

Endocrine-disrupting chemicals and female reproductive health: a growing concern

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Abstract

Female fertility and reproductive health depend on a series of developmental steps from embryogenesis through puberty, in addition to the proper functioning of the reproductive system in adulthood. Two important steps are the establishment of the ovarian reserve and development of the hypothalamic–pituitary–ovarian axis. During reproductive years, maintaining an adequate ovarian reserve of follicles as well as balanced neuroendocrine control of reproductive organs is crucial for fertility. Dysregulation of either of these events, during development or in adulthood, can lead to reproductive disorders. Over the past five decades, human fertility rates have declined, whereas the incidence of female reproductive disorders has risen, trends partially linked to environmental factors such as exposure to endocrine-disrupting chemicals (EDCs). Here we outline epidemiological and mechanistic evidence for how EDCs affect the ovarian reserve during early development, its maintenance during adulthood and the establishment of the hypothalamic–pituitary control of puberty and ovulation. Our Review not only reveals strong support for the role of EDC exposure in the development of female reproductive disorders such as abnormal puberty, impaired fertility, premature menopause or polycystic ovarian syndrome, but also highlights knowledge gaps, including the difficulty to prove causality between exposure and human disease manifestation.

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Key points

- The prevalence of female reproductive disorders is increasing globally, and exposure to chemicals that disrupt the hormone system (endocrine-disrupting chemicals; EDCs) are considered a contributing factor.
- There is evidence from epidemiological studies that links exposure to EDCs with reproductive disorders such as early puberty, early menopause and polycystic ovary syndrome.
- Experimental studies with animals clearly show that exposure to EDCs during early life as well as in adulthood can negatively affect ovarian reserve, folliculogenesis and the hypothalamic control of puberty and ovulation.
- Future studies are needed to better understand the effect of in utero exposure to EDCs on female reproductive health later in life and in future generations.

Introduction

Over recent decades, there has been a steady increase in the incidence of female reproductive disorders. Data from Europe and North America have documented a trend towards an earlier onset of puberty for the past 30 years^{1–4}, along with an increase in idiopathic central precocious puberty in human female individuals – that is, the unexplained appearance of secondary sexual characteristics before the age of 8 years^{5,6}. Population statistics also show a considerable increase in the prevalence of polycystic ovary syndrome (PCOS), which is a common hormonal endocrine disease in women of reproductive age⁷, and analyses carried out over the past 20 years suggest that the prevalence of premature ovarian insufficiency, defined as ovarian failure before the age of 40 years, is increasing, too⁸. These trends coincide with globally declining rates of human fertility and an increased use of medically assisted reproductive technologies across all age groups^{9–11}. Although it is well known that female fertility and reproductive health are influenced by multiple factors, including genetics, lifestyle, socioeconomic status, BMI and age, a growing body of evidence points to an important contribution from endocrine-disrupting chemicals (EDCs)^{12–18}.

EDCs are broadly defined as substances that can interfere with the endocrine (hormone) system and cause an adverse effect in living organisms or their offspring by mimicking, blocking or altering normal hormonal function(s)¹⁹ (Box 1). Humans are exposed to EDCs through various routes, including ingestion of contaminated food and water, inhalation of polluted air, dermal absorption from personal care products and household items²⁰, and in early life via placental transfer and breast milk. Consequently, EDCs can commonly be detected in human biological samples such as serum, urine, follicular fluid and amniotic fluid²⁰. Examples of EDCs currently identified by regulatory agencies in the EU and ubiquitous in our environment include plastic additives, such as some phthalates and bisphenols, and pesticides²¹. Many more chemicals, such as certain perfluoroalkyl and polyfluoroalkyl substances (PFAS), can disrupt hormonal processes and negatively influence reproductive health but are not currently classified as EDCs by regulatory agencies. Additionally, both cigarette smoke and paracetamol have been linked to endocrine-related disorders²²,

although the specific chemicals from cigarettes that confer endocrine disruption remain unclear²³.

Female reproductive health issues in adulthood can originate from disruption to hormone levels and function(s) during development²⁴, as a woman's reproductive health is largely established during embryonic and fetal development and puberty. In the transition from (unborn) child to an adult woman, the basic biology of the female reproductive system changes, as do the hormonal processes and tissues involved. Most notable among these changes occurs perhaps in the prenatal phase, where a complex interplay between the mother, the placenta, and the fetal adrenal glands and gonads determines steroid hormone levels that drive the phenotypical development of fetal tissues. Consequently, how EDC exposure affects the female reproductive system strongly depends on the age or life stage of exposure^{25,26}.

It is important to note that both reproductive health and fertility are broad terms that cover numerous dimensions. Reproductive health refers to complete physical, mental and social well-being in all matters relating to the reproductive system at all stages of life. Fertility, although specifically referring to the ability to conceive children, involves not only the physiological processes of producing viable gametes, successful fertilization and implantation of the embryo leading to a viable pregnancy, but also includes factors that affect reproductive potential, such as hormonal balance, reproductive organ health, and overall health, lifestyle and societal influences. As such, it is impossible to cover all these aspects in a single article as well as to consider the complex aetiology of the various female reproductive health issues. Instead, we will narrow the focus of this Review to specific female reproductive disorders where there is evidence to support a link to EDCs in humans and animal studies. These disorders include compromised ovarian function (through negative effects on ovarian reserve and follicular growth), delayed or early puberty, and PCOS (Fig. 1). The aim of this Review is to highlight links between environmental chemical exposure and selected female reproductive disorders to illustrate the necessity for better protection of female reproductive health. Hence, other female reproductive disorders and outcomes, such as preterm birth, endometriosis and breast cancer, will not be covered here, despite being associated with exposure to EDCs including phthalates, bisphenols, parabens and polychlorinated biphenyls (PCBs), as reviewed elsewhere^{27–33}. We will also highlight the difficulties in going beyond associations seen between EDCs and reproductive health issues to establish causality between EDC exposure and human disease manifestation.

Ovarian reserve

Female fertility depends on ovarian follicles, which have two main functions: generation of mature oocytes and synthesis of steroid hormones. In humans, all follicles form before birth via a series of events that starts during the second trimester of pregnancy when all germ cells undergo meiosis I; subsequently, the germ cells undergo meiotic arrest, forming primordial follicles. The total number of these prenatally formed primordial follicles is known as the ovarian reserve^{34,35}. Each surrounded by a single layer of flat granulosa cells and containing one immature oocyte, primordial follicles reside in the dense ovarian cortex where they can remain dormant for decades^{34,35}. Starting from their formation in the fetal ovaries, these follicles can follow one of three paths: continued dormancy, activation for growth or degeneration through atresia^{35,36}. Owing to continuous growth activation and atresia, the size of the ovarian reserve declines with age. When it is critically depleted, menopause commences, marking the end of natural fertility. Humans

are one of the few species known to undergo menopause, which leads to sterility in midlife, typically between the ages of 45 and 55 years^{37,38}.

Maintaining a careful balance between follicle dormancy, growth and degeneration is essential for age-appropriate ovarian reserve and normal reproductive lifespan. Age at menopause is heritable, with multiple genetic polymorphisms, particularly in genes involved in DNA damage repair, influencing its timing³⁹. However, various additional factors also influence age at menopause, including lifestyle factors such as smoking^{40,41} and nulliparity (not having given birth)⁴⁰. There are also regional differences, with earlier menopause observed in female individuals from African, Middle Eastern and some Latin American and Asian countries compared with individuals from Europe and Northern America⁴². If ovarian function ceases before the age of 40 years, it is considered as premature ovarian insufficiency⁴³. Some medical treatments, such as chemotherapy, are associated with an increased risk of premature ovarian insufficiency and reduced fertility due to their toxicity towards follicles, leading to premature depletion of the reserve⁴⁴. Associations between having a low birthweight or being a part of a multiple birth and subsequently undergoing early menopause (cessation of ovarian function before the age of 45 years) suggest that the fetal environment is important in establishing the ovarian reserve^{45–47}. Mathematical models further suggest a connection between the size of the ovarian reserve formed during fetal life and the length of the reproductive lifespan in humans³⁴. Consequently, individuals born with a smaller follicular pool might experience menopause earlier than those born with a larger pool. Clearly, therefore, chemicals that disrupt the establishment of the follicular pool or follicle homeostasis can affect the ovarian reserve and compromise fertility.

Evidence from human studies on EDCs and ovarian reserve

In utero exposure to EDCs. The events leading up to the formation of primordial follicles are sensitive and are expected to be vulnerable to EDC exposure. However, owing to the inherent challenges of studying human fetal tissues, with very limited access to the stages corresponding to meiosis I initiation in particular, investigating the effects of EDCs on these events is often unfeasible. Nevertheless, epidemiological studies indicate that establishment of the follicular pool is sensitive to EDCs. Convincing evidence in humans derives from the former use of the non-steroidal synthetic oestrogen medication diethylstilbestrol (DES), which aimed to prevent pregnancy complications; female individuals exposed to DES during their intrauterine development displayed a shortened reproductive lifespan in addition to a higher risk of infertility in adulthood (among many other adverse health outcomes)^{48–51}; surveys indicated that women exposed to DES in utero were more likely to experience earlier menopause than unexposed women^{48–51}. Potential causative mechanisms include a diminished follicular pool, accelerated follicular depletion, and changes in hormone biosynthesis and metabolism⁴⁸. Notably, potential associations between maternal smoking during pregnancy and age at menopause have been assessed in multiple studies, with inconclusive results^{46,47,52}.

Exposure to EDCs during adulthood. Ovarian reserve might be negatively affected by exposure to EDCs during adulthood as well as in utero. Epidemiological studies have shown that adult female individuals with greater exposure to EDCs, including some pesticides and cigarette smoke, face a higher risk of early menopause than those with lower exposure^{47,52–55}. Dose-dependent associations have been identified between lifetime exposure to cigarette smoke and earlier onset of menopause, with a study involving nearly 100,000 women in the USA

Box 1 | What is an EDC?

There is no globally established consensus on what defines an endocrine-disrupting chemical (EDC), but the most broadly used definition is “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)population”¹⁹. However, this definition potentially misses substances that disrupt the ‘programming’ and establishment of the endocrine system, which subsequently might alter the function of the endocrine system. This mode of action is covered by a subclause of the WHO (World Health Organization) definition: “A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations”, with support from a scientific consensus statement on the key characteristics of EDCs, which proposes that an EDC can alter tissue structure and organization by affecting events such as cellular proliferation, migration or differentiation²⁴⁹.

reporting that exposure to the highest levels of first-hand or second-hand smoking led to menopause being experienced 1.8 and 1.1 years earlier, respectively, than in women who had never smoked⁵³. Similarly, the National Health and Nutrition Examination Survey revealed dose-dependent associations between age at menopause and chemical exposure in adult female individuals, identifying 14 organochlorine pollutants and phthalates that potentially negatively affected age at menopause. Specifically, female individuals with the highest levels of combined exposure experienced menopause 1.9–3.8 years earlier than female individuals exposed to the lowest levels⁵⁵. Supporting a potential association between EDC exposure and smaller ovarian reserve, the presence of organochlorine compounds such as dichlorodiphenyltrichloroethane and PCBs in serum has been linked to a reduced density of dormant follicles in the ovaries of reproductive-aged female individuals in Sweden^{55,56}. This observation suggests that follicles might disappear more rapidly in adults exposed to higher levels of cigarette smoke and EDCs throughout their lives, leading to earlier reproductive senescence, compared with those with no or lower exposures.

Experimental evidence of EDCs and ovarian reserve

The effects of EDCs on ovarian follicles are often studied in rats and mice. However, despite their overall similar biology, there are some important differences between humans and rodents regarding ovarian follicles. In mice and rats, the formation of the ovarian reserve is completed postnatally and the ovarian cycle is shorter than in humans; in addition, rodents ovulate multiple oocytes at once. Notably, rats and mice never go through menopause; although rodents undergo reproductive senescence with declining fecundity as they age, this process does not correspond to menopause. Menopause, a phenomenon that is unique to humans among primates, is characterized by an extended post-reproductive lifespan owing to the complete cessation of ovarian function³⁸.

From primordial germ cell specification in the early embryo to primordial follicle formation (mid-gestation in humans and perinatally in mice), germ cells progress through several critical stages within a changing somatic environment to generate the ovarian reserve^{57,58}.

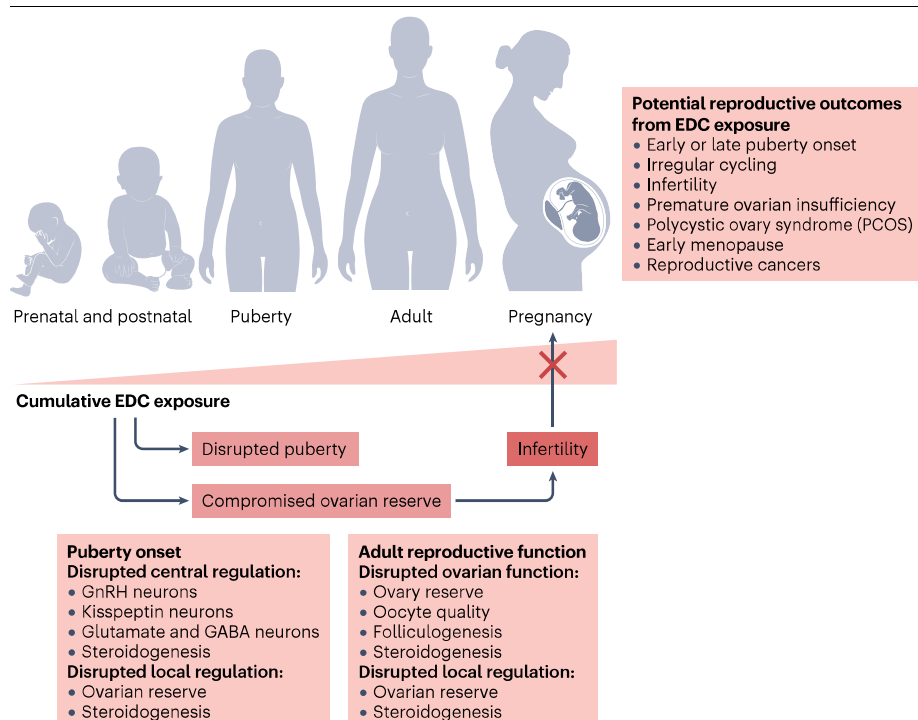


Fig. 1 | Female reproductive development and functions susceptible to perturbation by endocrine-disrupting chemicals. Female reproductive development begins in embryonic life with the specification and development of the germ cells, followed by ovarian differentiation. Concurrent brain development ensures subsequent establishment of the hypothalamic–pituitary–gonadal axis, which is essential for reproductive function. These processes can be sensitive to exogenous endocrine-disrupting chemicals (EDCs), which can disrupt development and affect reproductive function later in life, as well as directly influencing reproductive function during later life stages. GABA, γ -aminobutyric acid; GnRH, gonadotropin-releasing hormone.

The somatic milieu influences germline development, highlighting how EDCs could disrupt early ovary differentiation with lifelong consequences for fertility²⁴. For instance, chemicals such as tamoxifen that modulate oestrogen receptor (ER) activity can disrupt early somatic gonadal differentiation and consequently affect germ cells in mice^{59,60} (Box 2). Furthermore, aromatase-knockout mice display normal fetal ovary differentiation, but the germ cells are lost shortly after birth concomitant with signs of female-to-male somatic transdifferentiation, presumably as a result of the failure of androgens to be converted into oestrogens⁶¹. As discussed elsewhere, ovary differentiation in other mammals, such as sheep, goats and cows, relies on oestrogen signalling (Box 2), making this process susceptible to endocrine disruption⁶².

The germ cell population is particularly vulnerable during early developmental stages when undergoing mitotic and meiotic division in both mice and humans. Mitotic division increases the number of germ cells to form the basis for the establishment of the oocyte pool that will exist throughout the female reproductive lifespan⁶³. Subsequently, meiotic initiation and arrest in late prophase I are essential for the formation of the ovarian reserve and the ovulation of mature and developmentally competent oocytes after puberty. Disruption of these processes can lead, for example, to oocyte loss through apoptosis, or to the production of low-quality oocytes, potentially resulting in aneuploid gametes⁶⁴.

Disruption of meiosis. Disrupted meiosis can have profound effects on fertility but, although several studies suggest that meiosis is sensitive to EDCs, there is still a knowledge gap that warrants further investigation. A negative effect could arise from disrupting meiosis during fetal life, when oocytes enter prophase I, but also later during reproductive years, when meiosis II is completed. For example, oocytes from fetal mouse ovaries exposed to bisphenol A (BPA) displayed a

meiotic phenotype similar to that seen in oocytes from fetal ovaries of ER β -knockout mice, showing a high rate of synaptic aberrations and increased recombination^{65,66}. Similar effects of BPA on the fetal ovaries of rhesus monkeys⁶⁷ and sheep⁶⁸ and in cultured human fetal ovaries⁶⁹ are consistent with the loss of ER signalling, which is in contrast to its established ability to activate the ER^{33,34,70,71}. However, BPA has also been shown to inhibit ovarian steroidogenesis and consequently reduce ER activation^{72,73}. Mice exposed to diethylhexyl phthalate (DEHP) in utero during meiosis prophase I display disrupted meiotic progression^{74,75}. The herbicide atrazine, a known aromatase inducer, can disrupt meiosis and cause chromosomal abnormalities in mouse germ cells, affecting oocyte quality⁷⁶, suggesting a direct endocrine mode of action whereby meiotic progression and oocyte maturation are impaired^{77–79}. Indeed, a 2024 scoping review of the effects of bisphenols on oocyte health summarizes a large body of concerning data on how this chemical class can potentially disrupt meiosis I, meiosis II and other processes through various mechanisms of action⁶⁶. Disruption of meiosis I in fetal ovaries can lead to the formation of abnormal oocytes, which are typically cleared by atresia; accordingly, this process results in a reduced ovarian reserve. A prominent example of the negative effects of EDCs later in reproductive life comes from in vitro studies of oestradiol exposure, which was observed to cause abnormal spindle formation in adult mouse⁸⁰ and adult pig follicles⁸¹.

Both ER α and ER β are expressed in human fetal germ cells at the start of meiosis^{82,83}. This expression coincides with the peak in oestrogen synthesis observed just before meiosis is initiated in several mammalian species, including humans⁸⁴, although notably not in mice⁸⁵. Studies in aromatase-deficient rabbits have shown that oestrogen is dispensable for meiotic initiation, but the number of meiotic germ cells in the total germ cell pool is significantly lower in the knockout animals than in the control animals⁸⁶. This reduced number could be due to

meiotic germ cell loss, with oestrogen appearing important for germ and somatic cell proliferation and differentiation⁸⁶. Chemicals that disrupt oestrogen signalling during early fetal development could thus perturb establishment of the ovarian reserve by affecting ovarian cell proliferation and inducing meiotic germ cell loss. Human fetal ovaries start to produce steroid hormones, including oestrogens, early in development⁸⁷, with ovarian aromatase expression evident from week 10 to week 16 during gestation⁸³. Importantly, human fetal steroidogenesis involves the shuttling of steroids between the mother, the placenta, and fetal adrenals and gonads, meaning that EDCs might impact steroidogenesis in different tissues and compartments (for instance, the mother) that could still affect distant organs (for instance, the ovaries of the fetus)⁸⁸.

EDCs can also disrupt meiosis by mechanisms other than oestrogenic ones. For example, entry into meiosis depends on the timely activation of the transcription factor STRA8 by retinoic acid⁸⁹. Some EDCs, such as tributyltin, azole fungicides and BPA, can interfere with the retinoid system and potentially disrupt meiotic regulation⁹⁰. Analgesics such as paracetamol or indomethacin might also disrupt meiosis, as exposure has been shown to reduce oocyte numbers in rats, potentially through delayed meiotic entry evidenced by delayed *Stras8* expression⁹¹. Disruption of meiosis by EDCs might also involve oxidative stress causing DNA damage and meiotic defects^{92,93}. Although these latter effects might not be recognized as endocrine modes of action per se, they should nevertheless be considered, as they disrupt the formation of a key endocrine organ, the ovary.

In summary, numerous studies indicate that EDCs can affect meiosis in the developing ovary. It is plausible to assume that this effect leads to a reduced ovarian reserve, as supported by various mouse models of genes involved in meiosis that, when ablated, exhibit a diminished follicle pool or infertility^{94–99}.

Follicular atresia. The ovarian reserve is affected by EDCs even postnatally in experimental models, as certain exposures can directly cause follicular atresia. Follicular atresia has features of both apoptosis and autophagy, and is modulated by the balance between pro-survival (for example, BCL-2) and pro-apoptotic (for example, BAX) signals^{100,101}. Additionally, ferroptosis has been indicated in follicular atresia associated with ageing and oxidative stress¹⁰². Environmental factors can trigger atresia in primordial and early growing follicles through activation of the aryl hydrocarbon receptor. For instance, polycyclic aromatic hydrocarbons that activate the aryl hydrocarbon receptor (such as dimethylbenzanthracene and benzo(a)pyrene, both components of cigarette smoke) trigger the death of primordial and primary follicles in mouse ovaries at all developmental stages, as well as in xenografted adult human ovarian tissue, via the pro-apoptotic molecules Bax and Harakiri^{103–105}. Persistent organic pollutants such as organochlorine pesticides, PCBs, PFAS and phthalates have all been associated with increased follicular atresia in mice and rats, and in in vitro rodent and human follicle and cell cultures^{106,107}. Studies on human ovarian tissue in vitro demonstrate that exposure to hexachlorobenzene, *p,p'*-dichlorodiphenyldichloroethylene, 2,3,3',4,4',5-hexachlorobiphenyl and perfluorooctane sulfonate can increase follicular atresia by mechanisms that are likely to involve the upregulation of glycolysis, lipid metabolism, oxidative phosphorylation and ferroptosis, leading to the increased production of ATP and reactive oxygen species¹⁰⁷. Similarly, the DEHP metabolite monoethylhexyl phthalate can increase follicular atresia, probably by disrupting the cell cytoskeleton and the Hippo pathway¹⁰⁸. In adult rats, DEHP exposure lowers the levels of oestradiol,

luteinizing hormone (LH) and follicle-stimulating hormone (FSH), causing increased numbers of atretic follicles and prolonged oestrous^{109,110}, and rats exposed to BPA display increased follicular atresia, impacting overall fertility¹¹¹. These studies provide causal proof for the numerous reported associations between EDC exposure in adulthood, lower follicle density⁵⁶ and premature menopause^{54,55}.

Thus, not only can disrupted ovarian reserve occur during its establishment in fetal life, but also through accelerated depletion by atresia in adulthood. Both mechanisms can reduce the reproductive lifespan and induce early reproductive senescence. However, there are many knowledge gaps, particularly regarding the exact mechanisms of action.

Follicular growth

Whereas the establishment and maintenance of the follicular pool described above determine reproductive lifespan, follicular growth represents the next milestone necessary to attain normal fertility and complete reproductive function. Follicles continuously exit dormancy and enter the growing pool³⁵. The growth from the dormant primordial stage to ovulation takes up to a year in humans and can be roughly divided into two stages: gonadotropin-independent growth (from primordial to secondary follicles, occurring at all life stages until menopause) and gonadotropin-dependent growth (from antral (also known as tertiary) follicles) to ovulatory follicles, occurring only after puberty³⁵. Full folliculogenesis follows puberty, when the active hypothalamic–pituitary–ovarian axis supports the final growth of antral follicles to ovulation. Growing antral follicles provide an important source of steroid hormones, and the follicular microenvironment is crucial for the quality of the maturing oocytes⁸⁷. Human follicular fluid, like other bodily fluids, has been shown to contain complex mixtures of EDCs^{112–115}, raising questions about the potential influence of EDCs on follicle growth, steroidogenesis and oocyte quality^{112–114}.

Evidence from human studies on EDCs and follicular growth

Studying the gonadotropin-independent growth of follicles in humans is impractical; however, the gonadotropin-dependent growth phase can be readily followed during fertility treatment. Many studies in

Box 2 | Oestrogen signalling in ovary differentiation, steroidogenesis and germ cell development

Although critical for ovary differentiation in non-mammalian vertebrates, the exact role of oestrogen signalling in mammalian ovary development and function is less clear, and there are likely to be important differences between mammalian species²⁵⁰. Regardless, oestrogen signalling is essential for folliculogenesis and ovulation in the postnatal ovary, as evidenced by severe phenotypes in oestrogen receptor- and aromatase-knockout models^{61,65}. Oestrogens are also involved in regulating steroidogenesis, and control folliculogenesis and ovarian cyclicity via the hypothalamic–pituitary–ovarian axis. Oestrogen receptor subtypes are expressed in specific cell types in the mammalian ovary and disruption of oestrogen signalling during fetal life might lead to adverse reproductive effects in adulthood; germ cell meiosis, in particular, appears sensitive to the disruption of oestrogen signalling⁶⁵.

females undergoing medically assisted reproduction have suggested links between EDC exposure, reduced folliculogenesis and infertility. For example, two review articles conclude that the levels of persistent organic pollutants, BPA, phthalates, parabens and triclosan in females undergoing in vitro fertilization are associated with disrupted profiles of serum oestradiol and androgens, changes in antral follicle counts, a decreased likelihood of mature oocytes, decreased fertilization rates and overall reduced success rates of treatment^{113,116}. However, the associations are not consistent across studies, suggesting that the relationship between EDCs and folliculogenesis might be complex and influenced by additional factors such as region, lifestyle, socioeconomic or possibly earlier exposure to EDCs at pre-reproductive stage. Notably, many cohort studies are small and are likely to suffer from low statistical power, further complicating the picture. Additionally, outcomes such as fertilization rate and live birth rate also depend on semen quality, and so do not solely reflect female fertility.

Several studies have sought to disentangle the links between the presence of EDCs in follicular fluid and follicle growth in patients undergoing fertility treatment. By focusing on the ovarian sensitivity index, a measure of ovarian responsiveness to FSH during ovarian stimulation, notable associations have been found between follicle growth and the levels of persistent organic pollutants, parabens and phthalate metabolites in follicular fluid^{18,115}. As every individual is exposed to complex combinations of EDCs, a statistical model that considered the EDC mixture as a whole was used to show that patients with higher levels of EDCs in follicular fluid had lower ovarian sensitivity indexes than patients with lower exposure to EDCs¹⁸. In continued analyses, high levels of DEHP metabolites in follicular fluid were found to correlate with increased levels of molecular markers of inflammation and decreased cholesterol and steroid biosynthesis, possibly explaining the compromised follicle growth¹¹⁴.

Experimental evidence on EDCs and follicular growth

Mice and rats, although they are polyovular and have faster folliculogenesis compared with humans, share similar steroidogenesis and gonadotropin-independent and gonadotropin-dependent follicle growth stages to humans, and thus offer a system in which the effects of EDCs on folliculogenesis can be meaningfully studied. Numerous rodent studies have shown a decrease in the number of antral follicles and corpora lutea along with decreases in the levels of testosterone, oestradiol, LH and FSH on exposure to EDCs such as bisphenols and phthalates^{106,109–111,117–119}. Changes in folliculogenesis are often observed together with changes in oestrous cyclicity, meaning that fertility can be affected even months after exposure to EDCs is ceased¹²⁰. In vitro cultures of follicles exposed to phthalates and bisphenols typically show signs of dysregulated ovarian steroidogenesis^{73,121}. Obviously, the direct effects of EDCs on ovarian steroidogenesis are hard to disentangle from effects along the hypothalamic–pituitary–gonadal axis. This challenge has been extensively described for BPA, which has effects on ovarian steroidogenesis as well as on the pulsatory hypothalamic release of gonadotropin-releasing hormone (GnRH), leading to changes in ovarian cyclicity¹¹⁸.

Additional mechanisms might be involved in the disruption of follicle growth in response to EDCs. For example, DEHP can accelerate the activation of follicle growth by stimulating phosphatidylinositol 3-kinase (PI3K) signalling, or increase atresia of growing follicles through oxidative stress, depending on the concentration and timing of the exposure¹⁰⁶. As previously mentioned, transcriptomic studies in mouse and human ovarian cells indicate that phthalates might

target the cell cytoskeleton, Hippo signalling and various metabolic processes^{108,122}. Androgen signalling also carries out an important role in folliculogenesis; androgens can act directly via the androgen receptor predominantly in granulosa cells, influencing expression of the FSH receptor, insulin-like growth factor-1 and aromatase, as well as indirectly, through their aromatization to oestrogens^{123,124}. Phthalates, for example, are well-established anti-androgens that affect circulating levels of steroid hormones and ovarian aromatase expression depending on the experimental design, leading to disrupted folliculogenesis in rodent studies¹¹⁹; some studies suggest an association with PCOS in women¹²⁵. Androgen receptor antagonists such as flutamide and vinclozolin inhibit follicle development to antral stages in both in vivo and in vitro models¹²³, and decreased androgen receptor activity is associated with altered follicle growth patterns in women with PCOS or women with a poor ovarian response¹²³.

In summary, numerous experimental studies suggest that exposure to EDCs disrupts folliculogenesis and ovarian steroidogenesis in experimental animals and in humans^{119,121}. These disruptions include accelerated follicle growth activation, inhibited antral follicle growth and increased atresia, potentially leading to ovarian cycle irregularities in the short term and reduced fertility in the long run. Various EDC exposures correlate with markers of reduced fertility in females undergoing fertility treatments. Although the ultimate outcomes of such treatments (fertilization and live birth rates) also depend on male fertility, studies focusing specifically on ovaries provide strong evidence that EDCs negatively affect female fertility. However, it is important to note that human studies have primarily focused on patients undergoing fertility treatment, which constitute a selected population. It is also crucial to understand the extent of the negative effects that EDCs have on follicle growth and steroidogenesis in the general adult female population, as well as how susceptibility to EDCs might change in relation to biologically declining fecundity over a woman's lifespan.

Onset of puberty

Pubertal reactivation of the hypothalamic–pituitary–gonadal axis is essential for the acquisition of full reproductive capacity. In girls, puberty begins with breast development (thelarche) and progresses to first menstrual bleeding (menarche) and ovulatory cycles a few months or years later, signalling reproductive maturity. The normal age of puberty onset ranges widely (by 4–5 years) among female individuals, with genetic factors accounting for 50–80% of this variance^{126,127}. However, shifts in puberty timing among healthy populations over the past 30 years suggest that environmental factors can also have an influence¹. Such changes in pubertal onset timing might have an impact on public health and be an indicator of future reproductive health, as earlier puberty has been associated with increased risk of polycystic ovarian syndrome, obesity, type 2 diabetes mellitus and hormone-dependent cancers in female individuals^{128–133}.

A decrease in the age at thelarche has been observed worldwide since it was first documented in the 1990s in the USA¹³⁴. A systematic meta-analysis¹ of 30 studies published before 2019 revealed a decrease of nearly 3 months per decade in the age at thelarche from 1977 to 2013. Figure 2a illustrates the average age at thelarche in articles published during the past 10 years, and compares different time periods in the same geographical regions^{135–141}. Although limited, these data confirm the secular decrease in age at thelarche reported by the aforementioned systematic meta-analysis¹. Notably, another systematic review documented a drastic decrease in age at thelarche in China over the past 20 years¹³⁵, where it was also noted that median age at breast

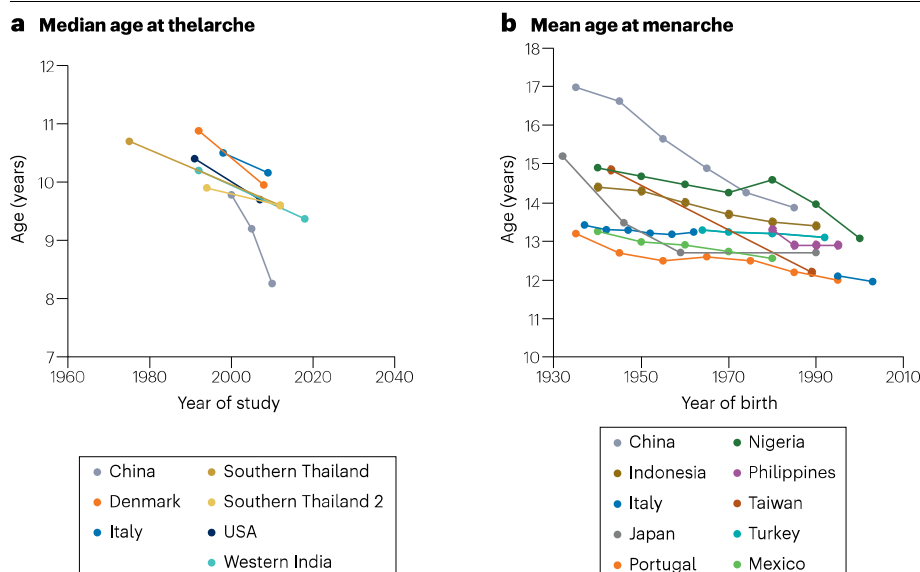


Fig. 2 | Secular trends in age at thelarche and menarche over past decades. **a**, A secular trend in median age at thelarche, based on year of study, in different geographical regions, from studies published after 2013 (refs. 135–141). **b**, A secular trend in age at menarche based on birth year, in different geographical regions, compiled from studies published after 2019 (refs. 137,147,149–155).

development significantly varied between urban (8.26 years) and rural areas (10.9 years)¹³⁵, again suggesting a role for environmental factors. Although obesity contributes to earlier onset of puberty (compared with a normal weight)¹⁴², some lean populations also show a secular trend towards earlier onset¹⁴³, suggesting that other environmental factors, including EDCs, might be in effect^{144,145}.

Age at menarche, normally a late marker of puberty, decreased in the USA and most of Europe from 1890 to 1960, coinciding with improved nutritional status and socioeconomic conditions⁴, but stabilized after 1960. However, it still continues to decrease in other parts of the world^{146–148}. Figure 2b summarizes studies published after 2019 documenting the average menarcheal age over a number of years in different geographical regions^{137,147,149–155}. Although very few studies have reported on secular trends over the past 20 years in Europe, data from Italy and Turkey seem to confirm the stabilization of age at menarche for girls born after 1960, as do data from Japan; however, China, Taiwan, Indonesia and Mexico report ongoing secular decreases.

Puberty begins with the reactivation of GnRH neurons in the hypothalamus after a period of postnatal quiescence. In rodents, GnRH cell bodies locate to the preoptic area and project to the median eminence, where they release GnRH in a pulsatile manner. This release stimulates the pituitary gland to produce LH and FSH^{156,157}. Research indicates that the pulse generator that drives GnRH release is not intrinsic to GnRH neurons but is located in the arcuate nucleus and mediobasal hypothalamus^{158–160}. Pubertal activation of this pulse generator involves a shift from inhibitory to excitatory inputs onto GnRH neurons. Although glutamate and γ -aminobutyric acid (GABA) are key modulators of GnRH neuron activity, additional critical factors, including the neuropeptide kisspeptin, its receptor GPR54, neurokinin B and makorin ring protein 3, have been identified¹⁶¹. The transcriptional activity of this extrinsic pulse generator appears particularly sensitive to sex steroids and energy balance-related hormones such as leptin or insulin, both at the end of gestation and during early postnatal life¹⁶². Kisspeptin, which drives puberty in both rodents and humans, is primarily secreted by two neuronal populations in rodents: those in the anteroventral periventricular nucleus, which are positively regulated

by oestrogens and mediate the preovulatory surge in LH, and those in the arcuate nucleus, which are negatively regulated by oestrogens¹⁶³. Leptin, produced by adipocytes, signals energy sufficiency to the hypothalamus and promotes puberty by acting on several hypothalamic neuronal populations, including kisspeptin and GABAergic neurons¹⁶⁴. These factors underscore the critical role of hormonal regulation in controlling GnRH release and initiating puberty. The organization of this neuroendocrine control of puberty has also been shown to be sensitive to environmental factors, such as EDCs, as illustrated by experimental data described later in this article. Extrapolating data from rodent models to humans requires caution owing to differences in endocrine sensitivity and neuronal organization between the organisms. Data from primates indicate that the mediobasal hypothalamus is the main site for positive feedback from oestrogen, but it remains unclear whether the negative and positive feedback effects of oestradiol are mediated by the same kisspeptin neurons in humans as they are in rats¹⁶⁵.

Evidence from human studies on EDCs and changes in the timing of pubertal onset

The aforementioned trends in the age of onset of puberty suggest that environmental contaminants might be important, as genetic factors alone do not explain the observed changes. Epidemiology studies linking early exposure to ubiquitous EDCs with altered thelarche and menarche timing in humans are challenging given the long delay between exposure and these milestones, as well as the multifactorial nature of the modulation of puberty by the environment. Research indicates that EDCs have mixed effects on the timing of pubertal onset in girls: for example, prenatal or peri-pubertal BPA exposure is associated with both early^{166,167} and late thelarche¹⁶⁸, but consistently with late menarche¹⁶⁸. This association between late menarche and BPA exposure is consistent with experimental studies documenting that prenatal or early postnatal low-dose exposure to oestrogenic compounds such as DES and BPA can delay puberty in female rats^{169,170}. Similarly, prenatal exposure to anti-androgenic compounds such as phthalates is associated with late menarche¹⁶⁸, suggesting a role for

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androgens in the regulation of female puberty. Hyperandrogenism during pregnancy, caused for example by a deficiency in 21-hydroxylase (CYP21), is associated with virilization, including central precocious puberty, ambiguous genitalia at birth and reduced fertility in female humans¹⁷¹. This virilization is considered to be the result of reduced fetal cortisol production, reduced negative feedback on the pituitary gland and subsequent increased production of adrenal androgen (DHEAS) in the female during gonadal differentiation^{172,173}.

An enduring question regarding EDC-induced disrupted pubertal timing is whether the effects originate from central or peripheral mechanisms (Fig. 3). Although some studies suggest that EDCs can directly affect breast development, alterations in menarcheal timing are more likely to reflect central disruptions by environmental factors on the hypothalamic control of puberty. The rising incidence of central precocious puberty supports this central mechanism hypothesis^{174–177}. Evidence for EDC-induced reprogramming of the GnRH network in humans is limited but supported by a study linking EDC exposure to changes in the methylome in the blood of peri-pubertal children¹⁷⁸. Specifically, urine levels of phthalate correlated positively with *TRIP6* promoter methylation and negatively with *TRIP6* protein levels. As *TRIP6* promoter methylation has been associated with pubertal transition¹⁷⁹, *TRIP6* methylation could be a target of EDCs involved in the pubertal changes observed in humans exposed to phthalates^{180–182}. Similarly, the increased methylation of genes known to be mechanistically associated with puberty, such as

TACR3 or *GNAS*, was associated with increased EDC levels in urine. However, causal links remain to be identified.

Experimental evidence of the influence of EDCs on the GnRH network

The GnRH network, crucial for regulating puberty, is highly sensitive to environmental factors, as illustrated by various animal models⁴. In rodents, oestrogenic and anti-androgenic EDC exposure can disrupt GnRH programming and puberty¹⁸³. In rats, the juvenile period (before puberty) appears particularly sensitive for detecting the effect of EDCs on GnRH release¹⁸³. Although late-stage exposure to EDCs can affect the activity of the adult hypothalamic–pituitary axis, such as disrupting the preovulatory LH surge^{109,184,185}, early developmental exposure appears to be particularly harmful in rats and mice.

EDCs can target key regulators within the GnRH pulse generator, such as GABA, MKRN3, oxytocin and kisspeptin¹⁸³. For example, perinatal exposure to BPA has been shown to impede the maturation of GnRH neurons and delay puberty in female rats¹⁷⁰. Additionally, kisspeptin neurons are particularly sensitive to endocrine disruption: BPA at high doses is associated with early puberty and a persistent disruption of kisspeptin neuron maturation¹⁸⁶, whereas the insecticide methoxychlor induces early pubertal onset in mice with early expression of kisspeptin neurons in the anteroventral periventricular region of the medial pre-optic area¹⁸⁷. Similarly, benzo[a]pyrene exposure reduces GnRH sensitivity to kisspeptin in primary cultures of human fetal hypothalamus¹⁸⁸.

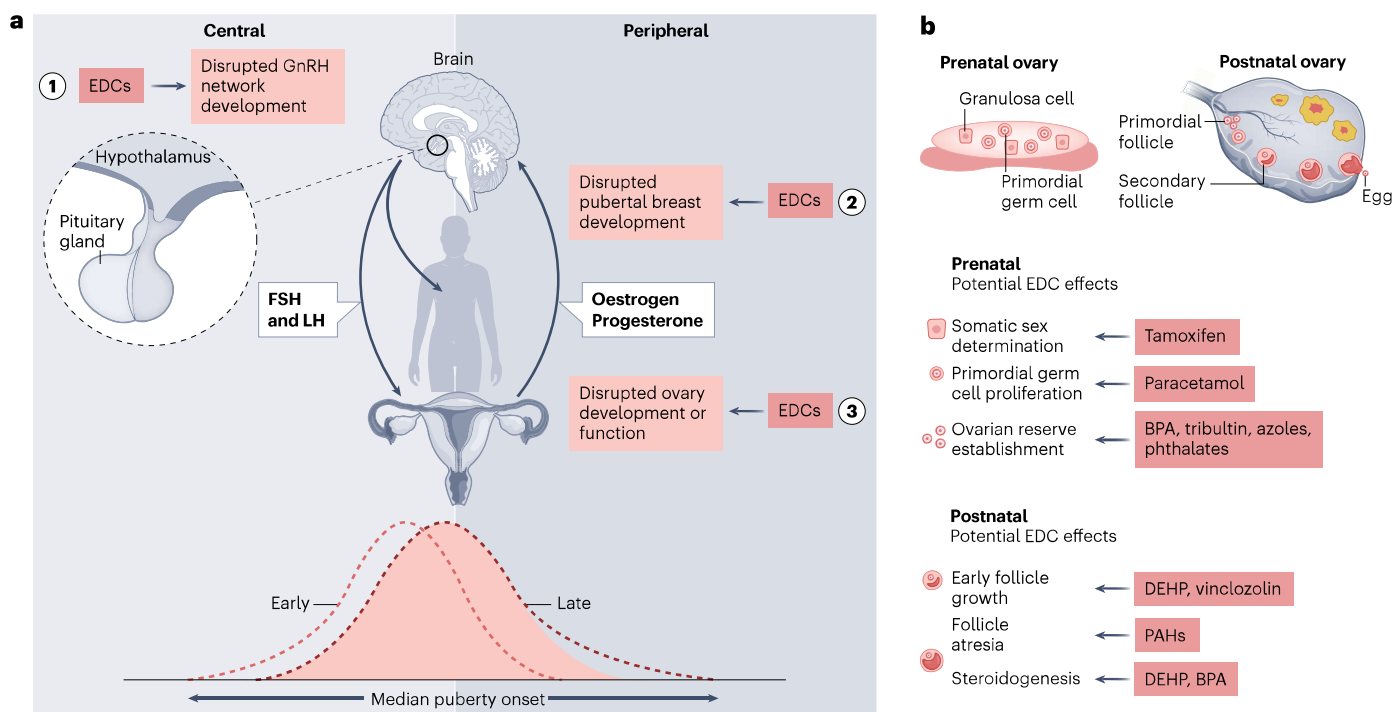


Fig. 3 | Central versus peripheral disruption of puberty timing. a, The distribution curve represents the classical pattern of age at puberty onset, the dotted red line indicates the secular trend in age at breast development (thelarche) and the dotted brown line shows the secular trend in age at onset of menstruation (menarche). There are several potential mechanisms by which endocrine-disrupting chemicals (EDCs) can mediate the secular trends seen in puberty onset: (1) disruption of the hypothalamic–pituitary–ovarian axis (central disruption),

(2) direct action of EDCs on breast tissue (peripheral disruption) and/or (3) direct action on ovarian pathways leading to oestrogen production (peripheral disruption). **b**, The effect of EDCs on prenatal and postnatal ovary development, with potential downstream effects on the peripheral regulation of puberty onset. BPA, bisphenol A; DEHP, diethylhexyl phthalate; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PAH, polycyclic aromatic hydrocarbon.

The mechanism of action through which EDCs would affect *KISS1* expression or action, however, remains to be determined.

Studies have revealed that EDCs can affect the timing of puberty, not only through ER activation but also by altering steroidogenesis. Inhibitors of aromatase or steroidogenesis, such as phthalates, fadrozole and ketoconazole¹⁸⁹, can disrupt the timing of puberty in female rodents, depending on the compound, exposure dose and timing of exposure^{190,191}. These experimental studies suggest that EDCs can reprogramme the GnRH network or affect ovarian steroid levels during puberty, which, in turn, could affect both the positive and negative feedback loops to the hypothalamus.

Research has highlighted the epigenetic regulation of the GnRH network during puberty and its disruption by developmental exposure to EDCs in rats¹⁹². Studies show that both individual EDCs and mixtures can transgenerationally affect the hypothalamic control of puberty in mice and rats^{192–195}. Notably, such disruption is often followed by oestrus cycle irregularities. For example, ancestral exposure to a mixture of 13 EDCs delayed puberty and GnRH maturation in the third generation of rats, affecting hypothalamic *Kiss1* expression. In third-generation female rats, the *Kiss1* promoter exhibited a disrupted histone configuration, with increased repressive H3K27me3 and decreased active H3K4me3 modifications, suggesting that delayed puberty resulted from altered epigenetic regulation of *Kiss1* transcription by Polycomb and Trithorax complexes¹⁹². These data illustrate that EDCs can alter the epigenetic programming of key puberty activating genes.

In summary, both epidemiological and experimental studies highlight that issues with puberty can represent an early indication of adult reproductive health issues caused by EDCs. The GnRH neuron micro-environment is highly sensitive to both direct and transgenerational EDC exposure, with effects potentially extending beyond classical oestrogenic modes of action to include additional alteration of steroid hormone levels or anti-androgenic actions, all of which can affect GnRH network activation during puberty. Transgenerational effects of EDCs on puberty control in humans as well as the mechanisms explaining the transmission of such effects remain to be identified.

PCOS

PCOS is a common endocrine disorder in premenopausal women, with prevalence rates of 5–10% worldwide but of up to 20% in some regions^{196–198}. The prevalence of PCOS seems to have increased over past decades, suggesting a potential role for environmental factors; however, this aspect is difficult to assess, considering the heterogeneity of symptoms experienced by women^{199,200} and increasing knowledge that has led to changes in clinical criteria for PCOS since the 1930s^{201–203}. The pathophysiology of PCOS remains unclear, but it is recognized as a multifactorial condition involving both genetic and environmental factors. Daughters of mothers with PCOS have a fivefold increased risk of developing the condition compared with daughters born to women without PCOS²⁰⁴. Genetic loci identified so far account for only about 10% of PCOS heritability, but growing evidence indicates that epigenetic alterations and developmental programming, triggered by hormonal imbalances in the maternal uterine environment, are important in the pathogenesis of PCOS²⁰⁴. The most common clinical symptoms of PCOS are anovulation and excess levels of androgens, although the spectrum of symptoms in women with PCOS is quite broad. PCOS is a typical multisystem disease, affecting ovarian function, hypothalamic–pituitary regulation and insulin regulation. Morphologically, PCOS is characterized by an accumulation of antral follicles and the failure to form one dominant follicle for ovulation. EDCs might affect these aspects

through alterations in the balance of hormones during fetal development, GnRH secretion, follicular growth and steroidogenesis, and thus increase the risk of developing PCOS.

Evidence from human studies on EDCs and polycystic ovarian syndrome

Although epidemiological data linking EDCs to PCOS are limited, some studies have found higher urinary or serum levels of BPA, dichlorodiphenyltrichloroethane, PCBs, pesticides and polycyclic aromatic hydrocarbons in women with PCOS than in women without PCOS^{205–210}. However, these studies are often limited by small sample sizes and single EDC measurements. Several large cohort studies have indicated an increased risk of PCOS following exposure to a mixture of PFAS^{211–213}. In a Swedish cohort of women aged 20–50 years, those who had ever lived in a highly PFAS contaminated area had a significantly higher hazard ratio (2.18; 95% confidence interval 1.43–3.34) for developing PCOS than women who lived in a ‘never high’ contaminated area²¹¹. Similarly, a US study found that women aged 18–45 years seeking fertility evaluation and treatment had a dose-dependent increased risk for PCOS by PFAS exposure, which was mostly driven by perfluorooctane sulfonate (odds ratio of 2.59 in the highest tertile compared with lowest tertile (95% confidence interval 0.93–7.53))²¹². Interestingly, PFAS have also been associated with increased antral follicle counts in females undergoing fertility treatment, suggesting a link between exposure levels and antral follicle number¹¹⁵. Although epidemiological studies have identified positive correlations between levels of EDCs during adulthood and the risk of PCOS, there is limited research on prenatal EDC exposure and risk of PCOS later in life; however, one study suggests that maternal phthalate exposure might confer a reduced risk for developing PCOS in daughters²¹⁴.

Experimental evidence on EDCs and PCOS

Animal models of prenatal exposure to testosterone or anti-Müllerian hormone (AMH; produced by growing follicles and considered a marker for ovarian reserve²¹⁵) demonstrate alterations similar to those observed in PCOS, highlighting the sensitivity of the hypothalamic–pituitary–ovarian axis to hormonal prenatal programming^{216,217}. Mammalian models of developmental exposure to testosterone most closely recapitulate the human PCOS phenotype; maternal exposure to testosterone in sheep, for example, results in a similar neuroendocrine phenotype to that seen in human PCOS (LH excess, hyperandrogenism and reduced oestradiol-feedback response)^{218,219}. Rodent models of PCOS provide very useful genetic tools but do not always exhibit increased levels of LH or testosterone, which are typically seen in women with PCOS. Nonetheless, considerable evidence links EDCs to PCOS-like phenotypes in rodents. For instance, neonatal exposure to tributyltin or BPA has been associated with a decreased number of corpora lutea, increased numbers of atretic follicles and cysts, as well as elevated testosterone and LH levels in rats^{220,221}. In mice, long-term effects of neonatal BPA exposure include the presence of paraovarian cysts, increased occurrence of cystic endometrial hyperplasia and decreased numbers of corpora lutea²²². DEHP exposure in adult rats resulted in hypoestrogenic anovulatory cycles, polycystic ovaries and prolonged oestrous cycles compared with control rats¹⁰⁹, whereas prenatal exposure to methoxychlor resulted in follicular cysts and irregular cycles in adulthood²²³. Adult exposure to BPA and its analogues bisphenol S and bisphenol F have been shown to reduce the numbers of antral follicles and corpora lutea in rats while altering steroid and gonadotropin hormone levels, depending on the dose and type of bisphenol^{111,117},

indicating potential sensitivity to develop PCOS-like phenotypes such as anovulation beyond the immediate postnatal period.

Experimental cell models give some additional explanation regarding the possible mechanisms of action of EDCs that lead to PCOS-like phenotypes. Studies have shown the potential for EDCs to affect ovarian steroidogenesis. For example, *in vitro* BPA⁷³ can decrease oestradiol production in H295R cells (the gold standard for assessing steroidogenesis²²⁴), the human granulosa cell line KGN⁷² or primary rat granulosa cells, while increasing testosterone production in primary rat theca interstitial cells²²⁵, possibly through the increased expression of steroidogenic enzymes. Likewise, phthalates can disrupt ovarian steroidogenesis in both *in vitro* human ovarian tissues and follicles²²⁶. PCOS, characterized by increased LH pulsatility²²⁷, can manifest with increased testosterone production by theca cells and an overactivation of the GnRH system in mice²²⁸. Elevated AMH levels *in utero* in women who developed PCOS²²⁹ and in experimental PCOS models²³⁰ suggest that neonatal exposure to excess AMH might lead to PCOS. AMH, produced by granulosa cells, can act on theca and granulosa cells to regulate LH- and FSH-mediated responses, as well as stimulate LH pulsatility and secretion in GnRH neurons²³¹, as all these cell types express the AMH receptor. BPA has been shown to affect the AMH signalling pathway in mouse granulosa cells *in vitro*, illustrating the sensitivity of AMH signalling to EDCs and its potential role in EDC-induced PCOS.

In summary, several studies report elevated levels of EDCs in the blood of women with PCOS, with the strongest associations shown for PFAS. Given the persistent nature of PFAS, the role of PFAS specifically and EDCs more broadly, it is pertinent to focus more research on prenatal EDC exposure and the development of PCOS. In light of the sensitivity of the GnRH network to endocrine disruption, further research is crucial to determine whether developmental exposure to EDCs disrupts GnRH programming and contributes to PCOS. Investigating how EDCs affect AMH signalling at both the hypothalamic and ovarian levels is warranted, especially considering the role of AMH in regulating neuroglial plasticity and the involvement of neuroendocrine dysregulation in women with PCOS²³². Studies on how EDCs might affect AMH signalling and PCOS should also consider the effects on the foeto-placental unit and, specifically, female fetal adrenal glands and the imprinting of the hypothalamic–pituitary–adrenal and/or hypothalamic–pituitary–gonadal axes, as hyperandrogenism during gestation leads to virilization of females in humans and animals and is linked to PCOS^{219,233}.

Future directions

Despite the increasing body of evidence linking EDC exposure to female reproductive disorders, a number of key knowledge gaps remain. Below, we outline several directions for study to improve our understanding of how EDCs influence female reproductive health.

Advances in high-throughput approaches have allowed the identification of new molecular pathways targeted by EDCs in the hypothalamus, pituitary and ovaries. Levels of proteins, mRNAs and metabolites show rapid changes after EDC exposure, whereas epigenetic modifications might explain some of the long-term effects²³⁴. Moving forwards, single-cell and spatial transcriptomics or proteomics approaches will help to characterize cell-specific responses to EDCs.

Future research should also focus on distinguishing how central and peripheral endocrine disruption affects puberty onset. Understanding the interplay between central and local endocrine control is crucial, as is determining the extent to which abnormal puberty timing due to EDC exposure can indicate future reproductive health issues.

It is also unclear whether EDCs primarily disrupt the development of the GnRH network and its microenvironment, which subsequently manifests as dysregulation, or whether EDCs primarily disrupt brain regulation at the time of puberty onset, or both. Similarly, it remains to be determined to what extent ovarian disruption by EDCs is due to developmental exposure with latent effects, disruptions at the onset of puberty or the continued negative effects of exposure throughout reproductive life. Given the global trend of postponing childbirth beyond peak fertile years, the impact of EDCs on ageing ovaries requires increased attention.

The placenta, a source of hormones and neurotransmitters essential for brain and reproductive tract development^{235,236}, is affected by EDCs²³⁷, influencing central brain control of puberty and female fertility. To what degree the influence of EDCs on the placenta contributes to the overall reproductive disease burden later in life, however, is not well characterized and deserves more attention. Furthermore, it is important to study how other regulatory pathways that are linked to neurological development, which can be affected by EDCs, influence female reproduction in relation to the exposome more broadly.

Interactions between the gut microbiome and the hypothalamic–pituitary–gonadal axis have been described in various endocrine-related diseases. Differences in gut microbiota have been described in girls with either central or peripheral precocious puberty and girls with normal puberty timing^{238–240}, as well as in women with PCOS²⁴¹ compared with female individuals without this disorder. It cannot be excluded, however, that differences in microbiota composition reflect a difference in hormonal status rather than being the cause of the disease. As EDCs are known to affect microbiota composition and metabolite production²⁴², future research should hopefully shed light on the effects EDCs might have on the gut–brain axis related to pathologies such as precocious puberty or PCOS. In addition, studies could explore the effects of EDCs on the microbiome within the reproductive tract, which has been associated with infertility in women^{243,244}. Considering the interplay between reproduction and energy balance, and the fact that dietary patterns can affect the gut microbiota^{245,246} and the placenta²⁴⁷, for example, the combined effect of dietary changes, metabolic diseases and EDCs on reproduction requires further exploration.

Concluding remarks

The potential link between EDC exposure and the rising incidence of female reproductive disorders has gained considerable attention owing to the ability of EDCs to disrupt the endocrine system. However, despite the ever-growing body of studies that link exposure to EDCs to female reproductive health effects, providing strong causal evidence in humans remains challenging. Major challenges include the complex aetiology of reproductive conditions, with many contributing factors (ranging from lifestyle and microbiome to genetics), as well as the long lag time between exposure during sensitive developmental windows (in utero to adulthood) and manifestation of adverse effects later in life (puberty and adult fertility). Confounding factors, such as general health of the mother during pregnancy, obesity status, presence of diabetes mellitus, recreational drug consumption, stress, socioeconomic status, genetic predispositions, access to healthcare and so forth, might all contribute to the observed effects and might not be appropriately accounted for in human studies. Nevertheless, this Review highlights some critical processes that are essential to female reproductive health and presents compelling evidence that EDCs disrupt ovarian development and function. EDCs can affect the ovarian reserve and folliculogenesis, as well as the maturation of the hypothalamic–pituitary–gonadal

axis and puberty onset in girls. Remaining knowledge gaps and ongoing discussions should not negate the urgency to act through coordinated strategies and demonstrably effective measures, prevent exposure to EDCs, and protect the reproductive health of women and future generations.

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