Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: https://www.tandfonline.com/loi/igye20

Bisphenol A (BPA) and its potential role in the pathogenesis of the polycystic ovary syndrome (PCOS)

Aleksandra Rutkowska & Dominik Rachoń

To cite this article: Aleksandra Rutkowska & Dominik Rachoń (2014) Bisphenol A (BPA) and its potential role in the pathogenesis of the polycystic ovary syndrome (PCOS), Gynecological Endocrinology, 30:4, 260-265, DOI: 10.3109/09513590.2013.871517

To link to this article: https://doi.org/10.3109/09513590.2013.871517

http://informahealthcare.com/gye
ISSN: 0951-3590 (print), 1473-0766 (electronic)

GYNECOLOGICAL ENDOCRINOLOGY

Gynecol Endocrinol, 2014; 30(4): 260–265
 DOI: 10.3109/09513590.2013.871517

informa healthcare

PCO

Bisphenol A (BPA) and its potential role in the pathogenesis of the polycystic ovary syndrome (PCOS)

Aleksandra Rutkowska and Dominik Rachoń

Department of Clinical and Experimental Endocrinology, Institute of Maritime and Tropical Medicine, Medical University of Gdańsk, Gdynia, Poland

Abstract

Polycystic ovary syndrome (PCOS) is the most common and the most heterogeneous endocrine disorder in premenopausal women. Apart from signs of hyperandrogenism such as acne, hirsutism and hair loss, women with PCOS usually present with menstrual irregularities and fertility problems.Additionally, they are often characterized by impaired glucose tolerance, which usually leads to the development of type 2 diabetes mellitus (T2DM). This review article describes current and novel approach to the pathomechanisms of PCOS and the potential role of an endocrine disrupting chemical (''endocrine disruptor'' – ED) – bisphenol A (BPA), which is commonly used as a plasticizer and due to its molecular structure can interact with estrogen receptors (ERs). Recent observations point to the higher levels of BPA in biological fluids of women with PCOS and its role in the pathogenesis of hyperandrogenism and hyperinsulinemia. It seems that mother's exposure to BPA during pregnancy may also lead to the development of PCOS in the female offspring.

Keywords

Bisphenol A, endocrine disruptors, hyperandrogenism, hyperinsulinemia, polycystic ovary syndrome

History

Received 9 June 2013
Revised 28 October 2013
Accepted 29 November 2013
Published online 7 January 2014

Introduction

Polycystic ovary syndrome (PCOS) is the most common and the most heterogeneous endocrine disorder in premenopausal women [1]. Its prevalence is estimated from 5 to 10% depending on the diagnosis' criteria [2]. Apart from signs of hyperandrogenism such as acne, hirsutism and hair loss [3]; women with PCOS usually present with menstrual irregularities [4] and fertility problems [5,6]. According to a consensus meeting sponsored by the European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM), PCOS can be diagnosed if two out of the following three criteria are fulfilled. These are: clinical and/or biochemical hyperandrogenism, chronic oligomenorrhea and/or anovulation, or the presence of polycystic ovaries on transvaginal ultrasonography [7]. Although this endocrinopathy has a great diversity of its clinical picture, it is also characterized by the presence of insulin resistance [8], which leads to the development of central obesity with its metabolic consequences [9]. Therefore, women with PCOS often present impaired glucose tolerance, which usually leads to the development of type 2 diabetes mellitus (T2DM) [10], atherogenic dyslipidemia (high serum triglycerides and LDL-cholesterol levels, low HDL-cholesterol levels) [11,12], higher blood pressure values and increased thrombotic activity [13,14]. Consequently, in most women with PCOS usually a concomitant diagnosis of the metabolic syndrome (MS) can be made, which in turn increases the risk of cardiovascular disease (CVD) development in these subjects [15]. Because of all these metabolic derangements, PCOS patients warrant a multidisciplinary approach, where apart from a gynecologist, an endocrinologist and a dietician are also involved.

The pathophysiology of PCOS still remains unclear. It seems that it is a multifactorial syndrome that may be caused by genetic factors, which could lead to tissue insulin resistance and its ensuing hiperinsulinemia and hyperandrogenism. However, recently in studies on the pathogenesis of PCOS an emphasis has been placed on the ethnic origin, geographic location, environmental factors and lifestyle, which also contribute to the variety of clinical pictures of this syndrome [16,17].

Endocrine disrupting chemicals and human health

Progressive urbanization, industrialization and consumerism have lead to the pollution of the environment, which affects wildlife and human health. Endocrine disrupting chemicals, so called ''endocrine disruptors'' (EDs), are defined by the Environmental Protection Agency (EPA) as ''. . . exogenous agents that interfere with the synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction and developmental processes . . .'' [18]. EDs belong to a heterogenic group of molecules (natural or synthetic), which very often due to their phenolic structure can interfere with steroid hormones synthesis and interact with their receptors. This in turn may usually lead to the development of many metabolic disorders or even hormone-dependent neoplasms (i.e. breast, uterine or prostate cancer). EDs encompass a variety of chemicals, including pesticides, plasticizers, industrial by-products and pollutants. The most common contaminators are bisphenol A (BPA), polychlorinated biphenyls (PCB), phthalates and dioxins (Figure 1). Due to their lipophilic structure, these compounds tend

Address for correspondence: Aleksandra Rutkowska, PhD, Department of Clinical and Experimental Endocrinology, Institute of Maritime and Tropical Medicine, Medical University of Gdańsk, Powstania Styczniowego 9B, 81-519 Gdynia, Poland. Tel: +48 349 1947. E-mail: olarynio@gumed.edu.pl

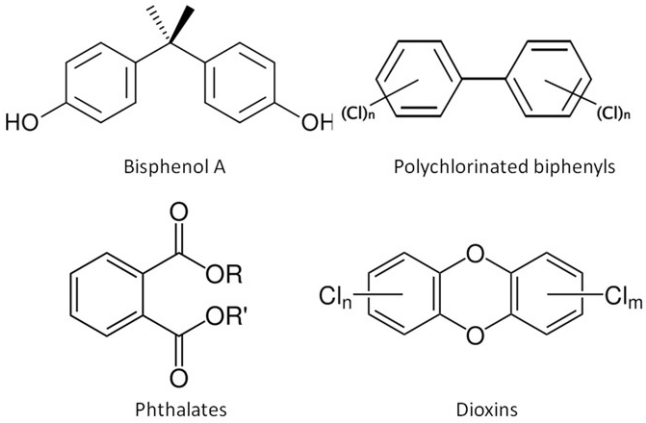

Figure 1. Chemical structures of the selected endocrine disruptors. 1. Bisphenol A (BPA), commonly used as a plasticizer, is an organic compound belonging to the group of diphenylmethane derivatives. 2. Polychlorinated biphenyls (PCB) belong to broad family of chlorinated hydrocarbons. 3. Phthalates are dialkyl or alkyl aryl esters of the phthalic acid. 4. Dioxins – chemicals with two phenyl groups fused onto a dioxin ring.

to bioaccumulate in the adipose tissue of all living organisms. Humans are at the end of the food chain, thus they are exposed to the highest doses of these compounds. EDs have been detected in human adipose tissue and biological fluids such as: serum [19], urine [20], milk [21] and amniotic fluid [22].

Bisphenol A (BPA) – a ubiquitous environmental xenoestrogen

BPA is one of the most abundant chemicals produced worldwide (>6 billion pounds produced each year) [23]. It was first synthesized by Alexander Pavlovich Dianin in 1891 and was then recognized in the 1930 by a British chemist Charles Edward Dodds as an artificial estrogen [24]. Soon after it has been tested in the prevention of the adverse pregnancy outcomes in women with a history of miscarriage until diethylstilboestrol (DES) was approved by the FDA for this indication in 1947 [25]. BPA is a diphenylmethane derivative formed by two phenol rings connected to two methyl groups (Figure 1). This phenolic structure allows BPA to interact with estrogen receptors (ER). Therefore, BPA and its metabolites are often regarded as xenoestrogens [26,27]. BPA can exert its biological effects through several pathways. Biochemical assays have confirmed its estrogenic activity via classical ER (ERα and ERβ); however, its affinity is 1000–10 000-fold lower than that of 17β-estradiol (E2) [28]. However, BPA shows approximately 10-fold higher affinity to ERβ compared to ERα [27,28]. There are also suggestions that BPA can interact with transmembrane ERs such as G protein coupled receptor 30 (GRP30) [29–31]. Data from recent experiments also show that BPA possesses high specificity and binding affinity to estrogen-related receptors gamma (ERRγ), which belong to the nuclear receptor family and are highly expressed in the placenta, developing fetus and the neonate [32]. Although the endogenous ligand for these receptors has not yet been identified, there are suggestions that they act as constitutive activators of transcription and play a role major in the maturation of the fetus. It has been also shown that BPA may upregulate foetal tissue ERRγ expression [33].

There is also evidence that BPA binds with the aryl hydrocarbon receptor (AhR), which is a ligand-dependent transcription factor expressed in a variety of tissues [34,35]. AhR is involved in the metabolism of xenobiotics and the modulation of their biological action, as well as steroid hormone synthesis and metabolism. Some studies have pointed to the cross-talk between AhR and other nuclear receptors such as ER, androgen receptors (AR) and the potential impact of BPA in these interactions. However, it has also been shown that BPA may exert anti-estrogenic actions by inhibiting the aromatase activity – an enzyme involved in the synthesis of estrogens [35].

In industry, BPA is used as a plasticizer. It is present in food packages, bottles (also baby bottles in the past), CDs, DVDs, electronic equipment, dental sealing, carbonless receipts, eye lenses and water pipes [36]. BPA is detected in the majority of examined individuals (95% of the human population). This is due to its high daily exposure as well as its leakage into foods from the packages [37]. Therefore, exposition to BPA is mainly through the contaminated foods and water as well as skin absorption. The liver plays an essential role in BPA metabolism and its excretion. Uridine 5'-diphospho-glucuronosyltransferase (UGT) is an enzyme responsible for BPA glucuronidation and conversion to metabolites with little or no estrogenic activity [20]. Some observations show that females compared to males are more likely to have higher levels of BPA sulfates than BPA glucuronides, which points to gender differences in its metabolism [38]. However, there are suggestions that non-conjugated BPA can accumulate and have a longer half-life than expected [39]. This in part may be explained by the down-regulation of the UGT activity by androgens [40].

Since BPA can interact with ERs it is obvious that it can impair female fertility. Ovarian cells seem to be a sensitive target for BPA, first of all because of its estrogen-like activity. BPA seems to act via classical ERα and ERβ [28], non-classical membrane estrogen receptors: GPR30 [30], ERRγ [41] and thus interfere with ovarian folliculogenesis [42,43] Ehrlich et al. (2012) have found that higher levels of urinary BPA correlate with the rate of implantation failure among women [44]. Higher concentrations of BPA, but not perfluoctane sulfonate (PFOS), mono-ethylhexyl phthalate (MEHP), and di-(2-ethylhexyl) phthalate (DEHP), were detected in the sera of women with fertility problems [45]. There are also reports about a dose–response association of BPA exposure and alteration of oocyte meiotic maturation and chromosome alignment in human oocytes [46].

The potential role of BPA in the pathogenesis of PCOS

The pathophysiology of PCOS is still not well understood and seems to be multifactorial. It has been shown that women with PCOS have an exaggerated gonadotropin-releasing hormone (GnRH) pulse generator activity with its consequent constant LH elevation, which in turn impairs follicular development and increases ovarian androgen production [47]. Data from the animal experiments have shown that neonatal exposure to BPA may upregulate the activity of GnRH pulse generator in adult life [48]. Additionally, it has been proven that BPA can also directly stimulate androgen synthesis in the ovarian theca-interstitial cells [49]. A correlation between increased serum testosterone levels observed in women with PCOS with serum BPA concentrations has also been found [50]. Although there are many reports on the effects of BPA on the ovarian steroidogenesis, their mechanisms are still not clear. Many results are controversial and seem to be dependent on the BPA dose and time of exposure, as well as cell type used in the experiment. However, some data from the studies on rats show that BPA has an ability to increase the testosterone synthesis in the theca-interstitial cells and decrease the estradiol production in the granulosa cells. These effects may be due to the upregulation of the Cyp17a1, Cyp11a1 and Star [51] and the down-regulation of Cyp19a1 activity – the key enzymes involved in the ovarian steroidogenesis [44]. What is more, BPA can also interact with the human sex hormone binding globulin (SHGB).

This protein may transport BPA through plasma and therefore modulate its bioavailability. On the other hand, BPA may also displace sex steroids from SHBG and therefore increase the amount of free testosterone [52].

Hiperinsulinemia is also a common feature in women with PCOS, which is usually aggravated by the presence of obesity [53]. Women with PCOS are more likely to have visceral adiposity [9], which exacerbate the existing insulin resistance leading to carbohydrate metabolism disorders (i.e. T2DM), CVD and reproductive dysfunction [5,54,55]. Data from numerous reports confirm the presence of a positive association between BPA exposure and BMI [56–58]. It is difficult, however, to state whether high serum or urine levels of BPA are a consequence or a cause of obesity. Nevertheless, the results obtained from the studies *in vitro* and *in vivo* have clearly shown a great potency of BPA for non-genomic activation of adipogenic transcription factors in 3T3-L1 preadipocytes [59], up-regulation of adipogenic genes [60], enhancement of adipocyte differentiation and lipid accumulation [61,62]. BPA seems not only to be involved in the molecular and cellular pathways of the development of obesity but also in the alteration of glucose homeostasis [63] and as a result the development of hyperinsulinemia and T2DM [64]. Several independent studies have shown, that urinary BPA as well as elevated serum BPA concentrations (>0.45 ng/mL) in women with PCOS were associated with severe insulin resistance [50,56,65]. The results from the studies on animals have shown that BPA can also increase insulin secretion [66]. These observations may be explained by a possible direct impact on the pancreas, which is a target receptor for BPA [67]. Quesada et al. found the activation of transcription factor CREB (cAMP response element binding protein) after the exposure of the islet cells to the low doses of BPA [68]. These cellular effects may then lead to the development of hyperinsulinemia as CREB activation is strongly associated with the expression of the insulin gene [69]. The altered Ca2+ cellular signaling may be another explanation for this BPA-induced metabolic derangements [70]. It may be triggered by BPA interactions with non-classical membrane estrogen receptors [71].

PCOS is also looked upon as a proinflammatory state, and this condition seems to be a key contributor to the PCOS pathogenesis. There are numerous studies reporting elevations of circulating inflammatory molecules in biological fluids of women with PCOS [72–75]. Chronic low-grade inflammation also seems to emphasize the ovarian dysfunction and the exaggerated theca cells androgen production [76]. BPA, by acting via estrogen receptors on adipocytes and macrophages infiltrating the adipose tissue, promotes inflammatory conditions. Recently, it has also been found that BPA may inhibit adipose tissue adiponectin secretion and additionally stimulate that of interleukin-6 (IL-6) and tumor necrosis factor alpha, which can further aggravate the disturbances of the carbohydrate metabolism and increase the cardiovascular risk in these women [77].

Maternal BPA exposure and PCOS development in the offspring

Data from several animal studies clearly show that fetal androgen exposure may be a triggering factor for the PCOS development in the offspring [78]. Results of the studies conducted in animals have shown that female murine embryos positioned next to males were more masculinized and higher testosterone levels were detected in their sera and the amniotic fluid [79,80]. Neonatal exposure of female rats to BPA via subcutaneous injection has promoted GnRH release in the hypothalamus of postnatal and adult rats [81]. This process may result in excess ovarian production of androgens [47]. Prenatal exposure of rodents to BPA has also resulted in abnormal ovarian folicullo- and steroidogenesis. Ovaries of animals treated with BPA were smaller, contained ovarian cysts [48] and abnormal oocytes [82] compared to control animals. BPA exposure of pregnant rodents also caused defeminization of the offspring's female brain, which was confirmed by the decrease in the number of dopamine neurons in the sexually dimorphic anteroventral periventricular nucleus of the hypothalamus [83]. These results may also explain the occurrence of impaired maternal behaviors [84] and aggressiveness in adult rodents [85] who were exposed to this ED during their fetal development. It has been shown that pregnant women with PCOS, apart from elevated serum testosterone concentrations, are also characterized by higher serum BPA levels. It has been postulated that the transfer of BPA through the maternal-fetal barrier may be facilitated via high placental ERR γ expression [32]. Significant concentrations of BPA have been found in the placenta, neonatal blood and the human amniotic fluid where they were five-fold higher than those found in the mother's serum [21,22,86]. It has been hypothesized that BPA exposure during early fetal development may be the underlying cause of the increased incidence of infertility, genital tract abnormalities and breast cancer observed nowadays in westernized populations [81]. Data from the studies on animals have shown that liver enzymes involved in the BPA metabolism such as the UGT2B1 isoform may be inactivated in the fetal as well as the maternal liver during pregnancy and lactation [20,87]. This explains the observations that after birth neonates are not able to inactivate BPA via conjugation with the glucuronic acid [88]. Additionally, in contrast to endogenous estrogens which in fetal live are bound with the alpha-fetoprotein [89], BPA does not show any affinity to it [90] and thus is readily available to interact with its target receptors.

Role of BPA in the DNA epigenetic modifications

The most worrisome are the reports about fetal and neonatal exposure to BPA and its effects on the epigenetic modifications [91]. Briefly, it concerns the heritable genome alterations such as nucleotide methylation or histone modification that play a significant role in gene expression without actual changes in the nucleotide sequence of the involved genes. Maternal exposure (F0) to this ED may also induce epigenetic effects in the fetus (F1 generation), fetal germ-cells (F2 generation) and subsequent transgenerational effects (F3 generation). There are some reports on the direct effects of BPA on the methylation of the DNA. BPA seems to influence the DNA structure in two different ways. Firstly, this ED may directly induce epigenetic changes in the genome, as it was observed in the studies on animals. Data from the experiments on mice have shown that maternal exposure to BPA-induced CpG methylation in the cells of the developing forebrain of the offspring [91]. Also, changes in CpG islands in Hoxa10 loci were reported in the uteri of CD-1 mice exposed to BPA during fetal life [92]. Secondly, it seems that androgens may also influence DNA methylation, which is further exacerbated by the presence of BPA and has been already confirmed by different studies. The epigenetic reprograming induced by hyperandrogenemia has been observed in women with PCOS. Qu et al. have documented a higher DNA methylation rate in the peroxisome proliferator-activated receptor gamma 1 (PPARG1) and the nuclear corepressor 1 (NCOR1) genes in the granulosa cells of women with PCOS compared to healthy controls [93].

Summary

Emerging clinical and experimental evidence indicates that BPA may play a major role in the PCOS pathogenesis via several pathways (shown in Figure 2). Additionally, BPA may also be a

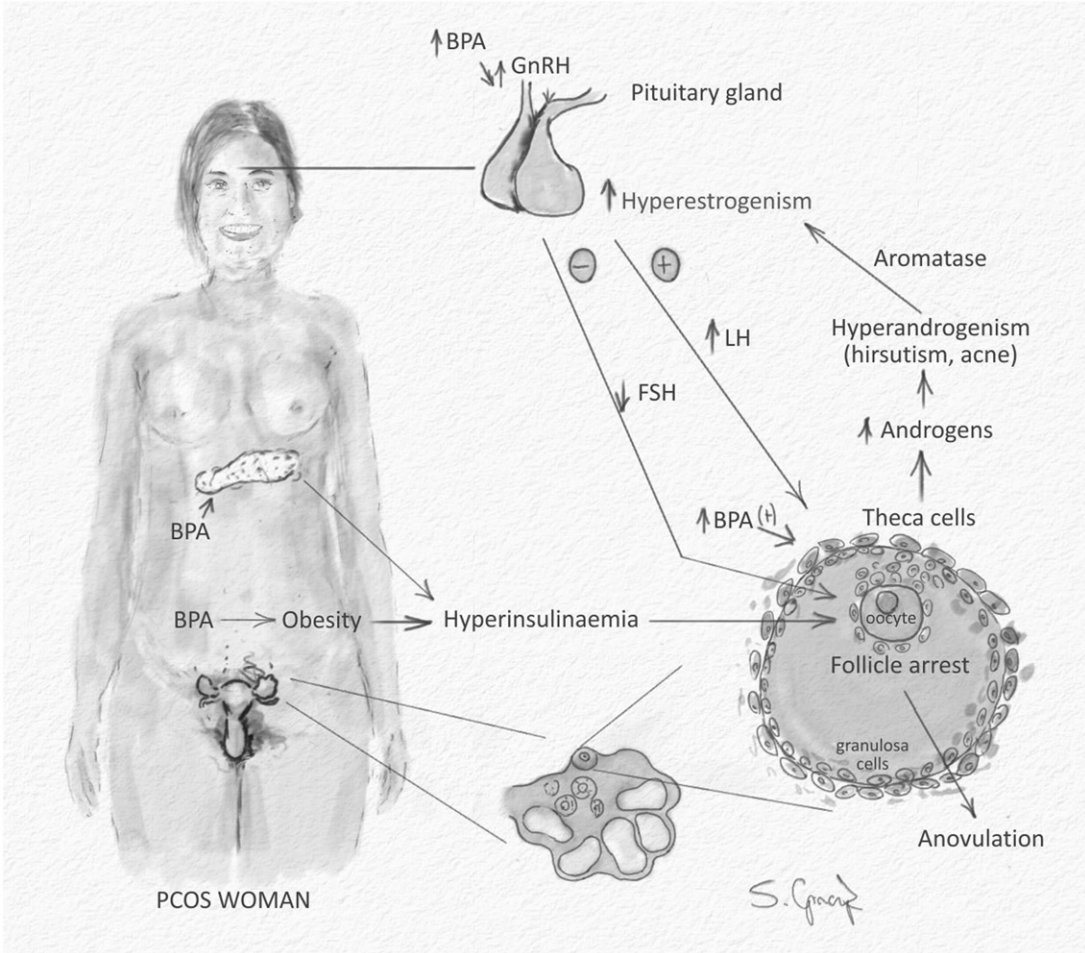

Figure 2. The potential role of BPA in the pathogenesis of PCOS. Hypothalamic BPA exposure activates GnRH pulse generator, which in turn leads to the increased LH and decreased FSH secretion by the pituitary and therefore promote ovarian hyperandrogenism. BPA can also directly stimulate androgen production in the ovarian theca cells leading to hyperandrogenemia and subsequent hyperoestrogenemia. BPA can also interact with the receptors in adipose tissue and stimulate pancreatic beta cells to insulin production which both result in increased lipid accumulation in the adipose tissue. All of these effects impair ovarian folliculogenesis leading to anovulation.

link between genetic factors (epigenetic changes), which in certain environment predispose to the development of hormonal disturbances typical for the PCOS.

Acknowledgements

Authors wish to thank Szymon Graczyk from the ''Studio Brainers'' for the preparation of Figure 2.

Declaration of interest

The authors declare no conflict of interests related to the content of this manuscript.

References

1. Azziz R, Woods KS, Reyna R, et al. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89:2745–9.
2. Adams J, Polson DW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. Br Med J (Clin Res Ed) 1986;293:355–9.
3. Moghetti P, Tosi F, Tosti A, et al. Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. J Clin Endocrinol Metab 2000;85:89–94.
4. Vutyavanich T, Khaniyao V, Wongtra-Ngan S, et al. Clinical, endocrine and ultrasonographic features of polycystic ovary syndrome in Thai women. J Obstet Gynaecol Res 2007;33:677–80.
5. Boomsma CM, Eijkemans MJ, Hughes EG, et al. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update 2006;12:673–83.
6. Brassard M, AinMelk Y, Baillargeon JP. Basic infertility including polycystic ovary syndrome. Med Clin North Am 2008;92:1163–92, xi.
7. Agrawal R, Sharma S, Bekir J, et al. Prevalence of polycystic ovaries and polycystic ovary syndrome in lesbian women compared with heterosexual women. Fertil Steril 2004;82:1352–7.
8. Legro RS, Castracane VD, Kauffman RP. Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. Obstet Gynecol Surv 2004;59:141–54.
9. Rachoń D, Teede H. Ovarian function and obesity – interrelationship, impact on women's reproductive lifespan and treatment options. Mol Cell Endocrinol 2010;316:172–9.
10. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999;84:165–9.
11. Strowitzki T, Halser B, Demant T. Body fat distribution, insulin sensitivity, ovarian dysfunction and serum lipoproteins in patients with polycystic ovary syndrome. Gynecol Endocrinol 2002;16:45–51.
12. Valkenburg O, Steegers-Theunissen RP, Smedts HP, et al. A more atherogenic serum lipoprotein profile is present in women with polycystic ovary syndrome: a case-control study. J Clin Endocrinol Metab 2008;93:470–6.

13. Amowitz LL, Sobel BE. Cardiovascular consequences of polycystic ovary syndrome. Endocrinol Metab Clin North Am 1999;28: 439–58, viii.
14. Legro RS, Urbanek M, Kunselman AR, et al. Self-selected women with polycystic ovary syndrome are reproductively and metabolically abnormal and undertreated. Fertil Steril 2002;78:51–7.
15. Shaw LJ, Bairey Merz CN, Azziz R, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health–National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. J Clin Endocrinol Metab 2008;93:1276–84.
16. Wijeyaratne CN, Seneviratne Rde A, Dahanayake S, et al. Phenotype and metabolic profile of South Asian women with polycystic ovary syndrome (PCOS): results of a large database from a specialist Endocrine Clinic. Hum Reprod 2011;26:202–13.
17. Lo JC, Feigenbaum SL, Yang J, et al. Epidemiology and adverse cardiovascular risk profile of diagnosed polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91:1357–63.
18. Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 1993;101:378–84.
19. Cobellis L, Latini G, De Felice C, et al. High plasma concentrations of di-(2-ethylhexyl)-phthalate in women with endometriosis. Hum Reprod 2003;18:1512–15.
20. Yokota H, Iwano H, Endo M, et al. Glucuronidation of the environmental oestrogen bisphenol A by an isoform of UDP-glucuronosyltransferase, UGT2B1, in the rat liver. Biochem J 1999;340:405–9.
21. Vandenberg LN, Hauser R, Marcus M, et al. Human exposure to bisphenol A (BPA). Reprod Toxicol 2007;24:139–77.
22. Ikezuki Y, Tsutsumi O, Takai Y, et al. Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. Hum Reprod 2002;17:2839–41.
23. Vandenberg LN, Chahoud I, Heindel JJ, et al. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. Ciencia Saude Coletiva 2012;17:407–34.
24. Erler C, Novak J. Bisphenol a exposure: human risk and health policy. J Pediatr Nurs 2010;25:400–7.
25. Vogel SA. The politics of plastics: the making and unmaking of bisphenol a ''safety''. Am J Public Health 2009;99:S559–66.
26. Ben-Jonathan N, Steinmetz R. Xenoestrogens: the emerging story of bisphenol a. Trends Endocrinol Metab 1998;9:124–8.
27. Gould JC, Leonard LS, Maness SC, et al. Bisphenol A interacts with the estrogen receptor alpha in a distinct manner from estradiol. Mol Cell Endocrinol 1998;142:203–14.
28. Kuiper GG, Lemmen JG, Carlsson B, et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology 1998;139:4252–63.
29. Watson CS, Bulayeva NN, Wozniak AL, Alyea RA. Xenoestrogens are potent activators of nongenomic estrogenic responses. Steroids 2007;72:124–34.
30. Thomas P, Dong J. Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: a potential novel mechanism of endocrine disruption. J Steroid Biochem Mol Biol 2006;102:175–9.
31. Watson CS, Bulayeva NN, Wozniak AL, Finnerty CC. Signaling from the membrane via membrane estrogen receptor-alpha: estrogens, xenoestrogens, and phytoestrogens. Steroids 2005;70:364–71.
32. Takeda Y, Liu X, Sumiyoshi M, et al. Placenta expressing the greatest quantity of bisphenol A receptor ERR{gamma} among the human reproductive tissues: predominant expression of type-1 ERRgamma isoform. J Biochem 2009;146:113–22.
33. Arase S, Ishii K, Igarashi K, et al. Endocrine disrupter bisphenol A increases in situ estrogen production in the mouse urogenital sinus. Biol Reprod 2011;84:734–42.
34. Kruger T, Long M, Bonefeld-Jorgensen EC. Plastic components affect the activation of the aryl hydrocarbon and the androgen receptor. Toxicology 2008;246:112–23.
35. Bonefeld-Jorgensen EC, Long M, Hofmeister MV, Vinggaard AM. Endocrine-disrupting potential of bisphenol A, bisphenol A dimethacrylate, 4-n-nonylphenol, and 4-n-octylphenol in vitro: new data and a brief review. Environ Health Perspect 2007;115: 69–76.
36. Chapin RE, Adams J, Boekelheide K, et al. NTP-CERHR expert panel report on the reproductive and developmental toxicity of bisphenol A. Birth Defects Res B Dev Reprod Toxicol 2008;83: 157–395.
37. Welshons WV, Nagel SC, vom Saal FS. Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. Endocrinology 2006;147: S56–69.
38. Kim YH, Kim CS, Park S, et al. Gender differences in the levels of bisphenol A metabolites in urine. Biochem Biophys Res Commun 2003;312:441–8.
39. Fernandez MF, Arrebola JP, Taoufiki J, et al. Bisphenol-A and chlorinated derivatives in adipose tissue of women. Reprod Toxicol 2007;24:259–64.
40. Takeuchi T, Tsutsumi O, Ikezuki Y, et al. Elevated serum bisphenol A levels under hyperandrogenic conditions may be caused by decreased UDP-glucuronosyltransferase activity. Endocrine J 2006; 53:485–91.
41. Matsushima A, Teramoto T, Okada H, et al. ERRgamma tethers strongly bisphenol A and 4-alpha-cumylphenol in an induced-fit manner. Biochem Biophys Res Commun 2008;373:408–13.
42. Newbold RR, Jefferson WN, Padilla-Banks E. Long-term adverse effects of neonatal exposure to bisphenol A on the murine female reproductive tract. Reprod Toxicol 2007;24:253–8.
43. Markey CM, Coombs MA, Sonnenschein C, Soto AM. Mammalian development in a changing environment: exposure to endocrine disruptors reveals the developmental plasticity of steroid-hormone target organs. Evol Develop 2003;5:67–75.
44. Erhlich S, Williams PL, Missmer SA, et al. Urinary bisphenol A concentrations and implantation failure among women undergoing in vitro fertilization. Environ Health Perspect 2012;120:978–83.
45. Skinner MK, Haque CG, Nilsson E, et al. Environmentally induced transgenerational epigenetic reprogramming of primordial germ cells and the subsequent germ line. PLoS One 2013;8:e66318.
46. Machtinger R, Combelles CM, Missmer SA, et al. Bisphenol-A and human oocyte maturation in vitro. Hum Reprod 2013;28:2735–45.
47. Barontini M, Garcia-Rudaz MC, Veldhuis JD. Mechanisms of hypothalamic-pituitary-gonadal disruption in polycystic ovarian syndrome. Arch Medical Res 2001;32:544–52.
48. Fernandez M, Bourguignon N, Lux-Lantos V, Libertun C. Neonatal exposure to bisphenol a and reproductive and endocrine alterations resembling the polycystic ovarian syndrome in adult rats. Environ Health Perspect 2010;118:1217–22.
49. Zhou W, Liu J, Liao L, et al. Effect of bisphenol A on steroid hormone production in rat ovarian theca-interstitial and granulosa cells. Mol Cell Endocrinol 2008;283:12–18.
50. Kandaraki E, Chatzigeorgiou A, Livadas S, et al. Endocrine disruptors and polycystic ovary syndrome (PCOS): elevated serum levels of bisphenol A in women with PCOS. J Clin Endocrinol Metab 2011;96:E480–4.
51. Nilsson E, Larsen G, Manikkam M, et al. Environmentally induced epigenetic transgenerational inheritance of ovarian disease. PLos One 2012;7:e36129.
52. Dechaud H, Ravard C, Claustrat F, et al. Xenoestrogen interaction with human sex hormone-binding globulin (hSHBG). Steroids 1999; 64:328–34.
53. Lord J, Thomas R, Fox B, et al. The central issue? Visceral fat mass is a good marker of insulin resistance and metabolic disturbance in women with polycystic ovary syndrome. BJOG 2006;113:1203–9.
54. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Human Reprod Update 2010;16:347–63.
55. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 1997;18: 774–800.
56. Wang T, Li M, Chen B, et al. Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance. J Clin Endocrinol Metab 2012;97:E223–7.
57. Galloway T, Cipelli R, Guralnik J, et al. Daily bisphenol A excretion and associations with sex hormone concentrations: results from the InCHIANTI adult population study. Environ Health Perspect 2010; 118:1603–8.
58. Zhao HY, Bi YF, Ma LY, et al. The effects of bisphenol A (BPA) exposure on fat mass and serum leptin concentrations have no impact on bone mineral densities in non-obese premenopausal women. Clin Biochem 2012;45:1602–6.

59. Phrakonkham P, Viengchareun S, Belloir C, et al. Dietary xenoestrogens differentially impair 3T3-L1 preadipocyte differentiation and persistently affect leptin synthesis. J Steroid Biochem Molec Biol 2008;110:95–103.
60. Somm E, Schwitzgebel VM, Toulotte A, et al. Perinatal exposure to bisphenol a alters early adipogenesis in the rat. Environ Health Perspect 2009;117:1549–55.
61. Masuno H, Iwanami J, Kidani T, et al. Bisphenol a accelerates terminal differentiation of 3T3-L1 cells into adipocytes through the phosphatidylinositol 3-kinase pathway. Toxicol Sci 2005;84:319–27.
62. Wada K, Sakamoto H, Nishikawa K, et al. Life style-related diseases of the digestive system: endocrine disruptors stimulate lipid accumulation in target cells related to metabolic syndrome. J Pharmacol Sci 2007;105:133–7.
63. Alonso-Magdalena P, Morimoto S, Ripoll C, et al. The estrogenic effect of bisphenol A disrupts pancreatic beta-cell function in vivo and induces insulin resistance. Environ Health Perspect 2006;114: 106–12.
64. Lang IA, Galloway TS, Scarlett A, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. JAMA 2008;300:1303–10.
65. Tarantino G, Valentino R, Di Somma C, et al. Bisphenol A in polycystic ovary syndrome and its association with liver-spleen axis. Clin Endocrinol 2013;78:447–53.
66. Jayashree S, Indumathi D, Akilavalli N, et al. Effect of bisphenol-A on insulin signal transduction and glucose oxidation in liver of adult male albino rat. Environ Toxicol Pharmacol 2013;35:300–10.
67. Alonso-Magdalena P, Ropero AB, Carrera MP, et al. Pancreatic insulin content regulation by the estrogen receptor ER alpha. PLoS One 2008;3:e2069.
68. Quesada I, Fuentes E, Viso-Leon MC, et al. Low doses of the endocrine disruptor bisphenol-A and the native hormone 17beta-estradiol rapidly activate transcription factor CREB. FASEB J 2002; 16:1671–3.
69. Jhala US, Canettieri G, Screaton RA, et al. cAMP promotes pancreatic beta-cell survival via CREB-mediated induction of IRS2. Genes Develop 2003;17:1575–80.
70. Alonso-Magdalena P, Vieira E, Soriano S, et al. Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. Environ Health Perspect 2010;118: 1243–50.
71. Alonso-Magdalena P, Laribi O, Ropero AB, et al. Low doses of bisphenol A and diethylstilbestrol impair Ca2+ signals in pancreatic alpha-cells through a nonclassical membrane estrogen receptor within intact islets of Langerhans. Environ Health Perspect 2005; 113:969–77.
72. Gonzalez F, Thusu K, Abdel-Rahman E, et al. Elevated serum levels of tumor necrosis factor alpha in normal-weight women with polycystic ovary syndrome. Metabolism 1999;48:437–41.
73. Kaya C, Akgul E, Pabuccu R. C-reactive protein and homocysteine levels are associated with abnormal heart rate recovery in women with polycystic ovary syndrome. Fertil Steril 2010;94:230–5.
74. Escobar-Morreale HF, Luque-Ramirez M, Gonzalez F. Circulating inflammatory markers in polycystic ovary syndrome: a systematic review and metaanalysis. Fertil Steril 2011;95:1048–58, e1041–2.
75. Kaya C, Pabuccu R, Berker B, Satiroglu H. Plasma interleukin-18 levels are increased in the polycystic ovary syndrome: relationship of carotid intima-media wall thickness and cardiovascular risk factors. Fertil Steril 2010;93:1200–7.
76. Gonzalez F, Rote NS, Minium J, Kirwan JP. Evidence of proatherogenic inflammation in polycystic ovary syndrome. Metab: Clin Experiment 2009;58:954–62.
77. Ben-Jonathan N, Hugo ER, Brandebourg TD. Effects of bisphenol A on adipokine release from human adipose tissue: implications for the metabolic syndrome. Mol Cell Endocrinol 2009;304:49–54.
78. Dumesic DA, Abbott DH, Padmanabhan V. Polycystic ovary syndrome and its developmental origins. Rev Endocrine Metabolic Disord 2007;8:127–41.
79. Diamanti-Kandarakis E, Piperi C. Genetics of polycystic ovary syndrome: searching for the way out of the labyrinth. Hum Reprod Update 2005;11:631–43.
80. Diamanti-Kandarakis E, Kouli CR, Bergiele AT, et al. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. J Clin Endocrinol Metab 1999;84: 4006–11.
81. Fernandez M, Bianchi M, Lux-Lantos V, Libertun C. Neonatal exposure to bisphenol a alters reproductive parameters and gonadotropin releasing hormone signaling in female rats. Environ Health Perspect 2009;117:757–62.
82. Susiarjo M, Hassold TJ, Freeman E, Hunt PA. Bisphenol A exposure in utero disrupts early oogenesis in the mouse. PLoS Genet 2007; 3:e5.
83. Rubin BS, Lenkowski JR, Schaeberle CM, et al. Evidence of altered brain sexual differentiation in mice exposed perinatally to low, environmentally relevant levels of bisphenol A. Endocrinology 2006;147:3681–91.
84. Palanza PL, Howdeshell KL, Parmigiani S, vom Saal FS. Exposure to a low dose of bisphenol A during fetal life or in adulthood alters maternal behavior in mice. Environ Health Perspect 2002;110: 415–22.
85. Kawai K, Nozaki T, Nishikata H, et al. Aggressive behavior and serum testosterone concentration during the maturation process of male mice: the effects of fetal exposure to bisphenol A. Environ Health Perspect 2003;111:175–8.
86. Vandenberg LN, Chahoud I, Heindel JJ, et al. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. Environ Health Perspect 2010;118:1055–70.
87. Matsumoto J, Yokota H, Yuasa A. Developmental increases in rat hepatic microsomal UDP-glucuronosyltransferase activities toward xenoestrogens and decreases during pregnancy. Environ Health Perspect 2002;110:193–6.
88. Taylor JA, Welshons WV, Vom Saal FS. No effect of route of exposure (oral; subcutaneous injection) on plasma bisphenol A throughout 24h after administration in neonatal female mice. Reprod Toxicol 2008;25:169–76.
89. Mannan MA, O'Shaughnessy PJ. Steroidogenesis during postnatal development in the mouse ovary. J Endocrinol 1991;130:101–6.
90. Vandenberg LN, Maffini MV, Wadia PR, et al. Exposure to environmentally relevant doses of the xenoestrogen bisphenol-A alters development of the fetal mouse mammary gland. Endocrinology 2007;148:116–27.
91. Yaoi T, Itoh K, Nakamura K, et al. Genome-wide analysis of epigenomic alterations in fetal mouse forebrain after exposure to low doses of bisphenol A. Biochem Biophys Res Commun 2008;376: 563–7.
92. Bromer JG, Zhou Y, Taylor MB, et al. Bisphenol-A exposure in utero leads to epigenetic alterations in the developmental programming of uterine estrogen response. FASEB J 2010;24: 2273–80.
93. Qu F, Wang FF, Yin R, et al. A molecular mechanism underlying ovarian dysfunction of polycystic ovary syndrome: hyperandrogenism induces epigenetic alterations in the granulosa cells. J Mol Med (Berl) 2012;90:911–23.