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Mini Review

Corresponding author
Hongjie Fan, PhD
Department of Obstetrics and Gynaecology, Li Ka Shing Faculty of Medicine, The University of Hong Kong Hong Kong SAR, China
Tel. +85239179378
Fax: +85228161947
E-mail: u30030120@connect.hku.hk

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Bisphenol Compounds on Human Reproduction Health

Hongjie Fan, PhD[1*]; Kai-Fai Lee, PhD[1,2]

[1]Department of Obstetrics and Gynaecology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

[2]Shen Zhen Key Laboratory of Fertility Regulation, The University of Hong Kong-Shenzhen Hospital, Haiyuan 1st Road, Futian District, Shenzhen, 518053, China

ABSTRACT

Bisphenol-A (BPA) is widely used in the plastic industry, and it is one of the well-studied endocrine disrupting chemicals (EDCs). Growing evidence raised the concern of BPA having weak estrogenic activity on human health including female reproductive functions and diseases. Serum BPA level is also associated with pregnancy loss, reproductive tract diseases and infertility. In fact, several countries restricted the use of BPA, and therefore substitutes which share similar chemical and physical properties with BPA were used. However, the effects of these bisphenols (e.g. bisphenol-F (BPF) and bisphenol-S (BPS)) on human reproductive health have not been fully investigated, and this mini-review summarized the recent data of these bisphenols on human reproductive health, and raise the concern on the safety and transgenerational effect of these bisphenols in humans.

KEY WORDS: Bisphenol-A; Bisphenol-F; Bisphenol-S; Pregnancy; Reproduction.

ABBREVIATIONS: BPA: Bisphenol-A; EDCs: Endocrine Disrupting Chemicals; PCOS: Poly-Cystic Ovary Syndrome; RSA: Recurrent Spontaneous Abortion; AFC: Antral Follicle Count; ERα: Estrogen receptor α; ERβ: Estrogen Receptor β.

INTRODUCTION

Endocrine disrupting chemicals (EDCs) are various chemicals mimicking hormones present in the body, and they bind and act through hormone receptors to modulate the functions of endocrine systems. In human, the target of EDCs in endocrine system include thyroid, pituitary, adrenal, mammary glands, ovaries, uterus in female, and prostate and testes in male.[1] EDCs with different hormone-like activities have diverse effect on endocrine systems,[2-4] which could be classified into persistent and non-persistent groups depending on their biodegradation and bioaccumulation properties (Table 1).

In various EDCs, bisphenol-A (BPA) is one of the well-studied chemical that might affect human health. Bisphenol compounds are a group of chemicals with two hydroxyphenyl groups, and most of which contains diphenylmethane structure. The naming of each bisphenol chemical is based on the reactant linking two hydroxyphenyls. For example, bisphenol-A has acetone as a bridge linking two phenols. As a result, bisphenol compounds share very simi-

Figure 1: Chemical Structures of Bisphenol Compounds.

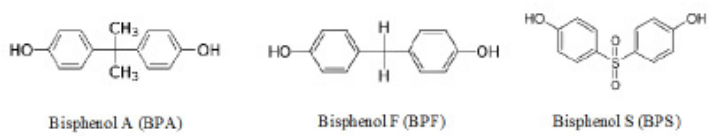

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Table 1: Main EDCs and their Effects in Endocrine Systems.

EDCs	Major hormonal effect	Endocrine effect
Persistent organic pollutants		
Polychlorobiphenyls (PCBs)	Thyroid	Alter ovarian steroidogenesis, oocyte development, reduce semen quality, learning disability, thyroid cancer, hypertension, diabetes
dichlorodiphenyltrichloroethane (DDT)	Estrogen	Reduced fertility, spontaneous abortion, type 2 diabetes, breast cancer, reduced bone mineral density
Dioxins	Anti-androgen	Alter steroid hormone metabolism, reduce semen quality, auto-immune disease, diabetes, breast/liver/ lung cancer, cancer mortality
Non-persistent organic pollutants		
Bisphenol A (BPA)	Estrogen	Alter steroidogenesis, reduced female and male fertility, reduced birth weight, asthma, increased children anxiety/depression, type 2 diabetes, breast/prostate cancer, obesity, hypertension
Phthalates	Estrogen	Reduced sperm quality and female fertility, endometriosis, preterm birth, pubertal delay, autoimmune disease, children abnormal behaviors
Isoflavones	Estrogen	Alter steroid hormone metabolism, autoimmune disease, increase bone mineral density, reduce prostate/breast cancer, anti-diabetes effect

lar chemical structure, and the difference is the reactant in the middle (Figure 1).

Among these bisphenols, BPA is the most commonly used chemical nowadays. BPA is heat resistant and has good elasticity. It has been widely used as plastic monomer in the manufacture of polycarbonate plastics and epoxy resins since 1950. Over 6 billion pounds of BPA are produced every year for manufacturing of plastic products, such as plastic bags, paper bags, bottles, microwave box, dental sealants, coated tins, paintings. BPA was firstly found to have the estrogenic effect in 1936.[5] Humans are exposed to BPA through dietary intake, dermal contact, and inhalation.[6] Since 1999, BPA were detected in human blood, urine, serum and placental tissue.[7] In last two decades, serval lines of evidence suggest adverse effect of BPA on human health including obesity, diabetes, abnormal behavior, and female and male reproductive functions.[2,8,9]

BPA Levels During Pregnancy

BPA could be detected in the serum of non-pregnant women, and pregnant women at early and late gestational stage, as well as in the fetal cord serum and amniotic fluid (1-2 ng/mL). For amniotic fluid at 15-18 weeks gestation, there was a 5-fold increase in BPA level (8.3 ng/mL).[10] After delivery, the placental BPA level was higher (11.2 ng/g tissue) when compared to the maternal serum and umbilical cord blood collected from the same subjects,[11] suggesting that BPA could be accumulated at the maternal-fetal interface that might affect fetal development during the whole gestational period.

The association of BPA and pregnancy-associated diseases was reported in several studies. Serum BPA level was much higher in patients with polycystic ovary syndrome (PCOS) than normal female.[12] Higher BPA level in follicular fluid (440 pg/ml) was also observed in PCOS patients compared with non-PCOS patients (338 pg/mL).[13] Similarly, patients with history of unexplained recurrent spontaneous abortion (RSA) have a significantly higher serum BPA level than normal women.[14,15] In women undergoing *in vitro* fertilization (IVF), BPA could be detected in most of the cases, and the higher urinary BPA concentrations were found in patients with lower antral follicle count (AFC) and number of oocytes retrieved.[16,17] A positive association was also found between BPA urinary concentrations and implantation failure.[18] However, it was also reported that IVF outcomes and endometrial wall thickness were not associated with urinary BPA concentrations,[19] but the spontaneous preterm birth rate[20] and the risk of low birth weight[21] were associated with higher urine BPA levels. In patients with uterine leiomyoma, their urine and plasma BPA levels were not different from the control group,[22] and endometriosis was not associated with urinary BPA level in infertile Japanese population.[23]

Mechanism of BPA in Female Reproduction

As an estrogen-like EDC, the activity of BPA was found to be 100 to 10,000-fold lower than that of 17β-estradiol (E2).[24-26] Estrogen receptor α (ERα) and estrogen receptor β (ERβ), and a transmembrane ER called G protein-coupled receptor 30 (GPR30) are the main targets of BPA when it carries out its effect.[27,28] Most of mechanism studies of BPA was performed in *in vitro* and *in vivo* animal models. In human, endometrial adenocarcinoma cell line Ishikawa is response to BPA with many genes modulated.[29] Human primary endometrial cell proliferation was inhibited by BPA,[30,31] BPA also induced the expression of decidualization makers and several hormone related mol-

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ecules in endometrial stromal cells.[32-34] BPA induces apoptosis, necrosis and the tumor necrosis factor-alpha (TNF-α) expressions in the human primary placental cells and the first trimester human chorionic villous explant.[35,36] Cell migration and invasion of trophoblast cell line HTR-8/SVneo and BeWo was reduced by BPA.[37,38] More detailed mechanism of BPA in animal study was reviewed elsewhere.[9,39,40]

Very few evidence support the detrimental effect of BPA on ovarian function. As mentioned previously, it was found that follicular fluid has a very low BPA level (1-2 ng/ml).[10] BPA at supra-physiological level altered the progesterone and estradiol synthesis in luteinized granulosa cells and reduced the expression of steroidogenesis enzymes, such as 3 beta-hydroxysteroid dehydrogenase (3 beta-HSD), CYP11A1 and CYP19A1 *in vitro*.[41] Human oocytes cultured in medium containing BPA (20 ng/mL to 20 μg/mL) exhibited abnormal meiotic maturation, changed spindle morphology and delayed chromosome alignment.[42] In sum, the synthesis of hormones and development of oocyte *in vitro* were significantly affected by BPA.

Other Bisphenols and Female Reproductive Functions

Due to the public concern about the risk of BPA in endocrine related diseases and infertility problems, the usage of BPA has been restricted in some products especially baby bottles in some countries, including Norway, Denmark, Germany, France and USA.[43] Several chemicals with similar structures with BPA were used as substitutes, such as bisphenol-F (BPF) and bisphenol-S (BPS), which lack thorough safety investigations.[44] Similar to BPA, these bisphenols could bind to the C-terminal ligand-binding domain of estrogen receptor and exhibit similar or weaker estrogenic activity as BPA.[45,46]

BPA, BPF and BPS are detected in our environment including water from rivers, sewage sludge and indoor air.[47-49] Receipts, paper products, and many canned food and soft drinks were found to have BPS and BPF.[50-57] In USA, BPF and BPS were detected in most of the human urine samples, albeit less frequent and lower concentrations than BPA in the same sample.[58,59] Low concentration of BPS was detected in some serum samples of pregnant women and the cord blood of the sibling,[60] suggesting BPS could also cross the placenta. Importantly, BPA, BPF and BPS could also be detected in breast milk.[61]

There is no published report regarding the association of BPF or BPS level and diseases related to pregnancy in humans. The potential effect of these bisphenols in reproduction was based on *in vitro* and *in vivo* animal studies. In porcine, BPS affected meiotic division of the oocytes and the expression and distribution of ERβ, ERα and aromatase.[62] BPS reduced egg production and the gonadosomatic index (gonad weight/body weight) in zebrafish.[63] BPS and BPF increased the uterine weight in rats,[64] but another study did not find the same effect.[65] In fact, the estrogenic and androgenic activities of BPF and BPS were found to have similar order of magnitude and mechanic action as BPA.[66,67] BPF and BPS also have genotoxicity and mutagenicity as BPA.[44] Although, the evidence of BPF and BPS on female reproduction is limited, the activity and mechanism of these two bisphenols is quite similar to BPA, leading to the adverse effect of bisphenols on female reproductive health could not be ignored.

CONCLUSION

It is widely recognized that BPA is harmful to human health and female reproduction. Whether BPA at current low environmental level poses chronic and transgenerational effect remains unknown.[68] Several countries have issued regulations to ban on the usage of BPA in specific products, such as baby bottles. Other bisphenols with similar structure to BPA are used to replace BPA in manufacturing process. Although compiling evidence of these bisphenols on female reproductive functions are lacking, concern about the safety of these bisphenols in public should be raised.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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