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Polycystic ovary syndrome: do endocrine disrupting chemicals play a role?

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Abstract

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder characterized by multiple endocrine disturbances and its underlying causes, although uncertain, are likely to be both genetic and environmental. Recently, there has been interest in whether endocrine disrupting chemicals (EDCs) in the environment, particularly Bisphenol A (BPA), may contribute to the disorder. In animal models, exposure to BPA during the perinatal period, dramatically disrupts ovarian and reproductive function in females, often at doses similar to typical levels of human exposure. BPA also appears to have obesogenic properties, disrupting normal metabolic activity and making the body prone to overweight. In humans, cross-sectional data suggests that BPA concentrations are higher in women with PCOS than in reproductively healthy women, but the direction of causality has not been established. As this research is in its infancy, additional work is needed to understand the mechanisms by which EDCs may contribute to PCOS as well as the critical periods of exposure, which may even be transgenerational. Future research should also focus on translating the promising work in animal models into longitudinal human studies and determining whether additional EDCs, beyond BPA, may be important to consider.

Keywords

PCOS; Bisphenol A; BPA; Endocrine Disrupting Chemicals; EDCs

PCOS and Endocrine Disrupting Chemicals

Although polycystic ovary syndrome (PCOS) affects 5–10% of reproductive age women, its underlying causes remain uncertain. The wealth of research on PCOS in recent years has made it increasingly apparent that genetic, epigenetic, endocrine, metabolic and

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environmental factors may all contribute to the development and presentation of this complex disorder [1–6]. Most commonly, the “environmental” contributors considered have been related to obesity and lifestyle, and indeed, there is extensive evidence that both play important roles in PCOS [7,8]. However recently, the range of potentially relevant environmental factors considered has broadened to include environmental chemicals, which could affect the pathogenesis and/or presentation of PCOS. [9,10]. The hormonal anomalies characteristic of PCOS, including androgen excess and insulin resistance, suggest that endocrine disrupting chemicals (EDCs) in the environment may be particularly relevant to consider. Here we focus on EDCs that are synthetically produced, although some naturally derived compounds share endocrine-disrupting properties and may be important to consider in the future [11].

Since World War II, advances in chemistry have exponentially increased the worldwide production and use of chemicals. For example the plastic industry has grown at a 6–12% yearly rate since 1940 [12]. Over 80,000 chemicals are now used in the United States alone and approximately 1500 new chemicals are introduced every year [13]. Of these, at least 870 are documented EDCs, and because most of chemicals in production have not been tested for adverse health effects, it is almost certain that there are many more EDCs yet to be identified [14]. EDCs can mimic endogenous hormones and/or interfere with the production, secretion, transportation, metabolism, binding action and excretion of natural hormones. Originally, EDCs were thought to act primarily by interfering with hormone binding at classical nuclear receptors. However today, it is well established that EDCs have numerous modes of action and can also interfere with transcriptional factors, non-steroid receptors (e.g. neurotransmitter receptors), orphan receptors (aryl hydrocarbon receptor), and enzymatic activity [15,16]. Their effects on the body can be extensive, altering reproductive function, neurodevelopment, cancer risk, and metabolism, among other things. Some EDCs, such as Bisphenol A (BPA) and certain phthalates, are found throughout the modern environments and virtually all Americans studied show measureable body burden of these chemicals [17,18]. Importantly, because many EDCs show a non-monotonic dose-response relationship, even exposure at low doses may be linked to adverse health effects [19]. Complicating the issue, the typical person has measureable levels of dozens of EDCs at once, and very little is known about the health risks associated with chemical mixtures [20].

Given the host of endocrine abnormalities associated with PCOS, it is worth considering the role that EDCs may play. PCOS-like symptoms were first documented in the historical literature in the 1700s [21], long before the rise of modern chemistry, thus EDCs are certainly not the primary causal agent in PCOS. However, it is plausible that EDCs may contribute to the etiology of PCOS along with other factors, or may modify the presentation of this highly heterogeneous disorder. Thus far, the preponderance of research has focused on a single EDC, BPA, and for that reason it is the focus of the current review. We start with an overview of the sizeable literature in animal models on early developmental exposure to BPA in relation to PCOS-like symptoms at reproductive maturity. We then assess the epidemiological evidence supporting an association between adult BPA exposure and PCOS symptoms, including associations with both ovarian and metabolic dysfunction. Finally, given that other EDCs can disrupt ovarian function, androgen activity, and metabolic

regulation, we conclude this review by briefly considering the limited evidence related to other chemicals, suggesting avenues for future research.

Introduction to Bisphenol A

BPA is a synthetic chemical that has been widely used in the manufacture of polycarbonate plastics and epoxy resins for decades and over 6 billion pounds are produced each year [22]. Although it is perhaps best known for its use in baby bottles and water bottles (from which it has largely been phased out), BPA is also a component of PVC, which lines many water pipes, and is used in manufacture of CDs, DVDs, and thermal receipt paper [23]. In addition, one of the primary sources of BPA exposure in humans is diet, particularly the consumption of canned and processed goods [23–26]. BPA can be ingested, inhaled, or pass through the skin and as such, human exposure to BPA is virtually ubiquitous, with over 90% of Americans having measureable levels of BPA in their urine [17].

Extensive evidence shows that BPA has weakly estrogenic properties. It binds to the classical nuclear estrogen receptors (ER- α and ER- β) as well as the non-classical membrane-bound ER receptor (necmER), a transmembrane ER called GPR30, and the aryl hydrocarbon receptor (AhR) [15,27]. It appears to have a particularly high affinity for the orphan nuclear receptor estrogen-related receptor- α or ERR- α [16]. The level of BPA activity in a cell, therefore, may be a product of the combination of estrogen receptor variants contained therein [27]. It is thought that BPA disrupts signaling pathways, perhaps by interfering with estrogen receptors influencing histone modification [28]. Given these modes of action, the ovary, as the main site of estrogen production in premenopausal women, is a prime target for BPA activity and indeed, BPA is commonly found in ovarian follicular fluid [29]. BPA also appears to stimulate ovarian theca-interstitial cells to produce androgens, possibly by regulating 17 β -hydroxylase, a key enzyme in gonadal steroid biosynthesis [30]. Dysregulation of that enzyme is believed to result in the overproduction of androgens by the ovary [31], suggesting one pathway by which BPA may contribute to the etiology of PCOS [32].

At the same time, BPA also acts on other hormone systems, most notably those involved in obesity, metabolism, and insulin regulation. BPA affects adipocyte differentiation [33], inhibits adiponectin release (which is protective against metabolic syndrome) [34], and increases expression of genes involved in adipocyte differentiation [35]. BPA also appears to activate glucocorticoid receptors, resulting in upregulation of 11- β -HSD-1, an enzyme that catalyzes the conversion of cortisone to cortisol, thus further promoting adipogenesis [36]. It induces pancreatic β -cells to increase insulin production *in vitro*, suggesting one route by which it may promote insulin resistance [37,38]. In fact, current evidence suggests that β -cell dysfunction caused by BPA exposure is mediated by mitochondrial activity and metabolic pathways. BPA also alters global DNA methylation in murine preadipocyte fibroblasts [39]. Taken together, these *in vitro* studies suggest many mechanisms by which BPA may alter androgen and metabolic activity, as well as induce epigenetic modifications.

Timing of exposure: a critical question

Given that BPA has been implicated in both ovarian and metabolic dysregulation, it is a logical EDC to study in relation to PCOS, a disorder typically marked by both reproductive and metabolic aberrations. Yet testing hypotheses and establishing associations has been challenging, partly because of uncertainty about the critical period(s) during which BPA exposure might contribute to PCOS (Figure 1). It is most straight-forward, for instance, to examine effects of exposure during adulthood. However, focusing on adulthood alone may be short-sighted, because we now know that for many EDCs, the period of exposure and clinical onset of disease not only may not coincide, but may be decades apart. For many chemicals, the greatest risk to health is during the prenatal and early postnatal period, during which body systems and endocrine homeostasis are established. For that reason, much of the animal research on BPA and PCOS has targeted perinatal chemical exposure, but analogous human studies looking at early exposure have been logistically difficult, for obvious reasons. An even greater challenge is to examine transgenerational effects. As we will discuss more, there is emerging evidence in animal models that individuals with no direct exposure to EDCs (even as germ cells) can show increased incidence of PCOS-like symptoms following EDC exposure generations earlier [40].

At the same time, timing of exposure is of utmost importance in understanding potential determinants of PCOS and it has been widely posited that the prenatal and early postnatal environment may play a role in the disorder. At least two hypotheses regarding the early origins of PCOS have been proposed. The first suggests that the roots of PCOS lie in excessive exposure to androgens *in utero* and is supported by extensive data from animal models. When pregnant sheep or primates are administered supra-normal levels of androgens, the resulting female offspring show PCOS-like symptoms including hyperandrogenism, gonadotropin dysregulation, insulin resistance, and anovulation [41–43]. By this “androgen excess” hypothesis, any exposure that results in elevated androgen levels or heightened androgen activity in the fetus could promote PCOS-like symptoms later in life, at least under certain postnatal conditions. Another potential early origins hypothesis (“adipose tissue expandability”) argues that intrauterine growth restriction followed by postnatal catch-up growth may alter adipose tissue function, contributing to later insulin resistance, and possibly PCOS [44,45].

Although these non-mutually exclusive hypotheses differ dramatically in mechanism, they share the central point that the perinatal environment is a key contributor to adult risk of disease. Both hypotheses are consistent moreover, with a possible influence of environmental chemicals, which could promote hypothalamic-pituitary-ovarian (HPO) axis dysregulation and/or change patterns of growth and metabolism in the fetus. The prenatal and early postnatal period is arguably the most plausible time during which exposure to BPA or other EDCs may promote subsequent development of PCOS and for that reason, much of the animal research has focused on those periods.

Early exposure to BPA: Effects on the developing female reproductive system

There has been extensive work in rodent models showing that exposure to BPA during critical prenatal and early postnatal windows results in extensive changes in reproductive physiology and development (Table 1). In fact, BPA may have more potent effects on some aspects of reproductive development than diethylstilbestrol [46] and genistein [47], two well-studied estrogenic compounds. Reproductive tract defects linked to early BPA exposure include ovarian cyst-adenomas, proliferative lesions of the oviducts, Wolffian remnants and squamous metaplasia of the uterus, and vaginal adenosis in adulthood [48,49]. Early exposure to BPA has also been linked to earlier pubertal timing [50,51]; altered estrus cyclicity [52,53]; changes of the HPO axis including lower luteinizing hormone levels [53], down-regulation of ER- α in the vagina, altered vaginal and uterine histology [54,55]; and changes in the mammary gland [52]. Perhaps of most relevance to the current discussion, rats exposed subcutaneously to high doses of BPA during the neonatal period (postnatal days 1–10) developed PCOS-like symptoms in adulthood including increased serum testosterone and estradiol levels, reduced progesterone, and ovarian cysts [22].

Although the earliest studies used supra-normal doses of BPA to elicit effects, more recently, many studies have used “environmentally relevant” doses, concentrations that approximate the level of exposure in the general human population [56–58]. Rodents perinatally exposed to environmentally relevant BPA levels showed earlier vaginal opening, impaired ovarian follicle development, elevated antral follicle counts, ovarian cysts, and reduced corpora lutea formation compared to controls [49,59,60]. Some reproductive organs appear to be more responsive to low doses of BPA than others. Whereas an uterotrophic response is elicited only at relatively high levels, perinatal exposure at extremely low doses can result in a decrease in the relative weight of the vagina and the formation of blood-filled ovarian bursae [61]. Using a range of exposure levels, a BPA-based rodent model of PCOS was developed. Animals given the Environmental Protection Agency’s BPA “reference dose”, (the amount deemed to be a maximum acceptable daily exposure, or 50 $\mu\text{g}/\mu\text{l}/\text{kg}/\text{day}$), showed reduced fertility, though no change in oocyte number at estrus. At significantly higher doses (500 $\mu\text{g}/\mu\text{l}/\text{kg}/\text{day}$), animals did not ovulate and were entirely infertile in adulthood, showing showed fewer corpora lutea, fewer antral follicles, and more atretic follicles than control animals [22]. At both at high and low doses, PCOS-like hormonal changes, including higher androgens, lower progesterone, and more frequent GnRH pulses were evident in adulthood in exposed animals compared to vehicle-administered controls [62].

Whether similar effects of perinatal exposure to BPA are found in humans remains to be seen. To our knowledge, no study of prenatal or early postnatal BPA exposure in humans has continued long enough to assess PCOS incidence in girls as they reach adolescence and adulthood, nor has any study assessed BPA in relation to markers of reproductive development in female infants and children. Studies have shown that other EDCs, for instance, the estrogenic compounds found in soy formula, may affect development of estrogen-sensitive organs in both boys and girls, but we know of no analogous study on

BPA [63]. Given the strong evidence from animal models that BPA may contribute to prenatal programming of endocrine and reproductive function, despite the inherent difficulties in such a study, it will be important to examine the relationship between early life exposure and development of PCOS in a longitudinal cohort.

Epidemiological evidence of a relationship between BPA and PCOS: adult exposure

Given these limitations, the human literature on BPA and PCOS has focused on adult exposure. A small number of studies have directly examined BPA exposure in relation to PCOS in human populations (Table 1). All of the studies have employed a case-control design, comparing circulating BPA levels in adult women with PCOS and reproductively healthy controls. The studies have all found that BPA levels are higher in women with PCOS than controls, however despite this consistency, cross-sectional studies cannot unravel causal relationships [64–66]. The study design cannot differentiate whether: (1) elevated exposure to BPA contributes to the development or presentation of PCOS; or (2) having PCOS impairs metabolism and excretion of BPA, thereby resulting in higher bioburden of the chemical. It is also possible, of course, that the relationship is bidirectional, with elevated BPA both an underlying cause as well as a consequence of PCOS or that another underlying factor explains the relationship between the two.

Circulating BPA concentrations are correlated with body mass index (BMI; $r=0.50$), moreover which may confound or modify the relationship between BPA and PCOS [65]. In one small study, both lean and obese women with PCOS had BPA levels similar to obese controls, but higher than lean controls [65]. However in a larger study stratified by BMI, BPA levels were significantly higher in women with PCOS than in controls in both the lean and overweight/obese strata [64]. Within women with PCOS, BPA levels appear to be comparable in lean and overweight groups [64–66].

BPA levels are also correlated with androgen levels in women. Among reproductively healthy women, serum BPA is strongly correlated with free testosterone ($r=0.56$), androstenedione ($r=0.48$), and DHEAS ($r=0.46$), however it is unclear from the existing literature whether that relationship holds true within women with PCOS [65]. The relationship between BPA and androgens is unlikely to be a simple, causal one. One possibility is that by binding to sex hormone binding globulin (SHBG), BPA displaces a proportion of the bound androgens, leading to higher free androgen levels [67]. Another possibility is that BPA interferes with androgen catabolism. Indeed, in rat liver, BPA administration reduces levels of enzymes needed for testosterone hydroxylation [68]. If androgen clearance were impaired by BPA exposure in humans as well, this could be one potential cause of androgen excess in PCOS.

At the same time, it appears that metabolism and excretion of BPA may be impaired in PCOS. Under normal conditions, the liver enzyme uridine diphosphate-glucuronosyl transferase (UGT) helps to clear BPA from circulation, catalyzing it so that it can be excreted in urine and feces. However, when androgen levels are high, UGT activity and transcription is reduced [69–71]. This may partly explain why BPA concentrations are

typically higher in males than in females in both humans and animals [72,73]. It may also partly explain why BPA concentrations are higher in women with PCOS than BMI-matched controls [64,65]. Taken in total, the evidence suggests that there may be a circular relationship by which testosterone and BPA each prevent normal metabolism and clearance of the other.

Role of BPA in PCOS-related metabolic dysregulation

In most cases, PCOS is not only a reproductive disorder, but a metabolic one as well, which suggests another mechanism by which BPA may be implicated. It is estimated that 60–80 percent of women with PCOS also have insulin resistance [74]. The ovary remains responsive to insulin, resulting in hypersteroidogenesis by the theca and granulosa cells [75]. Typically, women with classical PCOS [as defined by the original NIH criteria [76]] show more metabolic defects than women with non-classical PCOS [9], who may have normal insulin sensitivity and metabolic function. This is due, in part, to greater obesity among the former group [77], but even within BMI-matched groups, women with the classical phenotype tend to have greater abdominal adiposity, insulin resistance, and more irregular lipid profile than women with non-classical, or ovulatory, PCOS [78,79].

It is no surprise that of the environmental risk factors for PCOS, obesity and diet have received much attention. Obesity appears to exacerbate PCOS pathology, leading to greater insulin resistance and by extension, androgen excess [65,80,81], symptoms which may be ameliorated after diet-related weight loss [8]. However there is also growing recognition that certain chemicals in the environment, including BPA, may act as obesogens, agents that disrupt typical metabolic activity and make the body more prone to obesity [82,83]. Epidemiological studies have linked urinary BPA levels to obesity and overweight [84–87], central obesity [88]; cardiovascular disease [89–91], diabetes and prediabetes [92,93], insulin resistance [86,94], hypertension [95], and altered liver enzyme activity [93](Table 2).

There are multiple mechanisms by which BPA may exert these metabolic effects. First, BPA suppresses release of adiponectin, a hormone secreted by adipose tissue and which is protective against insulin resistance [96]. Second, BPA increases mRNA and enzyme activity of 11 β -HSD-1, an enzyme which catalyzes the conversion of cortisone to cortisol, thus promoting adipocyte differentiation and adipogenesis [36]. Interestingly, it appears that the BPA-mediated upregulation of 11 β -HSD-1 may occur through activation of glucocorticoid receptors, suggesting that the chemical acts on both the HPO and hypothalamic-pituitary-adrenal axes [36]. Third, BPA may disrupt glucose homeostasis. In adult mice, a single dose of BPA results in an immediate decrease in glycemia, an increase in insulin, and lowered metabolism, while a prolonged exposure increases beta-cell insulin concentrations, and results in chronic hyperinsulinemia and insulin resistance [97–99]. BPA also exacerbates normal pregnancy-related insulin resistance, resulting in reduced glucose tolerance and increased insulin, triglyceride, glycerol, and leptin levels (as well as increased weight) compared to controls even several months post-partum [100]. Fourth, BPA may slow metabolism, resulting in decreased food intake and activity concurrent with disrupted insulin signaling [97]. Finally, BPA exposure also leads to gross morphological changes in relevant organ systems, including increased liver weight and abdominal adipocyte mass

[101]. Notably, most of these studies focused on low doses of BPA in the range of environmentally relevant human exposure, and in some cases, effects were seen only at low doses and not at higher doses [19,101].

Fitting with animal models showing altered β -cell function after BPA exposure, women with PCOS show a positive relationship between BPA levels and insulin resistance as measured by both the Matsuda index [64] and HoMA index [66,102]. Among women with PCOS, compared to women with low BPA levels, those with high levels had more extreme insulin resistance and hyperandrogenism, as well as increased signs of inflammation, including spleen size and CRP and IL-6 levels [66]. It is worth noting that being overweight is not a defining characteristic of PCOS. Some women with PCOS are not overweight or obese, and among morbidly obese women with insulin resistance, nearly half do not have PCOS [103]. As such, it has been proposed that obesity is not a cause of PCOS, but rather it may impact its presentation, exacerbating any underlying predisposition to PCOS [104]. This is, of course, also a possible model for understanding the role of endocrine disruptors in PCOS. Exposure during critical periods may heighten an underlying predisposition towards PCOS, either by acting directly on the ovary, indirectly through metabolic effects, or both. Clearly additional research is needed to understand the complex interactions between BPA and obesity in humans, particularly in relation to PCOS.

Future directions: transgenerational effects and other EDCs

Among the most interesting and unexpected findings to emerge from recent research on EDCs are transgenerational effects of chemical exposure. In some animal models, prenatal exposure to EDCs has effects not only in the generation gestating at the time of exposure (F1) or their offspring (F2), who arose from gametes that may have been exposed, but the subsequent generation (F3), in which there was no direct exposure at all. A series of rodent studies on transgenerational inheritance of ovarian disease has considered exposure not only to BPA, but to other EDCs including anti-androgenic phthalates and vinclozolin (a fungicide), dioxin (TCDD), pesticides, and jet fuel (JP-8). All EDCs studied profoundly disrupted reproductive function in both the F1 and F3 generations, and many of the symptoms elicited were relevant to human PCOS. For instance, when pregnant rats were exposed to a plastics mixture (BPA as well as two phthalate esters), their female offspring in the F1 generation showed PCOS-like symptoms. The symptoms continued into the F3 generation, who had no direct exposure to the plastic mixture, and yet showed a decline in fertility, disrupted pubertal development, primordial follicle loss, polycystic ovaries and tumor development [105]. Findings were similar for the other chemicals studied. Jet fuel, vinclozolin, and dioxin exposure all resulted in increased incidence of polycystic ovaries in the F1 and/or F3 generations [11,106,107], while exposure to each of the chemicals was associated with reduced primordial follicle counts in the F1 and F3 generations compared to controls [108]. Vinclozolin-exposed animals showed a significant decrease in preantral follicles in the F1 generation as well. In the F3 generation, there was a significant decrease in large antral follicles and their granulosa cells showed epigenetic modification of a number of genes implicated in PCOS [108].

Notably, exposure to some chemicals also elicited relevant transgenerational metabolic effects. In lineages exposed to the aforementioned plastics mixture, F3, but not F1, animals showed increases in obesity and abdominal fat deposition accompanying the reproductive impairments at low, but not high, doses [105], and the F3 generation from the lineage exposed to jet fuel showed increased adult onset obesity [106].

Conclusions and future directions in EDC research

An extensive animal and *in vitro* literature implicates BPA in the development of metabolic and ovarian dysfunction similar to that seen in PCOS. A much more limited human literature points to associations between the two as well, however little is known beyond that women with PCOS appear to have higher BPA levels than reproductively healthy women and more research is needed to understand why [32]. On that basis, we propose three additional directions for future research. First, we raise the possibility that other EDCs may play a role in the etiology and/or presentation of PCOS. BPA has received the most attention from researchers thus far, however there are likely to be other environmental chemicals with the potential to disrupt estrogen, androgen, and metabolic pathways, causing PCOS-like symptoms. Second, in humans, unlike in most animal models, chemical exposure occurs in mixtures, raising the possibility that particular combinations of exposures contribute to the disorder. We are typically exposed to dozens of chemicals at once [18] and for this reason, research into “mixtures” of chemicals, while complicated to do, is more environmentally relevant [109]. In particular, future research should continue investigating the influence of low dose mixtures on reproductive disease. Finally, the recent transgenerational experiments suggest increased disease risk generations after the initial exposure and implicate epigenetics as a possible mechanism underlying PCOS.

These findings suggest that exposure to EDCs may promote epigenetic changes that promote PCOS-like symptoms for several generations after the initial exposure. This obviously presents a challenge for the research on human populations because of the long intergenerational interval as well as our virtually continuous exposure to EDCs in the modern environment. However it also suggests that looking for an epigenetic “signature” of PCOS may be a promising direction for future research.

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Abbreviations

BPA	Bisphenol A
EDC	Endocrine Disrupting Chemical
HPO	hypothalamic-pituitary-ovarian
PCOS	polycystic ovary syndrome

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Figure 1.

Critical periods during which exposure to endocrine disrupting chemicals (EDCs) may affect various aspects of reproductive and metabolic function, possibly contributing to PCOS.

Table 1
Summary of selected studies on EDCs exposure and reproductive outcomes relevant to PCOS.

EDC	Period of Exposure	Species (sample size)*	Dose	Health Outcome	References
BPA	Prenatal	Mice (21)	2.4 µg/kg/day	Prenatal exposure to BPA caused early onset of puberty.	Howdeshell et al. 1999
BPA and DES	Prenatal	Mouse (41–51)	BPA: 2, 20 µg/kg/day DES: 0.02, 0.2, 2 µg/kg/day	Low dose BPA and DES caused increased AGD in females and altered estrus cyclicity.	Homma et al. 2002
BPA	Perinatal	Rat (12–34)	0.1 mg/kg/day or 1.2 mg/kg/day	BPA increased body weights and altered estrous cyclicity. The low dose had a more persistent life-long influence on body weight.	Rubin et al. 2001
BPA	Neonatal	Rat (9–11)	Average 5 mg/kg/day or 50 mg/kg/day	BPA exposure altered hypothalamic hormone action, lower GnRH induced LH, and estrus cyclicity.	Fernandez et al. 2009
BPA	Prenatal	Mouse (6–10)	25 or 250 µg/kg/day	BPA exposure led to early onset of puberty, increased body weight, decreased absolute vaginal weight, increases in blood-filled ovarian bursae, and increase in antral follicles.	Markey et al. 2003
BPA	Prenatal and Neonatal	Mouse (5–12 prenatal; 7 neonatal)	Prenatal: 10 or 100 mg/kg/day Neonatal: 15 or 150 µg/pup/day	Number of corpora lutea was reduced after prenatal BPA exposure. Neonatal exposure to high dose BPA caused a significant increase in polyovular follicles.	Suzuki et al. 2002
BPA	Neonatal	Mouse (16–23)	10, 100, 1000 µg/kg/day	Para-ovarian cysts of mesonephric origin and cystic endometrial hyperplasia increased in all exposed groups. Corpora lutea decreased in a dose-dependent manner.	Newbold et al. 2007
BPA	Prenatal	Mouse (13–16)	0.1, 1.0, 10, 100, 1000 µg/kg/day	A significant increase in number of ovarian cysts was seen at BPA 1.0 µg/kg/day.	Newbold et al. 2009
BPA	Adult	Human (71 PCOS; 100 controls)	—	BPA levels were significantly higher in PCOS women compared to controls. Testosterone and Androstenedione were positively associated with BPA. Finally, BPA was positively correlated with insulin resistance.	Kandaraki et al. 2011
BPA	Adult	Human (6 PCOS; 28 abnormal cycles; 26 controls)	—	Women with PCOS and over-weight women without PCOS had higher circulating levels of BPA. Non-obese women and women with other menstrual disease did not show an increase in BPA. BPA was associated with elevated testosterone, androstenedione, and DHEAS.	Takeuchi et al. 2004

* In some cases, different treatment groups had different sample sizes and in those cases, the minimum and maximum are noted.

Table 2

Summary of selected studies on EDCs exposure and metabolic outcomes relevant to PCOS.

EDC	Period of Exposure	Species (sample size) ^a / cell type	Dose	Health Outcome	References
BPA	—	Mouse Beta TC-6 cells	100 ng/mL	BPA induced insulin production, increased Hsp70 production and decreased the expression of GRP78	Makaj et al. 2011
BPA	—	Mouse Pancreatic Islets of Langerhans	100 µg/kg/day	BPA up-regulated the production of insulin mediated by ERα.	Nadal et al. 2009
BPA	—	Rat INS-1 cells	0.002, 0.02, 0.2, 2.0 µM dissolved in DMSO	Dose dependent decrease in cell viability and increased apoptosis was identified. Insulin production, mitochondrial activity including ATP production, gene expression was altered with increasing BPA.	Lin et al. 2013
DES, BPA, TCDD, PCB-153, HCB, BDE-47	—	Mouse Preadipocytes	10 µM DES, 10 µM BPA, 0.1 µM TCDD, 10 µM PCB-153, 1 µM HCB, 10 µM BDE-47	DES, BPA, TCDD, BDE-47, PCB-153, HCB, all decreased methylation. BPA, BDE-47, and TBT increased adipocyte differentiation.	Bastos Sales et al. 2013
BPA	Prenatal	Mouse (9–14 litters)	5, 50, 500, 5000, 50,000 µg/kg/day	Low, but not high, dose BPA exposure was associated with increased gonadal, renal and abdominal fat, low serum leptin, and decreased adiponectin levels and glucose tolerance.	Angle et al. 2013
BPA	Adult	Rat (6)	0.005, 0.5, 50, 500 µg/kg/day	BPA at doses as low as 5ng/kg/day significantly lowered insulin in reproductive tissues.	D'Cruz et al. 2012
BPA	Adult	Human (40 PCOS cases, 20 controls)	—	Women with PCOS showed evidence of metabolic dysfunction, including increased insulin resistance, high hepatic steatosis, increased spleen size and inflammation compared to controls, adjusting for BMI.	Tarantino et al. 2013
BPA	Adult	Human (1455)	—	High BPA concentrations were associated with diabetes, cardiovascular disease, and abnormal liver enzyme concentrations.	Lang et al. 2008
BPA	Prenatal/ child	Human (311)	—	Prenatal BPA was associated with lower BMI in pre-pubertal girls. However, current high BPA was associated with increased waist circumference and BMI.	Harley et al. 2013

* In some cases, different treatment groups had different sample sizes and in those cases, the minimum and maximum are noted.