Developmental programming refers to processes that occur during early life that may have long-term consequences, modulating adult health and disease. Complex diseases, such as diabetes, cancer and cardiovascular disease, have a high prevalence in different populations, are multifactorial, and may have a strong environmental component. The environment interacts with organisms, affecting their behaviour, morphology and physiology. This interaction may induce permanent or long-term changes, and organisms may be more susceptible to environmental factors during certain developmental stages, such as the prenatal and early postnatal periods. Several factors have been identified as responsible for inducing the reprogramming of various reproductive and nonreproductive tissues. Among them, both natural and synthetic steroids, such as endocrine disruptors, are known to have either detrimental or positive effects on organisms depending on the dose of exposure, stage of development and biological sexual background. The present review focuses on the action of steroids and endocrine disruptors as agents involved in developmental programming and on their modulation and effects on female neuroendocrine functions.

**KEYWORDS**
developmental programming, endocrine disruptors, glucocorticoids, gonadal steroids
INTRODUCTION

Certain developmental stages, such as the prenatal and early postnatal periods of an organism’s life, represent windows of susceptibility during which the environment can have a major impact on the embryo or the infant and might regulate health status during adult life. During these windows of susceptibility, different factors, such as lifestyle, diet, environmental pollutants, medical and pharmaceutical interventions, may affect organisms, altering their development (Figure 1). Developmental programming refers to processes by which stimuli or insults produce permanent effects on the structure and functions of the organism, which could be a result of epigenetic mechanisms or stable changes in gene expression. Developmental plasticity is a phenomenon that allows a developing organism to change its structure and function in response to environmental cues. The Developmental Origins of Health and Disease hypothesis, which is based on animal models and epidemiological evidence from several multifactorial and complex pathologies such as obesity, diabetes, polycystic ovary syndrome (PCOS) and neuronal disorders, describes how early-life experience influences the health and disease risk later in life.

Steroids are lipophilic molecules that participate in the regulation and establishment of the hypothalamic-pituitary-gonadal axis in the case of gonadal steroids (such as testosterone and 17β-oestradiol [E2]), as well as the hypothalamic-pituitary-adrenal axis in the case of glucocorticoids. Because of the lipophilic nature of these compounds, most of them and their metabolites may be able to cross the blood-brain barrier and placenta during prenatal life.

Gonadal steroids and glucocorticoids are synthesised mainly by the gonads and adrenal glands during gestation, as well as by the foeto-placental unit. These hormones are all derived from cholesterol and the many enzymes involved in their synthesis are strictly regulated. The first step in steroid synthesis involves the formation of pregnenolone. Then, 2 different pathways may lead either to progesterone, which acts as a precursor for the synthesis of androgens, oestrogens and glucocorticoids, or to 17α-hydroxypregnenolone, which leads to the formation of androgens and oestrogens. Oestrogen production depends on androgens as substrates (Figure 2). All of these compounds share a common structure, and their formation is dependent on pituitary hormone signalling in the different target tissues.

Several studies have reported that male and female susceptibility to different complex diseases is not the same and that parental life experience could affect offspring development, particularly as a result of maternal effects. Because steroids play several roles in sexual development and the maintenance of biological differences, we aim to review the effects of steroids as actors involved in the effects of developmental programming on the female neuroendocrine system.

GONADAL STEROIDS

2.1 Androgens and PCOS as a clinical case

In females, androgens play an important role in the regulation of fertility. Although they had been assumed to be detrimental or
dispensable in normal folliculogenesis and ovarian functions, more recently, they have been shown to have positive functions on these processes because they are expressed at all stages of follicular development.\textsuperscript{13} It has been shown that alterations in androgen levels may be involved in disorders such as PCOS, endometrium cancer and endometriosis.\textsuperscript{14} Testosterone, which is the main androgen, not only exerts its actions mainly via the androgen receptor (AR), but also can induce biological effects via its main active metabolites: dihydrotestosterone and E\textsubscript{2}. Dihydrotestosterone also binds to AR, although its action is more potent, and E\textsubscript{2} can act via its own receptors.\textsuperscript{15}

In women, androgens are produced in the ovaries and adrenal glands. The most important androgens are testosterone and androstenedione, although females also produce dehydroepiandrosterone and dehydroepiandrosterone sulphate, which are weaker androgens.\textsuperscript{16} Testosterone is important for mammalian brain development.\textsuperscript{10} Although testosterone levels in females are higher during foetal life than in adulthood, male foetuses always show higher testosterone levels than females during early development.\textsuperscript{17} Androgens play important roles during prenatal life and in the early postpartum period, being fundamental for brain development and sexual differentiation.\textsuperscript{17-19} Both sexes express the AR but, during development, there is a lack of androgens in females, which leads to the formation of the genital tubercle into a clitoris and the urogenital swellings into the labia majora.\textsuperscript{20} Studies in different animal models have shown that, during late embryonic life and early postnatal life, there is a window of programming that is susceptible to androgens, and that these can affect sexual organ function, brain structure and behaviour. It has also been seen that puberty is another window of susceptibility and that androgens (as well as oestrogens) affect body composition by affecting muscle build up, but do not affect not genitalia.\textsuperscript{20} In postnatal life, androgens play a key role in women reproduction not only because they act as oestrogen precursors, but also because they are key for ovarian follicle development.\textsuperscript{21}

In 1959, Phoenix et al.\textsuperscript{22} showed that prenatal treatment of guinea pig females with testosterone had long-term effects on behaviour, as well as on phenotypic reproductive outcomes. Testosterone exposure in females has been related to several alterations. Among them, one of the most important is PCOS, an endocrine-metabolic disorder that affects 5%-10% of women of reproductive age. This disorder is characterised by menstrual irregularities (oligomenorrhoea or amenorrhoea) and clinical and/or biochemical hyperandrogenism in the presence or absence of polycystic ovaries, with more than half of the patients being overweight or obese.\textsuperscript{23}

PCOS is considered a multifactorial pathology but its aetiology remains controversial. Current theories emphasise on genetic and intrauterine origins coupled with environmental factors such as diet and altered lifestyle patterns.\textsuperscript{24} Because gene candidates for PCOS can explain only part of the heritability of the syndrome, an environmental role and an epigenetic contribution have also been suggested. It has been reported that prenatal androgen exposure is able to induce polycystic ovaries features in rats,\textsuperscript{25-27} mice,\textsuperscript{28} monkeys,\textsuperscript{29,30} and sheep,\textsuperscript{31} and also that foetal programming, mediated by prenatal hyperandrogenism, is related to hyperinsulinaemia, dyslipidaemia, insulin resistance, cardiovascular disease and metabolic syndrome, all of which are found in high incidence in women with PCOS.\textsuperscript{25-26,32-33}

It has been proposed that PCOS mothers may give birth to children who show alterations in their metabolic and reproductive characteristics.\textsuperscript{34-36} Different studies have shown that both daughters and sons from PCOS mothers demonstrate an altered metabolic function.\textsuperscript{34-36,37} Nevertheless, reproductive disturbances have only been found in the daughters of PCOS women,
showing evidence of an increased follicular mass, and higher luteinising hormone (LH) and testosterone levels at the end of puberty.37

In animal models, prenatal and neonatal androgen excess can lead to the development of PCOS-like features. Hyperandrogenism leads to reproductive changes in females during pubertal and adult life, causing alterations in follicular development, ovarian steroidogenesis and uterine features, as well as changes in behaviour. Androgen excess also leads to metabolic alterations, affecting the liver, adipose tissue and other organs.25-27,38-41

Although there are controversial results about the levels of LH and follicle-stimulating hormone (FSH) in PCOS patients, many patients present LH hypersecretion, which can be blunted in the adult patient as a result of an increased body mass index. In addition, after leuprolide stimulation, 2- to 3-month-old PCOS daughters show increased LH secretion.42 This effect disappears during childhood when the hypothalamic-gonadal axis is dormant and reappears at the end of puberty.37 By contrast, in the sheep model, the increased LH secretion in the offspring of androgenised mothers appears to be related to the metabolic component that appears later in life and is not modulated by prenatal interventions.43 The fact that animal models do not replicate all human PCOS traits makes it difficult to fully understand PCOS pathogenic mechanisms. Abbott et al.44 recently reported the existence of a hyperandrogenic population of female rhesus monkeys that exhibit PCOS traits. These findings suggest that the syndrome may have a possible ancient origin and that its features may naturally affect other species beyond humans, and indicate the role of androgens in female biology. In addition, under laboratory conditions, gestational exposure of female monkeys to androgens induces several PCOS-like neuroendocrine, reproductive and metabolic features in adult life.44 These findings, together with the fact that rhesus monkeys share over 90% of their genome with humans, are consistent with the hypothesis that PCOS pathogenesis is determined not only by genetic components, but also by epigenetic mechanisms, in which androgens play a major role during development.54

In most of these models, the third trimester of pregnancy appears to be the most important window of programming (Figure 3). PCOS mothers treated with metformin throughout pregnancy improve their hormonal and metabolic parameters during the third trimester, and their female offspring lack the markers of ovarian programming observed in the nontreated PCOS group.42 Thus, appropriate management of these pregnancies appears to be key with respect to avoiding the perpetuation of this condition. On the other hand, in rodent models, the first few postnatal days of life are also a window of susceptibility for programming because androgen administration during this period may also lead to long-term alterations and the appearance of PCOS-like features.45 Taken together, these results highlight the importance of androgens in females and suggest that the levels of androgens are tightly regulated during development because alterations in their levels during prenatal or early postnatal life lead to long-term consequences that affect both reproduction and metabolism.

### 2.2 Oestrogens

In the steroidogenic process, the aromatisation of androgens results in oestrogens. The most abundant and potent oestrogen in females is E2. E2 acts mainly via the oestrogen receptor (ER), which not only has 2 different isoforms, ERx and ERβ, but also may act via GPER, a G protein-coupled membrane receptor.15,46 Oestrogens have multiple metabolic actions that take part via their target tissues. They can influence glucose homoeostasis in the liver, adipose tissue and skeletal muscle.47 In the pancreas, they can influence insulin secretion, whereas, at the hypothalamic level, they may modulate food intake.47 They are important in female reproductive functions. In mammals, ovarian folliculogenesis is a process dependent on E2 bioavailability, with E2 contributing to the maintenance of pregnancy and controlling the release of gonadotrophins at the hypothalamic level.48

Because E2 plays different functions, it has been proposed that it has a modulatory effect during development. Thus, alterations in its levels may lead to consequences during postnatal life. Most of the relevant studies in this respect show that E2 has a potent action in rodents and other animal models such as sheep, during the first few days of postnatal life when the ovarian follicle population is established, and also that it can lead to PCOS-like features in adult life41,49-51 (Figure 3). Puttabyatappa et al.52 reported that prenatal E2 administration in sheep does not reproduce the neuroendocrine disruptions caused by testosterone. This indicates that the effects of testosterone on programming reproductive alterations may be caused by androgenic effects during prenatal life43 and/or that androgens act via oestrogenic pathways as a result of testosterone aromatisation.41,52 Puttabyatappa et al.52 also noted that the dose of E2 administered was not sufficient to generate a disruption. Thus, prenatal oestrogenic effects remain to be explored. Because many pollutant components act as oestrogenic-like compounds, several studies have explored the action of oestrogens during development and the windows of susceptibility during foetal life.

Much more is known about the oestrogenic action during early postnatal life. Sotomayor et al.54 have shown that a single injection of oestradiol valerate on postnatal day 1 alters the oestrous cycle, leading to the development of polycystic ovaries with a reduction of primordial and preantral follicles, and also increases androgen biosynthesis. It was also found that this treatment leads to alterations in body weight gain. In other studies, the action of oestradiol valerate was suggested to involve ovarian sympathetic activity and hypothalamus alterations that affect reproductive functions and ovarian development.54,55

Taken together, these results suggest that, although androgens and oestrogens may induce developmental programming in females and lead to long-term detrimental effects in both metabolic and reproductive functions, the susceptibility window for each of them appears to be different. According to the evidence from animal models,
FIGURE 3  Metabolic and reproductive outcomes of different models of developmental programming of polycystic ovary syndrome (PCOS). AMH, anti-Müllerian hormone; GD, gestational days; T, testosterone; DHT, dihydrotestosterone; EV, oestradiol valerate. The pink arrow indicates the offspring. In such cases, exposure to androgen or oestrogen is directly on the offspring during postnatal life.
females are more susceptible to androgens during prenatal life and more susceptible to oestrogens during early postnatal life.

2.3 | Gonadal steroids and their neuroendocrine effect on the predisposition to drug addiction

Androgens and oestrogens play important roles in the central nervous system. In females, they can alter reproductive and metabolic pathways via the modulation of hypothalamic and pituitary processes, which involves modulating the release of gonadotrophins and acting as neuromodulators in the dopaminergic system. It has also been shown that androgens and oestrogens can alter behaviour and susceptibility to certain drugs and alcohol as they act on the dopaminergic system. Although both males and females may become addicted to drugs, females may initiate drug use at earlier ages, show enhanced responses to drugs of abuse, be more vulnerable to addictions, and experience more difficulties in abstinence processes.

It has been proposed that E2 may act as a facilitator, at least in part, in a vulnerability to drugs of abuse, affecting the brain reward system, which is dependent on the dopaminergic transmission from the ventral tegmental area to the nucleus accumbens. In ovariectomised rodents, the delivery of E2 has been shown to increase cocaine consumption, thus suggesting a hormonal-dependent pathway. In addition, Calipari et al. showed that there is an oestrous cycle-dependent mechanism controlling increased cocaine reward in females, which involves a regulation of the dopamine transporter (DAT) via E2 levels. Because E2 levels change in an oestrous cycle-dependent way, at the oestrous stage, when E2 levels are high, this hormone increases dopamine activity in the ventral tegmental area, leading to conformational changes in DAT via Thr53 phosphorylation by extracellular signal-regulated kinase.

Cruz et al. have reported that, in adulthood, rat females neonatally exposed to oestradiol valerate show alterations in brain areas involved in the production of movement and reward, nigrostriatal and mesocorticolimbic pathways, respectively. It was found that, in the striatum and substantial nigra-ventral tegmental area, neurotransmitters are altered, showing an increase in dopamine in both areas, although, in the striatum, there is only an increase in noradrenaline content and a decrease in DAT levels. Because dopamine is involved in the reward system, the response to amphetamines in these females during adulthood was also tested, and it was proposed that, because exposure to oestradiol valerate at neonatal life exerts changes in the nigrostriatal pathway, this may affect the rewarding effects when these animals are exposed to drugs of abuse. Cruz et al. concluded that exposure to oestrogens during early-life periods may be a factor of vulnerability to drug addiction.

Because endocrine disruptors might mimic the action of gonadal steroids, they may affect the modulation of the dopaminergic system. For example, bisphenol A (BPA) administration at prenatal and early postnatal life affects the dopamine system, including the dopamine receptor and DAT. Thus, BPA may also affect drug reward susceptibility and behavioural patterns, although further research is needed to clarify this issue.

3 | NONGONADAL STEROIDS

Nongonadal steroids include corticosteroids, which are lipophilic compounds produced mainly in the adrenal glands, although it has been suggested that some of them may also be produced in the brain. They act as principal mediators in stress signalling and can be divided into 2 groups: glucocorticoids, among which the most important are cortisol (in primates) and corticosterone (in rodents), and mineralocorticoids, such as aldosterone.

During late foetal development, corticosteroids play important roles in the development of the brain and several other organs. Exposure to these compounds before the late surge during gestation may have detrimental effects on the embryo, either through maternal origin (such as corticosterone from maternal origin as a result of stress) or treatment with synthetic glucocorticoids.

Some synthetic glucocorticoids are used during pregnancy either to reduce the risks of early premature birth between weeks 24 and 34, in that they help with lung maturation, or to manage congenital adrenal hyperplasia. One of the common glucocorticoids used in antenatal treatment is betamethasone. Its administration is assumed to mimic the foetal surge of glucocorticoids and to stimulate foetal lung maturation, thus helping to reduce the morbidity and mortality related to respiratory pathologies. Borges et al. found that, in rodents, exposure to betamethasone during gestational days, when the reproductive organs are being developed and the brain is becoming sexually mature, leads to a low birthweight and affects reproductive outcomes in female offspring, causing alterations in the regularity of the oestrous cycle, delay of puberty onset, increase in LH serum levels and alterations in the uterine structure. It was also shown that betamethasone alters the sexual behaviour of animals, expressed as a reduction of the lordosis quotient. Even more, betamethasone-treated animals show postimplantation problems and a reduced weight of their offspring during in utero life, a marker of intrauterine growth alteration.

Moisiadis et al. have shown that prenatal treatment with glucocorticoids leads to intergenerational and transgenerational effects on stress-associated behaviours affecting the hypothalamic-pituitary-adrenal response to stress, via maternal and paternal transmission for at least 3 generations.

Studies in human populations have also shown that the administration of glucocorticoids used for antenatal treatment is associated with smaller size at birth and also neurological and behavioural consequences because these children may present a thinner cortex, primarily in the rostral anterior cingulate cortex, leucomalacia and a high risk of some disorders such as hyperactivity and distractibility. In a recent study, Kiguti et al. observed a clear male-over-female effect of betamethasone exposure during prenatal life on cardiac parameters and thus suggested that the alterations were sex-dependent. It was also suggested that the results observed were probably a result of the reduced intrauterine testosterone in the betamethasone-exposed male progeny. These results once again highlight the importance of studying the hormonal context in a sex-dependent manner.
Endocrine disruptors are compounds that may interfere with the endocrine system, causing alterations in metabolism and reproduction, as well as changes in the brain and behaviour, in addition to affecting other neuroendocrine pathways. Furthermore, the endogenous hormones that act to program neuroendocrine functions during development, some xenobiotics, environmental and chemical substances, such as pesticides, fungicides, industrial chemicals, plastics and plant-derived products (eg, phytoestrogens), can interfere with the hormonal signalling because they act as hormone agonists or antagonists via ERs (xenoestrogens) and ARs (xenoandrogens). Because endocrine disruptors are ubiquitous and are part of the daily life, they may exert their actions during critical windows of development, leading to programming and long-term effects. It is of great interest to study their effects because they can be transferred from maternal-foetal interactions, as well as via lactation, and are also found in food sources. The present review focuses on the case of bisphenols, phthalates and parabens, which are found in plastics and also in some common pesticides (Figure 4).

### 4.1 Bisphenols, phthalates and parabens

Bisphenols, phthalates and parabens are found in plasticisers, solvents and additives. Worldwide populations are exposed to these compounds in daily life because they are found in several industrial and consumer products, mainly food and drink. One of the most common bisphenols is BPA, which is found in polycarbonate plastic containers, including baby bottles. Thus, humans are exposed to BPA from the early postnatal period of life onwards. BPA is known to bind competitively to ERs, with high affinity for ERβ, although it can also act via oestrogen-independent pathways.

Phthalates are diesters of phthalic acid, which are used in wrapping materials and food processing. Thus, humans are exposed to them throughout life. They act as anti-androgenic compounds. In both humans and rodents, there is evidence that exposure to phthalates causes developmental and reproductive alterations. There is also evidence that mixtures of BPA and phthalates have additive interactions in their anti-androgenic activity, showing synergistic effects at high concentrations and antagonistic activities at low concentrations.

In vitro and in vivo models have shown that alterations mediated by bisphenols and phthalates involve epigenetic mechanisms and present intergenerational and transgenerational effects. Studies in human populations and animal models have shown that BPA levels in pregnant females correlate with increased androgen levels, high levels of leptin and low levels of adiponectin (two adipocytokines), nitrosative stress, dyslipidaemia, liver damage, hormonal imbalance, and ovarian dysfunctions in their female progeny. It has been shown that PCOS women, independent of their body weight, have high levels of serum BPA. Thus, because this compound can mimic the actions of natural steroids, it may be considered as a factor involved in the etiopathogenesis of the syndrome. In addition, given the evidence of animal models suggesting that BPA exposure may lead to PCOS-like features, the current high rates of this syndrome may be also explained by the effect of this endocrine disruptor. BPA may also have a role as an environmental component in PCOS pathogenesis.

Some studies have shown that maternal administration of methyl donors, such as folic acid or vitamin B12 during pregnancy or melatonin during early-life periods, might partly reverse the effects of BPA in the offspring. These results show that the susceptibility periods of life for programming should be considered as good windows for medical interventions that aim to reverse, at least partially,
the detrimental effects of exposure to oestrogenic and androgenic compounds.

Parabens are also found in plastics and in other daily life sources such as cosmetics, pharmaceutics and food industries. They are known to have oestrogenic activity and can bind to ERs. Because they are lipophilic, they can cross the brain barrier and accumulate in the skin and adipose tissue. The human population presents a high concentration of these compounds in serum, urine and breast milk samples. Rodent studies have shown that high doses of parabens can affect female fertility and, if the exposure is in utero, they can also affect the offspring, acting as endocrine disruptors, being able to cross the placenta. In a recent study, Guerra et al. have shown that exposure during prenatal life to low doses of butylparaben does not affect the female offspring reproductive parameters but does affect brain sexual development in that they reported more than 50% of treated animals not being sexually receptive to males.

Because human populations are exposed to these compounds in daily life, it is of great interest to evaluate metabolites of these compounds in pregnant women so that medical interventions and follow-up could be performed in their offspring. As noted above, interventions can include the administration of compounds as melatonin or folic acid, which are known to have no effect on the developing organism and may also have positive effects on maternal-foetal health from early life onwards.

4.2 | Pesticides

Pesticides, such as insecticides, herbicides and fungicides, are widely used for agricultural and medical purposes. Thus, the worldwide population is at high risk of exposure to pesticides and it has been suggested that some cases of cancer, neurological disorders, poisoning, allergies and reproductive disorders might be related to pesticide exposure. Moreover, although some of them are no longer used, their effects persist in the environment. Thus, studies have investigated some of the intergenerational and transgenerational effects of some pesticides and found that they are able to act through epigenetic mechanisms. There are different classes of pesticides. Some of the most common are synthetic organochlorine and organophosphorus compounds. Although they are not steroidogenic compounds, they share lipophilic and chemical structural similarities, which allow them to act via ARs and ERs, either mimicking or inhibiting their action.

4.2.1 | Organochlorine pesticides

Organochlorine pesticides such as dichlorodiphenyltrichloroethane (DDT), methoxychlor (MXC) and endosulfan are among the most used pesticides. Because most of them have lipophilic structures, they may bioaccumulate and persist for years, thus being among the most frequent contaminants. Furthermore, given their structure, they can cross the placenta, thus affecting developing embryos. It has also been shown that they can affect female fertility by disrupting the oestrous cycle, the development of ovarian follicles and the hormone levels.

DDT has been banned in many countries because of its toxic effects, although it is still used as a malaria vector control in some places of Africa. It has been reported that DDT may lead to developmental and reproductive abnormalities, neurological disorders and cancer. DDT has also been shown to have transgenerational effects, including ovarian diseases, obesity, metabolic alterations and cancer susceptibility in adult life, via epigenetic mechanisms. Furthermore, it has been reported that exposure to DDT during pregnancy leads to subfertility in the female offspring.

Subsequent to the prohibition of DDT, MXC has been used in its replacement. However, MXC also persists in the environment after its use and has been shown to have strong oestrogenic and anti-androgenic effects. Human epidemiological and rodent model studies have shown that constant exposure to MXC during adulthood affects cycling and ovulation and leads to fertility issues. Several studies have indicated that MXC can have a developmental programming effect, causing alterations in epigenetic processes, such as changes in methylation patterns. When rodents are exposed to MXC during foetal or early postnatal life, the effects in females persist until adulthood, with alterations in reproductive outcomes, such as pubertal acceleration, an irregular oestrous cycle, and alterations in folliculogenesis and cyst formation. The effects of prenatal administration of MXC have also been tested in sheep, and the results obtained showed that it can alter the LH surge at postnatal life, generate cycle disruption and lead to a low birthweight in the female offspring.

Endosulfan has also been found to have long-term effects on the population. It has been described as a xenoestrogenic compound that can interact and activate ERs. Because endosulfan can be stored in adipose tissue, mothers exposed to it during their life may affect their children during pregnancy via the placenta and umbilical cord. Endosulfan has also been reported to influence fertility, as well as glucose metabolism, affecting the pancreas and plasma glucose levels, as well as liver oxidative stress and functions.

4.2.2 | Organophosphorus pesticides

Organophosphorus pesticides (among which some of the most used are dichlorvos and chlorpyrifos) exert their toxicological action via inhibition of the enzyme acetylcholinesterase. This enzyme is expressed in several tissues, including the central nervous system and the ovary, and participates in the regulation of folliculogenesis. Thus, organophosphorus pesticides may affect not only the nervous system at brain level, but also the local ovarian system, although further research is needed to clarify this.

Chlorpyrifos has been shown to have neurotoxic effects, to be able to alter placental tissue, and to have negative effects on trophoblast development and neural development, as well as on ovarian, kidney and liver development. The worldwide population is exposed to this compound because it is found in the environment,
water, fruits and vegetables, although women living in agricultural communities are more exposed and may thus accumulate this compound, showing high levels of it in urine and blood. In addition, it is important to remain aware that this compound can have intergenerational effects. In a murine model, Mansour and Gamet-Payráste showed that the effects of the indirect exposure to chlorpyrifos during prenatal and early postnatal life (by lactation) could be ameliorated by the administration of vitamin E.

5 | CONCLUSIONS

Complex diseases are currently a main concern in clinics. Currently, human populations are exposed to several hormonal and hormone-like compounds in the form of environmental pollutants and pharmaceutical compounds. Because environmental components are included among the factors contributing to the aetiology of these pathologies, it is important in clinical, epidemiological and basic research to be aware of the concept of developmental programming. As described in the present review, although steroids play many physiological actions, their excess (or absence) may lead to several pathologies that affect the neuroendocrine and reproductive systems. Because there are sex differences in the steroid regulation axis, it is also important to study the effects caused by steroid imbalances in more detail. Finally, it is also important to expand our knowledge of the epigenetic mechanisms of action that may lead to intergenerational and transgenerational effects resulting from steroid derangements because they can be used as targets with respect to the therapeutics of complex pathologies and disorders.

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