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Developmental programming of the female neuroendocrine system by steroids

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Abstract: Developmental programming refers to processes that occur during early life, which 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 behavior, 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 non-reproductive 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.

1.-Introduction

Certain developmental stages, such as the prenatal and early postnatal periods of an organism's life, are windows of susceptibility during which the environment can have a major impact on the embryo or the infant and might regulate the health status during adult life [1]. During those windows of susceptibility, different factors such as the lifestyle, diet, environmental pollutants, medical and pharmaceutical interventions may affect organisms, altering their development [2] (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 due to epigenetic mechanisms or stable changes in gene expression [3-5]. 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 (DOHaD) 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 [6], describes how early life experience influences the health and disease risk later in life [2].

Steroids are lipophilic molecules that participate in the regulation and establishment of the hypothalamus-pituitary-gonadal axis, in the case of gonadal steroids (such as testosterone (T) and 17-B-estradiol (E_2)), and the hypothalamus-pituitary-adrenal axis, in the case of glucocorticoids. Due to the lipophilic nature of these compounds, most of them and their metabolites may be able to cross the blood-brain barrier as well as the placenta during prenatal life [7].

Gonadal steroids and glucocorticoids are synthesized mainly by the gonads and adrenal glands, during gestation, also by the fetoplacental 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, two different pathways may lead either to progesterone, which acts as a precursor for the synthesis of androgens, estrogens and glucocorticoids, or to 17-alpha-hydroxypregnenolone, which leads to the formation of androgens and estrogens. Estrogen production depends on androgens as substrates (Figure 2). All these compounds share a common structure and their formation is dependent on pituitary hormone signaling in the different target tissues.

Several studies have described that male and female susceptibility to different complex diseases is not the same [8-10] and that parental life experience could affect offspring development, particularly due to maternal effects [11, 12]. As steroids play several roles in sexual development and in the maintenance of biological differences, here we propose to review the effects of steroids as actors involved in the effects of developmental programming on the female neuroendocrine system.

2.- 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, in the past years, they have been shown to have positive functions on these

processes as they are expressed at all stages of follicular development [13]. It has been shown that alterations in androgen levels may be involved in disorders such as PCOS, endometrium cancer and endometriosis [14]. T, which is the main androgen, exerts its actions mainly through the androgen receptor (AR), but it can also induce biological effects through its main active metabolites: dihydrotestosterone and E_2. Dihydrotestosterone also binds to AR but its action is more potent and E_2 can act by its own receptors [15].

In women, androgens are produced in the ovaries and adrenal glands. The most important androgens are T and androstenedione, but females also produce dehydroepiandrosterone and dehydroepiandrosterone sulfate, which are weaker androgens [16]. T is important for mammalian brain development [10]. Although T levels in females are higher during fetal life than in adulthood, male fetuses always show higher T levels than females during early development [17]. Androgens play important roles during prenatal life and in the early postpartum period, being fundamental for brain development and sexual differentiation [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 [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 affect sexual organ function, brain structure and behavior. It has also been seen that puberty is another window of susceptibility and that androgens (as well as estrogens) affect body composition, by affecting muscle build up, but not genitalia [20]. In post-natal life, androgens play a key role in women reproduction, not only because they act as estrogen precursors but also because they are key for ovarian follicle development [21].

In 1959, Phoenix et al. [22] showed that prenatal treatment of guinea pig females with T had long-term effects on behavior as well as on phenotypic reproductive outcomes. T 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 characterized by menstrual irregularities (oligomenorrhea or amenorrhea) 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 [23].

PCOS is considered a multifactorial pathology but its etiology remains controversial. Current theories emphasize on genetic and intrauterine origins coupled with environmental factors such as diet and altered lifestyle patterns [24]. As 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 [25-27], mice [28], monkeys [29, 30] and sheep [31], and that fetal programming, mediated by prenatal hyperandrogenism, is related to hyperinsulinemia, dyslipidemia, insulin resistance, cardiovascular disease and metabolic syndrome, all of which are found in high incidence in women with PCOS [25, 26, 32, 33].

It has been proposed that PCOS mothers may give birth to children who may show alterations in their metabolic and reproductive characteristics [34-36]. Different studies have shown that both daughters and sons from PCOS mothers show an altered metabolic function [34, 36, 37]. Nevertheless, reproductive disruptions have only been found in PCOS

women`s daughters, showing evidence of an increased follicular mass, and higher luteinizing hormone (LH) and T levels at the end of puberty [37].

In animal models it has been shown that 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, uterine features and changes in behavior. 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 due to increased Body Mass Index (BMI). In addition, after leuprolide stimulation, 2-3-month-old PCOS daughters show increased LH secretion [42]. This effect disappears during childhood when the hypothalamus-gonadal axis is dormant and reappears at the end of puberty [37]. In contrast, in the sheep model, the increased LH secretion in the offspring of androgenized mothers seems 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. (2017) have recently reported the existence of a hyperandrogenic population of female rhesus monkeys that exhibit PCOS traits [44]. These findings suggest that the syndrome may have a possible ancient origin and that its features may naturally affect other species beyond humans, and remark the role of androgens in female biology. Besides, in 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 [44].

In most of these models, the third trimester of pregnancy seems 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 non-treated PCOS group [42]. Thus, appropriate management of these pregnancies seems to be key to avoid the perpetuation of this condition. On the other hand, in rodent models, the first postnatal days of life are also a window of susceptibility for programming, as androgen administration in the first days of life 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, as alterations in their levels during prenatal or early postnatal life lead to long-term consequences that affect both reproduction and metabolism.

2.2-Estrogens

In the steroidogenic process, the aromatization of androgens results in estrogens. The most abundant and potent estrogen in females is E_2. E_2 acts mainly through the estrogen receptor (ER), which has two different isoforms known as alpha (ERα) and beta (ERβ), but may also

act through GPER, a G-protein-coupled membrane receptor [15, 46]. Estrogens have multiple metabolic actions that take part via their target tissues. They can influence glucose homeostasis 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 of great importance in female reproductive functions. In mammals, ovarian folliculogenesis is a process dependent on E_2 bioavailability, and E_2 contributes to the maintenance of pregnancy and controls the release of gonadotropins at hypothalamic level [48].

As E_2 plays different functions, it has been proposed that it may play a modulatory effect during development. Thus, alterations in its levels may lead to consequences during postnatal life. Most studies regarding this point have shown that E_2 has a potent action in rodents and other animal models such as sheep, during the first days of postnatal life when the ovarian follicle population is established, and that it can also lead to PCOS-like features in adult life [41, 49-51] (Figure 3)**.** Puttabyatappa et al. (2016) [52] showed that prenatal E_2 administration in sheep does not reproduce the neuroendocrine disruptions caused by T. This shows that the effects of T on programming reproductive alterations may be caused by androgenic effects during prenatal life [53], and/or that androgens act via estrogenic pathways due to T aromatization [41, 52]. Puttabyatappa et al. (2016) [52] also mentioned that the dose of E_2 administered was not enough to generate a disruption. Thus, prenatal estrogenic effects are yet to be explored. As many pollutant components act as estrogenic-like compounds, several authors have explored the action of estrogens during development and the windows of susceptibility during fetal life.

More is known about the estrogenic action during early postnatal life. Sotomayor et al. (2008) [54] have shown that a single injection of estradiol valerate on postnatal day 1 alters the estrous cycle, lead to the development of polycystic ovaries with a reduction of primordial and preantral follicles, and increases androgen biosynthesis. These authors also found that this treatment leads to alterations in body weight gain. In other studies, they have shown that the action of estradiol valerate may 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 estrogens 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 seems to be different. According to the evidence from animal models, females seem to be more susceptible to androgens during prenatal life and more susceptible to estrogens during early post-natal life.

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

Androgens and estrogens play important roles in the central nervous system. In females, they can alter reproductive and metabolic pathways through the modulation of hypothalamic and pituitary processes, i.e. by modulating the release of gonadotropins and acting as neuromodulators in the dopaminergic system. It has also been shown that androgens and estrogens can alter behavior and susceptibility to certain drugs and alcohol

as they act on the dopaminergic system [15]**.** 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 [56-58].

It has been proposed that E_2 may act as a facilitator, at least in part, in the 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 [59-61]. In ovariectomized rodents, the delivery of E_2 has been shown to increase cocaine consumption, thus suggesting a hormonal-dependent pathway [61, 62]. In addition, Calipari et al. (2017) [58] showed that there is an estrous cycle-dependent mechanism controlling increased cocaine reward in females, which involves a regulation of the dopamine transporter (DAT) via E_2 levels. As E_2 levels change in an estrous cycle-dependent way, at the estrous stage, when E_2 levels are high, this hormone increases dopamine activity in the ventral tegmental area, leading to conformational changes in DAT via Thr53 phosphorylation by the ERK kinase.

Cruz et al. (2014) [49] have shown that, in adulthood, rat females neonatally exposed to estradiol valerate show alterations in brain areas involved in the production of movement and reward, nigrostriatal and mesocorticolimbic pathways, respectively [49]. These authors found that, in the striatum and substantial nigra-ventral tegmental area, neurotransmitters are altered, showing an increase in dopamine in both areas but only an increase in noradrenaline content in the striatum and a decrease in DAT levels. As dopamine is involved

in the reward system, they also tested the response to amphetamines in these females during adulthood, and proposed that as exposure to estradiol valerate at neonatal life exerts changes in the nigrostriatal pathway, then it may affect the rewarding effects when these animals are exposed to drugs of abuse. They concluded that exposure to estrogens during early life periods may be a factor of vulnerability to drug addiction.

As endocrine disruptors might mimic the action of gonadal steroids, they may affect the modulation of the dopaminergic system. For example, it has been shown that BPA administration at prenatal and early postnatal life affects the dopamine system, including the dopamine receptor and DAT [63]. Thus, BPA may also affect drug reward susceptibility and behavioral patterns, but further research is needed to clarify this issue.

3.- Non-gonadal steroids

Non-gonadal steroids include corticosteroids, which are lipophilic compounds produced mainly in the adrenal glands, although it has been suggested that part of them may also be produced in the brain [64, 65]. They act as principal mediators in stress signaling and can be divided in two groups: glucocorticoids, among which the most important are cortisol (in primates) and corticosterone (in rodents), and mineralocorticoids, such as aldosterone.

During late fetal 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 due to stress) or treatment with synthetic glucocorticoids [66].

Some synthetic glucocorticoids are used during pregnancy either to reduce the risks of early premature birth between weeks 24 and 34, as they help in lung maturation, or to manage congenital adrenal hyperplasia [67]. One of the common glucocorticoids used in antenatal treatment is betamethasone. Its administration is supposed to mimic the fetal surge of glucocorticoids and to stimulate fetal lung maturation, thus helping to reduce the morbidity and mortality related to respiratory pathologies [67, 68]. Borges et al. (2017) [68] 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 birth weight and affects reproductive outcomes in female offspring, causing alterations in the regularity of the estrous cycle, delay of puberty onset, increase in LH serum levels, and alterations in the uterine structure. These authors also showed that betamethasone alters the sexual behavior of animals, expressed as a reduction of the lordosis quotient. Evenmore, betamethasone-treated animals show post-implantation problems and a reduced weight of their offspring during *in utero* life, a marker of intrauterine growth alteration[68].

Moisiadis et al. (2017) [66] have shown that prenatal treatment with glucocorticoids leads to intergenerational and transgenerational effects on stress-associated behaviors affecting the hypothalamic-pituitary-adrenal response to stress, via maternal and paternal transmission for at least three generations.

Studies in human populations have also shown that administration of glucocorticoids used for antenatal treatment is associated with smaller size at birth [69] and neurological and behavioral consequences, as these children may present a thinner cortex primarily in the rostral anterior cingulate cortex, leukomalacia and high risk of some disorders such as hyperactivity and distractibility [70-72]. In a recent study, Kiguti et al. (2017) [73] 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. They also suggested that the results observed were probably due to the reduced intrauterine T in the betamethasone-exposed male progeny. These results highlight, once again, the importance of studying the hormonal context in a sex-dependent manner.

4-Endocrine disruptors

Endocrine disruptors are compounds that may interfere with the endocrine system, causing alterations in metabolism, reproduction, brain and behavior changes and other neuroendocrine pathways. Besides the endogenous hormones that act programming neuroendocrine functions during development, some xenobiotics, environmental and chemical substances such as pesticides, fungicides, industrial chemicals, plastics and plant-derived products (such as. phytoestrogens) can interfere with the hormonal signaling as they act as hormone agonists or antagonists via ERs (xenoestrogens) and ARs (xenoandrogens) [74]. As endrocrine 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 as they can be transferred from maternal-fetal interaction as well as via lactation and are also found in

food sources [75, 76]. The present review will focus on the case of bisphenols, phthalates and parabens, which are found in plastics and in some common pesticides (Figure 4).

4.1 Bisphenols, phtalates and parabens

Bisphenols, phthalates and parabens are found in plasticizers, solvents and additives. Worldwide populations are exposed to these compounds in daily life as they are found in several industrial and consumer products, mainly food and drink [77]. One of the most common bisphenols is bisphenol A (BPA), which is found in polycarbonate plastic containers, including baby bottles. Thus, humans are exposed to BPA since early postnatal periods of life. BPA is known to bind competitively to ERs, with high affinity for ERβ, but it can also act via estrogen-independent pathways [78].

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 antiandrogenic compounds. In both humans and rodents, there is evidence that exposure to phthalates causes developmental and reproductive alterations [79]. There is also evidence that mixtures of BPA and phthalates have additive interactions in their antiandrogenic activity, showing synergistic effects at high concentrations and antagonistic activities at low concentrations [80].

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) [81], nitrosative stress, dyslipidemia, liver damage, hormonal imbalance and ovarian dysfunctions in their female progeny [82]. It has been shown that PCOS women, independently of their body weight, have high levels of serum BPA [83]. Thus, as 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 that suggest that BPA exposure may lead to PCOS-like features, the high rates of this syndrome nowadays may be also explained by the effect of this endocrine disruptor. BPA may also have a role as an environmental component in PCOS pathogenesis [83].

Some studies have shown that maternal administration of methyl donors, such as folic acid or vitamin B12 [84, 85] during pregnancy or melatonin [86] 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 to reverse, at least partially, the detrimental effects of exposure to estrogenic 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 estrogenic activity and can bind to ERs. As they are lipophilic, they can cross the brain barrier and accumulate in the skin and adipose tissue. It has been shown that the human population presents a high concentration of these compounds in serum, urine and breast milk samples [87]. 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 [88]. In a recent study, Guerra et al. (2017) [89] 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, as they found that over 50% of the treated animals were not sexually receptive to males.

As human populations are exposed to these compounds in daily life, it could be of great interest to evaluate metabolites of these compounds in pregnant women, so that medical interventions and follow-up could be done to their offspring. As mentioned before, intervention can include the administration of compounds as melatonin or folic acid, which are known not to affect the developing organism and may also have positive effects on maternal-fetal health since early life.

4.2 Pesticides

Pesticides, 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 [90]. Moreover, although some of them are no longer used, their effects persist in the environment. Thus, some authors have studied 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 ones 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.

-A) Organochlorine pesticides

Organochlorine pesticides such as dichlorodiphenyltrichloroethane (DDT), methoxychlor (MXC) and endosulfan are among the most used pesticides. As most of them have lipophilic structures, they may bioaccumulate and persist for years, thus being among the most frequent contaminants. Besides, given their structure, they can cross the placenta, thus affecting the developing embryos [91]. It has also been shown that they can affect female fertility by disrupting the estrous cycle, the development of ovarian follicles and the hormone levels [92].

DDT has been banned in many countries because of its toxic effects, but is still used as malaria vector control in some places of Africa [93]. It has been described that DDT may lead to developmental and reproductive abnormalities, neurological disorders and cancer [93-95]. It has also been shown that DDT has transgenerational effects, including ovarian diseases, obesity, metabolic alterations and cancer susceptibility in adult life, via epigenetic

mechanisms [93, 96, 97]. It has also been reported that exposure to DDT during pregnancy leads to subfertility in the female offspring [98].

Since 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 estrogenic and anti-androgenic effects [90, 99, 100]. Human epidemiological and rodent model studies have shown that constant exposure to MXC during adulthood affects cycling and ovulation and leads to fertility issues [99, 101, 102]. Several studies have described that MXC can have a developmental programming effect [102-104], causing alterations in epigenetic processes, such as changes in methylation patterns [99]. When rodents are exposed to MXC during fetal or early postnatal life, the effects in females persist until adulthood, with alterations in reproductive outcomes, such as puberty acceleration, irregular estrous cycle and alterations in folliculogenesis and cyst formation. The effects of prenatal administration of MXC have also been tested in sheep, and results showed that it can alter the LH surge at postnatal life, generate cycle disruption, and lead to low birth weight in the female offspring [105].

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. As 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 affect fertility as well as glucose metabolism, affecting the pancreas and plasma glucose levels, as well as liver oxidative stress and functions [91, 106].

-B) Organophosphorus pesticides

Organophosphorus pesticides, among which dichlorvos and chlorpyrifos are some of the most used, exert their toxicological action via inhibition of the enzyme acetylcholinesterase [107]. This enzyme is expressed in several tissues, including the central nervous system and the ovary, and participates in the regulation of folliculogenesis [108]. Thus, organophosphorus pesticides may be affecting not only the nervous system at brain level but also the local ovarian system, but 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, neural development as well as on ovarian, kidney and liver development [109-111]. The worldwide population is exposed to this compound because it is found in the environment, water, fruits and vegetables, but 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, as this compound can have intergenerational effects, it is of great importance to be aware of this [112]. In a murine model, Mansour and Gamet-Payraste (2016) [110] have shown 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 one of the main concerns in clinics. Nowadays, human populations are exposed to several hormonal and hormone-like compounds as environmental pollutants and pharmaceutical compounds. As these pathologies have

environmental components among their factors contributing to their etiology, it is of great importance in clinical, epidemiological and basic research to be aware of the developmental programming notion. As described, although steroids play many physiological actions, their excess (or absence) may lead to several pathologies that may affect the neuroendocrine and reproductive systems. As there are gender differences in the steroid regulation axis, it is also of great importance to deepen the study of the effects caused by steroid imbalances. Finally, it would be important to deepen the knowledge of the epigenetic mechanisms of action that may lead to intergenerational and transgenerational effects caused by steroid derangements, because they can be used as targets for the therapeutics of complex pathologies and disorders.

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Figure 1: Windows of susceptibility to environmental insults that may affect developing organisms throughout life. Developmental programming consequences may lead to epigenetic and gene expression changes and physiological adaptations that affect the susceptibility to adult diseases.

Figure 2: Schematic overview of the main steps of the steroidogenic process. Progestins and androgens (Dehydroepiandrosterone=DHEA, androstenedione and testosterone) are part of adrenal and ovarian steroidogenesis. Mineralocorticoids (e.g. aldosterone) and glucocorticoids (e.g. cortisol and corticosterone) are products of adrenal steroidogenesis, whereas estrogens (estradiol and estrone) are products of the ovarian steroidogenic process.

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=estradiol valerate. The pink arrow indicates the offspring. In those cases the exposure to androgen or estrogen is directly on the offspring, at postnatal life.

Figure 4: Most common endocrine disruptors and their action during early life programming. In purple: Examples of bisphenols, parabens and phtalates. In green: Examples of organochlorine pesticides. In yellow: Examples of organophosphorus pesticides.