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Effects of Environmental Chemicals and Drugs on Reproductive Endocrine System

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Abstract
Commonly found in ecosystems, endocrine disruptors are a large group of natural or synthetic compounds and xenobiotics that are toxic to the endocrine system of a living organism. The pesticides, herbicides, and hormonally active substances that are widely used in agriculture and industrial compounds are among the endocrine disruptors. Endocrine disrupters interfere with the immune system, thyroid functions, reproductive systems, and intrauterine life of a living organism. Endocrine disruptors show their oestrogenic, anti-oestrogenic, antiandrogenic, and androgenic effects by activating hormone biosynthesis, secretion, transport, degradation, receptors, or postreceptors. Effects of endocrine disruptors on male genital tract can be observed in estrogenic effects that cause delayed puberty, and, more importantly, reduction in androgen production of Leydig cells. Promycine, linuron, vinclozin, p,p'DDT, dioxin, phthalates, genistein, resveratrol, and bisphenol A are among the natural or synthetic chemicals that alter Leydig cell function. On the other hand, endocrine disruptors such as diethylstilbesterol, dichlorodiphenyltrichloroethane/dichlorodiphenyl-dichloro ethylene , methoxychlor, bisphenol A, polychlorinated biphenyls A, polychlorinatedbiphenyl, dioxins, and phthalates cause premature thelarche and precocious puberty with their estrogenic effects in girls. Atrazine, trenbolan acetate, lead, and vinclozis are among the other endocrine disruptors that may cause late puberty in girls. This article is a review of the recent publications that study the influences of endocrine disruptors on endocrine systems during puberty and adolescence, the growth and development periods of children.
Key Words: Endocrine Disruptors; Reproductive System; Children.

Cinsel Gelişimi Etkileyen Çevresel Faktörler ve İlaçlar

Özet
Ekosistem üzerinde çok yaygın olarak bulunan ve sayıları giderek artan doğal veya sentetik, hormonal olarak aktif, endokrin sisteme toksik olan maddelere ve ksenohormonlara endokrin bozucular denmektedir. Çevrede bulunan veya tarımda kullanılan haşere ilaçları, bitki koruyucular, bitkilerin hızlı büyümesini artıran hormonal ilaçlar ve endüstriyel maddeler endokrin bozucuların listesini oluşturmaktadır. Endokrin bozucular intrauterine döneme etki ederek konjenital malformasyonlara yolaçabildiği gibi; postnatal dönemde üreme, immun sistem ve tiroid fonksiyonlar üzerine de olumsuz etki gösterirler. Endokrin bozucular hormonların biyosentezini, salınımını, transportunu veya yıkımını reseptör veya postreseptör aktivasyon yoluyla etkileyerek; östrojenik, antiöstrojenik, antiandrojenik veya androjenik etkiler ile gösterirler. Endokrin bozucuların erkek genital sistem üzerine etkileri, östrojenik etkilerinden dolayı daha çok gecikmiş puberte olarak gözükmektedir ve en önemli etkisini Leydig hücrelerinin androjen üretimini azaltarak göstermektedir. Özellikle promycine, linuron, vinclozin, p,p'DDT, dioxin, fitalatlar, genistein, resveratrol ve bisphenol A Leydig hücre fonksiyonunu etkileyen doğal veya sentetik kimyasallar arasında yer almaktadır. Kızlarda ise diethylstilbesterol, dichlorodiphenyltrichloroethane /dichlorodiphenyl-dichloro ethiylene, methoxyklor, bisphenol A, polychlorinatedbiphenyl, dioxinler ve fitalatlar gibi endokrin bozucular, östrojenik etkileri ile erken telarş ve puberte prekoksa neden olmaktadır. Kızlarda geç puberteye neden olan endokrin bozucular ise atrazin, trenbolan asetat, kurşun ve vinclozindir. Bu yazı endokrin bozucuların, hızlı büyüme dönemindeki çocukluk çağı ve adölesanların sürekli gelişim ve değişim halinde olan endokrin sistemleri üzerine etkilerini son yayınlar ışığında gözden geçirmektedir.
Anahtar Kelimeler: Endokrin Bozucular; Cinsel Gelişim; Çocuklar.

Sexual development gains momentum in the embryonic period and adolescence. Environmental factors that affect human ecosystems have potential influence on especially these two processes in life in terms of endocrine function and, particularly, of sexual development (1). Increasing in number with a widespread effect on humans, these natural or synthetic, and hormonally active substances and xenohormones are called endocrine disruptors (ED). EDs are toxic substances to the endocrine system (2). The list of EDs includes environmental and crop protection substances like insecticides and pesticides as well as hormonal drugs and industrial substances which allow rapid growth of plants (3, 4). Because they experience constant physiological change and are in a process of growing up all the time, children are more prone to get affected by such a toxically charged environment (5). In addition, because genes in children that enable cellular development, DNA replication, and DNA repair along with genes that control the metabolism of endogenous and exogenous agents are more easily influenced by EDs, children have more susceptibility to these agents (6, 7).

In the last 10 years, especially, there have been extensive studies on EDs. Under several subtitles and

with clinical findings like infertility, obesity and so on, these studies have focused on investigating the effect of EDs and determining the effect mechanisms and environmental contamination of some synthetic and steroidal substances that act like endocrine disruptors on the molecular level (8).

While EDs may cause congenital malformations by affecting the fetus in the intrauterine phase, they may also have toxic effects on reproductive and immune systems as well as thyroid functions in the postnatal period that can even lead to an increase in obesity in childhood (6). By influencing endocrine and reproductive systems, EDs affects the human body through enzymatic means such as nuclear receptors, steroid hormone receptors (estrogen receptors), neurotransmitter receptors (serotonin, dopamine, norepinephrine receptors), orphan receptors (aryl hydrocarbon receptor), and steroid biosynthesis and/or metabolism (9). Through receptor or post-receptor activation, EDs affect the biosynthesis, release, transport, or destruction of hormones; in this way, they create oestrogenic, anti-oestrogenic, androgenic, or antiandrogenic effects (10-12). Mimicking numerous hormonal effects in a very good way, therefore, EDs show different clinical signs in boys and girls (13) (Table 1).

Table 1. The potential effects of endocrine disruptors on genital system.

	Fetal/Neonatal	Prepubertal	Pubertal
Male	Intrauterine growth restriction Undescendent testes Hypospadias	Premature pubarch	Small testes and high FSH Early puberty Delayed puberty
Female	Intrauterine growth restriction	Premature thelarche Peripheral precocious puberty Premature pubarch	Secondary central precocious puberty Polycystic ovary syndrome Delays in ovulatory cycles

FSH: Follicle stimulating hormone

The effects of endocrine disruptors on male sexual development:

The occurrence of secondary sexual characteristics in males before the age of 9 is defined as early sexual maturation (14). Most endocrine disruptors have oestrogenic effects; they employ androgenic effects less. Therefore, ED-related early puberty is less common in males; delayed puberty, however, is a more common condition in boys (13) (Table 2).

Table 2. The effects of some specific EDs on male genital system.

	Effects on animal models	Potential effects on humans	Potential effect mechanism
Vinclozolin	Hypospadias, undescendent testes		Delay in DNA metilation of germ cells (Epigenetics)
DES	Hypospadias, undescendent testes, micropenis	Hypospadias, undescendent testes, micropenis, epididymal cyst	Increase in oestrogen receptor expression in the epididyme, increase in IGFB3 levels
DDT	Decrease in fertility	Undescendent testes	
DDE		Undescendent testes	
Phthalates	Dcerease in anogenital distance, undescendent testes, oligospermia	Dcerease in anogenital distance and leydig cell functions, hypospadias	Decrease in testosterone synthesis
PCB	Decrease in spermatogenesis, delayed puberty	Decrease in penis size, delayed sexual maturation, decrease in fertility, cancer in fetal testes	
BPA	Abnormal growth in prostate and urethra		Increase in oestrogen in the hypothalamus, increase in androgen receptor expression in the prostate

DES: diethylstilbestrol, DDT: dichlorodiphenyltrichloroethane, DDE: dichlorodiphenyldichloroethylene, PCB: polychlorinated biphenyls, BPA: bisphenol A, IGFB3: insulin-like growth-binding protein 3

Endocrine disruptors have various effects on male reproductive system and the most important of these is reducing the androgen production in Leydig cells (10). Experiments on humans and animals have both shown that males may suffer from inadequate masculinization and malformation of the genitalia due to ED-affected fetal Leydig cell dysfunction. Inadequate development of Leydig cells in the adolescence may also manifest itself as decreased libido and spermatogenesis (10). EDs affecting Leydig cell function are shown in Table 3 (13):

By inhibiting the binding of androgen to androgen receptors and inhibiting steroidogenesis in Leydig cells, EDs specified in the table bring about incomplete masculinization. EDs are one of the reasons of the diseases defined under the title "testicular dysgenesis syndrome." This syndrome may surface in the form of cryptorchidism, hypospadias, testicular cancer, and decrease in semen quality (10).

Since obesity is now a common phenomenon all over the world with an increasing rate of frequency and prevalence, it does not only effect humans but also animal species by increasing the average weight. This has caused an increase in the number of studies concentrating on the relationship between ED and obesity. Some of these publications have attempted to explain this relationship by EDs influence in reducing Leydig cell function and increased oestrogenic effects (15).

Table 3. Natural and synthetic chemicals that effet Leydig cell formation.

Chemicals	Effect mechanism	Area of use and sources
Procymidone	Androgen receptor antagonist	Fungicide
Linuron	Androgen receptor antagonist	Herbicide
Vinclozolin	Androgen receptor antagonist	Fungicide
p,p'DDT	Androgen receptor antagonist	Pesticide
Dioxin	Aryl hydrocarbon receptor antagonist	Carbon hydrocarbons
Phthalates	Peroksizom proliferator activated receptors (PRARs)	Plastic materials
Genistein	Oestrogen receptor stimulator	Soy-based food
Resveratrol	Oestrogen receptor stimulator	Red wine, red grapes
Bisphenol A	Oestrogen receptor stimulator	Polycarbonate plastic materials

McGray et al. have demonstrated the androgen receptor antagonist effects of pesticides like procymidone, linuron, vinclozolin, and p,p'-DDT on quails (16,17). Phthalates, which is especially commonly used in plastic toys, create adverse effects on male reproductive system during certain stages of development by inhibiting steroidogenesis of the Leydig cells (10).

A member of the polychlorinated dibenzop-dioxin groups, 2, 3, 7, 8 tetra chlodibenzo-p-dioxin (TCDD) is an industrial product that affects Leydig cells by disrupting steroidogenesis and decreasing sex steroids and LH receptor expression. It also causes inactivation in steroid hormones through cytochrome P450 induction (10, 18).

Cheng CY et al.'s 2011study has shown that environmental toxic substances like Bisphenol A and cadmium distort the occludin/20-1/focal adhesion kinase (FAK) complex in the blood-testis barrier while also affecting the Sertoli cells (19). Again, Haeba et al. have conducted a study to examine the effect of vinclozolin on vertebrates by applying the substance on Dapnia Manga, a plankton. This study has demonstrated that vinclozolin has antiandrogenic effects on male Dapnia Manga as it reduced the rate of reproduction (20).

Methoxychlor (MXC) leads to damage in the sexual behaviours of adult male quails. After a study conducted on Japanese quails for two generations, Ottinger et al. have pointed out that MXC-exposed male quails have shown abnormalities in sexual behaviour while also these males have had less hypothalamic, catecholamine, and plasma steroid hormones (21). Having replaced DDT, methoxychlor is an insecticide that has been in use in fruit and vegetable production for years. By injecting MXC to quail eggs, Ottinger et al. have also shown that this substance causes impaired sexual behaviour in male offsprings in the long term (21). The reason for selecting quails in this type of studies is the well-defined reproductive endocrinology and reproductive behaviours of the quail.
Ottinger et al. have investigated the effects of estradiol, ethinyl estradiol, atrazine, methoxychloro DES, genistein, vinclozolin, p.p'DDE, and trenbolone acetate on male reproductive function and reproductive behaviours and concluded that these substances limit reproductive behaviours. However, they have also pointed out that the effect may change according to EDs and dose, even creating inverse effects at times (10).

It is known that catecholamines have stimulant effects on reproductive function and behaviours. As much as it affects water balance, vasopressin, for instance, is known to have a modulatory effect on sexual behaviour (10). Because as studies on invertebrates have proved, vasopressin and vasotocin found in the stria terminalis and amygdala of the male brain contain more neuronal cells with a higher intensity. For example, vasotocin has a direct effect on the sexual behaviours of male quails (22).

To investigate the effect of alcohol as an ED, Anderson et al. have conducted a research on adolescent males during puberty (23). As a result of this research, they have concluded that alcohol decreases testis weight, sperm count and motility, and the effect of sperms on fertilisation while it also causes an abnormal increase sperm incidence.

Biologically natural phytoestrogens, isoflavone found in soybean and genistein found in other plants are 1000-fold less active than normal oestrogen (E2). However, when injected into male quail egg embryos, these substances impair sexual development; these embryo subjects have also shown a decrease in immunostaining due to arginine vasotocin (AVT) in the hypothalamus (24). Similarly, after being injected into embryos, DDE and 2,2-bis (4-chlorophenyl)-acetic acid (DDA), two

active metabolites of DDT, have reduced mating ability (24, 25).

The effects of endocrine disrupters on female sexual development:

The development of secondary sexual characteristics in females before the age of 8 is defined as early sexual maturation (14). Many EDs have oestrogenic effects and they may result in early thelarche and precocious puberty in girls (13) (Table 4).

Table 4. The effects of some specific EDs on female genital system.

	Effects on animal models	Potential effects on humans	Potential effect mechanism
Vinclozolin	Multisystemic malfunction, tumours		Affected DNA metilation of germ cells (Epigenetics)
DES	Susceptibility to malignincies	Vaginal adenocarcinoma in babies whose mothers use DES during pregnancy	Increase in oestrogen receptor expression in the epididyme, decrease in IGFB3 levels
DDT/DDE	Precocious sexual maturation	Precocious puberty, increase in breast cancer risk	Neuroendocrine effects through aryl hydrocarbon receptors and oestrogen receptors
BPA	Breast ductus anomalies, precocious puberty	Abortions	Apoptotic activity inhibition in breast tissues
PCB	Neuroendocrine effects, behavioural shifts		Effects on oestrogen and neurotrasmitter receptors
Dioxins	Breast ductus development anomalies		Aryl hydrocarbon receptor inhibition through cytokinesis 2
Phthalates		Premature thelarche	

DES: diethylstilbestrol, DDT: dichlorodiphenyltrichloroethane, DDE: dichlorodiphenyldichloroethylene, PCB: polychlorinated biphenyls, BPA: bisphenol A, IGFB3: insulin-like growth-binding protein 3

EDs with estrogenic effects in females have been identified by many researchers. These are estradiol (an endogenous oestrogen receptor (ER) agonist), diethylstilbestrol (a medicament), genistein (a soy phytoestrogen), methoxychlor (a pesticide), and PCB-126 (an industrial substance) (8).

It has been reported that oestrogen given to rodents before the onset of sexual maturation causes early opening of the vagina, which corresponds to breast development in humans (11, 26). It has also been pointed out that some phytoestrogens that contain isoflavones such as genistein (found in soybeans and soy-based products) and daidzein give rise to early vaginal opening and increase in the uterus width (25, 26). For example, the daidzein, genistein, and total isoflavone were significantly high in the serum of Korean girls with central pubertas praecox (27). However, some studies suggest that isoflavones do not distinctly lead to early puberty in girls (28). Still, it is accepted that the oestrogen-dependent tissues of children who feed on a isoflavone-rich diet are affected by isoflavones. However, once affected, these tissues do not always result in early puberty (as in the case of increase in uterine elevation in mice), proliferation of the vaginal epithelium, or increase bone density. In light of all these studies on various effects of EDs such as phytoestrogens, which have estrogenic effects, have led researchers to study the effect mechanisms of phytoestrogens. Bateman et al. have detected decrease in GnRH secretion in mice that were exposed to phytoestrogens. They have explain this with the decrease in the fibre density in anteroventral periventricular and arcuate nucleus stimulated by kisspeptin, a peptide that is normally located in the hypothalamus and stimulates GnRH (29). Methoxychlor (MXC) is a pesticide that has been used as an alternative to DDT for a long time. Experiments in rats have shown that subjects exposed to MXC in the fetal period have early vaginal opening in future sexual development (30).

Bisphenol A (BPA), which can be found in plastic toys and plastic bottles, causes early vaginal opening and early puberty in female rats despite the fact that it has weak oestrogenic effects (31). In addition to these effects, BPA is also known as a teratogen and carcinogen substance. It is known that mice are under higher risk of breast cancer in adulthood when they are exposed to oestrogen for long periods of time in fetal period. As a carcinogen substance, BPA, when applied to fetuses in long terms, gives rise to maturity in the mammary glands in mice. Early prepubertal BPA exposure accelerates the onset of puberty in female mice. The effects of Bisphenol A, all of which are carried out through its impact on the hypothalamus, influence oestrogen receptors and accelerate the onset of puberty in female rats (32). As Bisphenol A brings about an increase in the density of the fibres of paraventricular, ventromedial, and arcuate nuclei in the hypothalamus, it results in changes in the reproductive functions of mice. As a result, the effect of BPA is focused on these certain nuclei in the hypothalamus, which in turn, gives rise to increase in weight gain in female rats and, thus, impairs the reproductive function. The morphogenesis of the mammary glands of fetuses exposed to perinatal BPA

also changes (33). Of course, this effect is also created by influencing oestrogen receptors.

Phthalates are a type of EDs usually found in soaps, shampoos, plastic items, cosmetic ingredients, and intravenous and PVC medical tubes (11, 34). Phthalates have systemic impact. The effects of phthalates have been a subject of research in recent years and through these studies it has been proved that they have adverse effects on the course of pregnancy, semen quality, thyroid functions, respiratory system, and neuromotor development of children while they also cause precocious puberty especially in girls (35). It has also been reported that they even increase the risk of allergies and asthma prevalence, reduce muscle mass in boys, and cause hypersensitivity. But its effects on reproductive functions are of greater importance. Studies have pointed out that phthalates reduce LH, free testosterone, and sex hormone binding protein levels (35). Indeed, there were high levels of phthalate in the urine samples of girls with precocious puberty and early thelarche (34-36). Another study has shown that phthalates give way to early vaginal development and an increase in the size of the uterus in girls (37).

Kakeyema et al. have shown that giving dioxin and polychlorinated dibenzodioxins in small doses to female mice has resulted in precocious puberty. Their study has proven that dioxin type EDs cause early maturation of hypothalamo-pituitary axis and early development of genitalia (38). A study conducted on immigrants living in Belgium reports that they have found high levels of p,p'-DDE, a DDT metabolite, in the urine samples of 84% of the girls with precocious puberty. This ED effect has been explained by the stimulation of the hypothalamo-pituitary axis due to weak oestrogenic effect. To analyse the effect mechanism of p,p'-DDE, some researchers have studied the impact of this metabolite on the Mullerian duct in girls during the gonadal development (39).

The toxic effects causing the increase in delayed puberty in girls in the last decades have been explained by EDs such as lead, vinclozolin (a fungicide with an androgenic effect), DDT and its metabolite DDE, trenbolone acetate (a anabolic androgen receptor agonist), and atrazine (a herbicide).

Some researchers have reported that, once applied to embryos trenbol acetate influences female reproductive functions and causes delayed puberty (40). Toxic effects of lead, which is another ED causing late onset of puberty in girls, have been the subject of several studies. For example, lead, even at very low doses, delays puberty in female mice (41). In another outstanding research, Mendola et al.'s survey of PubMed data base articles published between 1997 and 2007 has reported lead to be the most influential toxic substance that effects reproductive system of girls (42). Another study analysing the relationship between blood lead levels and puberty prolongation has pointed out that the onset of puberty varies depending on blood lead levels (43). There is an inverse relationship between high blood lead levels in girls during puberty and inhibin B hormone, a sign of follicular development (44). Although these studies indicate that high lead levels delay follicular growth and puberty, low inhibin B levels in girls with delayed puberty should be regarded as a warning sign to check lead levels. However, in contrast to these findings, another study on 192 healthy girls has demonstrated that lead does not have any effects in breast development (45).

Another ED that is toxic for female reproductive system is atrazine. Particularly those with agricultural jobs are exposed to atrazine. The amount of atrazine in the drinking water also poses a problem for public health. To investigate the toxic effects of atrazine in patients, it is adequate enough to study the urinary atrazine mercapturate levels (46). The toxic effect of atrazine manifests itself by disrupting the oestrogen-based hormonal balance of the female reproductive system in favour of androgens. Some researchers assert that this effect may also manifest itself by increasing the rate of preterm births (47). A study conducted in Illinois, the United States, has demonstrated that females between the ages of 18 and 40 who were exposed to atrazine had irregularities in menstrual cycles, elongation in the follicular phase, and increase in infantile ovulatory cycles (48).

Other EDs that may cause late onset of puberty in girls are vinclozolin and Bisphenol A (BPA). It has been found out that while vinclozolin reduces the gestation period and number of pregnancy as well as increases the percentage of abortions, and BPA also has an increasing effect on the number of abortions (49).
Parallel to the time spent in urban life, the amount of toxic substances that threaten public health also increases. Toxic substances effect all systems of human health in varying degrees. Such toxic substances are especially effective during the fetal period, period of rapid growth in childhood, and adolescence along with the ever changing endocrine system during these periods. Endocrine disruptors (EDs) have oestrogenic, anti-oestrogenic, androgenic, and antiandrogenic effects. EDs usually manifest themselves by disrupting the hypothalamo-pituitary axis and changing the hormone balance. Clinically, these effects may point to early puberty or late puberty. Although there are many drugs and toxins that have been identified as EDs, it is for sure that we still live in a world of many unidentified substances that we are exposed to in our everyday lives. To see the effect of these substances on future generations, there is need for extensive research and experiments on humans and animals.

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