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Review

Endocrine-disrupting chemicals in polycystic ovary syndrome: an evidence-based minireview

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Abstract. Polycystic ovary syndrome (PCOS) is a plurifactorial endocrine disorder, affecting 5-10% of women of reproductive age to result in hyperandrogenia, anovulation and infertility, metabolic syndrome and enhanced cardiovascular risk. Animal experiments unraveled that pre- and early postnatal exposure of female offspring to testosterone or bisphenol A (BPA), one synthetic, organic plasticizers component may induce a PCOS-like developmental pattern in adulthood. In contrast to other endocrine-disruption chemicals, information on BPA exposure in biological indicators and wildlife is scarce. On the other hand, the ability of BPA to alter ovarian steroidogenesis has been demonstrated in several cell culture models. In line with that, preliminary clinical studies demonstrated elevated serum and urinary BPA levels in PCOS patients. Nonetheless, a causative role of BPA in PCOS is still under debate and further studies on the topic are warranted.

Key Words: endocrine disruption, bisphenol A, polycystic ovary syndrome, androgens, insulinresistance, biological indicator

Rezumat: Sindromul ovarelor polichistice (PCOS) reprezintă o endocrinopatie plurifactorială, afectând 5-10% din femeile în etapa reproductivă, ce asociază hiperandrogenie, anovulație și infertilitate, sindrom metabolic și risc cardiovascular crescut. Cercetările pe modele animale au semnalat dezvoltarea unui fenotip PCOS-like la animale adulte expuse în perioada prenatală sau precoce postnatal la testosteron sau bisfenol A (BPA), un compus sintetic de natură organică ce intră în componența maselor plastice. Spre deosebire de alți disruptori endocrini, informațiile privind expunerea la BPA la specii indicatori biologici sau specii sălbatice sunt reduse. Pe de altă parte, proprietatea BPA de a interfera cu steroidogeneza ovariană a fost demonstrată în numeroase experimente pe culturi celulare. În concordanță, studii clinice preliminare demonstrează concentrații serice și urinare crescute ale BPA la paciente cu PCOS. Totuși, rolul cauzal al BPA în patogeneza PCOS este incert, impunând extinderea cercetărilor în domeniu.

Cuvinte cheie: disruptie endocrina, bisfenol A, sindromul ovarelor polichistice, androgeni, insulinorezistenta, indicator biologic

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Introduction

With industrialization, a large number of man-made chemicals entered the environment to exert deleterious effects on wildlife and human. Undoubtedly, a series of these substances, named endocrine-disrupting chemicals (EDC) interfere at several points with endogenous hormones signal transduction pathways to disturbe cell metabolism and cell-to-cell communication (Georgescu *et al* 2004, Georgescu *et al* 2006). As a result, EDC act either as endocrine agonists or antagonists to disrupt the biological activity of endogenous hormones, chiefly sex and thyroid hormones. Besides in vitro experiments and animal researches, epidemiological studies in man alerted on possible implication of EDC in the pathogenesis of endocrine-related neoplasia (e.g. breast, ovary, testicular, prostate and colon cancer), sex differentiation disorders, oligoastenozoospermia and infertility, thyroid dysfunction and, more recently, type 2 diabetes mellitus, obesity and the polycystic ovary syndrome (PCOS).

According to the National Institutes of Health (NIH), PCOS is reported as the most common endocrine disorder in women of reproductive age, clustering androgen excess, menstrual irregularities (oligo/amenorrhea) and infertility, insulinresistance and obesity. Although the clinic of PCOS is extremely heterogenous, a characteristic endocrine feature across all patients with PCOS is clinical and/or biochemical hyperandrogenia, in accordance with the most recent AE-PCOS Society outlines (Azziz *et al* 2009). Both lean and obese PCOS patients develop hyperinsulinemia as a response to insulinresistance. Furthermore, hyperinsulinemia behaves as a major determinant of altered androgen secretion and metabolism (Pepene 2011). PCOS patients are at increased cardiovascular risk (Pepene *et al* 2011), although higher prevalences of main cardiovascular morbidities such as angina pectoris, acut myocardial infarction or stroke in the postmenopausal period remain uncertain (Wild *et al* 2000; Schmidt *et al* 2011). Nonetheless, up to the date, PCOS remains a disorder of unknown pathogenesis.

Endocrine-disrupting mechanisms of bisphenol A in cell culture studies

Bisphenol A (4,4′-dihydroxy-2,2-diphenylpropane, BPA) is a colorless, organic compound which is poorly soluble in water

but highly lipophilic and constitutes one main component of polycarbonate plastics and epoxy resins and, hence, one of the most widely spread EDC worldwide. It leaches from baby-bottles, particularly when subjected to temperatures above 50°C, reusable water bottles and food-containers, water supply pipes, cardboards, compact-discs etc. Traditionally, BPA acts estrogen-mimetic (xenoestrogen) as a ligand of estrogen receptors (ERs) in various tissues, to induce specific, estrogen-dependent genes expression. Apart from direct activation of ER-α, there is evidence of BPA activation of non-classical transduction pathways such as the membrane-bound GPR30, a protein which belongs to the G-protein coupled class of receptors (Thomas *et al* 2006). In a similar fashion in which ERs are bound and activated, BPA appears to bind to GPR30 and induce estrogen-like effects (Thomas *et al* 2006). BPA functions as a ligand for both ER-α and ER-β but, notably, different types of coactivators expression may vary in dependance to the type of receptor bound. Therefore, it has been proposed that differences in the ability of ER-α or ER-β to recruit coactivators may be involved in the tissue-specific responses subsequent to BPA exposure (Whetherill *et al* 2007). It is suspected that BPA may additionally function as a ligand for the estrogen-related receptor-gamma (ERR-gamma), an orphan nuclear receptor with high constitutive activity (Takanyanagi *et al* 2006) and for the aryl hydrocarbon receptor (AhR), a quasi-ubiquitary transcription factor strongly activated by numerous xenobiotics including BPA, polychlorinated dibenzodioxins, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, benzopyrene etc. (Swedenborg *et al* 2009). The AhR interplays with other hormones receptors and hormones signal transduction pathways, including the ER, thereby contributing to endocrine-related effects of BPA.

In order to test for estrogenicity, proliferation studies on an estrogen-dependent cell line such as the human breast cancer cell line MCF-7 (E-SCREEN test) can be used. The E-SCREEN test is based on the dose-response relationship between the proliferation of MCF-7 cells and the amount of estrogen to which the cells are exposed. By comparing the effects of an xenoestrogen and estradiol, the relative estrogenic potency of a compound can be determined. Estrogen effects on human breast cancer cells can also be monitored after transfection of cells with an ER-mediated luciferase gene construct (Legler *et al* 2002). Moreover, under laboratory condition, BPA was able to transform the human breast epithelial cells MCF-10F which are ER-negative into ER-positive (Fernandez *et al* 2010). In microarray studies, BPA induces a specific gene expression pattern, with up-regulation of oncomiR-21 by both estradiol and BPA, consistent with increased expression of miR-21 from breast cancer biopsies (Sempere *et al* 2007). Inhibition of testicular steroidogenesis by BPA has been linked to its intervention as androgen antagonist (Akingbemi *et al* 2004).

Apart from breast cancer cells, BPA enhances insulin production by β-pancreatic islet cells and inhibits adiponectin release from adipocytes (Hugo *et al* 2008). Exposure of 3T3-L1 adipocytes to various concentrations of BPA was associated with increased adipogenesis (Taxvig *et al* 2012), however, the intimate mechanisms by which BPA promotes adipogenesis are less clear. While expression of PPAR-gamma in various adipocytes culture models remains unchanged (Taxvig *et al* 2012) or even decreased (Yee *et al* 2012), in a recent study of human visceral adipocytes exposure to BPA it was established that even at the lowest concentration employed (i.e. 10 nM), an increase in PPAR-gamma and lipoprotein lypase mRNA expression was induced (Wang *et al* 2012). Concomitantly, by acting upon the glucocorticoid receptor, BPA significantly enhanced mRNA expression and enzymatic activity of type 1 11-β-hydroxyster oiddehydrogenase, an enzyme responsible of cortisone to hormone-active cortisol conversion in the adipose tissue (Wang *et al* 2012). Experimental work revealed BPA may disrupt thyroid hormones activity by preventing the binding of T3 to thyroid hormones nuclear receptor, nonetheless, its affinity for this receptor is severalfold lower than its affinity for ERs (Moriyama *et al* 2002). In addition, inhibition of adiponectin and enhanced release of pro-inflammatory cytokines TNF-α and IL-6 from human adipocytes may be added as contributive mechanisms to endocrine disruption caused by BPA (Hugo *et al* 2008, Ben Jonathan *et al* 2009).

Exposure to bisphenol A in wildlife and laboratory animal studies. The relevance of biological indicators

In contrast to other EDCs, reports on the effects of BPA contamination in wildlife are scarce, mainly due to lack of massive, accidental exposure. As for other EDC, the consequences of BPA exposure have been studied in several kinds of species used as biological indicators in the evaluation of endocrine disruption (Georgescu *et al* 2005, Georgescu 2006). Of vertebrates, fish and amphibians were largely studied. In accordance to the estrogen-like biological activity of BPA, exposure was followed by increased vitellogenin (VTG) mRNA levels in the liver and VTG protein production, to attest for feminization in numerous species such as the carp, the fathead minnow or the rainbow troat (Lindholst *et al* 2001; Mandich *et al* 2005, Brown *et al* 2005), however, effects were reported at concentrations above those usually reported in aquatic environments. At lower levels, the circulating estrogen to androgen ratio is diminished, probably due to aromatase activity inhibition (Crain *et al* 2007). Phenotypically, exposure to BPA has been shown to determine sexual ambivalence, alterations in the spermatogenesis process with abnormal sperm quality, anovulation and delayed breeding (Mandich *et al* 2007). Early exposure of *X. laevis* embryos to BPA (before stages 9-10 of development) affects the survival rate and exerts teratogenic effects whereas later exposure may cause feminization and sex revearsal with elevated VTG synthesis (Oehlmann *et al* 2009). In addition to that, in amphibians, BPA interferes with T3-induced expression of both thyroid hormone receptors α and β (Iwamuro *et al* 2006), even at low levels (i.e. μg l−1), thereby promoting tissue resistance to thyroid hormones.

Implication of Bisphenol A in human health

Mounting evidence points out towards a potential implication of xenoestrogens including BPA in the complex pathogenesis of hormone-related neoplasia, in particular of the breast, the ovary and the prostate. Nevertheless, most of studies are based on mechanistic designs in various cell cultures and animal models whereas epidemiological data in humans are practically lacking.

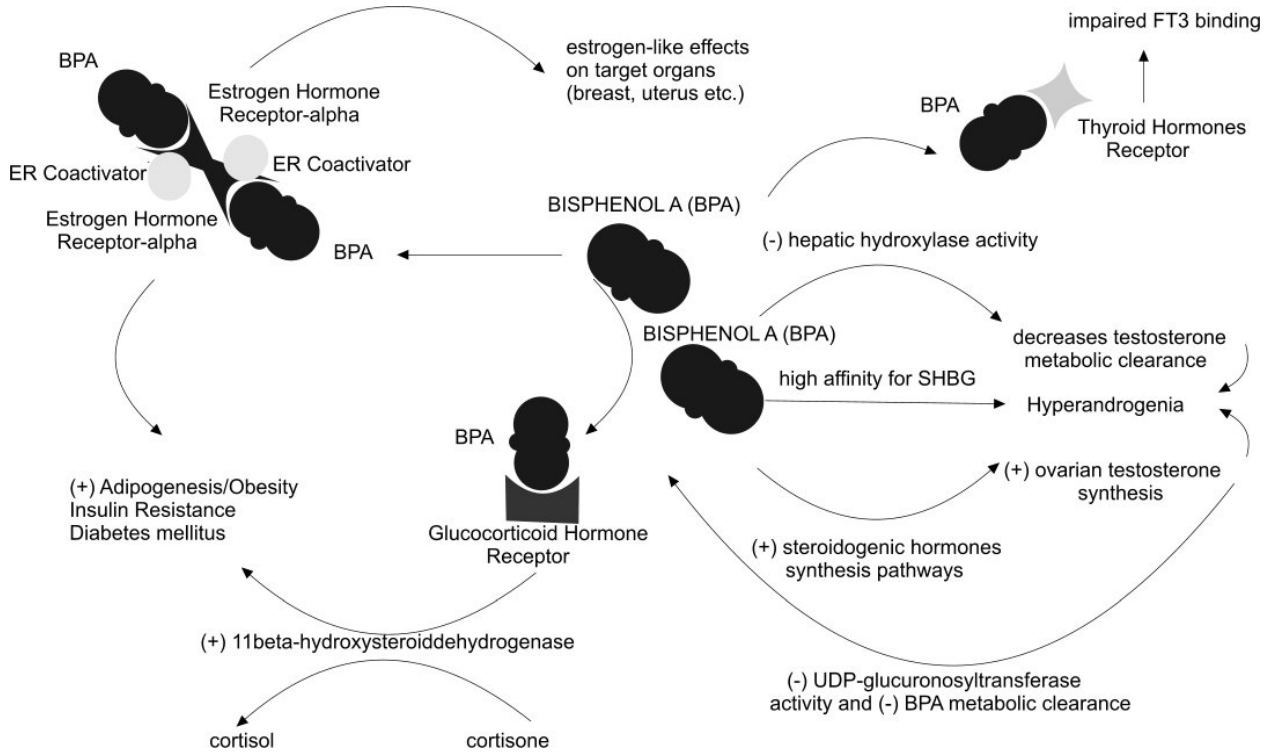

Figure 1. Mechanisms of bisphenol A (BPA)-induced endocrine disruption relevant to the pathophysiology of polycystic ovary syndrome (PCOS). A prerequisite for the development of PCOS-like features is fetal and/or early neonatal exposure to BPA. Increased testosterone production and activity and low testosterone clearance explain hyperandrogenia induced by BPA, however, the relationship is reciprocal since testosterone impairs BPA clearance. BPA also interferes with estrogen hormone receptors and glucocorticoid hormone receptor to promote increased adiposity with insulin resistance and estrogen-like effects on hormone-sensitive organs. Thyroid hormone binding to the thyroid hormones receptor is impaired.

In mouse studies of breast cancer, either by concomitant fetal exposure to BPA or by postpartum-induced mammary carcinogenesis models, BPA exposure significantly increases breast cancer risk (Vandenberg *et al* 2007, Lozada *et al* 2011). In Wistar rats, BPA leads to increased susceptibility to carcinogen-induced mammary tumors, even though no spontaneous tumors were observed (Betancourt *et al* 2010). Consistent with in vitro studies, epidemiological evidence of BPA playing the role of an obesogen begin to accumulate. In that sense, few large observational studies suggest associations of urinary BPA with abdominal obesity and insulin resistance (Carwile *et al* 2011, Wang *et al* 2012). In a clinical research, Lang *et al* (2008) found a positive relationship between high BPA exposure and the development of type 2 diabetes and cardiovascular disease in humans. In a more recent survey, including a large group of apparently healthy persons in a follow-up of more than ten years, a higher urinary BPA excretion was related to coronary artery disease incidence in multivariate adjustments, independently of traditional cardiovascular risk factors (Melzer *et al* 2012), although neither the significance nor the mechanism of this association is yet clarified.

Bisphenol A in the pathogenesis of polycystic ovary syndrome: new perspectives on environmental determinants of endocrine disorders

The concept of in utero exposure to abnormal hormone environment playing a role in the etiopathogenesis of PCOS developed from animal studies showing that fetal exposure to androgen excess is associated with PCOS features in pubertal primates (Eisner *et al* 2002). Likewise, sheep exposure to testosterone excess during the fetal stage of development results in adult animals in features that closely resemble to the PCOS phenotype: hyperandrogenism, blunted preovulatory LH surge and cycle defects, low fertility, hypertension and insulinresistance. Interestingly, in the same research, only testosterone but not dihydrotestosterone administered prenatally was able to induce the abovementioned phenotype, hence, a physiopathologic role for aromatase, the enzyme involved in testosterone conversion to estradiol, is suspected (Padmanabhan *et al* 2010). Further, the potential role of BPA as a determinant of PCOS was raised by evidence that exposure of rats to high BPA levels immediately after birth, during brain differentiation, was followed by altered GnRH secretory pulses in addition to anovulation and increased ovarian testosterone production during adulthood (Fernandez *et al* 2010). Animals showed a polycystic ovaries appearance and were infertile (Fernandez *et al* 2010). In sheep, prenatal exposure to BPA, which resulted in maternal levels which approximated twice the highest levels found in human maternal circulation, led to reproductive anomalies in offspring characterized by altered preovulatory LH peak and elevated FSH and LH levels (Padmanabhan *et al* 2010) that are alike to endocrine abnormalities noticed in patients with PCOS. In clinical, observational studies, serum BPA concentration was reported as significantly higher in women with PCOS compared to healthy women (Takeuchi *et al* 2002, Kandaraki *et al* 2011) both of the lean and the obese phenotypes (Kandaraki *et al* 2011). Moreover, a positive correlation of serum BPA with

androgen excess as determined by total and free serum testosterone and serum androstendione was observed (Takeuchi *et al* 2002, Kandaraki *et al* 2011) as well as with the degree of insulinresistance (Kandaraki *et al* 2011).

Apart from endocrine dysregulation, several lines of evidence show that women with the PCOS associate chronic low-grade inflammation and elevated risk of metabolic syndrome, liver dysfunction and cardiovascular disease (Ilie *et al* 2010, Ilie *et al* 2012). High-sensitivity C-reactive protein, a traditional inflammation marker, insulin resistance and the ultrasonographic pattern of hepatic steatosis in patients with PCOS appear to be closely related to serum BPA levels, independently of obesity (Tarantino *et al* 2012).

The maternal-fetal placental unit plays a capital role in fetal metabolism (Georgescu *et al* 2011). Detectable BPA concentrations have been confirmed in maternal serum and ovarian follicular fluid as well as in fetal plasma thus indicating transplacental passage of the compound (Schönfelder *et al* 2002). As with other EDC (Georgescu *et al* 2011), continuous contaminaton takes place after birth since about 95% of children and adults test positive for BPA contamination, a phenomenon linked to its widespread use. The relevance of increased BPA load in women with the PCOS to the physiopathological course of the syndrome remains unclear, mostly because of the reciprocal relationship between BPA and androgen hormones. In vitro, rat ovarian theca-interstitial cells exposed to BPA synthesize excessively testosterone (Zhou *et al* 2009), a finding which is in agreement with the development of PCOS-like syndrome after both pre- or neonatal exposure of animals to BPA (Newbold *et al* 2009, Fernandez *et al* 2010). It appears that BPA intervenes by up-regulation of the activity of enzymes involved in the steroidogenic pathway to accelerate androgen production (Zhou *et al* 2009), a finding previously reported as an intrinsec defect in patients with PCOS (Nelson *et al* 2001). Additionally, BPA decreases the activity of enzymes involved in testosterone metabolic pathways and exhibits affinity for sex hormone-binding globulin (SHBG) and temporarily increases the levels of serum free testosterone (Hanioka *et al* 1998). On the other hand, androgens clearly influence BPA metabolism by impacting on BPA clearance by hepatic uridine diphosphate-glucuronosyltransferase activity, thereby increasing serum levels of BPA (Takeuchi *et al* 2006) (Fig. 1).

Conclusions

To conclude, experimental and some epidemiological data unravel the link between BPA contamination and PCOS. Nonetheless, several questions remain unsolved. Future studies should clarify if the association between exposure to BPA and PCOS is based on a cause-effect relationship and if so, what cumulative exposure dose cutoff has to be considered. Apart from endocrine abnormalities, there is unclear if the association of serum BPA with insulinresistance, metabolic alterations and chronic inflammation is due to BPA per se or rather circumstantial. As BPA is part of EDCs acting as obesogens, increased exposure to this compound presumably contributs to the aggravation of obesity and androgen excess in women with PCOS, thereby entertaining a vicious physiopathological circle in PCOS.

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