Mini Review

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Bisphenol-A and polycystic ovary syndrome: a review of the literature

https://doi.org/10.1515/reveh-2020-0032
Received March 13, 2020; accepted May 22, 2020; published online July 14, 2020

Abstract: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age with reproductive, metabolic and endocrine implications. While the exact pathophysiological mechanisms of the syndrome are unknown, its heterogeneity suggests a multifactorial causal background. In the last two decades, numerous environmental chemicals, including Bisphenol-A (BPA) that is used in the synthesis of polycarbonate plastics, have been proposed as potential contributors to the aetiology of PCOS. This review provides a holistic overview of the available data regarding the possible relation of PCOS with BPA exposure. We have included a total number of 24 studies. Eleven human case-control and 13 animal studies provided data regarding this potential relation. Accumulating evidence suggests that a correlation between high levels of BPA and the presence of PCOS may exist. Contradicting results from human and animal studies, however, render it difficult to conclude on the exact role of BPA in the pathogenesis of PCOS. BPA may constitute a consequence of the syndrome rather than a cause, but further research is still needed to clarify this. Continued efforts to study the early origins of PCOS, using prospective-designed studies, are required to identify the exact effect of BPA on women with PCOS.

Keywords: environment; gynaecology; health; human; polycystic ovarian syndrome; chemical disruptors.

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Introduction

Polycystic ovary syndrome (PCOS) constitutes the most common endocrinopathy among women in reproductive age [1]. PCOS is associated with a great number of reproductive, endocrine and metabolic features such as anovulation, infertility, hyperandrogenism, obesity, hyperinsulinism, increased risk of type 2 diabetes and cardiovascular disease, all of which render it a complex and heterogeneous condition [2–4].

During the last two decades, many inherited and acquired causal factors have been suggested as contributors to the aetiology of PCOS but it is still unclear which of these factors initiates the pathophysiological cycle of anovulation, androgen excess and hyperinsulinemia that are encountered in the syndrome [3]. Familial distribution of PCOS patients suggests that genetics play an important role in the development of the syndrome and around 250 different candidate genes have been identified in databases and linked with PCOS [5, 6]. Therefore, the pathophysiology of PCOS seems to be affected by multiple different factors [7, 8].

Recently published data on the pathogenesis of the syndrome emphasizes on the role of ethnic origin, geographic location, lifestyle and environmental factors, which also affect the heterogeneity of clinical presentation [9, 10]. Many studies have focused on the potential role of environmental chemicals, such as bisphenol- F, bisphenol- S and phthalates, which could affect the pathogenesis and/or presentation of the syndrome [11]. Among these chemicals, Bisphenol-A (BPA) has been proposed as an aetiological factor for PCOS due to its ability to act as an endocrine disruptor by mimicking the function of oestrogen [12].

The aim of this review was to provide a holistic overview of the currently available literature from both animal and human studies on the relation of Bisphenol-A and polycystic ovary syndrome and explore the potential role of Bisphenol-A in the pathogenesis and pathophysiology of the syndrome.

Introduction to Bisphenol-A

BPA is an organic synthetic compound which belongs to the group of diphenylmethane derivatives and bisphenols (4,40-dihydroxy-2,2-diphenylpropane) [13]. BPA is formed by two phenol rings connected to two methyl groups and available evidence suggests that BPA has oestrogenic properties due to its similar structure with oestrogens (Figure 1) [14].

Initially, BPA was developed as a synthetic oestrogen in the 1890s and chemical industries have used it since for multiple applications. These applications included its use as a monomer to manufacture polymers (e.g. polycarbonate and epoxy resins), an antioxidant, an inhibitor of polyvinyl chloride polymerization as well as a means to synthesise a flame retardant [15]. Nowadays, BPA is massively produced in industry, constitutes an abundant environmental chemical in our daily lives and can be found in many consumer products, such as internal coating of food and drink containers, reusable plastic bottles, medical devices and dental materials [16–19]. These products constitute the sources for human BPA exposure.

BPA can be ingested, inhaled, or pass the epidermis and then migrate to the saliva, urine and blood [20]. According to studies conducted in North America and Europe human exposure to BPA is common and the majority of people have detectable levels in urine. It is thought that food is the main contributor to the overall BPA exposure, whereas plastics and dental surgery contribute to a minor extent [21, 22]. Based on toxicological *in vivo* studies, the US Food and Drug Administration and the European Food Safety Authority have concluded that human exposure to BPA is under the safe Tolerable Daily Intake (TDI) value of 4 mg per kg of body weight per day (mg/kg bw/day).

BPA has been previously linked with several harmful health effects such as asthma, diabetes, obesity, behavioural changes, cancer and alterations in immune function and neurodevelopment in children [23–26]. However, the most common disorders caused by BPA are related to the female reproductive system [27–29]. Nowadays, an increasing number of studies suggests that BPA may have a role in the pathogenesis of PCOS [30, 31].

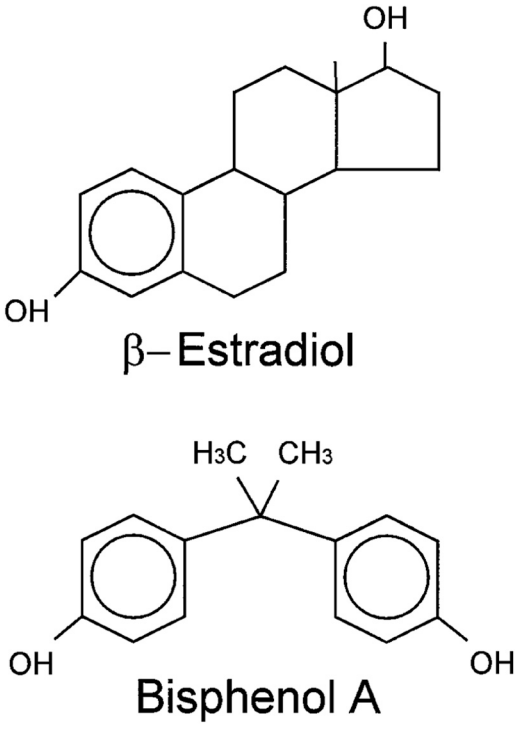

Figure 1: Chemical structures of β-oestradiol and Bisphenol-A (BPA).

Bisphenol-A as an endocrine disruptor

The available data suggests that BPA acts as a weak oestrogen. It binds to both nuclear oestrogen receptors (ER-a and ER-b) but it has 1000–2000 times less affinity to the ERs compared to the most active oestrogen, 17 b-estradiol [14, 32]. BPA has the ability to bind to the membrane bound ER receptor (ncmER), the G protein-coupled receptor 30 (GPR30), the aryl hydrocarbon receptor (AhR) and the oestrogen-related receptor-a (ERR-a) [33–35]. Consequently, the ratio of different oestrogen receptors in a population of cells may be related to the impact of BPA in this specific cell population [34]. As a result, BPA can act either as an oestrogen agonist or antagonist under different molecular environments [36]. Based on these findings, the ovary, which is the main site of oestrogen production andoestrogen receptor expression, is hypothesised to be the primary target for BPA activity [37]. In accordance to this assumption, BPA is regularly found in the fluid of ovarian follicles, a finding that also leads to the hypothesis that BPA may affect ovarian follicles and reduce ovarian reserve [38, 39].

BPA can stimulate ovarian theca cells and as a result increase the production of androgens. In this process the function of 17ß-hydroxylase (P450c17), a key enzyme in gonadal steroid biosynthesis, is possibly altered due to BPA [40]. Hyperexpression of that enzyme, which increases 17-hydroxyprogesterone levels (a key feature of PCOS), is thought to cause the excessive production of androgens by the ovary, suggesting one possible mechanism through which BPA may lead to PCOS [9, 41]. Furthermore, apart from theca cells BPA can also affect granulosa cells. An *in vitro* study, demonstrated the ability of BPA to amplify FSH-stimulated progesterone synthesis while suppressing FSH-induced oestradiol production when administered in granulosa cells for 3 days [42]. The possible capacity of BPA to influence granulosa cells may constitute another putative pathway linked to increased androgen production by the theca cells in PCOS due to the paracrine actions that granulosa cells exert on theca cell steroidogenesis [43, 44]. This idea is also supported by the fact that ovarian androgens were increased as a response to FSH injections in PCOS patients, although FSH does not act directly on theca cells [44]. Therefore, BPA may contribute directly or indirectly to increased androgen levels by interacting with theca cells, the main source of intraovarian androgens, and granulosa cells respectively [45].

BPA can also bind to the human sex hormone binding globulin (SHGB). This protein may transport BPA through plasma, change its biological availability and as a result its effect on target tissues that express oestrogen receptors. BPA may also dislocate sex hormones from SHBG and therefore increase the amount of free androgens [46].

At the same time, BPA acts on other hormonal pathways as well. These pathways are related to obesity, metabolism, and insulin regulation. BPA has an effect on adipocyte differentiation through gene regulation, inhibits the release of adiponectin which acts protectively against metabolic syndrome and increases the secretion of interleukin-6 and tumour necrosis factor alpha [47–49]. BPA promotes inflammatory conditions by acting via oestrogen receptors on adipocytes and macrophages infiltrating the adipose tissue. Chronic low-grade inflammation seems to emphasize the ovarian dysfunction and the exaggerated theca cells androgen production.

Additionally, BPA appears to activate glucocorticoid receptors which lead to the upregulation of 11-ß-HSD-1. This enzyme facilitates the conversion of cortisone to cortisol and as a result promotes adipogenesis [50]. Moreover, BPA can increase insulin production *in vitro*, by affecting pancreatic ß–cells directly. The sustained hyperinsulinemia produced by BPA affects peripheral tissues, producing insulin resistance, possibly due to the down-regulation of insulin receptors [51–53].

Recent data suggests that BPA affects signalling pathways and influences also the epigenetic mechanisms of the cell [54]. Specifically, early life exposure to BPA has been associated with prostate carcinogenesis mediated by changes in DNA methylation and altered gene expression in hypothalamus via DNA methylation and histone acetylation [55, 56]. As a result, the epigenetic regulation of specific genes during the early stages of development may alter their expression patterns or activity later in life, predisposing individuals to disease in adulthood and affecting health and disease across generations [57–59].

Taken together, generated data proposes many putative mechanisms by which BPA may affect endocrine/metabolic activity and induce epigenetic modifications.

Bisphenol-A and polycystic ovary syndrome: animal studies

The effects of the exposure to endocrine-disrupting compounds such as BPA have been examined in animal models. A summary of these studies can be found in Table 1. A common finding in animals exposed to BPA during early developmental stages is the alteration of ovarian morphology which resembles the appearance of polycystic ovaries.

In a mouse study, the changes that were noticed in the tissue morphology and function of the genital tract after prenatal BPA exposure (age of vaginal opening, ovarian follicular development, oestrous cyclicity, presence of ovarian blood-filled bursae) led the authors to hypothesize that BPA is acting by disrupting the hypothalamic-pituitary-gonadal axis by directly affecting the oestrogen-target tissues and organs [60]. Similarly, rat prenatal exposure, even in small quantities of BPA, have been shown to alter the patterns of oestrous cyclicity and decrease the levels of luteinizing hormone in plasma [61].

A decrease in the area occupied by the corpora lutea and multiple cystic follicles in the ovary were found in animals after the administration of 1 mg of BPA during neonatal period [62]. Similarly, in a very well-designed study published in 2009, rat neonatal exposure to BPA disrupted the ovarian development. The effects were dose dependent and included the formation of cysts resembling large antral follicles [63]. A similar study reported altered ovarian morphology (large number of cysts) after BPA exposure in rats [64]. These findings demonstrate the ability of BPA, when given during neonatal period, to cause

Table 1: Animal studies examining the effects of Bisphenol-A exposure on animal models.

Author Year	Study type	Model used	BPA dose	Period of exposure	Route of exposure	Outcome
Howdeshell 1999	In vivo	CF-1 mice	2.4 μg/kg	prenatal	orally (mother)	Significantly reduced the number of days between vaginal opening and first vaginal oestrus, which is highly correlated with first post-pubertal ovulation
Rubin 2001	In vivo	Sprague–Dawley rats	0.1, 1.2 mg/kg	prenatal	orally (mother)	Altered patterns of oestrous cyclicity and decreased levels of plasma luteinizing hormone
Suzuki 2002	In vivo	ICR/Jcl mice	10, 100 mg/kg	prenatal/ postnatal	subcutaneously (mother)	Ovary-independent vaginal epithelial changes when given postnatally but not prenatally
Honma 2002	In vivo	ICR/Jcl mice	2, 20 μg/kg	prenatal	subcutaneously (mother)	Early vaginal opening, no affect in first breeding reproductive functioning
Markey 2003	In vivo	CD-1 mice	25, 250 μg/kg	prenatal	subcutaneously (mother)	Increase in the percentage of ovarian tissue occupied by antral follicles
Kato 2003	In vivo	Sprague–Dawley rats	0.25, 1, 4 mg	neonatal	subcutaneously	Multiple cystic follicles in the ovary
Newbold 2007	In vivo	CD-1 mice	10, 100, 1000 μg/kg	neonatal	subcutaneously	Increase in cystic ovaries and severe pathologies of oviduct and uterus
Newbold 2009	In vivo	CD-1 mice	0.1, 1, 10, 100, 1000 μg/kg/day	prenatal	subcutaneously (mother)	Elevated incidence of ovarian cysts
Adewale 2009	In vivo	Long-evans rats	50 μg/kg and 50 mg/kg	neonatal	subcutaneously	Disrupted ovarian development but not disrupted ability of GnRH neurons to respond to steroid-positive feedback
Fernandez 2010	In vivo	Sprague–Dawley rats	500μg/50 μL and 50μg/50 μL	neonatal	subcutaneously	Altered ovarian morphology / large number of cysts
Veiga-Lopez 2013	In vivo	Sheep	0.5 mg/kg	prenatal	subcutaneously (mother)	Alterations in fetal ovarian steroidogenic gene and microRNA expression related to gonadal differentiation, folliculogenesis and insulin homeostasis
Patisaul 2014	In vivo	Wistar rats	NG	lifetime	orally	Key features of PCOS induced
Veiga-Lopez 2014	In vivo	Sheep	0.05, 0.5, and 5 mg/kg	prenatal	subcutaneously (mother)	Changes in ovarian follicular dynamics and defects in time interval between estradiol rise and preovulatory LH release

NG: not given, BPA: Bisphenol-A, PCOS: polycystic ovary syndrome.

changes in the ovary which create a polycystic morphology. However, the polycystic morphology caused by BPA administration has different fundamental morphological features compared with the morphology seen in PCOS ovaries, which consist primarily of numerous small to medium sized non-dominant follicles [65].

Apart from cystic ovaries, neonatal BPA exposure can cause long-term adverse effects in the rest of the reproductive tract, such as progressive proliferative lesions of the salpinx and uterine atypical hyperplasia [66]. BPA exposure during the third trimester has also the potential to alter transcriptional signals and influence the function of the uterus in primates and affect ovarian follicular dynamics and gene expression related to steroidogenesis in sheep [67–69]. Moreover, not only subcutaneous injection but also BPA enriched diet can induce key features of PCOS (cystic follicles, irregular oestrus, elevated body weight) in rats [70].

When given to pregnant mice, BPA crosses the placenta and reaches fetal organs. A few animal studies have examined the effect of prenatal exposure to BPA and reported changes such as increased incidence of ovarian cysts, delayed first ovulation and reduced number of corpora lutea [71–74].

Fetal alpha-fetoprotein, which is characterised as the main defense against oestrogen, binds oestrogen to reduce its activity. Moreover, the maternal liver through cytochrome P450s degrades oestrogens enzymatically and through glucuronosyl-transferase decreases BPA [74]. Given that this enzyme cannot be expressed by the fetus,

and that BPA crosses the placenta, the fetus may be unprotected and susceptible to the effects of this exogenous oestrogen [75, 76].

Overall, BPA exposure, especially during early stages of development, can cause anomalies in the morphology and function of the female reproductive tract in animals. While many of the effects resemble the anatomical characteristics of PCOS further research is required to clarify the mechanisms by which BPA disrupts the molecular mechanisms of normal female reproductive tract development.

Bisphenol-A and polycystic ovary syndrome: human studies

Human studies on the correlation of PCOS with BPA exposure are scarce in the literature. Overall, 11 studies have examined the association of PCOS with BPA and these are summarised in Table 2. These case control studies compared the levels of BPA in serum or urine of patients with PCOS and healthy asymptomatic women. Nine studies showed increased BPA levels in patients with PCOS. Moreover,7 studies reported a correlation between BPA and androgen levels.

Higher BPA levels in PCOS women compared to controls ($p<0.001$) and a statistically significant positive association between androgens and BPA concentrations were observed in a large cross sectional study published in 2011 [77]. Similarly, a Turkish study, which included 112 PCOS patients, concluded that adolescents with PCOS had higher BPA levels in serum than controls ($p=0.001$). Also, in the same study high BPA levels were significantly correlated with androgen levels [78]. Reaching similar conclusions, a research group from Poland reported significantly higher serum BPA concentrations in PCOS patients compared to asymptomatic women ($p=0.035$) and a positive correlation with serum total testosterone and free androgen index [79]. These results suggest a potential role of BPA in the pathogenesis of PCOS and more specifically a contribution to the ovarian hyperandrogenism seen in women with PCOS possibly due to the altered metabolism of androgens or their dislocation from SHBG.

The increased concentration of BPA follows similar trends in women with PCOS not only in blood but also in urine samples. In a subgroup of Iranian women BPA levels were significantly higher in PCOS group when compared with the control group ($p<0.001$) proposing a correlation between BPA exposure and PCOS [80]. However, there is one publication which unlike the previous studies, found no association between PCOS and increased BPA levels in urine [81].

In 2013, a study proposed the presence of the liver–spleen axis in polycystic ovary syndrome. In this study higher BPA levels in PCOS women were associated with higher grades of insulin resistance, hepatic steatosis, free androgen index, inflammation and spleen size. At multivariate analysis, spleen size and free androgen index were the best predictors of the increased BPA levels [82]. Apart from the common role of BPA as endocrine disruptor, a pathway involving low-grade inflammation, hyperandrogenism and liver–spleen axis in the pathogenesis of PCOS is also possible. BPA could act as a pro-inflammatory triggering factor and lead to spleen enlargement. This finding, which is a marker of inflammation, is in line with the immune derangement in women with PCOS [83].

A study conducted in Japan in 2002 showed differences between genders in serum BPA concentrations. This finding is possibly due to differences in the metabolism of BPA which is affected by androgen levels. In this study serum BPA concentrations were significantly higher in the normal men group ($p<0.001$) and PCOS group ($p<0.05$) compared to the normal women group supporting the possible relation of BPA with increased androgen levels [84]. Two years later, the same research group, compared the levels of BPA in healthy women and patients with PCOS, divided in obese and non-obese, and concluded that there was an association between serum BPA and androgen levels in both groups [85]. Interestingly, BPA was increased in both PCOS patients and healthy obese individuals suggesting that PCOS and obesity are two different aspects of the same metabolic disease [86].

Based on these findings, some studies have concluded that PCOS can lead to higher levels of BPA, in contrast to the initial belief that BPA is one of the PCOS causal factors. This hypothesis derives from the fact that the amount of circulating testosterone of women with PCOS is elevated and high androgen levels can reduce BPA clearance [87, 88]. This assumption stems from the mechanism of BPA clearance. Under physiological circumstances, the liver enzyme uridine diphosphate-glucuronosyl transferase (UGT) drives the degradation and clearance of BPA from circulation. High androgen levels, however, result in the decrease of the activity and the transcription of uridine diphosphate-glucuronosyl transferase [89, 90].

Despite the consistent results regarding the association of PCOS with high BPA levels, which are also supported by a recent meta-analysis, it remains unclear whether this relation is caused by BPA or is a consequence of PCOS [91]. Moreover, a two-way pathophysiological phenomenon with high BPA levels causing PCOS and PCOS causing further increase of BPA levels cannot be excluded [28].

Table 2: Human case control studies examining the relation of BPA and PCOS.

Author Year	Study design	Study scope	Sample type	Sample timing	PCOS patients	BPA levels in patients	Controls	BPA levels in controls	P value	Correlation between BPA and androgen levels
Takeuchi 2002	case control study	Investigate human exposure to BPA	blood	midfollicular phase	16	0.64 + 0.1 ng/mL	14	1.04 + 0.1 ng/mL	<0.05	Yes
Takeuchi 2004	case control study	Investigate serum levels of BPA in women with ovarian dysfunction	blood	midfollicular phase	13	1.05 + 0.1 ng/mL	19	0.71 + 0.09 ng/mL	<0.05	Yes
Tsutsumi 2005	case control study	Investigate the metabolism of endocrine disruptors such as BPA	blood	NG	NG	1.04 ± 0.10 ng/mL	NG	0.64 + 0.10 ng/mL	<0.05	Yes
Kandaraki 2011	case control study	Determine BPA levels in PCOS women	blood	NG	71	1.05 + 0.56 ng/mL	100	0.72 + 0.37 ng/mL	<0.001	Yes
Tarantino 2013	case control study	Evaluate the contribution of increased serum BPA levels to low-grade chronic inflammation and hyper-androgenism in women with PCOS	blood	NG	40	0.7 ng/mL	20	0.1 ng/mL	<0.0001	Yes
Vagi 2014	case control study	Investigate the association between BPA and PCOS	urine	NG	52	1.6 µg/l	50	2.1 µg/l	NG	NG
Akin 2015	case control study	Investigate the role of BPA in PCOS	blood	early follicular phase	112	1.1 + 0.1 ng/mL	61	0.8 + 0.1 ng/mL	=0.001	Yes
Vahedi 2016	case control study	Evaluate serum BPA in two women groups with and without PCOS	blood	NG	62	0.48 ± 0.08 ng/mL	62	0.16 ± 0.04 ng/mL	<0.05	NG
Wang 2016	case control study	Investigate the effect of BPA on the aromatase expression and estradiol synthesis in the granulosa cells from PCOS and non-PCOS patients	follicular fluid	36 h after hCG administration	21	338.00 ± 57.88 pg/mL	17	440.50 ± 63.70 pg/mL	<0.05	NG
Rashidi 2017	case control study	Investigate the association of PCOS with urinary BPA	urine	NG	51	3.34 + 2.63 ng/mL	51	1.43 + 1.57 ng/mL	<0.001	NG
Konieczna 2018	case control study	Investigate serum levels of BPA	blood	midfollicular phase	106	0.202 ng/mL	80	0.154 ng/mL	=0.035	Yes

NG: not given, BPA: Bisphenol-A, PCOS: polycystic ovary syndrome.

Conclusion

While the exact pathophysiology and triggering factors of polycystic ovary syndrome (PCOS) are unclear, it could be suggested that there is a possible contribution of environmental factors in its manifestation. Bisphenol-A (BPA), one of the most abundant endocrine disruptor chemicals in daily life, may play a role in the pathogenesis of PCOS by affecting different molecular mechanisms. However, it is not yet established whether the observed associations between increased BPA levels and PCOS suggest an etiological factor or whether the disorder's endocrine profile alters the storage and clearance patterns of BPA, which subsequently leads to increased serum measurements in PCOS patients. Finally, while the aetiology of this syndrome remains largely unknown, further comparative case studies are necessary to elucidate the possible effects of BPA exposure and its interactions with androgens.

Research funding: None declared.
Author contributions: All authors contributed to the design and implementation of the research, literature search, data collection, discussion of the findings and to the writing of the manuscript.
Competing interests: The authors declare no conflict of interest.
Informed consent: Not applicable.
Ethical approval: Not applicable.

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