REVIEW

The influence of various endocrine disruptors on the reproductive system

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Abstract

Various stimulants (VS) are chemicals that disrupt the endocrine system — endocrine homeostasis of the reproductive system — which also known as endocrine-disrupting chemicals (EDCs). These substances are found in the human body, in both the blood and urine, amniotic fluid, or, among others, the adipose tissue.
This article presents the current state of knowledge of the effect of EDCs and additional factors such as smoking, alcohol consumption, and cannabis on the gonads.
The article is an overview of the impact of EDCs and their mechanism of action, with particular emphasis on gonads, based on databases such as PubMed, EMBASE and Google Scholar, and Web of Science available until May 2022.
The impact of human exposure to bisphenol A (BPA) is not fully understood, but it has been shown that phthalates show a negative correlation in anti-androgenic activity in the case of men and women for the anti-Müllerian hormone (AMH). Smoking cigarettes and passive exposure to tobacco have a huge impact on the effects of endocrine disorders in both women and men, especially during the reproductive time. Also, the use of large amounts of cannabinoids during the reproductive years can lead to similar disorders. It has been documented that excessive alcohol consumption leads to disturbed function of the hypothalamus–pituitary–gonadal axis (HPG). Excess caffeine consumption may adversely affect male reproductive function, although this is not fully proven.
Therefore, the following publication presents various stimulants (BPA, phthalates, nicotine, alcohol, cannabis) that disrupt the function of the endocrine system and, in particular, affect the function of the gonads.

Key words: alcohol; bisphenol A; cannabidiol; coffee consumption; endocrine disruptors; endocrine system; reproductive system; female and male infertility; ultraviolet (UV); UV filters; tobacco and e-cigarettes

Introduction

Endocrine-disrupting compounds (EDCs) are chemicals with properties that interfere with the body's hormonal homeostasis. These compounds may disturb the work of the hypothalamic–pituitary–gonadal axis (HPG). It has been proven that most EDCs have a wide range of effects and, above all, sometimes a significant negative effect on the endocrine system [1].

So far, the negative impact of EDCs has been detected in compounds including pesticides, dioxins, polychlorinated biphenyls (PCBs), polybrominated diethyl ethers (PBDE), plasticisers like bisphenol A (BPA) and phthalates, UV filters, or nicotine. Some of these are formed as products during the incineration of municipal waste or even in volcanic eruptions (dioxins). They can be ingredients in cosmetics or paper, or used in plant or animal protection (pesticides). Phthalates are components necessary for the production of, for example, varnishes or phthalic paints, laminates, or adhesives. However, some, such as phytoestrogens, alcohol, or marijuana, sometimes have beneficial effects but not for male and female gonads [1–3].

The operation of EDCs is still not well understood. It is known that they can disturb the endocrine system, in both the female and male gonads [1–3]. It has been

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proven that in the case of female gonads, changes may occur, including oestrogen (E) signalling pathways and interact via oestrogen receptors (ER). The same is true of the male gonads, where EDCs can disrupt "healthy" hormones via androgen (A) and the androgen receptor (AR). It has been shown that EDCs can act as agonists or "mimic" a natural hormone. In addition, they also bind and activate various hormonal receptors, such as 1. AR; 2. ER; 3. oestrogen-related receptor (ERR); or 4. aryl hydrocarbon receptor AhR), chimeric antigen receptor (CAR), or pregnane X receptor (PXR). EDCs can be antagonistic by binding to these various receptors without activating them. In addition, EDCs significantly affect the concentration of hormones, their transport, synthesis, metabolism, or elimination [4–7].

The publication presents the current state of knowledge on how BPA, phthalates, androgenic EDCs, alcohol, nicotinism, marijuana, and UV light affect both male and female fertility. The authors of this work discuss the issues related to the influence of the dose of these agents, and the duration of use on the occurrence of changes at the gonadal and hormonal levels. The influence of abstinence on changes caused by the chronic use of alcohol, cigarettes, or marijuana is also discussed. Understanding the mechanisms leading to the development of sexual dysfunctions at the cellular, hormonal, and psychosocial levels may contribute to the improvement of diagnostic methods and the implementation of preventive and therapeutic measures. Compulsive consumption of various substances is one of the modifiable risk factors for infertility in both women and men. The publication additionally presents the impact of coffee consumption on the fertility process and, above all, the current state of knowledge regarding, inter alia, magnesium and calcium.

The purpose of this review is to discuss the influence of various stimulants and UV filters on the reproductive system. The article is an overview of the impact of reproductive disruptors on the male and female reproductive systems based on the medical databases PubMed, Web of Science, EMBASE, and Google Scholar, available until 28 May 2022. Publications in Polish and English were considered. During the search of the relevant literature, the following keywords and their combinations were used: "endocrine disruptors", "bisphenol A", "phthalates", "male gonads", "female gonads", "UV filters", "tobacco and e-cigarettes", "alcohol", "cannabis", and "coffee". Original research papers and review papers related to the presented topic were qualified for the review.

Bisphenol A

Bisphenol A (BPA) is an oestrogenic monomer (it occurs in the formation of, among others, epoxy resins and polycarbonate plastics) [8], and studies conducted on women with polycystic ovary syndrome (PCOS) showed its significantly increased level compared to healthy women. Moreover, in women with PCOS, a positive correlation was found between insulin resistance and serum BPA concentration [9], with serum BPA levels in those diagnosed with PCOS significantly higher compared to women without PCOS [9–12].

In addition, an association was found between body mass index, total testosterone (T), free T, dehydroepiandrosterone, and dehydroepiandrosterone sulphate (with and without PCOS) and BPA. However, no correlation between serum BPA and any other sex hormone [luteinizing hormone (LH), follicle-stimulating hormone (FSH), and oestradiol (E2)] was confirmed [13-14].

It has now been shown that BPA crosses the placental barrier and has been detected in the foetus (serum) and in the amniotic fluid as a potential hazard [15–16]. The highest concentration of BPA was found in the amniotic fluid in the middle of pregnancy, and it is then destroyed during the maturation of the foetal liver [16].

Animal study
In rodents, BPA reduced fertility in the offspring by exposing the uterus and ovaries [17]. The greatest danger, however, is in the prenatal period [18–20].

Human study
The effect of human exposure to BPA is not fully investigated; however, studies on other EDCs have shown that they may influence the development of oestrogen-sensitive organs [21].

Future research directions proposed by this field include the use of developmental biomarkers, in particular those involved in reproductive development, to investigate this association in infants and female children in a longitudinal cohort [18, 22].

Phthalates

Phthalic acid esters (PAEs) are compounds that increase the plasticity of polyvinyl chloride (PVC). PAEs are mainly used in cosmetology (cosmetics, toiletries, food packaging), medical products (including intravenous tubes), beverage containers, and plastic toys [18, 23–29]. It has been proven that DBPs (phthalates) have anti-androgenic effects [18].

Animal study
Rodent studies have shown that PAEs lower fertility and thus increase visceral obesity [30]. Dibutyl phthalate (DBP) is more dominant during prenatal exposure than in mature animals [31]. In rodents, it was found that

the concentrations of DBP, BPA, and di(2-ethylhexyl) phthalate (DEHP) increased significantly during pregnancy, which resulted in significantly more PCOS [32].

Human study

Recent studies have shown that DEHP is highly toxic, especially during reproduction and growth, both in animals and humans [33–34]. On the other hand, recent studies have shown that exposure to DEHP causes impaired ovarian steroidogenesis as well as low levels of progesterone (P) [35–36]. Phthalates also show a reversely proportional (negative correlation) anti-androgenic effect, related in particular to the concentration of testosterone (T) [37]. Moreover, it was also shown that the phthalate metabolite was negatively correlated with the concentration of AMH [38].

Prenatal androgen exposure and environmental androgens

Prenatal androgen exposure

Human study

A foetus that is exposed to excess androgens develops PCOS during adolescence. Additional studies on female offspring showed an increase in AMH levels in female offspring [39]. However, paradoxically, in the cohort study, the same researchers did not confirm this increase.

Animal study

Prenatal studies on rats (Wistar breed) showed cystic ovarian follicles, an increased number of preantral and antral follicles [40], and therefore ovulation and menstrual disorders, i.e. PCOS (increased levels of androgens and LH) [41]. Prenatal androgen exposure in female monkeys demonstrated the presence of PCOS and insulin resistance even in infancy [42–43].

Environmental androgens

The environmental androgens include triclocarban (TCC), i.e. 3,4,40-trichlorocarbanilide. TCC is often used as an antimicrobial agent. It can be found in toys, pacifiers, school supplies, brooms, clothes, and plastics [44]. Pycke et al. [45] detected TCC in umbilical cord plasma. TCC itself has almost no androgenic effect, but in the presence of T via the AR, increased transcription of AR occurs and, as a result, bioactivity of endogenous T is increased [46].

UV filters and gonads

UV filters are a heterogeneous group of chemical compounds that can be divided into 2 main types:

physical filters which include, among others, zinc oxide and titanium dioxide, and chemical filters, such as 3-benzophenone (BP-3), 3-benzylidene camphor (3-BC), 4-methylbenzylidene camphor (4-MBC), 2-ethylhexyl 4-methoxycinnamate (OMC), octocrylene (OCT), 2-ethylhexyl 4-dimethylaminobenzoate (OD-PABA), and 4-aminobenzoic acid (PABA) [47-48].

Modern filter compositions contain substances to block or absorb UV-B and UV-A radiation, and consequently they largely protect against the development of basal and squamous cell carcinomas of the skin and melanoma, the development of which is associated with exposure to UV-A radiation [49-52]. Together with the spread of public awareness of the dangers of exposing the skin to radiation and the ever-increasing incidence of melanoma, the use of sunscreen has become common [51].

Mechanistic studies

It has been shown that chemical filters, in particular, have a significant effect on the reproductive system [47]. One of the findings was the oestrogenic properties of BP-3, which has the ability to stimulate oocytes through the ER. Under the influence of BP-3, follistatin mRNA expression was induced, stopping oocyte maturation, which may be a compensatory mechanism in response to the disruptive action of BP-3. Also, the percentage of p27 molecules inhibiting primordial vesicle activation was decreased by the low concentration of BP-3 (5.8 nM), which is an example of the induction of an imbalance between follicle maturation and BP-3-induced activation of early oocyte forms [53].

Human studies

The effect of BP-3 on the male reproductive system was successfully assessed in humans, where the concentration of these compounds in the urine was determined and compared to the tested blood and semen samples. It transpired that in 97% of healthy volunteers, the presence of compounds from the BP-3 group was detected in the urine. A positive relationship has been demonstrated between the concentration of benzophenones in the urine and the concentration of FSH. The concentration of benzophenone-1 was positively related to the T/E ratio and negatively related to the inhibin b/FSH ratio. However, the influence of compounds from the benzophenone group on changes in the quantity and quality of male sperm [54] has not been demonstrated. Extremely interesting conclusions can be drawn from the study of the influence of 3-benzophenone on female fertility. BP-3 was also found in 98% of the urine samples from the female group. It turned out that the higher concentration of BP-3 in women was associated with a higher probability of implantation and pregnancy,

and successful labour than in women with lower concentrations of BP-3. However, such surprisingly positive results of the effect of BP-3 were limited to the group of women declaring they spend more time outdoors and perform moderately hard work. Due to the inability to properly isolate the effect of physical activity on fertility in these women, there is a need to continue research into the isolated effect of BP-3 on fertility [55].

Tobacco and e-cigarette smoking

Smoking cigarettes and passive exposure to tobacco has a huge impact on the endocrine disruption effects in women of reproductive age, both in the menstrual and luteal phases, and most importantly it has a negative effect on female fecundity [56–61]. However, the Oxford Family Planning Association presents interesting observations that demonstrate the return to normal fertility of ex-smokers [62]. Studies by Barbieri et al. [63] suggest that smoking inhibits a major steroidogenic pathway, including the inhibition of granulosa cell aromatase and the induction of the oxidative metabolism of Es [64]. In smokers, significantly reduced levels of AMH were found, especially in patients prepared for in vitro fertilisation (IVF) [65–67].

Since the 1980s, many meta-analyses and cohort studies have been conducted related to the number of cigarettes smoked and the menstrual cycle, which showed increased nicotinism in the luteal phase [67]. Apart from nicotine addiction, Craig et al. [68] observed an additional problem which also appeared in our research, namely that female smokers tended to drink alcohol before menstruation, which probably increased the number of cigarettes smoked in the luteal phase.

The research was further confirmed in a study by Sakai and Ohashi [69], which showed that the number of cigarettes smoked by young Japanese women and the CO level in their exhaled air increased significantly in the luteal phase.

The study was additionally confirmed by Hughes et al. [70], who showed that quitting smoking significantly improved fertility. This method included research involving several minutes of consultation, education, and encouragement at each clinical visit, according to the patient's individual readiness to stop smoking cigarettes.

Electronic cigarettes
Electronic cigarettes (e-cigarettes, e-cigs) are nowadays an alternative that can help in reducing the number of cigarettes smoked or in cessation of smoking.

Male reproductive system
Research by Wetendorf et al. [71] on sham mice showed a negative impact on the success of implantation and the future health of a foetus exposed to nicotine contained in e-cigarettes. It should be noted that exposure to e-cigarettes in the uterus reduces weight ($p = 0.006$).

Despite the scarcity of existing literature on the subject, very interesting observations were made by Golli et al. [72] in the testis of Wistar rats, in which it was proven that e-cigarette refill liquid (e-liquid) containing nicotine disturbed the oxidative balance and reduced the 2 main enzymes of steroidogenesis: 1. P450 side-chain cleavage (scc) (cytochrome 450 scc), and 2. 17b-hydroxysteroid dehydrogenase (17b-HSD) mRNA level. Experimental studies were carried out on sperm collected from the tail epididymis, which showed a significant decrease in the number and viability of sperm. Nicotine-free e-cigarette fluid (low voltage steam) disrupted the enzymes involved in steroidogenesis (3β-HSD and 17β-HSD) and those related to the activity of the seminal epithelium, which can lead to impairment of the reproductive system.

Inhibition of the expression of 2 key enzymes contained in the synthesis of steroids, 3β-HSD and 17β-HSD, was observed after exposure to e-vapour. As a result, the activity of the marker nuclei of sorbitol dehydrogenase (SDH) and the enzyme glucose-6-phosphate dehydrogenase (G6PDH) was significantly impaired, whereas the marker tissue damaging lactate dehydrogenase (LDH) increased slightly. There are currently no data on the effects of e-cigarette use on sperm [73]. Nevertheless, Helen O'Neill [74] showed that e-cigarettes may impair male fertility through toxic chemicals (flavourings). She presented the results of an experiment in which male sperm were exposed to the aromas of cinnamon and chewing gum introduced into the medium. The concentration of the aromas used in the experiment was similar to the average consumption of occasional and heavier e-cigarette users. The results indicated that cinnamon flavours can significantly reduce sperm motility by causing slower cell movement.

Wawryk-Gawdy et al. [75] showed that in male rats, exposure to smoke and e-vapour caused morphological and functional changes in the seminal epithelium (including vacuolisation, decreased spermatogenesis) and increased apoptosis of spermatogonia and spermatocytes. Additionally, slight changes in sperm morphology were found.

Female reproductive system
The effect of smoking on female fertility has already been studied, and it has been proven that active, prolonged smoking with high intensity significantly reduces fertility and has harmful effects during pregnancy [76–77]. Currently, there are no precise data on

the influence of the inhalation and exhalation of e-cigarette vapours on folliculogenesis and gamete efficiency. There are also a lack of detailed data on the prenatal exposure of pregnant women and the embryo/foetus to e-cigarettes [78].

Transcriptome analysis by Wetendorf et al. [71] showed that exposure to e-cigarettes modulated the gene expression necessary for uterine receptivity (pathway: integrin, prostanoid biosynthesis, proliferation, Janus kinase (JAK), and chemokine signalling). The protein claudin 10 (CLDN10) was overexpressed in the superficial and glandular epithelium of the uteri in women exposed to e-cigarettes, with elevated RNA levels. The role of CLD10 in the uterus is not well established; it is known to play a pivotal role in the kidney and is related to epithelial ion transport. Hence, maternal inhalation of e-cigarette vapour regulates the pathways crucial for uterine receptivity, which includes the genes responsible for ion transport. In contrast, *in utero* exposure of female mice resulted in a reduction in body weight gain. The results clearly showed a negative impact of e-cigarettes. It has been shown that embryo implantation led to an abnormal pregnancy, affecting the health of the offspring. When applied to women, these results would indicate that e-cigarette use when of reproductive age may directly influence conception and have a detrimental effect on the embryo and the foetus.

Research by Smith et al. [79] was carried out on pregnant mice (C57BL/6J) that had been exposed to nicotine fumes from e-cigarettes. The experimental results showed that exposure of mice to nicotine-containing fumes during a period of rapid brain development may cause permanent behavioural changes. Studies in animal models have shown that the exposure of the foetus during intrauterine life, or of puppies after birth, to e-cigarette fumes containing nicotine led to weight and body length reduction. However, there are no evaluative studies yet on the reproductive impact of e-cigarette use by pregnant women [80]. Despite this, the use of e-cigarettes can deliver levels of nicotine and its metabolites similar to, or even higher than, those provided by traditional cigarettes with a similar systemic retention [82]. The literature results indicate that the use of electronic nicotine delivery systems (ENDS) by pregnant women is not safe for foetuses [80-84].

Cannabis and the endocrinal-gonadal system

The hemp plant is one of the oldest herbs in Central Asia. It has been used since antiquity for therapeutic, recreational, and even religious purposes. There are 2 types of this plant: indica and sativa. Both types have many different forms; they can be dried as seeds, flowers, stems, or leaves. Currently, in addition to alcohol and tobacco, marijuana is one of the most common psychotropic drugs [85], and its prevalence has grown significantly. According to the World Health Organization, the annual prevalence of cannabis use is around 2.5% of the world's population [86].

A 'cannabinoid' is a compound of the cannabis plant or its derivatives (phytocannabinoids, endocannabinoids, and synthetic cannabinoids) [87]. The most abundant phytocannabinoids are Δ-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) [88]. On the other hand, cannabis is divided into 3 chemical variants depending on the cannabinoid content: Type I (THC dominance), Type II (CBD and THC), and Type III (CBD dominance) [89]. Endogenous cannabinoids (eCBs) are substances produced naturally in the body that work through cannabinoid receptors. eCBs contain lipophilic neurotransmitters: arachidonoylethanolamine (anandamide, AEA), 2-arachidonoyl glycerol (2-AG), 2-arachidonoyl glyceryl ether (noladin ether), virodhamine, and N-arachidonoyl glycerol (NADA). Contrary to eCBs, there are synthetic cannabinoids (THC analogues) [90].

The influence of cannabis on the female and male hypothalamic–pituitary–gonadal axis

Adolescents often use cannabinoids in their reproductive years, so the influence of marijuana on the reproductive system, especially on fertility, should be taken into account [91–93].

Animal study

Chronic administration of cannabinoids to rodents resulted in a reduction in gonadotropin-releasing hormone (GnRH) release in female animals. THC reduced the release of GnRH which was stimulated by norepinephrine and dopamine [94–96]. Similar reactions occurred with chronic cannabis administration, where GnRH receptors were expressed in the pituitary gland [97].

High levels of cannabinoids not only affect the hypothalamus, but also may disturb both the Graafian follicle maturation process and ovulation (the level of vascular cells) [98–99]. It has been shown that endocannabinoids negatively affect the male reproductive system. Endocannabinoids have CB1Rs receptors in the hypothalamus, pituitary gland, testis, Leydig cells, and sperm [91, 100, 101]. It has been shown that the administration of THC results in a reduction in plasma LH, T, and FSH [102]. THC has direct and indirect multiple effects on the inhibition of GnRH release, which causes an inhibition in LH pulsatility [96, 103].

Moreover, it has been found that CBD can inhibit the 7α hydroxylase enzyme, which is necessary in the synthesis of androgen in the rat testis. The dysfunction of this enzyme leads to a decrease in testosterone production by the Leydig cells in the testis [91]. An experiment on mice resulted in a 47% decrease in sperm motility after administering 1 mM of THC for 15 min and a 67% decrease after administering 10 mM of THC for 15 min [104]. Testicular atrophy and a decrease in the seminiferous tubule diameter were also seen after the administration of AEA and THC [103-104].

Human data

Cannabinoids exert a negative effect on the female reproductive system [103]. During pregnancy, THC may cross the placental barrier, which may lead to the birth of a child with low birth weight or even premature delivery [105–106], and an increased risk of pregnancy loss has also been observed [107]. Continuous consumption of marijuana (during conception, throughout pregnancy) has even resulted in sudden infant death syndromes [108].

CB1R agonists significantly reduce the concentration of prolactin, and cannabinoids increase the release of dopamine in the hypothalamus, and as a result the release of prolactin is inhibited [109]. But in the case of chronic marijuana use, there is a 'rebound phenomenon', leading to significant hyperprolactinaemia [110]. Research by Crume et al. [111] showed that the use of marijuana during lactation was associated with its shortening.

There is currently a lack of accurate data related to PCOS and cannabinoid consumption. Currently, the relationship between the endocannabinoid system and the development of PCOS has been proven, and this is also found in non-obese people. Moreover, an increased level of AEA has been shown in PCOS patients [112]. It has also been postulated that ECS activation and CB1R overexpression is associated with insulin resistance in women with PCOS. Research by Juan et al. [113] showed increased expression of AEA, 2-AG, CB1R, and CB2R mRNA in those with PCOS compared to healthy patients.

The latest research by Lammert et al. [114] showed that women who use cannabis and tobacco have a shortened luteal phase, in comparison to females who only use tobacco. A very interesting and innovative study (a randomised, placebo-controlled trial test) was conducted by Sherman [115] in a group of 8 heavy cannabis users, 3 of whom received micronised progesterone (200 mg; n = 3), while the rest received a matching placebo (n = 5), in the early follicular phase of their menstrual cycle during cannabis withdrawal. Among the women receiving progesterone, all tests were negative, which was further confirmed by cannabis abstinence.

Cannabinoids exert a negative effect on the human reproductive system [103]. Recent studies have shown that the human sperm expresses both cannabinoid receptors: CB1RS and CB2RS [101]. Cannabinoids and eCBs have been shown to negatively affect sperm function. THC activates CB1RS on sperm and results in a reduction in the lifespan and motility of the sperm [103]. In addition, THC hinders the induction of capacitation by the acrosome reaction inhibiting penetration to the zona pellucida and inhibiting the fertilisation capacity [116–118]. An association between marijuana use and a decrease in sperm count and concentration has been made based on the results of these studies [119, 120]. Men who use marijuana have shown a poor sperm morphology when presented for infertility evaluation [121]. Long-term use of marijuana can lead to disturbances in erectile function [122]. The latest studies have shown that there is an association between the use of cannabis and an increase in testicular germ cell tumours, especially non-seminomatous tumours [123–124].

Effects of alcohol on the genitals

Excessive and continuous consumption of alcohol leads to multifactorial and polygenic disorders that can result in various phenotypic addictions [125–126]. Alcohol, in addition to its influence on the liver, cardiovascular system [127], immune disorders, mental disorders, and some neoplasms [128], causes numerous hormonal disorders [126, 129].

The influence of alcohol on the hypothalamic-pituitary-adrenal axis

Alcohol activates the hypothalamic–pituitary–adrenal (HPA) axis, which results in an increase in the concentration of adrenocorticotropic hormone (ACTH) and glucocorticoids [126].

Animal study

In rats, acute administration of ethanol increases the levels of ACTH and corticosterone in the plasma, and it has additionally been proven that females show a greater response after the administration of ethanol than males [130]. Rivier et al. [131] showed that under the influence of ethanol the concentration of corticotrophin-releasing hormone (CRH) from the hypothalamus increases. It has been noted that the paraventricular nucleus (PVN) is damaged significantly, but this does not abolish the stimulating effect of ethanol on ACTH release [131]. Hence, additional regions of PVN and/or, for example, vasopressin have

been shown to mediate the stimulation of ACTH release by ethanol [132]. In the case of chronic alcohol administration, the response to cortisol and ACTH is reduced [133]. Additionally, the CRH system has been proven to play an important role in alcoholism, limiting the expression of CRH mRNA in the PVN [134] and reducing the pituitary response to CRH [135]. It has also been shown that mice lacking the CRH1 receptor show an increase in alcohol consumption, even for the rest of their lives [136, 137].

Human study
Alcohol produces both sedating and stimulant effects in humans. Several studies have shown a stimulating effect of alcohol on the HPA axis [138] and increased urinary cortisol levels in men [139]. In alcoholics, the HPA axis function is disturbed [133, 140–141].

In addition, it has been shown that decreased opioid activity as a result of alcoholism or genetically associated with the risk of alcoholism can induce hypercortisolaemia alter mesolimbic dopamine (DA) production and lead to inappropriate ethanol enhancement [140, 142].

Alcohol and the hypothalamic-pituitary-gonadal axis
Alcohol abuse and alcoholism are associated with impaired reproductive function in both men and women. The HPG axis and its hormones are essential for the proper functioning of the reproductive system. It has been shown that in people with excessive alcohol consumption, HPG dysfunction is associated with decreased libido, infertility, and gonadal atrophy. Several studies have clearly documented that alcohol has a detrimental effect on all 3 components of the HPG axis: the hypothalamus, pituitary, and gonads. We will review some of these studies on the acute and chronic effects of alcohol on the male and female reproductive systems [126]. Dysregulation of the HPG axis can therefore lead not only to reproductive dysfunction, but also to other serious health problems such as mood and memory disorders, osteoporosis, and muscle atrophy [126, 143, 144].

The influence of alcohol on the hypothalamic-pituitary-gonadal axis in puberty
Moderate alcohol consumption in puberty girls causes low E levels [145]. Boys also experience hormonal changes when consuming alcohol. First, there is a significant reduction in the levels of testosterone and pituitary hormones (LH and FSH) [146]. Under the influence of alcohol, alcohol-induced HPG axis activity is disturbed, which results in reproductive and growth disorders [147].

Animal study
Studies in rodents and monkeys have shown that alcohol reduces hypothalamic LHRH secretion and increases the concentration of growth hormone releasing hormone (GRH) [148], which was associated with a decrease in circulating growth hormone (GH) [147]. The decrease in GH under the influence of alcohol was associated with the decrease in insulin-like growth factor 1 (IGF-1), i.e. with disturbed growth in animals [149].

In female monkeys, alcohol caused a significant reduction in LH, E, and IGF-1 but did not affect FSH and leptin levels [150].

Alcohol and the female and the male hypothalamic-pituitary-gonadal axis
Premenopausal alcohol consumption leads to menstrual disorders, reproductive disorders (decreased ovarian reserve), anovulatory cycles, increased risk of spontaneous abortions, and early menopause or hyperprolactinaemia [151–155]. In the case of hormone replacement therapy, oestradiol metabolism disorders (decreased oestradiol conversion to oestrone) occurred in women who consumed alcohol [156]. Dysregulation of the HPG axis may therefore lead not only to reproductive dysfunction, but also to other serious health problems, such as mood and memory disorders, osteoporosis, and muscle wasting [126, 143, 144].

Consuming ethanol, both acute and chronic, causes a decrease in testosterone and progesterone levels, and an increase in FSH, LH, and E, which results in a decrease in semen, sperm count, and motility [157]. In the case of cirrhosis of the liver caused by alcoholism, hypogonadism (increase of oestradiol and oestrone) is observed [158].

Animal study
Studies conducted on young rats subjected to acute and chronic exposure to ethanol showed a decrease in testosterone levels and abnormalities in LH and FSH levels [159–160].

Alcohol and prolactin
Alcohol consumption has been shown to induce hyperprolactinaemia in animals and in humans. Animal studies (in female macaques) have shown an increased concentration of prolactin (PRL) during chronic alcohol administration [161, 162]. It has also been shown in rats that ethanol increases plasma PRL levels and pituitary weight in cyclic female rats and ovariectomised rats [163], and leads to the formation of a prolactinoma tumour induced by elevated oestradiol (alcohol induction) [164].

The effect of caffeine (found in coffee, tea, and cocoa drinks) on the female and male reproductive system

It was observed during the pandemic that there was a decrease in ready-to-eat meals (25%) and alcohol (12%) compared to what was consumed before the pandemic. Increased consumption of vegetables and fruits may result from greater care for the supply of essential vitamins for fear of viral infection [165]. Retrospective studies by Silva et al. [166] and Salman et al. [167] confirmed the increase in fruit and vegetable consumption during the pandemic.

Excess caffeine consumption may adversely affect male reproductive function, possibly through DNA damage (aneuploidy, DNA breakage) of sperm, although these studies are not entirely consistent. As a result, it was proven that in most studies, caffeine consumption had no effect on sperm parameters [165, 168, 169]. It is true that some studies have shown that drinking coffee by women was associated with a longer time required to become pregnant [165].

A study by Rivera-Calimlim in a 6-week-old infant who was breastfed by a mother drinking 4–5 cups of coffee and about 480 ml of cola daily showed hand tremors and an increase in muscle tone in this child. These symptoms were significantly reduced when the mother stopped the caffeine consumption [170–172]. The authors concluded that a limit of 300 mg of caffeine per day is reasonable [173].

Breastfeeding mothers who consumed a lot of coffee (more than 450 mL per day), delivered infants with lower birth weight and decreased haemoglobin and haematocrit at birth. Iron levels in breast milk were also lower among coffee drinkers, and their infants' haemoglobin and haematocrit values were lower up to one month after delivery [174].

A review of studies conducted from 2000 to 2020 by Olechno et al. based on PubMed and Google Scholar showed that drinking coffee, from 3 to 4 cups a day, is a source of magnesium and potassium, as opposed to calcium, sodium, and phosphorus [175].

Conclusions

Certain chemicals in modern living environments have been shown to significantly disrupt EDCs [18, 176].

EDCs are found, in particular in PCBs, flame retardants, perfluorinated compounds, and, primarily, in phthalates and phenols. Mitro et al. [177] proved that these compounds cross the placental barrier. These compounds are especially dangerous in the prenatal period [178, 179]. Studies conducted on pregnant rats exposed to EDCs (a mixture of phthalates, BPA [32], jet fuel [180], vinclozolin [181], or a mixture of N, N-diethyl-meta-toluamide (DEET), and permethrin [182]) lead to the development of PCOS in both the first and third generations. On the other hand, disorders of the menstrual cycle and *in vitro* implantation (IVF) disorders have been shown in humans [24].

Stimulants, such as cannabis, cigarettes, alcohol, coffee, and UV filters, are disruptive regardless of the endocrine system, especially gonads. However, these factors are subject to constant modification. In this publication, particular attention was paid to their frequent or constant consumption (e.g. habitual alcohol or marijuana consumption). Demographic and socio-economic factors affect fertility in women and men. The problem of infertility results from many factors, including those related to lifestyle: smoking, alcohol consumption, use of other psychoactive substances, obesity, mental stress, improper diet, and caffeine intake [159, 160, 175, 183]. Expanding knowledge about changes in the reproductive system due to the effect of chronic alcohol consumption, as well as other modifiable risk factors for infertility, will allow for the implementation of early prophylaxis.

However, it has been observed that the use of e-cigarettes rises sharply in pregnant women, as well as in women of childbearing age, because it is believed that it is healthier than smoking regular cigarettes and useful as an aid in reducing and quitting smoking. The current effects of e-cigarettes on human development are completely unknown [184]. So, promoting awareness among the public and service providers about the risks and benefits of the use of e-cigarettes by pregnant women [185] has been suggested. Guidelines and evidence-based research on the use of e-cigarettes during pregnancy must also be prepared by global healthcare organisations. Animals that were exposed to e-vapours at critical developmental periods, as in the research conducted by Lee et al., showed this can interfere with the development of the genital organs, leading to damage [186].

It is important to spread this knowledge not only among patients of infertility treatment clinics or addiction centres, but also among family doctors, who are usually the first point of contact for the patient. Awareness in the Polish population of the interrelationship of these important issues should enable implementation of comprehensive treatment, not only directed at the problem with which the patient presents to the doctor, but also at what can cause it to be reversed.

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