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REVIEW ARTICLE

Demystifying Bisphenol A-Induced Alterations in Hypothalamic-Pituitary-Ovarian Functions Leading to Polycystic Ovarian Syndrome

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Abstract In recent decade, polycystic ovarian syndrome (PCOS) has become one of the main fertility disorders in females. Other than genetic factors, the etiology of this disease includes environmental factors, especially endocrine disrupting compounds (EDC). Bisphenol A (BPA) is a prominent EDC enormously used in manufacturing of various substances. Increased exposure to these substances on a daily basis throughout life, from prenatal to adult stages, has resulted in deleterious changes in female reproductive system. These changes include PCOS-like phenotypes such as hyperandrogenism, cystic ovaries and anovulation. Although studies in human are limited, several reports are available in animal models wherein BPA has been shown to directly affect ovarian development, folliculogenesis and steroidogenesis, thereby causing PCOS-like symptoms. Hypothalamus and pituitary are considered to be the most significant endocrine tissues involved in maintaining the structure and functions of ovary. BPA being an endocrine disruptor severely affects these tissues by modulating the synthesis and release of gonadotropin releasing hormone and gonadotropins from hypothalamus and pituitary, respectively. However, in light of reports available, effect of BPA on hypothalamus and pituitary do not corroborate with those on ovary. The current review suggests that BPA-induced PCOS-like phenotypes might be due to its direct action on ovary while alteration in hypothalamo-pituitary-ovarian axis seems to play a minor role. The authors through this review also intend to direct the attention of readers and policy makers towards the fact that despite the well-known negative effects of BPA exposure, manufacturing and use of BPA-containing substances is continuing, especially in developing countries.

Keywords Polycystic ovarian syndrome · Bisphenol A · HPO axis · GnRH · Gonadotropins · Sex steroids

Introduction

Polycystic ovarian syndrome (PCOS), a disorder resulting from the alteration of reproductive, endocrine and metabolic functions, is worldwide considered as the most common reproductive disorder in women of fertile age (Fenichel et al. 2017; Liu et al. 2021). In India, the occurrence of this disorder ranges from 3.7 to 22.5% and it has been observed that urban women have 0.1 times higher odds of developing the disorder than their rural counterparts (Ganie et al. 2019; Joshi et al. 2014; Gill et al. 2012; Bharathi et al. 2017). The prevalence of PCOS has been shown to be associated with obesity, type 2 diabetes, glucose tolerance, abdominal adiposity, cardiovascular diseases and lifestyle (Escobar-Morreale 2018). Since the clinical manifestations of this syndrome are diverse, there was a need to set a basis for its diagnosis. While in 1990, the National Institute of Health considered hyperandrogenism and ovulatory dysfunctions (including altered menstrual cycles) as the diagnostic parameters for PCOS, the Rotterdam criteria of 2003 added a third feature i.e., presence of polycystic ovarian morphology (Zawadski and Dunaif 1992; Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004). Currently, the clinical

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diagnosis is based on whether an individual meets at least two of the three above mentioned phenotypes. In recent years, in addition to genetic and metabolic determinants, the endocrine disrupting chemicals (EDCs) have emerged as major environmental factor in inducing PCOS. Various synthetic chemicals have been categorized under EDCs as these molecules have the capacity of mimicking the action of natural hormones and in turn causing endocrinopathy (Crisp et al. 1998). These range from commercial plasticisers (bisphenol A and pthalates), paints (tributyltin), drug ingredients (diethylstilbesterol) to polyhalogenated aromatic hydrocarbons used in pesticides and herbicides (biphenyls and dioxins) (Palioura and Diamanti-Kandarakis 2013; Rutkowska and Diamanti-Kandarakis 2016).

Among EDCs, bisphenol A or 2,2-Bis(4-hydroxyphenyl)propane (BPA) is an omnipresent molecule that mimics estrogenic action. It has been shown to adversely affect a wide range of female reproductive functions such as development of ovary and other reproductive tissues, menstrual/estrous cycle, folliculogenesis, ovarian steroidogenesis, ovulation, fertilization, implantation, and survival as well as development of zygote (Palioura and Diamanti-Kandarakis 2015; Pivonello et al. 2020). The link between BPA and PCOS has been largely drawn based on population studies wherein women with PCOS showed high serum and urinary BPA concentrations (Takeuchi et al. 2004; Hossein et al. 2017; Akin et al. 2015; Tarantino et al. 2013; Vahedi et al. 2016). To elucidate the specific role of BPA in causing PCOS, several in vivo, ex vivo and in vitro experiments have been conducted in animal models. These experiments have explicitly shown that BPA exposure causes structural and functional changes in the ovary similar to those observed in PCOS. Also, BPA alters secretion of gonadotropin releasing hormone (GnRH) and gonadotropins from hypothalamus and pituitary, respectively. However, BPA-induced changes at the level of ovary in most of the studies do not correspond with changes in hypothalamus and pituitary. The present review is aimed to answer whether BPA-induced PCOS-like changes in ovary is due to direct action or by altering hypothalamic-hypophyseal functions or both.

Bisphenol A: Routes of Exposure, Accumulation and Action

The endocrine disruptor BPA is a major constituent in food packaging materials, bottles, flame retardants, water supply tanks and pipes. BPA is capable of leaching into consumables such as food and water on exposure to heat (Vandenberg et al. 2007). Therefore, humans are exposed to it largely through food and water that accounts for almost 90% of the overall route of exposure (Geens et al. 2012). Intake of BPA can also occur through air or mere surface contact via exposure to BPA-containing non-dietary products such as aerosol, medical equipment, thermal paper, etc. (Abraham and Chakraborty 2020; Vahedi et al. 2016).

The metabolism and bioaccumulation of BPA has been schematically represented in Fig. 1. Liver is the main site for metabolism of BPA wherein enzymes uridine diphosphate glucuronosyltransferase and phenol sulfotransferase are reported to cause glucuronidation and sulfonation of the BPA molecule, respectively (Yokota et al. 1999; Pritchett et al. 2002). This conjugation process makes BPA hydrophilic and inactive, thus allowing its excretion via urine. The half-life of the conjugated BPA is $\sim$ 5.3 h (Völkel et al. 2002) which is sufficient enough to cause its deconjugation in tissues such as lung, liver, kidney and placenta by a critical enzyme beta-glucuronidase, thereby making the molecule active again. The active form of BPA gets released into the circulation leading to its bioaccumulation in certain tissues (Ginsberg and Rice 2009). For instance, it has been reported that fat accumulates approximately triple the amount of BPA than other tissues due to BPA's lipophilic nature (Csanády et al. 2002). Hence, tissues such as ovary that are surrounded by large amount of fat become more susceptible to being exposed to BPA (Fernandez et al. 2007) and is probably one of the main reason for pronounced deleterious effect of BPA on female reproduction than male reproduction.

Dodds and Lawson (1936) for the first time described the estrogenic property of BPA while investigating its role in maintenance of the vaginal estrus phase in ovariectomised rats. Competitive binding assays have shown that BPA binds to human estrogen receptors (ER) with lesser affinity as compared to 17β-estradiol (Chapin et al. 2008). This decrease in affinity is due to structural differences causing steric hindrance in attachment of BPA to the ligand binding domain of the ERs. BPA acts as estrogen agonist via ER alpha (ERα) (Ascenzi et al. 2006) and is capable to translate its effect through genomic as well as non-genomic pathways (Nadal et al. 2000). During non-genomic actions, BPA generally involves ERK/MAPK (extracellular regulated kinase/mitogen-activated protein kinase), PI3K-AKT (phosphatidylinositol 3-kinases - serine/threonine protein kinase) and cytoplasmic Ca^{2+}-dependent signalling pathways (Bolli et al. 2008; Marino et al. 2012). In addition to ERα, agonistic action of BPA is mediated through a non-classical estrogen receptor G protein-coupled receptor 30 following intracellular Ca^{2+} signalling mechanism (Alonso-Magdalena et al. 2005). Interestingly, BPA also acts as an antagonist to sex steroids when it binds to ER beta (ERβ) (Ascenzi et al. 2006) and androgen receptor (AR) (Xu et al. 2005; Wang et al. 2017). Other receptors employed by bisphenols are aryl hydrocarbon receptor (AHR), pregnane X receptor and peroxisome proliferator-

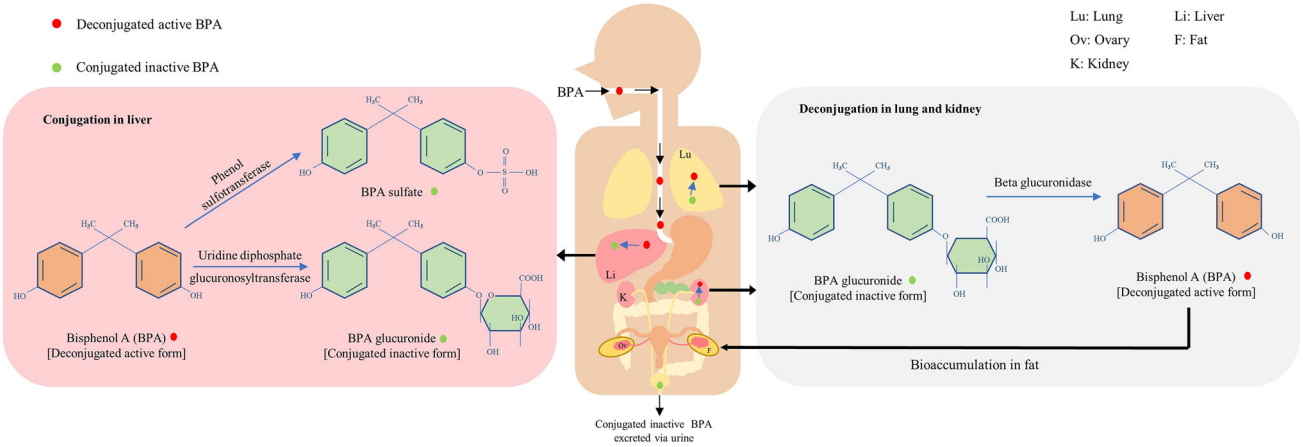

Fig. 1 Metabolism and bioaccumulation of bisphenol A (BPA) in human (schematic representation in a female body). BPA is converted into inactive form following conjugation in liver. This is catalysed by enzymes uridine diphosphate glucuronosyltransferase and phenol sulfotransferase. The conjugated BPA is either excreted out via urine or deconjugated by an enzyme beta-glucuronidase in various tissues, importantly lung and kidney. The deconjugated BPA which is active gets accumulated in fat

activated receptor (PPARγ) that are reported to inhibit follicle growth, induce hypercholesterolemia and cause proliferation of pre-adipocytes, respectively (Riu et al. 2011; Sui et al. 2012; Ziv-Gal et al. 2013; Boucher et al. 2014).

Based on a three generation study in rats, World Health Organization, Food and Drug Administration (2009) labelled the BPA dose of 5 mg/kg bw/day as 'No-observed-adverse-effect-level' (NOAEL), the highest concentration that has no adverse morphological effect. Thereafter, up to the dose of 50 mg BPA /kg bw/day has been considered as 'lowest-observed-adverse-effect-level' (LOAEL) by the United States Environmental Protection Agency (US EPA 2010). It is noteworthy to mention that several studies in animal models are now available that have shown the detrimental effects of BPA even at doses many times lower than NOAEL. The tolerable daily intake value for BPA has been deduced to be 0.05 mg/kg bw/day which is greater than the highest daily intake of BPA as seen in adolescents (European Food Safety Authority, EFSA 2015). However, such permissible levels do not take into account the cumulative effect that BPA has on the health of an individual exposed to it during its lifetime. Eventually, due to toxic nature of BPA, restriction has been imposed by developed nations on its use in various products with special emphasis on baby items (Ministry of Environment and Energy, MOEE 2012). In spite of toxic effect of BPA, it is still being used in India (Shrinithivihahshini et al. 2014) though policy has been formulated to prevent BPA usage (Mahamuni and Shrinithivihahshini 2017). In lieu of BPA, some alternative analogues such as BPS [bis-(4-hydroxyphenyl)sulfone] and BPF [4,4'-dihydroxydiphenyl methane] have been introduced worldwide. However, these molecules are also reported to have antiandrogenic, estrogenic and thyroidogenic actions (Rochester and Bolden 2015) and hence, their use is debatable.

Effect of BPA on Hypothalamo-Pituitary-Ovarian Axis

GnRH and Gonadotropins

The hypothalamo-pituitary axis plays pivotal role in regulating the female reproductive system. Gonadotropin releasing hormone (GnRH) released from hypothalamus in pulsatile manner is under the control of various endogenous factors, importantly kisspeptin (Oakley et al. 2009) which is secreted from neurons of anteroventral periventricular nucleus (AVPV) and arcuate nucleus (ARC) of brain (Fig. 2). Thereafter, GnRH stimulates the production and release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from gonadotrophs of anterior pituitary. Low frequency pulses of GnRH stimulate the synthesis and release of FSH while high frequency leads to production and release of LH (Ferris and Shupnik 2006). The gonadotropins in turn regulate the ovarian functions including folliculogenesis, steroidogenesis and ovulation. Estrogen produced from ovary regulates GnRH and gonadotropin secretion via feedback mechanisms, either directly at the level of hypothalamus and pituitary, or indirectly by regulating KISS production (Fig. 2).

The effect of BPA on secretion of KISS, GnRH and gonadotropins is summarized in Fig. 2. It has been shown that BPA increases the number of KISS1-secreting neurons of AVPV region (Naulé et al. 2014), and upregulates the expression of KISS1 mRNA and ERα protein in these

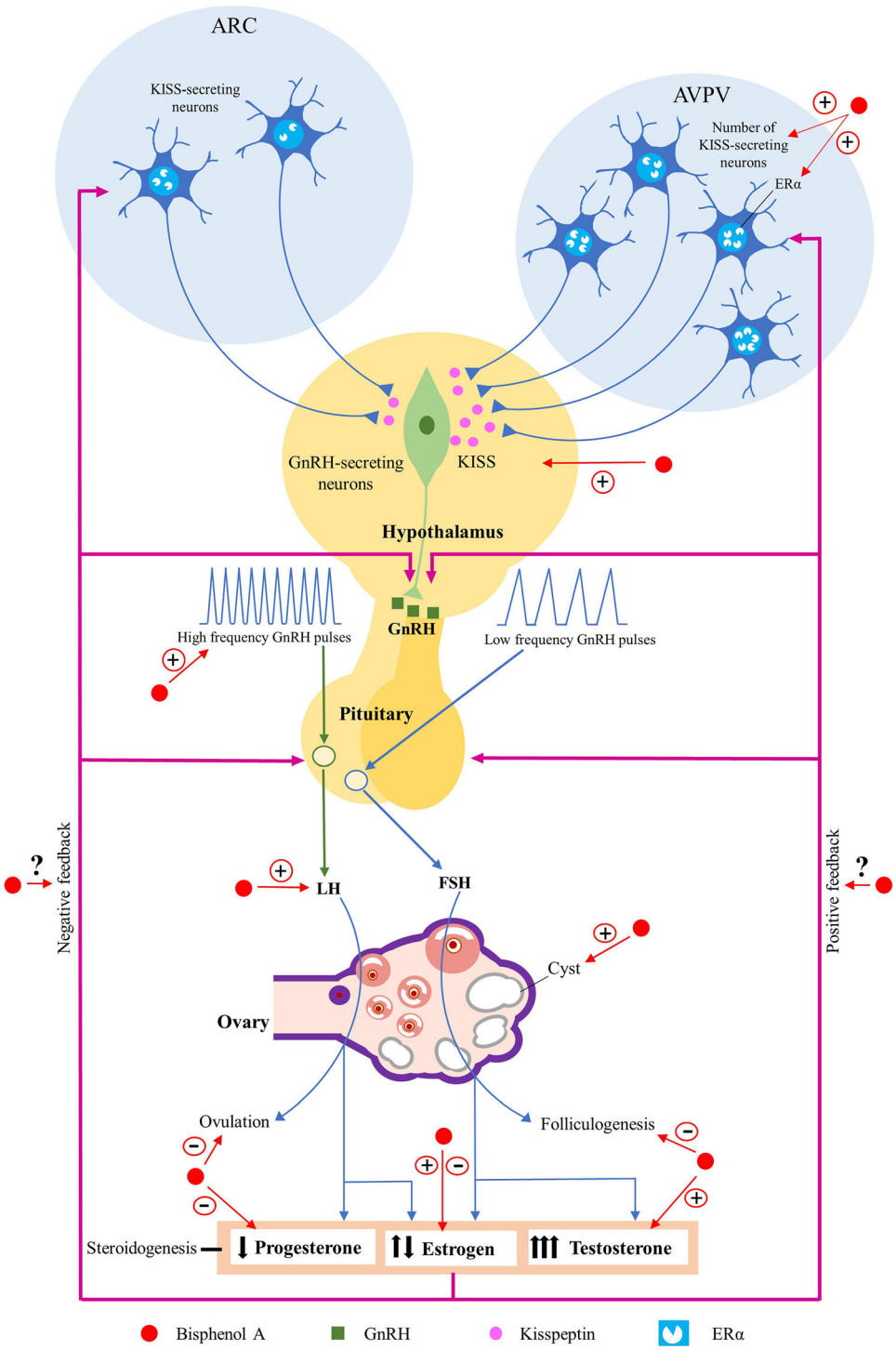

Fig. 2 Bisphenol A (BPA) effect on hypothalamo-pituitary-ovarian axis. BPA induces an increase in number of kisspeptin (KISS)-secreting neurons located in anteroventral periventricular nucleus (AVPV) and secretion of KISS peptide. These neurons exhibit an upregulation in expression of estrogen receptor alpha (*ERα*) after BPA exposure. BPA enhances KISS-induced pulse frequency of gonadotropin releasing hormone (GnRH) secretion from hypothalamic neurons and thereby production of luteinising hormone (LH) from anterior pituitary. At the level of ovary, BPA inhibits folliculogenesis, causes cyst formation and promotes anovulation. On steroidogenesis, it had differential effects on estrogen, stimulatory on testosterone and inhibitory on progesterone. The effect of BPA on estrogen feedback pathways is largely unexplored. [arcuate nucleus, ARC; follicle stimulating hormone, FSH]

neurons (Monje et al. 2010; Xi et al. 2011; Wang et al. 2014b, a). Since BPA binds with ERα, it is possible that by increasing the expression of this receptor it is enhancing its own effect on KISS-secreting neurons. In addition to effect on KISS, exposure to BPA at perinatal, postnatal, pubertal or adult stages in different animal models is reported to cause an increase in GnRH pulse frequency (Fernández et al. 2009; 2010; Gámez et al. 2015), upregulation in expression of GnRH mRNA (Xi et al. 2011; Wang et al. 2014b, a) and enhancement in post-transcriptional processing of GnRH mRNA (Monje et al. 2010). Parallel to GnRH, many of these studies report an increase in level of LH (Monje et al. 2010; Lee et al. 2013; Wang et al. 2014b, a; Zhou et al. 2014; Gámez et al. 2015). In case of

PCOS patients, a positive association is observed between serum level of BPA and LH (Vahedi et al. 2016; Rutkowska et al. 2020). On the contrary, a few studies report the decrease in serum level of LH after BPA exposure (Savabieasfahani et al. 2006; Fernández et al. 2009; Zaid et al. 2018). Since GnRH regulates the release of LH by upregulating inositol trisphosphate pathway (IP3) and BPA causes decrease in IP3 production, Fernández et al. (2009) have speculated that decrease in LH production after BPA exposure could be due to inhibition of release mechanism and not the synthesis. Besides, BPA is shown to delay and reduce the amplitude the preovulatory LH surge in adult rat (López-Rodríguez et al. 2019). In the same study, GnRH regulator phoenixin and clock genes such as period circadian regulator 1 (*Per1*) and brain and muscle ARNT-like 1 (*Bmal1*) are also shown to be downregulated by BPA, thereby leading to disruption of LH surge (Loganathan et al. 2019; López-Rodríguez et al. 2019).

With regard to the effect of BPA on production and release of FSH, the reports are contradictory. BPA has been reported to have stimulatory (Xi et al. 2011; Wang et al. 2014b, a; Zhou et al. 2014), inhibitory (Zaid et al. 2018) and no effect (Fernández et al. 2009; Lee et al. 2013; Gámez et al. 2015) on FSH mRNA and serum level. The inhibitory or no effect of BPA could be seen in light of the fact that GnRH pulse frequency increases under the effect of BPA, and FSH synthesis and release depends on slow pulsatile release of GnRH. However, the reason behind the stimulatory effect of BPA on FSH level is not clear and needs further investigation. Nevertheless, it is evident from these studies that BPA has the potential to disrupt the KISS1-GnRH-gonadotropin production.

Ovarian Functions

The effect of BPA on ovarian functions, folliculogenesis and steroidogenesis, either directly or via modulating hypothalamo-hypophyseal axis is depicted in Figs. 2 and 3.

Folliculogenesis

Primordial germ cells originating from epiblast migrate to genital ridge during embryonic stage and give rise to oogonia. These germ cells enter into meiosis which gets arrested at diplotene stage of prophase I to form primary oocytes. They are required to break off from the germ cell nest and get surrounded by a single layer of follicular cells to form primordial follicles (Pepling 2006; Tingen et al. 2009). A few primordial follicles from its pool are selected for growth and transformation into antral follicles. It is noteworthy to mention that transformation from primordial to secondary/preantral follicle is independent of gonadotropins. Under the influence of gonadotropins, preantral follicles are transformed into antral/Graffian follicles and eventually into preovulatory follicles. Prior to ovulation, meiosis which was arrested at diplotene stage of prophase I is resumed and gets arrested again at metaphase II. These secondary oocytes/ova are released out from preovulatory follicles at the time of ovulation.

Numerous studies have shown the association between BPA, oocyte formation, follicular development and ovulation (Pivonello et al. 2020). These associations have been schematically represented in Fig. 3. BPA is shown to adversely affect the transformation of oogonia into primary oocytes by inhibiting germ cell nest breakdown (Zhang et al. 2012; Zhao et al. 2014; Miao et al. 2015; Berger et al. 2016). Germ cell nest is maintained by estrogen and its breakdown occurs due to upregulation of anti-apoptotic factors and downregulation of pro-apoptotic factors (Sarraj and Drummond 2012). The balance between apoptotic and anti-apoptotic factors gets disrupted due to exposure of BPA. In vitro treatment of postnatal mice ovary with BPA has resulted in a significant increase in expression level of two prominent anti-apoptotic factors, B-cell lymphoma 2 (*Bcl2*) and B-cell lymphoma extra-large (*Bclxl*) (Zhou et al. 2015). The same study also reports decrease in expression of extrinsic apoptotic pathway factors, FAS cell surface death receptor (*Fas*) and Caspase 8 (*Casp8*). A similar observation has been made in another study wherein level of Bcl2 is shown to increase concomitantly with decrease in pro-apoptotic factors of intrinsic apoptotic pathway, BCL2-like protein 4 (*Bax*) and BCL2 Antagonist/Killer 1 (*Bak1*) (Wang et al. 2014b, a). Often incomplete germ cell nest breakdown leads to the appearance of multiovular follicles (MOFs) in adult ovary (Pepling 2006; Tingen et al. 2009) and number of such malformed follicles is shown to increase post BPA exposure in mice and lamb (Suzuki et al. 2002; Rivera et al. 2011). In BPA-exposed postnatal lamb ovary, an increase in ERs with an increase in MOFs tempted them to speculate that extended action of estrogen via its receptor would have caused inhibition in germ cell nest breakdown leading to formation of the malformed follicles. In addition to impairment of oogenesis and induction of abnormal follicles formation, BPA reduces the pool of primordial follicles by enhancing its premature transformation into primary follicles (Rodríguez et al. 2010; Rivera et al. 2011; Zhao et al. 2014). In vitro treatment of rat postnatal ovary with BPA is reported to upregulate PI3K-AKT pathway that is known for its involvement in follicular development (Liu et al. 2006; Cecconi et al. 2012). Another study corroborates the BPA-induced acceleration in number of primordial follicle entering into growth (Hu et al. 2018). In this study in mice, treatment with BPA inhibited phosphatase and tensin homologue (*Pten*), the transcription factor known to

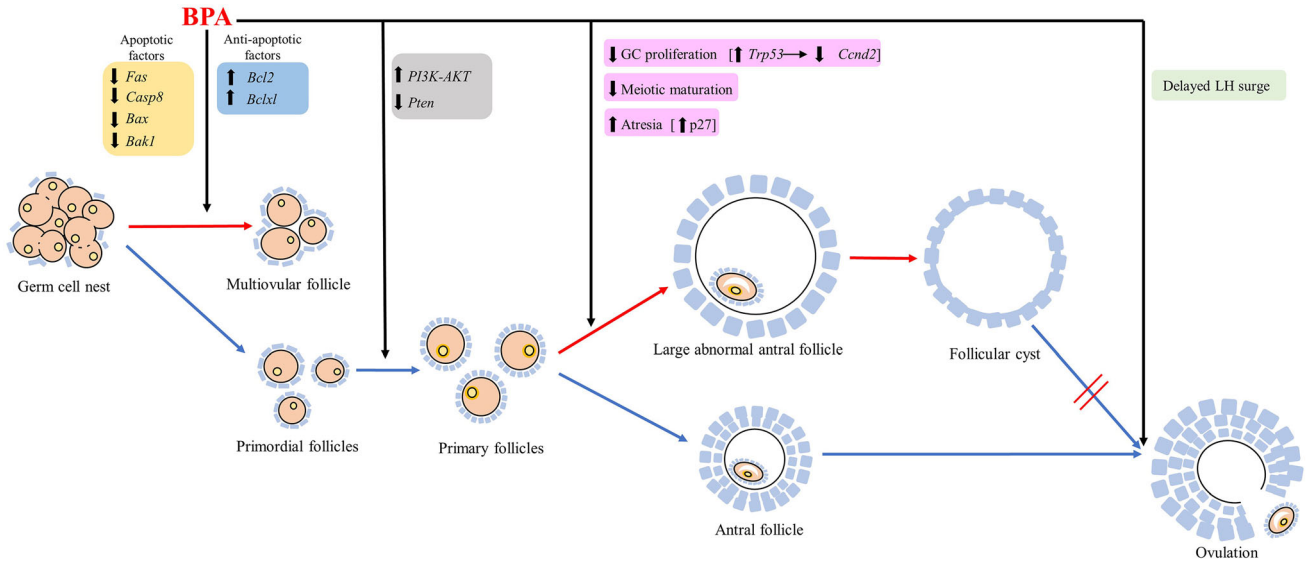

Fig. 3 Bisphenol A (BPA)-induced changes in ovarian folliculogenesis. Exposure to BPA disrupts the natural process of folliculogenesis. BPA inhibits germ cell nest breakdown by upregulating anti-apoptotic factors and downregulating apoptotic factors leading to formation of multiovular follicles. The premature transition of primordial follicles to primary follicles is enhanced by BPA via PI3K-AKT signalling pathway that decreases the expression of transcription factor *Pten* involved in maintaining the pool of primordial follicles. Further, BPA induces the formation of large abnormal antral follicles by increasing its antral cavity and inhibiting granulosa cell (GC) proliferation and meiotic maturation. The abnormal antral follicles get transformed into cysts. Besides BPA increases number of atretic follicles by upregulating expression of p27, and it alters LH surge thereby causing anovulation. [FAS cell surface death receptor, *Fas*; caspase 8, *Casp8*; B-cell lymphoma 2, *Bcl2*; BCL2-like protein 4, *Bax*; BCL2 antagonist/killer 1, *Bak1*; B-cell lymphoma extra-large, *Bclxl*; phosphatidylinositol-3-kinase and serine/threonine protein kinase pathway, PI3K-AKT; phosphatase and tensin homologue, *Pten*; cyclin D2, *Ccnd2*; transformation-related protein 53, *Trp53*; cyclin dependent kinase inhibitor, p27; luteinising hormone, LH]

maintain the pool of primordial follicles (Reddy et al. 2008).

In addition to affecting the pool of primordial follicles and follicular selection, BPA adversely affects the development of antral follicles (Fig. 3). After exposure to BPA, antral follicles become abnormally large-sized due to enlarged antrum (Adewale et al. 2009; Zaid et al. 2018) thereby contributing in formation of cysts (Zaid et al. 2018), the characteristic feature of ovary in case of PCOS. BPA has been reported to reduce granulosa cell proliferation of preantral and antral follicles (Xu et al. 2002; Lenie et al. 2008; Peretz et al. 2012). Since ER antagonists could not block this effect on antral follicles even though BPA enhances ovarian *ER* expression, it has been suggested that BPA would have carried out its effect on development of antral follicles following nongenomic/non-estrogenic pathway (Peretz et al. 2012). Probably, BPA might have caused abnormal antral follicle development via AHR as expression of this receptor is reported to increase in gonads after *in utero* exposure to BPA (Nishizawa et al. 2005). Further, in *Ahr* knockout mice, BPA failed to induce abnormal follicular growth (Ziv-Gal et al. 2013), corroborating the involvement of AHR by BPA in translating its effect at the level of antral follicles. In farm animals in which androgen is shown to play important role in later stages of follicular development (Sen and Hammes 2010; Prizant et al. 2014), BPA-induced decrease in expression of ovarian ARs suggests that BPA affects antral follicles by inhibiting the action of endogenous androgen (Rivera et al. 2015; Santamaría et al. 2016). BPA-induced abnormal growth of follicles could be due to alteration in cell cycle regulators that leads to reduction in the proliferation of granulose cells. Peretz et al. (2012) identified two such factors, cyclin D2 (CCND2) and transformation-related protein 53 (TRP53), in antral follicles of mice. It has been reported that BPA upregulates TRP53 that in turn downregulates CCND2 and results in inhibition of granulosa cell proliferation in antral follicles (Peretz et al. 2012). For comprehensive understanding, influence of BPA on genetic regulation of folliculogenesis is summarized in Fig. 3.

BPA not only affects the granulosa cells, it also inhibits meiotic resumption and maturation of oocytes (Hunt et al. 2003; Can et al. 2005; Susiarjo et al. 2007; Lawson et al. 2011; Chao et al. 2012). BPA exposure is reported to cause aneuploidy due to improper centrosome and spindle microtubular organization (Hunt et al. 2003; Can et al. 2005; Chao et al. 2012), and inhibition of germinal vesicle breakdown (Lenie et al. 2008; Chao et al. 2012). BPA-induced acceleration in number of growing follicles eventually leads to their atresia (Rivera et al. 2011; Peretz et al.

2012; Lee et al. 2013; Gámez et al. 2015; Zaid et al. 2018). The increased expression of p27 in oocytes and granulosa cells of antral follicles has been highlighted as one of the main reasons for their atresia in lamb exposed postnatally to BPA (Rivera et al. 2011). It is noteworthy that p27 can activate caspases in oocyte and granulosa cells thereby causing cell death (Rajareddy et al. 2007). Taken together, it can be speculated that the above mentioned effects of BPA on ovary at the level of germ cell nest breakdown, formation of follicles, development and maturation of oocytes, and atresia of follicles ultimately lead to reduction in number of antral follicles or formation of abnormal antral follicles not capable of ovulation (Fig. 3). As a result, the histological observation of these ovaries often showed reduced number of corpora lutea (Takeuchi et al. 2004; Adewale et al. 2009; Zaid et al. 2018; López-Rodríguez et al. 2019) due to reduced ovulation or anovulation, another characteristic feature of PCOS patients. In conclusion, BPA-induced PCOS-like features in ovary could be due to lack of factors favouring folliculogenesis and excess production of factors inducing cell death.

Steroidogenesis

It is a matter of debate whether hyperandrogenism is the cause or effect of PCOS. Nonetheless, elevated serum testosterone and high BPA level in urine and serum have been observed in women with PCOS (Takeuchi and Tsutsumi 2002; Konieczna et al. 2018; Akin et al. 2015). A similar observation has been made in girls showing precocious puberty (Lee et al. 2014). In addition, BPA has been reported to increase serum level of free testosterone in PCOS patients (Kandaraki et al. 2011; Tarantino et al. 2013) which might be due to its property of displacing testosterone from sex hormone binding globulin (Déchaud et al. 1999). The increased level of testosterone is shown to decrease clearance of BPA from circulation; thereby hyperandrogenism is suggested to have an additive effect on BPA titre in PCOS patients (Takeuchi et al. 2006). The correlation between androgen and BPA has been examined using animal models. In postnatal rats, treatment with BPA has resulted in an increase in serum level of testosterone (Fernández et al. 2010). This was further validated by in vitro experiment where BPA had positive effect on steroid acute regulatory proteins (*StAR*), steroidogenic enzymes such as cholesterol side chain cleavage enzyme (*Cyp11a*) and 17α-hydroxylase, and testosterone production by thecal cells isolated from immature rat ovary (Zhou et al. 2008). On the contrary, in mice, high concentration of BPA is shown to downregulate the expression of *StAR* and *Cyp11a* and consequently, testosterone production by antral follicles (Peretz et al. 2011; Peretz and Flaws 2013).

Efforts have also been made to examine correlation between BPA and estrogen, and the results are contradictory. A positive correlation has been suggested in BPA-exposed women factory workers in which high level of serum estrogen has been recorded as compared to unexposed individuals (Miao et al. 2015). Similarly, high urinary BPA and serum estrogen levels have been reported in girls with precocious puberty (Lee et al. 2014). In contrast, the analysis of estrogen serum level along with urinary BPA level in women facing infertility issues and undergoing in vitro fertilization treatment showed a negative correlation (Mok-Lin et al. 2010; Bloom et al. 2011; Ehrlich et al. 2013). This gets support from in vitro studies where human granulosa cells treated with BPA exhibited downregulation of aromatase expression (*CYP19A*) and estradiol production (Kwintkiewicz et al. 2010; Wang et al. 2017). The relationship between BPA and estrogen levels remains controversial even in non-human animal models. In vivo studies in rat and mice have shown that exposure to BPA, whether in prenatal, postnatal or in adult stages, have upregulated the expression of *Cyp19a* and serum level of estrogen (Fernández et al. 2010; Xi et al. 2011; Naulé et al. 2014; Wang et al. 2014b, a; Gámez et al. 2015; Zaid et al. 2018). On the other hand, in vitro studies report decrease in *Cyp19a* expression and estradiol production under the effect of BPA (Zhou et al. 2008; Peretz et al. 2011). In another in vitro study in which human granulosa cell line (KGN) was used, BPA is shown to upregulate the expression of *PPARγ* that in turn inhibited the FSH-induced *CYP19A* expression (Kwintkiewicz and Giudice 2008). The difference in results of in vitro and in vivo studies might be because the latter involves interplay of endogenous factors and hypothalamo-hypophyseal-ovarian (HPO) axis with BPA.

With regard to effect of BPA on another female sex steroid progesterone, in vivo as well as in vitro studies in human and several animals revealed its inhibitory effect on production of progesterone (Zhou et al. 2008; Fernández et al. 2010; Grasselli et al. 2010; Peretz et al. 2011; Peretz and Flaws 2013; Mansur et al. 2016; Samardzija et al. 2018; Zaid et al. 2018; Qi et al. 2020). Surprisingly, expression of *StAR* and several steroidogenic enzymes such as *Cyp11a*, *Cyp17a* and 3β- hydroxysteroid dehydrogenase (*3β-Hsd*) are reported to increase in response to BPA (Zhou et al. 2008; Samardzija et al. 2018; Qi et al. 2020). The decrease in production of progesterone despite increased expression of steroidogenic enzymes could be seen in light of a study where exposure to BPA is demonstrated to enhance the expression of ATP binding cassette subfamily A member 1 (*ABCA1*) which is known to cause efflux of cholesterol, thereby decreasing the availability of substrate for steroid biosynthesis (Qi et al. 2020). This gets support from a study in PCOS patients in whom an increase in

ABCA1 gene polymorphism is seen as compared to normal individuals (Karadeniz et al. 2011). In response to BPA exposure, sequestering of cholesterol in the perinuclear areas of steroidogenic cells also needs to be considered as a probable reason for decrease in progesterone production (Samardzija et al. 2018). In addition, we propose that BPA-induced decline in number of corpora lutea resulting from disrupted follicular growth and ovulation needs to be taken into account for decreased progesterone production since luteinised follicular cells are the main source of progesterone in an adult female. However, it is not yet clear how production of testosterone and estrogen increases when level of cholesterol decreases due to its efflux or sequestering.

Conclusion

The endocrine disruptor BPA enhances the synthesis of GnRH by directly regulating the GnRH-secreting neurons and also indirectly by altering the production of KISS from its neurons of AVPV region. An increased level of GnRH in turn stimulates LH secretion though contradictory results are reported with regard to its effect on FSH secretion. In addition, both in vivo and in vitro exposure to BPA causes structural and functional abnormalities of ovary that are often similar to PCOS-like phenotypes such as hyperandrogenism, formation of cysts and anovulation. It appears that BPA causes PCOS-like symptoms by directly affecting the ovary and also indirectly through HPO axis. However, many of the BPA-induced changes at the level of hypothalamus and pituitary have not been seen in accordance with the functional changes in ovary in response to BPA. The increased production of GnRH and gonadotropins after exposure to BPA instead of stimulating folliculogenesis, production of female sex steroids and ovulation in ovary, caused reduction in number of primordial follicles, formation of abnormal and atretic follicles, decrease in testosterone to estrogen ratio, inhibition in production of progesterone, and restriction on ovulation.

It is to be noted that majority of studies dealing with the effect of BPA on reproductive axis are focused on non-primates. In human, reports are limited to correlating plasma and urinary BPA levels with PCOS symptoms. BPA seems to have species-specific effects and hence, conclusions derived from non-human studies should not be extrapolated to humans. Well-designed in vivo and in vitro studies in human are required for investigating the involvement of HPG axis in BPA-induced PCOS-related changes in ovary. Also, the dose of BPA and route of administration has significant impact on its effect and therefore should be carefully considered while designing these experiments. In addition, studies need to be directed towards understanding molecular mechanisms of BPA action leading to PCOS-like symptoms. Nonetheless, enough evidence is available to mark this EDC as a highly dangerous chemical affecting female fertility. Despite this, developing and under-developed countries are still far away from putting a cap on the use of BPA-containing substances. In the interest of human and animal welfare, research needs to be focussed on developing mechanisms to antagonizing the effect of BPA and enhancing its clearance from the body.

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