Reproductive Sciences
2017, Vol. 24(1) 19-27

DOI: 10.1177/1933719116654992
journals.sagepub.com/home/rsx
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Prenatal Exposure to Endocrine Disruptors: A Developmental Etiology for Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common and complex endocrinopathies among reproductive-age women. Polycystic ovary syndrome is characterized by symptomatology of oligomenorrhea and androgen excess, with or without presence of polycystic ovarian morphology. The etiology of PCOS is multifactorial, including genetic and environmental components. It has been previously established that prenatal androgen exposure results in a PCOS phenotype in experimental animal models and epidemiologic human studies. Investigators hypothesize that prenatal exposure to endocrine-disrupting chemicals (EDCs) may contribute to PCOS development. This review examines the emerging research investigating prenatal exposure to 3 major classes of EDCs—bisphenol A (BPA), phthalates, and androgenic EDCs—and the development of PCOS and/or PCOS-related abnormalities in humans and animal models. Highlights of this review are as follows: (1) In rodent studies, maternal BPA exposure alters postnatal development and sexual maturation;, (2) gestational exposure to dibutyl phthalate and di(2-ethylhexyl)phthalate results in polycystic ovaries and a hormonal profile similar to PCOS; and (3) androgenic EDCs, nicotine and 3,4,4'-trichlorocarbanilide, create a hyperandrogenic fetal environment and may pose a potential concern. In summary, prenatal exposure to EDCs may contribute to the altered fetal programming hypothesis and explain the significant variability in severity and presentation.

Keywords

polycystic ovary syndrome, prenatal exposure, endocrine disruptors

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among reproductive–age women. The estimated prevalence of PCOS ranges between 4% and 12% worldwide.[1-3] The 2003 Rotterdam criteria for diagnosis of PCOS includes 2 of the following 3 criteria (1) oligo- or anovulation, (2) clinical or biochemical evidence of hyperandrogenism, and (3) polycystic ovarian morphology on ultrasonography.[4] Androgen excess has been associated with health risks such as insulin resistance and long-term risk of metabolic syndrome.[5-9] The etiology of PCOS remains multifactorial with emerging literature on genetic pathways and environmental factors.

Although the initial signs and symptoms of PCOS present during or just prior to the onset of puberty, clinical diagnoses are difficult to establish accurately and often are not made until later on in life.[10-12] There have been no studies on the time it takes from first presentation of symptoms to a diagnosis of PCOS, but it has recently been suggested that diagnosis of adolescent PCOS should wait until at least 2 years after menarche.[13] Additionally, as a syndrome, PCOS is characterized by variable symptom severity and clinical presentation and may dynamically change in phenotype across the reproductive life span.[14]

Fetal programming is a process where biological or exogenous signals or insults at critical stages of development induce permanent changes in tissue structure or function.[15] These alterations may be a manifestation of adaptive responses to the *ex utero* environment. It is well known that the critical developmental stages that take place *in utero* are times of significant cellular proliferation, differentiation, and functional maturation. Intrauterine exposures may have profound effects based not only upon the type of exposure but also upon the timing of

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exposure, even at low doses. A study conducted by Webber et al[16] proposed that these adaptations to exogenous insults take place *in utero* during ovarian development and oogenesis. Furthermore, a subset of women with adult-onset PCOS may be attributable solely to intrauterine exposures that may ultimately induce its metabolic and reproductive sequelae.[17]

Concern over endocrine-disrupting chemicals (EDCs) as a health hazard has increased as their exposure is ubiquitous within the modern living environment. Research findings have shown that they may pose the greatest risk during prenatal development by causing irreversible changes to differentiating tissues.[18,19] In particular, extensive work has been done on 6 major classes of EDCs (phthalates, phenols, perfluorinated compounds, flame retardants, polychlorinated biphenyls [PCBs], and organochlorine pesticides) to prove that these EDCs do indeed cross the placental barrier.[20] In addition, harm may be potentiated as the fetal liver has not matured to detoxify these substances during ovarian/reproductive organogenesis. There is additional concern as EDC exposure is widespread, is poorly regulated, and can bioaccumulate up the food chain and also in maternal fat stores. Studies have shown that prenatally exposing gestating rats to either a mixture of phthalates and bisphenol A (BPA),[21] jet fuel,[22] and vinclozolin[23] or a mixture of N,N-diethyl-meta-toluamide (DEET) and permethrin,[24] all lead to PCOS-like characteristics as far as the third generation. In human studies, PCB exposure was associated with menstrual cycle abnormalities[25] and dose-dependent implantation failure in human in vitro fertilization (IVF).[26] The organochlorine pesticide, hexachlorobenzene, was associated with reduced odds of implantation after embryo transfer during human IVF.[27]

In an effort to elucidate the current and emerging findings, this review will discuss 3 major classes of EDCs—BPA, phthalates, and androgenic EDCs and will conclude with a discussion of research challenges and suggested directions that show promise for further investigation.

Prenatal Androgen Exposure and the Development of PCOS

Prior research in both humans and animals has examined the effect of increased exposure to androgens *in utero* and its association with the incidence of PCOS. The role of excess androgens in the development of PCOS has long been known.[28,29] There is evidence that hyperandrogenism in girls is temporally associated with (precedes) premature pubarche and polycystic ovaries following puberty,[30] while premature pubarche also increases the risk for hyperandrogenism and polycystic ovaries.[31]

Studies in humans. There are few recent studies on the effect of fetal exposure to excess androgens in humans. One study describes a cohort of daughters born to mothers with PCOS.[32] These daughters have an increased risk of developing the syndrome as adults.[32] In studies of both women with and without PCOS, increased maternal testosterone (T) levels at midgestation (18 weeks) have been shown to predict increased anti-Mullerian hormone (AMH) levels in female offspring at adolescence, a clinical feature characteristic of both adolescents and adults with PCOS.[33,34] Increased AMH levels are also prevalent among infants born to mothers with PCOS.[35,36] However, in a prospective cohort study, investigators found no correlation between midgestational maternal blood concentrations of androgens in pregnant women and the development of PCOS traits in female offspring during adolescence.[37] Analysis of prenatal exposure to excess androgens is performed by assessment of serum T concentrations in (1) maternal blood, (2) umbilical cord blood, or (3) amniotic fluid. Any of these compartments alone may present an incomplete hormonal profile at the time of critical fetal programming.[38-40]

Studies in rats. Studies with prenatally exposed Wistar rats found cystic ovarian follicles and elevated numbers of preantral and antral follicles ($P = .07$ and $P < .01$, respectively) compared to unexposed offspring.[41] In this rat model, lower numbers of corpora lutea were also observed in exposed versus unexposed offspring ($P < .05$).[41] The offspring also had significantly altered T levels (1.12 ± 0.08 ng/mL in experimental vs 1.33 ± 0.05 ng/mL in controls; $P < .05$) and luteinizing hormone (LH) levels (1.87 ± 0.14 mIU/mL in experimental vs 2.29 ± 0.14 mIU/mL in controls; $P < .05$).[41] Ovulatory dysfunction and menstrual disorders are a common feature of PCOS,[4] and Sprague-Dawley rats with prenatal androgen exposure have developed irregular and prolonged estrous cycles, decreased numbers of preovulatory ovarian follicles, higher levels of LH and progesterone (P), and significant reductions in ovulation compared to unexposed female rats.[42]

Studies in monkeys. Prenatally exposed female rhesus monkeys possess a hormonal profile similar to that of PCOS (increased serum LH and androgens) as well as insulin resistance in infant to adult stages of life.[43,44] Regardless of timing of exposure (early or late), prenatally exposed female rhesus monkeys had ovulatory dysfunction and decreases in menstrual cycle length by 40% to 50% compared to unexposed female monkeys.[17] Another study demonstrated that prenatal excess androgen exposure resulted in increased numbers of small-, medium-sized, and primary follicles.[45]

Studies in sheep. The PCOS phenotype has also been recreated in sheep, with prenatally androgenized ewes meeting the diagnostic criteria for PCOS, in addition to having other abnormalities characteristic of PCOS including insulin resistance, LH hypersecretion, and reduced negative feedback of P secretion.[46] Prenatally administered androgen had a virilizing effect both on ewe external genitalia (yielding a penis and scrotal tissue but no testicular tissue) and on internal genitalia (yielding remnants of Wolffian ducts and a dilated uterus with secretions).[47] The exposed ewes' ovaries were also larger and contained an increased number of large antral follicles, follicular cysts, or increased stroma.[47] Ovarian biopsies of the ewes' ovaries showed a significantly lower number of

primordial follicles in exposed ewes compared to controls (46.9% vs 71.1% at the primordial stage, respectively).[47]

Environmental Androgens

Due to the existing data on prenatal exposure to excess androgens, it is worth investigating the role of environmental androgens in creating a hyperandrogenic fetal environment. One agent with androgenic activity is 3,4,4′-trichlorocarbanilide, also known as triclocarban (TCC), a widely used antimicrobial found in soaps, clothing, carpets, plastics, toys, school supplies, and pacifiers.[48] Triclocarban has been detected in umbilical cord plasma.[49] Alone, TCC has little to no androgenic activity; however, in the presence of T, TCC amplifies the effects of T at the level of the androgen receptor (AR) by increasing AR-mediated transcriptional activity, leading to a 45% increase in T-induced signal transcriptional activity.[50] Such a synergistic effect increases the bioactivity of endogenous T, resulting in a physiological environment not unlike that created by increased serum androgen concentrations.

Perfluoroalkyl acids (PFAAs) are a group of chemicals that have surfactant properties and are widely used in industrial and commercial products.[51] One study demonstrated that members of the PFAA chemical group (perfluorooctane sulfonic acid [PFOS], perfluorooctanoic acid [PFOA], and perfluorohexane sulfonic acid [PFHxS]) have androgenic activity. Adjusted total T concentrations were on average 0.18 nmol/L higher in daughters of mothers with very high PFOS exposure compared to daughters with very low exposure.[51] Similar significant trends were seen for daughters prenatally exposed to PFOA ($\beta = 0.24$; 95% confidence interval [CI]: 0.05-0.43) and PFHxS ($\beta = 0.18$; 95% CI: 0.00-0.35).[51]

Another compound with androgenic activity is nicotine. Nicotine has been shown to cross the placental barrier and accumulate in amniotic fluid at a concentration 88% greater than in maternal plasma.[52] Nicotine has complex and multifactorial effects. Women smokers have an elevated T due to the nicotine. A study conducted among women with PCOS by Cupisti et al[53] found that smokers had increased free T levels (0.03 [0.02-0.05]) compared to nonsmokers (0.04 [0.02-0.06]; $P = .02$). The literature on age at menarche among daughters of maternal smokers is mixed. Studies have found that daughters of mothers who smoked during gestation had an earlier age at menarche compared to daughters of mothers who did not.[54-56] However, 2 studies found that heavy maternal smoking (>20 cigarettes a day) led to a later age at menarche in female children.[57,58]

Maternal smoking has also been shown to increase human fetal estrogen levels, dysregulate cytochrome P450 (which is involved in the biosynthesis of androgens and metabolism of nicotine[59,60]), alter the expression of follicle-stimulating hormone (FSH) receptors, and increase the number of primordial follicles compared to controls.[61] A study in rats also showed that prenatal exposure to nicotine results in chronically increased levels of serum T in female offspring.[62]

During gestation, both elevated maternal sex hormone–binding globulin (SHBG) and placental androgen metabolism function to protect the fetal environment from excess androgen exposure.[63] It is not known whether SHBG provides similar protection from environmental androgens.

Phthalates

Phthalates, a class of compounds with antiandrogenic activity, are used to soften plastic and vinyl.[64] Phthalates are found in numerous consumer products, such as cosmetics, toiletries, shower curtains, wallpaper, food packaging, and medical products, such as intravenous tubing.[64] The prevalence of phthalate exposure is considered to be widespread in the United States, as most people in the general population have detectable levels of 13 different phthalates and phthalate metabolites in their urine.[65] A study on maternal urine and amniotic fluid levels of common phthalates and phthalate metabolites confirmed that this class of EDCs can cross the placental barrier.[66] In addition, 1 study of infants admitted to the neonatal intensive care unit (NICU) showed that urine phthalate and phthalate metabolite concentrations corresponded with categorized levels of exposure to NICU phthalate-containing plastics due to leaching of the phthalates from the medical equipment (IV tubing, feeding tubes).[67] In rodent studies, phthalate exposure was associated with increased visceral adiposity and reduced fertility.[68]

Dibutyl phthalate. Findings from animal studies indicate that susceptibility to the adverse reproductive effects of dibutyl phthalate (DBP) is greater during prenatal exposure compared to adult exposure.[69] In rodents, high level of DBP exposure during pregnancy is associated with reproductive system and organ abnormalities in female offspring.[69] Another study in rats gestationally exposed to DBP and di(2-ethylhexyl)phthalate (DEHP), as well as BPA, found that all of the females among the first-generation (F1) and third-generation (F3) offspring had a significantly higher incidence of polycystic ovaries characterized by an increased number of ovarian cysts.[21] Although these results indicate that such exposure contributes to a transgenerational establishment of PCOS in offspring, the study did not verify whether these effects were associated with combined exposure to both phthalates and BPA or to DBP exposure alone. Additionally, the dosage of exposure was over 10 000 times the average daily human exposure encountered in the environment.[21]

In light of these results, the published research on DBP warrants further investigation. More specifically, additional animal studies should be conducted that exclusively assess the effects of gestational exposure to DBP at environmentally relevant exposure levels before further investigations involving exposures that include a combination of DBP and other EDCs. Although an examination of composite EDC exposures has been proposed to be more representative of human exposure,[70] the effect of DBP exposure alone must first be elucidated in order to determine its impact on PCOS pathogenesis.

Di(2-ethylhexyl)phthalate. Although studies show that DEHP is a reproductive and developmental toxicant in humans and animals,[71,72] the current literature reports conflicting findings regarding the actions of DEHP on female reproduction. Animal studies have shown that DEHP exposure is associated with altered ovarian steroidogenesis and low levels of P.[73] In adult rats, studies show that DEHP exposure is associated with (1) decreases in serum estradiol (E2) levels and (2) cessation of ovulation.[74] These actions are hypothesized to be carried out by the major metabolite of DEHP, mono(2-ethylhexyl) phthalate (MEHP), which has been proposed to directly inhibit ovarian production of E2, resulting in anovulation.[74] Polycystic ovarian morphology has also been described in adult female rats after adult exposure to DEHP.[73] A study of gestational exposure to DEHP at environmentally relevant levels in mice found that the ovarian weights of female offspring were approximately 35% higher compared to offspring without prenatal DEHP exposure.[75]

Phthalates have also demonstrated antiandrogenic effects in humans. A study conducted by Main et al[76] found that serum T concentration in infants was inversely associated with serum phthalate concentrations. In women carrying female fetuses, log serum levels of DEHP and the metabolite of DBP, monobutyl phthalate (MBP), have been found to be inversely correlated with log total T concentrations (-0.15, 95% CI: -0.26 to -0.04, $P = .04$ for DEHP and -0.20, 95% CI :-0.39 to -0.01, $P = .01$ for MBP) and log free T concentrations (-0.15, 95% CI: -0.27 to 0.03, $P = .01$ for DEHP and -0.21, 95% CI: -0.42 to 0.004, $P = .05$ for MBP).[77] In a human study, women with relatively higher creatinine-adjusted urinary concentrations of MEHP and MBP had lower odds of having PCOS in comparison to controls with normal levels of the metabolite.[78] Additionally, the only cohort study known thus far to examine the impact of *in utero* phthalate exposure on PCOS development in offspring found that relatively higher maternal serum levels of phthalate metabolites, including MEHP, were associated with a lower prevalence of PCOS among their daughters ($P = .005$).[79] However, this study also found that maternal levels of another phthalate metabolite, monoethyl phthalate, were negatively associated with levels of AMH ($r = -.21$, $P = .031$).[79]

The literature on DEHP and MEHP exposure *in utero* is conflicting with regard to ovarian effects. This may be due to studies using different measures of ovarian function. Classic cases with PCOS exhibit an ovarian morphology consisting of many peripheral small antral follicles with relatively larger stroma compared to normal ovaries as well as an increased number of primary and preantral follicles.[80] There is also hyperplasia[81] of the theca cells around the follicle that accounts for the production of excess ovarian androgens in PCOS cases.[82] Rodent studies on DEHP and MEHP have shown that exposure accelerates the rate of primordial follicle recruitment, leading to lower numbers of primordial follicles and increased numbers of antral and preantral follicles.[83] Furthermore, DEHP was associated with an increased number of mature ovarian follicles.[83] However, DEHP exposure also decreases the number of primary and secondary follicles, likely via induced follicular atresia.[83] In addition, in a recent study of *in utero* DEHP exposure in rats, the ovaries of exposed female offspring exhibited a decreased theca cell layer thickness compared to unexposed offspring.[84] In addition, exposure resulted in significantly increased serum FSH levels and no apparent changes in offspring fertility.[84] Such findings imply that *in utero* exposure to DEHP does not appear to be implicated in the pathogenesis of PCOS. However, the study was not able to accurately assess the levels of serum LH or the patterns of LH secretion in offspring. Since increased levels of LH along with a decreased periodicity of its secretion are a hallmark of PCOS, additional studies are warranted. Given the discrepancies from the available literature, further animal studies are needed in order to better establish the effects of prenatal phthalate exposure in offspring.

Bisphenol A

Bisphenol A is an estrogenic monomer largely used in the making of polycarbonate plastics and epoxy resins with exposure considered to be ubiquitous in the general population due to detectable levels of BPA in urine at all ages and percentile levels.[65] As BPA has been associated with metabolic issues, researchers have begun to investigate its potential contribution to the pathophysiology of PCOS. A study in women found that serum BPA concentrations in those diagnosed with PCOS were significantly higher compared to women without PCOS (1.05 ± 0.56 ng/mL vs 0.72 ± 0.37 ng/mL, respectively; $P < .0001$).[85] A study in an adolescent female cohort found that having a diagnosis of PCOS was the main factor in predicting elevated levels of serum BPA ($P = .029$).[86] In this adolescent cohort, serum BPA levels were significantly elevated in girls with PCOS compared to the control group (1.1 ± 0.4 ng/mL vs 0.8 ± 0.3 ng/mL, respectively; $P = .001$).[86] Another study reported a positive correlation between BPA levels and the severity of insulin resistance in women with PCOS (1.39 ± 1.35 ng/mL in women with insulin resistance vs 0.57 ± 1.11 ng/mL in controls; $P = .0003$).[87] Women with PCOS were found to have a higher serum BPA mean concentration of 0.7 ng/mL, with a range of 0.1 to 6.0 ng/mL compared to 0.1 ng/mL with a range of 0.1 to 0.6 ng/mL in controls, along with more severe cases of insulin resistance (homeostatic model assessment score of 3.0 ± 1.2 in women with PCOS vs 1.4 ± 0.3 in controls).[87] Increased insulin resistance has been reported to be prevalent among cases with PCOS; PCOS is present in a majority of obese women and up to 30% of nonobese women with the syndrome.[88] Genome-wide association studies in China and Europe have also found specific susceptibility loci for PCOS that involve the insulin receptor,[89,90] suggesting that PCOS and insulin resistance are closely related. Bisphenol A has also been proven to induce insulin resistance, with an odds ratio of 2.43 (95% CI: 1.35-4.38; $P = .006$).[91] Additionally, serum BPA levels positively correlated with body mass index, total T, free T, dehydroepiandrosterone, and dehydroepiandrosterone

Table 1. Reported Effects of Prenatal Exposure to Bisphenol A (BPA) in Rodent Models.[a]

Species	Developmental Stage of Exposure	Dosage	Effects	References
Mouse	Days 11-17 (organogenesis)	2.4 μg/kg/d (environmentally relevant)	Advanced onset of first estrous	Howdeshell et al[99]
Mouse	Days 11-birth (ovarian development)	0.5 μg/kg/d (mimics exposure from bottle feeding)	Decreased number of primordial follicles; shortened estrous period; decreased fertility (impaired ovulation)	Wang et al[95]
		20 μg/kg/d (previously shown to disrupt oocyte meiosis)	Decreased number of primordial follicles; shortened estrous period; decreased fertility (impaired ovulation)	
		50 μg/kg/d (EPA referenced safe dose)	Decreased number of primordial follicles; advanced puberty onset; decreased fertility (impaired gestation)	
Mouse	Days 11.5-18.5 (oocyte maturation)	20 μg/kg/d	Increased incidence of meiotic aberrations in oocytes	Susiarjo et al[96]
Mouse	Days 11-12, 12.5, 13.5, and 14.5	20 μg/kg/d	Changes in oocyte gene expression within 24 hours of exposure onset; increased incidence of meiotic aberrations in oocytes	Lawson et al[97,b]
Rat	Days 6-21	50 mg/kg/d (NOAEL)	Longer estrous cycles	Schönfelder et al[98]
Mouse	Days 11-17	20 μg/kg/d	Advanced onset of first estrous	Honma et al[100]

Abbreviations: EPA, Environmental Protection Agency; NOAEL, no observed adverse effect level.
[a]The effects of BPA exposure during fetal development vary by dosage in micrograms or milligrams per kilogram per day (μg/kg/d or mg/kg/d) and prenatal developmental stage of exposure. Reported reasoning for dosage and timing of exposure are listed, as available.
[b] Exposure measured over multiple lengths of time. Results apply to all durations of BPA exposure.

sulfate for both women with and without PCOS; however, no such correlation between serum BPA and any other sex hormone (LH, FSH, and E2) concentrations was found.[85,92] Bisphenol A therefore seems to be uniquely estrogenic in its receptor binding and androgenic in its correlated hormone profile.

Currently, BPA has been identified as a possible hazard to fetal development.[93] Bisphenol A has been identified in fetal serum and full-term amniotic fluid, confirming its ability to pass through the placental barrier.[94] Additionally, the fetus may be susceptible to BPA bioaccumulation during the first half of fetal development as BPA concentration in amniotic fluid assayed at 15 to 18 weeks gestation was found to be 5 times higher than maternal serum samples collected during early pregnancy as well as maternal serum samples collected during late pregnancy.[94] The precise mechanism of prenatal metabolic clearance of BPA is unknown—it is unknown whether the placenta or fetal liver/fetal kidney participates in BPA metabolism. Bisphenol A accumulates in amniotic fluid into midterm gestation. Amniotic fluid concentrations of BPA then decrease as fetuses reach full term, possibly indicating that the fetus gradually metabolizes BPA as fetal liver function matures.[94]

In a study investigating BPA in rodents, *in utero* exposure during early ovarian development resulted in decreased fertility among the F1 offspring.[95] The effect of such exposure has also been proposed to span across generations, as impaired oocyte meiotic maturation has also been reported to occur.[96,97]

For many chemical hazards, the time of exposure that poses the greatest risk to health and future development is during the prenatal period when organ systems and physiological homeostasis are being established. For example, prenatal exposure of female rats to the no observed adverse effect level (NOAEL) of BPA established by the Environmental Protection Agency was observed to have a greater percentage of longer estrous cycles compared to controls.[98] Additionally, mouse studies of prenatal exposure at levels far less than the NOAEL for BPA found that female offspring had a significantly earlier onset of puberty.[99,100]

While the findings from animal studies appear to correlate with the research on adult BPA exposure and the incidence of PCOS (Table 1), the effects of human prenatal exposure to BPA remain largely unknown. As of this review, no human studies on prenatal BPA exposure have been published to investigate its potential longitudinal association with PCOS development during adolescence or adulthood. However, studies of other EDCs have shown that those with estrogenic activity may affect the development of estrogen-sensitive organs.[101] Taking into account the findings from animal studies, which indicate that BPA impacts prenatal programming and thus leads to alterations in endocrine and reproductive function, future research should longitudinally examine the relationship between prenatal exposure in humans and the development of PCOS. Future research directions proposed by the field include the usage of developmental biomarkers, particularly those involved in reproductive development, to explore this association in female infants and children in a longitudinal cohort.[102]

Transgenerational Inheritance Reaching From Prenatal Exposure

Aside from the study of phthalates and BPA mentioned earlier,[21] other studies have shown that prenatal exposure to

different EDCs can induce epigenetic transgenerational inheritance of PCOS. Gestating F0 female rats exposed to jet fuel (a hydrocarbon mixture with known toxicologic effects) during the fetal gonadal development period led to significantly increased numbers of ovarian cysts in F1 and F3 rats and significantly increased levels of E2 in F3 rats.[22] Increased pubertal abnormalities (either early or late onset of puberty) were seen in both F1 and F3 rats but did not reach significance.[22]

Another study exposed gestating F0 female rats to vinclozolin (a fungicide known to cause transgenerational epigenetic diseases such as prostate disease, kidney disease, and female reproductive defects).[23] Researchers found that all F1 to F3 female rats had a significant increase in ovarian cysts that had a predominant theca cell layer but were lacking in granulosa cells and oocytes.[23]

Another study exposed gestating F0 female rats to vinclozolin, a mixture of permethrin (the most commonly used insecticide that can cause minor toxicologic effects in mammals) plus DEET (an insect repellant with negligible toxic effects), a plastics mixture (BPA, DBP, and DEHP), dioxin, and jet fuel.[24] The F1 and F3 generations all had significantly decreased primordial follicles regardless of their exposure.[24] Only the F3 generation showed a significant increase in total number of large and small ovarian cysts as well as number of small cysts regardless of exposure.[24] An increase in the number of large cysts in the F3 generation was seen in the vinclozolin, pesticide, low-dose plastics mixture, and jet fuel treatment groups.[24] The F1 generation exposed to the low-dose plastics mixture, jet fuel, or vinclozolin showed a significant increase in small antral follicles.[24] Finally, only the F3 generation from the vinclozolin lineage showed significantly elevated androgen levels compared to controls.[24]

Conclusion

Although this review examined literature on 3 major classes of EDCs that are well studied, it is clear that their role in the pathogenesis of PCOS via prenatal exposure is still far from being defined. In addition, the effect that prenatal exposure to other EDCs has on the development of PCOS needs to be determined, particularly since there is a vast array of EDCs that can cross the placental barrier and affect fetal development.

Further investigations are necessary to resolve currently discrepant findings, to explore other pathways of biological influence (including 2-hit models of exposure at different susceptible time windows[103]), to clarify mechanisms of action, and to determine more effective methods of exposure and outcome assessment. In order to improve accuracy of exposure assessment, future human studies should better characterize the critical periods in fetal development and use the best tools for exposure assessment. Longitudinal cohort studies show promise in efforts to analyze associations between fetal exposure to particular EDCs and the incidence of PCOS.

Authors' Note

All work on the article was done at Boston University School of Medicine. All authors have made substantial contributions at all levels, from conception to revision and final edits. M.H. drafted this review, E.C. added significant portions, and all authors critically revised it for intellectual content. The final version of this review has been approved by all authors for publication.

Acknowledgments

We would like to acknowledge Dr. Vasantha Padmanabhan for her guidance and mentorship in the area of polycystic ovary syndrome research as well as for bringing attention to key initial literature pertaining to the hypothalamic-pituitary-ovarian axis and PCOS for this paper.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: S.M. is supported by the Reproductive Scientist Development Program from the NIH/NICHD Grant K12 HD000849.

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