShafeiA, RamzyM, HegazyA, HussenyA, EL-hadaryU, TahaM, MosaA.The molecular mechanisms of action of the endocrine disrupting chemical bisphenol A in the development of cancer. Gene2018; 647:235–243.

5. VandenbergL, HuntP, MyersJ, Vom SaalF. Human exposures to bisphenol A: mismatches between data and assumptions. Rev Environ Health 2013;28:37–58.

6. Konieczna A, Rutkowska A, Rachoń D. Health risk of exposure to Bisphenol A (BPA). Rocz Panstw Zakl Hig2015; 66:5–11.

7. BarbonettiA, CastelliniC, Di GiammarcoN, SantilliG, FrancavillaS, FrancavillaF.In vitro exposure of human spermatozoa to bisphenol A induces pro-oxidative/apoptotic mitochondrial dysfunction. Reprod Toxicol2016; 66:61–67.

8. Mínguez-AlarcónL, HauserR, GaskinsA. Effects of bisphenol A on male and couple reproductive health: a review. Fertil Steril2016; 106:864–870.

9. Zheng H, Zhou X, Li DK, Yang F, Pan H, Li T, *et al.* Genome-wide alteration in DNA hydroxymethylation in the sperm from bisphenol A-exposed men. PLoS One. 2017 Jun 5;12(6):e0178535.

10. PivnenkoK, PedersenGA, ErikssonE, AstrupTF. Bisphenol A and its structural analogues in household waste paper. Waste Manage2015; 44:39–47.

11. CorralesJ, KristofcoL, SteeleW, YatesB, BreedC, WilliamsE, BrooksB. Global assessment of bisphenol A in the environment: review and analysis of its occurrence and bioaccumulation. DoseResponse2015; 13:1–29.

12. FleischA, SheffieldP, ChinnC, EdelsteinB, LandriganP.Bisphenol A and related compounds in dental materials. Pediatrics2010; 126:760–768.

13. Centers for Disease Control and Prevention. National Center for Environmental Health. Atlanta, GA: Fourth National Report on Human Exposure to Environmental Chemicals, Executive Summary; 2009. 3.

14. Lee J, Choi K, Park J, Moon HB, Choi G, Lee JJ, *et al.* Bisphenol A distribution in serum, urine, placenta, breast milk, and umbilical cord serum in a birth panel of mother-neonate pairs. Sci Total Environ. 2018 (1);626:1494-1501..

15. YamasakiH, NagakeY, MakinoH. Determination of Bisphenol A in effluents of hemodialyzers. Nephron2001; 88:376–378.

16. CalafatA, WeuveJ, YeX, JiaL, HuH, Ringer S, *et al.* Exposure to bisphenol A and other phenols

in neonatal intensive care unit premature infants. Environ Health Perspect2009; 117:639–644.

17. BiedermannS, TschudinP, GrobK. Transfer of bisphenol A from thermal printer paper to the skin. Anal Bioanal Chem2010; 398:571–576.

18. LoganathanS, KannanK. Occurrence of bisphenol A in indoor dust from two locations in the eastern United States and implications for human exposures. Arch Environ Contamin Toxicol2011; 61:68–73.

19. GaoH, YangB, LiN, FengL, ShiX, ZhaoW, LiuS. Bisphenol A and hormone-associated cancers. Medicine2015; 94:e211.

20. SeachristD, BonkK, HoS, PrinsG, SotoA, KeriR.A review of the carcinogenic potential of bisphenol A. Reprod Toxicol2016; 59:167–182.

21. Tang-PéronardJ, AndersenH, JensenT, HeitmannB. Endocrine-disrupting chemicals and obesity development in humans: a review. Obes Rev 2011; 12:622–636.

22. Amin MM, Ebrahim K, Hashemi M, Shoshtari-Yeganeh B, Rafiei N, Mansourian M, Kelishadi R. Association of exposure to Bisphenol A with obesity and cardiometabolic risk factors in children and adolescents. Int J Environ Health Res. 2019; 29(1):94-106.

23. XuJ, HuangG, GuoT.Developmental bisphenol A exposure modulates immune-related diseases. Toxics2016; 4:23.

24. LindP, LindL.Endocrine-disrupting chemicals and risk of diabetes: an evidence-based review. Diabetologia2018; 61:1495–1502.

25. ShengZ, TangY, LiuY, YuanY, ZhaoB, ChaoX, ZhuB. Low concentrations of bisphenol a suppress thyroid hormone receptor transcription through a nongenomic mechanism. Toxicol Appl Pharmacol2012; 259:133–142.

26. Andrianou XD, Gängler S, Piciu A, Charisiadis P, Zira C, Aristidou K, *et al.* Human Exposures to Bisphenol A, Bisphenol F and Chlorinated Bisphenol A Derivatives and Thyroid Function. PLoS One. 2016; 26;11(10):e0155237.

27. Chailurkit L, Aekplakorn W, Ongphiphadhanakul B. The association of serum bisphenol A with thyroid autoimmunity. Int J Environ Res Pub Health 2016; 13:1153.

28. LeonardiA, CofiniM, RiganteD, LucchettiL, CipollaC, PentaL, EspositoS. The effect of bisphenol A on puberty: a critical review of the medical literature. Int J Environ Res Pub Health 2017; 14:1044.

29. WilsonC. Bisphenol A and PCOS. Nat Rev Endocrinol 2011; 7:187–187.

30. ZhouW, FangF, ZhuW, ChenZ, DuY, ZhangJ. Bisphenol A and ovarian reserve among infertile women with polycystic ovarian syndrome. Int J Environ Res Pub Health2016; 14:18.

31. LaRoccaJ, BoyajianA, BrownC, SmithS, HixonM. Effects of in utero exposure to Bisphenol A or diethylstilbestrol on the adult male reproductive system. Birth Defect Res2011; 92:526–533.

32. JorgensenEM, AldermanMH, TaylorHS. Preferential epigenetic programming of estrogen response after in utero xenoestrogen (bisphenol-A) exposure. FASEB J2016; 30:3194–3201.

33. Lassen TH, Frederiksen H, Jensen TK, Petersen JH, Joensen UN, Main KM, *et al.* Urinary bisphenol A levels in young men: association with reproductive hormones and semen quality. Environ Health Perspect. 2014; 122(5):478-84.

34. ManfoF, JubendradassR, NantiaE, MoundipaP, MathurP.Adverse effects of bisphenol A on male reproductive function. Rev Environ Contam Toxicol2014; 228:57–82.

35. BaeJ, KimS, KannanK, Buck LouisGM.Couples' urinary bisphenol A and phthalate metabolite concentrations and the secondary sex ratio. EnvironRes2015; 137:450.

36. Li DK, Zhou Z, Miao M, He Y, Wang J, Ferber J, *et al.* Urine bisphenol-A (BPA) level in relation to semen quality. Fertil Steril. 2011; 95(2):625-30.e1-4.

37. MeekerJD, YangT, YeX, CalafatAM, HauserR. Urinary concentrations of parabens and serum hormone levels, semen quality parameters, and sperm DNA damage. Environ Health Perspect 2011; 119:252–257.

38. SrivastavaS, GuptaP. Alteration in apoptotic rate of testicular cells and sperms following administration of Bisphenol A (BPA) in Wistar albino rats. Environ Sci Pollut Res2018; 25:21635–21643.

39. ChitraK, RaoK, MathurP.Effect of bisphenol A

and co-administration of bisphenol A and vitamin C on epididymis of adult rats: a histological and biochemical study. Asian J Androl2003;5:203–208.

40. El-BassounyD, HindawyM. The adverse effects of bisphenol 'A' on some reproductive organs of the male albino rat. Egypt J Histol2013; 36:564–578.

41. Cariati F, D'Uonno N, Borrillo F, Iervolino S, Galdiero G, Tomaiuolo R. "Bisphenol a: an emerging threat to male fertility". Reprod Biol Endocrinol. 2019; 20;17(1):6.

42. Tomza-Marciniak A, Stępkowska P, Kuba J, PilarczykB.Effect of bisphenol A on reproductive processes: a review of in vitro, in vivo and epidemiological studies. J Appl Toxicol 2017; 38:51–80.