REVIEWS

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The Effect of Using Estrogens in the Light of Scientific Research

Skutki stosowania estrogenów w świetle badań naukowych

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Abstract

Estrogens are female sex hormones, belonging to a group of steroid hormones, derivatives of cholesterol. These hormones can be divided in terms of origin: natural and synthetic. Biologically, the most active is estradiol (E_2). Estrogens are responsible for the development of tertiary sexual characteristics and a number of metabolic processes. In our environment there are many substances, metals and toxins which can mimic the biological functions of estrogens. Due to its characteristics, it can induce cell proliferation and stimulate tumor development. Estrogens are subject to a complex metabolism that, inadequately controlled, can lead to toxic derivatives. Catecholestrogens quinones (CE-Q) interact with DNA and form depurinating adducts disturbing cellular processes. By affecting cell proliferation, it can stimulate the formation of mutation and carcinogenesis, by stimulating the production of free radicals exhibiting genotoxicity. Estrogens are mostly used in hormone replacement therapy and hormonal contraception. There are three main sources of administration of preparations containing estrogen: oral, vaginal and percutaneous. The latter two are characterized by a lack of a so-called "first pass effect". Numerous studies carried out on estrogens (both natural and synthetic) demonstrate the possibility of their detrimental function on the human body. Through its impact on clotting factors, it increases the risk of thrombosis and is considered to participate in the formation of cancer of the breast and uterus. That is why the introduction of estrogen therapy should always be preceded by a careful assessment of individual circumstances and the balance between potential benefits and risks (**Adv Clin Exp Med 2012, 21, 4, 535–543**).

Key words: estrogen, cancer, HRT, contraception, tobacco smoking.

Streszczenie

Estrogeny są żeńskimi hormonami płciowymi należącymi do grupy hormonów steroidowych, pochodnych cholesterolu. Hormony te można podzielić pod względem pochodzenia na naturalne i syntetyczne. Biologicznie najbardziej aktywny jest estradiol (E_2). Odpowiadają one za rozwój trzeciorzędowych cech płciowych oraz wiele procesów metabolicznych. W środowisku występuje wiele związków, metali i toksyn, które mogą naśladować biologiczne funkcje estrogenów. Dzięki temu mogą wpływać na proliferację komórek i stymulować rozwój nowotworów. Estrogeny podlegają złożonym przemianom metabolicznym, które nieodpowiednio kontrolowane mogą prowadzić do powstawania toksycznych pochodnych. Chinony katecholoestrogenów (CE-Q) mogą oddziaływać z DNA i tworzyć depurynowe połączenia, zaburzając procesy komórkowe. Wpływają także na proliferację komórki, co może powodować powstawanie mutacji oraz proces nowotworzenia. Pobudzając tworzenie wolnych rodników, oddziałują genotoksycznie. Estrogeny najczęściej są stosowane w hormonalnej terapii zastępczej oraz antykoncepcji hormonalnej. Można wyróżnić trzy główne drogi podawania preparatów zawierających estrogeny: doustną, dopochwową i przezskórną, z czego dwie ostatnie charakteryzują się brakiem tzw. efektu pierwszego przejścia. Liczne badania przeprowadzone nad estrogenami (zarówno naturalnymi, jak i syntetycznymi), sugerują możliwość ich szkodliwego oddziaływania na organizm ludzki. Wpływają na czynniki krzepnięcia, zwiększając ryzyko zachorowania na zakrzepicę oraz mają udział w procesie powstawania nowotworów piersi, jajnika czy macicy. W połączeniu z paleniem tytoniu ich negatywne właściwości wzmagają się. Wprowadzenie więc terapii estrogenowej zawsze powinno być poprzedzone starannym wywiadem oraz indywidualną oceną potencjalnych korzyści i ryzyka ich zastosowania (**Adv Clin Exp Med 2012, 21, 4, 535–543**).

Słowa kluczowe: estrogen, nowotwór, HTZ, antykoncepcja, palenie tytoniu.

Estrogens (ES) are female sex hormones, belonging to a group of steroid hormones, derivatives of cholesterol. They are synthesized in the ovary, placenta, testes and adrenal cortex. They are substances that contribute to the development and growth of female genital gender and female sex characteristics, and cause endometrial growth [1]. Estrogens are considered to be one of the etiological factors of breast, uterine and ovarian tumors [2]. It is also believed that they have an impact on other disorders, such as thromboembolic disease [3].

Estrogens – Their Construction and Function

Estrogens can be divided, in terms of origin, into natural (animal and phytoestrogen) and synthetic. Synthetic can be divided into those with a steroid construction and nonsteroidal [4].

Natural estrogens are 18-carbon steroids with an aromatic ring, containing the CH_3 group in 13 carbon. There are three basic, biologically active estrogens: estrone (E_1), 17-β-estradiol (E_2) and estriol (E_3). Among women at reproductive age, the main estrogen with the highest biological activity is 17-β-estradiol. Estrone, is about 5–10 times less active than 17-β-estradiol, and only a small amount is produced in the ovaries. It mainly arises from the peripheral conversion of androstenedione. The least active estrogen is estriol. Almost in its entirety, it is metabolized in the liver from E_2 and E_1, although it cannot be excluded that it also arises in the ovaries [4].

Synthetic estrogens were synthesized for the first time in 1938 by the Inhoffen team in Berlin. The resulting 17α-etynyloestradiol had a strong estrogen biological activity. Over the following years, further modifications of estradiol were carried out leading to more or less biologically active derivatives [4].

The direct precursors of estrogens are the androgens androstenedione and testosterone. Their conversion in the human body create estrone and estradiol, respectively. This reaction occurs not only in glands of internal secretion but – less – in hepatic, adipose tissue, breast glands and other [4].

The functions of estrogens are very broad. In addition to their impact on the reproductive system by stimulating the development of external genitalia and breasts, they have a lot of other activities. They regulate lipid profile by reducing LDL and total cholesterol while increasing HDL; change the levels of blood clotting factors; and affect the economy of carbohydrates. These hormones have an influence on thyroid economy by increasing the TBG (thyroxine binding globulin) and the need for the thyroid hormone in hypothyroid women [1, 5].

An interesting aspect are environmental estrogens. In our environment there are many substances, metals and toxins which can mimic the biological function of estrogens. It seems to be a big problem because exposure to potentially neutral substances may induce hormone-dependent cancers. Among the common substances that can mimic estrogens, there are: phytoestrogens (eg. Genistein contained in soy), xenoestrogens (eg. Biseptol A or dicholorodiphenyltrichloroethane (DDT)) and metalloestrogens. While phytoestrogens exert a protective effect, especially for breast cancer, xenoestrogens and metalloestrogens may induce cancers. In the group of metalloestrogens there are many ordinary heavy metals and metalloids which humans come into contact with every day, such as: cadmium, copper, chromium, lead, mercury, nickel, nitrite and more [6].

An especially interesting metal which mimics estrogen is cadmium. This heavy metal is widely used in industry, but the main source of cadmium in the body is smoking. There are many ways in which it potentially induces cancers: by induction oxidative stress, aberrant gene expression and inhibition of DNA damage repairs, inhibition of apoptosis and stimulating proliferation by reaction with estrogen receptor alpha (ERα) [7]. Johnson et al., in his publication, proved that cadmium mimics estrogen by binding onto ERα. This stimulation increases epithelial density in mammary ducts and secretory lobuloalveolar structures in rats. The rat's uterine weight after stimulation by this heavy metal was similar to stimulation by estrogen. What is more, this effect was present even in rats exposed to small, non-toxic doses, which is important when we recall that cigarette smoking significantly increases the amount of cadmium in the body [8].

Metabolism

The metabolism of estrogens occurs in two ways, by intramolecular steroid transformation and conjugation with glucuronides and sulphates. During metabolism of A-ring estrogens, it comes to the formation of catecholestrogens (CE), which are inactivated by:

– sulfate conjugation by cytosolic sulfotransferase enzymes (SULT),

– glucuronidation catalyzed by several members of a superfamily of microsomal UDP-glucuronosyltransferase enzymes (UGT),

– methylation catalyzed by a member of a superfamily of methyltransferase enzymes (COMT) [4, 9].

Catecholestrogens are major metabolites of steroid estrogens. Both the 2- and 4-hydroxy CEs can be further oxidized to CE quinines (CE-Qs) or semiquinones. These oxidation products play an important role in mutagenesis. To avoid potential harm, these metabolites are coupled to, respectively:

– parent estrogens to glucuronide and sulfate conjugates (by UGT and SULT),

– catechol estrogens to glucuronide, sulfate and methyl conjugates (by UGT, SULT and COMT),

– catechol estrogens quinines to glucuronide conjugates (by UGT) [9].

Like in other enzymatic pathways, these conjugation pathways, are characterized by high interpersonal variability [9]. For some of the allelic variants mentioned, a link was found between the enzymes and the occurrence of various cancers. For example, the transition at codon 213 (CGC/Arg to CAC/His) SULT1A1, which is one of the most important members of the SULT family, shows a positive association between homozygote His/His and the risk of breast cancer. On the other hand, there are many publications where correlation with the activity of some other enzymes like COMT and cancer risk are uncertain. For instance, in some research (Lavigne et al., 1997) this correlation occurs but in other (Bergman-Jungeström et al., 2001) this association is denied [10]. This shows that polymorphisms of estrogens metabolizing enzymes have an effect on the formation of harmful derivatives, but this is not the sole influence.

Estrogens and Carcinogenesis

Epidemiological studies in humans and biological studies in animals have shown E_2 as a carcinogen. Small elevations of circulating estrogen levels caused by increased endogenous production or by taking them as a drugs may lead to breast or uterine cancer [2, 10]. There are many ways in which ES can affect organisms to promote carcinogenesis. They are shown in Fig. 1.

One of the direct influences of estrogens on target cells is caused by combining the steroid receptor complex with DNA. In that way, it can regulate the expression of genes and transform protooncogenes into oncogenes [2]. Estrogens have two kinds of receptors – ERα and ERβ. They belong to the nuclear receptor superfamily of transcriptional activators [11]. The affinity of receptors is different to different ligands, e.g. estradiol has a higher affinity for ERα than ERβ. The effect of these ligands is also variable. The same substrate acting on a different type of receptor may be either an agonist or antagonist. The mechanism of action, binding a hormone with its target receptor (ERα or ERβ) and translocation to a nucleus, is called a genomic action. It is possible due the conformational modifications of the receptor and the exposure of nuclear localization sequences. Then receptor undergoes homodimerization (α-α or β-β) or heterodimerization (α-β) and binds to the estrogen response element (ERE) on the pro-

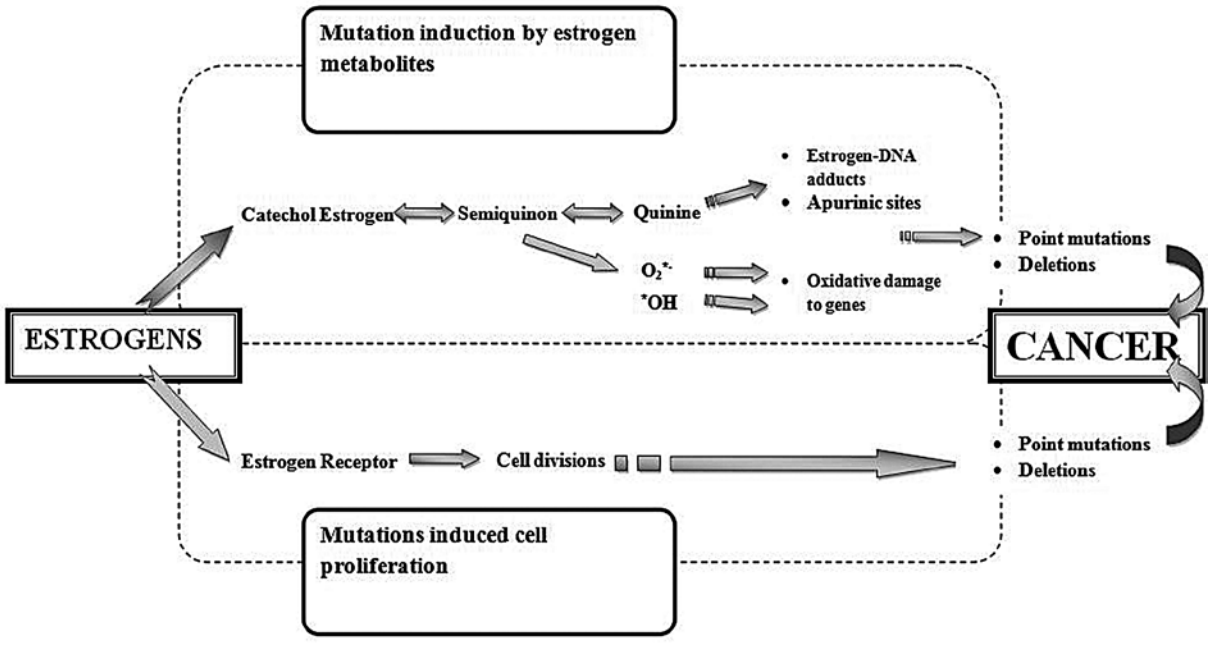

Fig. 1. Pathways potentially responsible for estrogen carcinogenesis [14]

Ryc. 1. Potencjalne ścieżki odpowiedzialne za wpływ estrogenów na nowotworzenie [14]

Table 1. Genomic and non-genomic estrogen action [1]

Tabela 1. Działanie genomowe i niegenomowe estrogenów [1]

Genomic action mechanisms	Non-genomic action mechanisms
Binding with receptor ERα or ERβ	Activation/repression of other pathways than receptor ERα or ERβ
Late response after exposure to the hormone	Fast response after exposure to the hormone
Gene expression, mRNA and new protein synthesis	Rapid adaptation to changes in the milieu

moter regions of target genes [1]. The first estrogen receptor discovered was ERα. The gene coding it is ESR1, and is regulated by seven different promoters. It is not known whether all splice variants result in functional proteins. ERα is regarded as an important factor affecting the biology of breast cancer [12]. Until recently, the formation of breast cancer was thought to be caused by the ER-mediated proliferation of epithelial cells. Continuous stimulation increases the chances of the occurrence of spontaneous mutations [13]. Since discovering the absence of ER in proliferating human breast epithelial cells, the search has begun for other routes to oncogenicity.

For the non-genomic actions of estrogens, estrogen receptor responses are located in the cell membrane. The differences between genomic and non-genomic actions are presented in Table 1.

One of the theses of tumorgenesis in the non-genomic route is that estrogen stimulates the induction of several histone modifications in ERα target gene promoters like phosphorylation, acetylation and methylation [14]. What is more, ER has been recognized as having an impact on:

– G-protein-coupled receptors (GPCRs),
– tyrosine kinases and mitogen-activated protein kinases (MAPKs),
– cell membrane ion channels,
– activation of adenylate cyclase production,
– phospholipase C (PLC) activation.

Through the above-mentioned path, estrogens may regulate many processes such as gene expression or proliferation of cells in tissues where there are no traditional targets of these hormones, e.g. in the vascular wall or central nervous system [1].

Another pathway involved in the carcinogenic process is insufficient conjugation of estrogens and their metabolites. Estrone and estradiol are not capable of forming adducts with DNA, while the oxidation products of catechol estrogens are able to bind covalently to bases of DNA and to the nucleophilic sites of the proteins. 4-hydroxy CE-Qs is believed to make depurinating adducts, which can lead to apurinic DNA sites and permanent mutations. This consequently leads to tumorgenesis. This adducts were found in various target tissues of cancer. Studies on animals showed a higher level of adducts in the liver cancer of male Sprague Dawley rats treated with stilbene estrogen and in the mammary tissue of rats who were induced by equine estrogen metabolite – 4-hydrozyequilenin. On the other hand, the catechol ethinyl E_2-DNA adduct and catechol equilenin-DNA adduct were detected in both human breast tumor tissues and healthy ones [10].

Oxidative damage to genes is another example of the negative effect of estrogens on the cells. The oxidation of the estradiol's catechols and 17α-ethinylestradiol by Cu^{2+} and the production of hydroxyl radicals was shown by Seacat et al. in 1997. Alternatively, estrogen's semiquinone may react with molecular oxygen and form superoxide radial and quinone. This free radical damage induced by estrogens may lead to 8-hydroxylation of the purine bases of DNA, strand breakage and lipid hydroperoxide-mediated DNA modification [10, 13].

Mitochondria are very important for estrogens – estrogen biosynthesis occurs there and, what is more, estrogens administered exogenously are also transported there. They have both ERα and ERβ. Several studies have demonstrated inhibition of mitochondrial respiratory complex I, II, III, IV and mitochondrial ATP synthase by estrogens. Inhibition of mitochondrial respiratory complex I may lead to the generation of ROS (Reactive Oxygen Species). The induction of some isoforms of NOS (Nitric Oxide Synthase) by this hormone can lead to inhibition of cytochrome c oxidase and thus the formation of O_2^- [1, 15]. Roy et al. suggest that ROS formation upon E_2 exposure might explain oxidative damage to hormone-dependent tumors and subsequent genetic alternations [10].

Estrogens and Usage

The main reasons for using estrogens include hormone replacement therapy (HRT) and hormonal contraception. In appropriately selected small doses, they can be used to regulate the menstrual cycle. Large doses of estrogen are used to in-

hibit ovulation, premenstrual syndrome, puerperal lactation and bleeding function. Estrogens are also given in cases of deficiency or when they may have beneficial effects on the body e.g. in the treatment of infertility or premature ovarian expiration. In the past, they were also used to treat osteoporosis and cardiovascular disorders, but because of serious side effects it is now not recommended [4].

Currently, there are three main routes of administration of preparations with estrogen: oral, vaginal and transdermal. With oral administration of estrogen, the adverse so-called "first pass effect„ may occur. It is characterized by converting approximately 60% of the absorbed dose to estrone, and then to 13-estradiol glucuronide, which has no metabolic activity. A further consequence of the "first pass effect" is enhanced synthesis of hepatic protein, renin substrate and proteins involved in blood clotting. This effect is not observed after vaginal administration. Estrogens given in this way are absorbed quickly into the bloodstream, and reach higher blood levels than similar doses administered orally. Absorption depends on the medium in which the hormone is suspended, and the vascularity of the vagina. It can be administered as globules, creams or rings worn on the uterine cervix. The least common way of administration of estrogens is a transdermal application of creams, gels and patches. Given in this way, estradiol reaches the therapy level within 4 hours, and after removing the patch, its level returns to baseline within 24 hours [4]. This route of administration is particularly beneficial because it avoids the peaks and troughs of estrogen levels which occur in oral therapy. It also doesn't affect the biliary cholesterol saturation index, and avoids local gastrointestinal irritation [16].

Hormonal methods of contraception are the most effective and most convenient methods of contraception. The correct application gives almost one-hundred percent efficiency (Pearl index 0.3). In addition to taking daily doses of hormones (whether orally, transdermally or vaginally), the contraception can also be used "on demand" (the so-called "morning after pill", up to 72 hours after intercourse). The classic two-component pill is a combination of estrogen and progestagen. Such COCs (Combined Oral Contraceptives) are mostly used in therapy, but pills containing only progestagens are also available. The estrogen used in almost all preparations is Ethinylestradiol (EE) or, rarely, estradiol valerate. The contraceptive effect depends primarily on the suppression of gonadotropin release. In addition, this method of contraception has additional benefits. For example, women suffering from menorrhagia have a reduction of blood loss by at least 50%. This therapy can be used to treat acne, hirsutism and dysmenorrhea [17, 18].

HRT are hormone preparations used for the treatment for endocrine gland deficiencies. This deficiency also occurs during menopause because of the depletion of their natural reproductive and hormonal functions. Hormone replacement therapy should be personalized, and can be applied via 3 regimens: estrogen alone, estrogen plus cyclical progestin or estrogen plus continuous progestin. Because of the higher risk of endometrial hyperplasia and cancer when using unstrained estrogen replacement, this kind of therapy is reserved for women who have undergone a hysterectomy. A combination of estrogen with progestin in HRT is the choice for women who have not had a hysterectomy. The benefits of HRT depend on improving the quality of life – elimination the symptoms of menopause (hot flashes, mood swings, nocturnal sweat, etc.) – and on preventing diseases such as osteoporosis [19, 20]. The list of negative side effects of HRT includes nausea, weight gain, migraines and severe disorders such as hypertension, thrombosis, or gallstones. One of the biggest risks of this therapy is an increased risk of developing breast, ovarian and endometrial cancer [4].

Estrogens and Pathology

Despite of the advantages of estrogen therapy, the influence of these hormones on a woman's body carries a lot of controversy and danger. It is thought that they are involved in the formation of breast and uterine cancer. Due to the numerous spheres of estrogens' effects, it is believed that special care should be taken in dosage formulations containing it, especially when there are aggravating factors for the patient (high BMI, smoking, genetic mutation predisposition to the occurrence of cancer or thrombosis, etc.) [2, 18].

Estrogens and Breast Cancer

The female mammary gland is under hormonal control, where the main role seems to be played by estrogen. There is significant evidence that breast cancer incidence is increased in current users of menopausal hormone therapy [21, 22]. Obviously, there is a difference among the risks and the preparation used. A WHI (Women's Health Initiative) trial found a higher risk of breast cancer incidence with the use of CCE+MPA, but little or no risk when estrogen-only preparations were used [23]. Similar observations were made in a Million Women Study, which showed that using

combined hormone therapy was associated with higher breast cancer mortality. The risk is also associated with the duration of use of estrogen-progestin preparations [22, 23].

Estrogens may be associated with promoting the operation of an existing process of carcinogenesis in the breast. However, estrogens and their metabolites may directly or indirectly induce free radical DNA damage, genetic instability and cell mutations. They may take part in the preinitiation processes. On the other hand, there are many different effects of estrogens on the breast which reduce the risk of cancer. For example, in women who were pregnant before age 20, this hormone has a protective effect. It is achieved through activation by estrogen of a number of tumor suppressor genes such as p53 or BRCA1, responsible for DNA repair. Such a correlation is only possible when in the breast hasn't begun the process of carcinogenesis [21].

Estrogens and Ovarian Carcinoma

The ovary is the main source of the female reproductive steroid hormones [24]. Research data suggests that malignant transformation in the ovaries may be the result of disturbances in hormonal homeostasis, since the top incidence of ovarian cancer has been observed in women around- and postmenopausal [25]. Epidemiologic findings on HRT and the risk of epithelial ovarian cancer (EOC) are conflicting. In three studies, HRT use was associated with reduced risk of EOC, whereas other studies showed no association or moderately increased risk [26]. Other clinical studies like Cancer Prevention Study II, the Breast Cancer Detection Demonstration Project and the Swedish Study showed that estrogen replacement therapy (ERT) and estrogen-progestin therapy increases the risk of ovarian cancer [25]. That research includes the suggestion that this risk is when taking ERT more than 10 years, and can persist up to 29 years after cessation of use [27, 28]. In contrast, usage of oral contraceptive (a combination of estrogens and progestins) reduces the risk of developing ovarian cancer by up to 40% and this protection is long lasting and may persist for 15 years or more [24].

Estrogens and Endometrial Carcinoma

Endometrial cancer is the most common gynecological malignancy, which is strongly associated with estrogen exposure [29]. Estrogens have an effect within the endometrium via the insulin-like growth factor (IGF-1), produced locally by stromal cells. Progesterone reverses the effects of estrogen by stimulating the local synthesis of the enzymes dehydrogenase 17-β-hydroxysteroid and sulfotransferases. They convert estradiol into the less active form of estrogen, estrone, and bind with sulphates. The risk of developing endometrial cancer depends on the ratio between estrogen and progestin. An increased level of estrogen relative to progestagens has a negative effect on the endometrium [30]. Lukanova et al. and Zeleniuch-Jacquotte et al. observed that postmenopausal women at the highest quartiles of plasmatic 17-β-estradiol and estrone levels have an increased risk of this cancer [29].

While the increased risk of endometrial cancer in postmenopausal women using estrogen therapy (ET) is being considered, the use of combined estrogen-progestin therapy (EPT) still remains unclear. When the large cohort study WHI and other clinical trials (Anderson et al. 2003; Hulley et al. 2002) showed a null or inverse association between the use of continuous-combined EPT and the risk of endometrial cancer, a cohort study made by Lacey J et al. and other case-control studies (Newcomb P et al. 2002) suggest that this risk is apparent [31–33]. Razavi et al. demonstrated a statistically significant increase in risk associated with long-term use of continuous-combined estrogen-progesterone therapy (EPT), which was limited to women with BMI < 25 kg/m^2. Estrogen-only therapy and long-term use of short-sequential EPT were associated with a notable increased risk of endometrial cancer both in thinner and heavier women [31].

Estrogens and Thromboembolic Disease

One of the most serious complications of oral contraceptive and hormone replacement therapy is thromboembolic disease. The main manifestion of this is a deep venous thrombosis (DVT) with or without pulmonary embolism (PE). Other symptoms can be superficial venous thrombophlebitis, upper extremity and intraabdominal DVT or cerebral sinus thrombosis [3, 20].

Estrogens were initially considered as a factor reducing the risk cardiovascular disease because of its influence on lipid metabolism. Estrogen therapy in women after menopause shows a reduced level of total cholesterol, LDL cholesterol, apoliportotein AII, apolipoprotein B, and rising HDL cholesterol and triglycerides. They also have an effect on the vascular wall by regulating vasomo-

tor tension. They block calcium channeling in the wall and increase secretion of NO and prostacyclin. They can also promote proliferation collagen fibers [34, 35].

In 1998, the first randomized research HERS (Heart and Estrogen/Progestin Replacement Study) showed that HRT doesn't prevent cardiovascular disease but it raises numerous adverse events. In a group taking conjugated equine estrogen (CCE) at a dose of 0.625 mg/day with medroxyprogesterone acetate (MPA), in the first year, a 50% higher incidence of cardiac events was observed, and a 3-fold higher risk of thromboembolic disease than in a group taking placebos. Similar projects like ERA (Estrogen Replacement and Atherosclerosis Trial), WHI (Women's Health Initiative) or WEST (Women's Estrogen for Stroke Trial) showed congenial results. The higher risk of heart events was observed in the first year, then the risk systematically declined, and after four years equalized with a control group. A higher risk was observed in a group of women who had hereditary thrombofilia [3, 34]. Studies have shown that the use of conjugated estrogen is associated with a lower risk of coronary heart disease than the use of combined estrogen with progestin [36]. In the postmenopausal estrogen-progestin interventions-trial (PEPI), research was shown that using only estrogen in therapy slightly decreases the concentration of fibrinogen [19]. The prothrombotic effect of progestin still remains unclear [3].

As opposed to HRT, using OCP (Oral Contraceptive Pills) is associated with a marginal risk of myocardial infarction [18]. The overall observational data is consistent, pointing to a 3- to 6-fold increased risk of VTEs among all OCP used compared to non-users. In woman taking HRT, this risk is 2- to 4-fold compared with non-users [20].

Research has shown that usage of oral estrogen increases the level of factor VII and factor IX, but does not affect the concentration of factor VIII. In addition, treatment increasing the concentration of fragments F1 + F2 formed by activation of prothrombin, reduces antithrombin activity, concentration of tissue plasminogen and a decrease activity of inhibitor activity plasminogen type 1 (PAI-1). The influence on the concentration of protein S and protein C remain unclear. They often have lower concentrations, however there were reports of no change or growth [3, 37].

Estrogens and Immunological Aspects

It is believed that females have higher immunological response and more often suffer from autoimmune disease than males. It is suggested that female sex hormones play a major role in this heightened immune response. An epidemiological study based on a questionnaire suggests that exposure to DES (diethylstilbestrol) increases the chance of getting asthma, lupus, arthritis and respiratory-track infections [10].

Sex hormones such as estrogens influence both immature (by affecting the thyroid and bone marrow) and mature immune cells. Sex steroids act on the immune system in a variety of ways by altering the function and phenotype of T and B cells, immunoglobulin levels and possibly the kinetics of Ig synthesis or synthesis of cytokines. It has been shown that neonatal exposure to DES and E_2 has a strong influence on the immune system in immunoprivileged tissues [10].

Estrogens can change the indicators of immune activation: myeloperoxidase (MPO) and proinflammatory cytokines like IL-6, TNF-α, IL-1β, INF-γ and GM-CFS. Induction releasing MPOs from inactivated cells by E_1, E_2, E_3 and 16-α-hydroxyestrone stimulate generation of oxidants in the absence of pathogens. This effect can also be achieved by hormone replacement therapy [10].

Estrogens and Tobacco Smoking

Tobacco smoking is one of the factors influencing hormonal changes. Current literature has conflicting data on the effect of cigarette smoking on estrogen serum concentration and its effects on that hormone. That inconsistent data may be wrong due to methodology and too much confidence in relation to the respondents. A study made by the Endogenous Hormones and Breast Cancer Collaborative Group (2011), in cross-sectional analyses in 13 prospective studies, showed higher concentrations of sex hormones (i.e. estradiol and estrone) whereas SHBG (Sex Hormone Binding Globulin) did not vary significantly for women who smoked 15+ cigarettes per day than those who never smoke [38]. Different results were obtained by Soldin et al. (2011) in his study. He divided 293 women into active smokers, passive smokers, and non-smokers. The conclusion was in contrast to the previous group: smoke exposure decreased serum hormone concentrations. This inconsistent data can be due to reliance on self-reported smoking status, not confirmed in many cases by checking levels of cotinine. Soldin et al. proved differences in the declarations of people about smoking. In many cases, smoking status differed from levels of estimated cotinine. Tobacco smoking affects the secretion, synthesis, metabolism, distribution and

excretion of hormones. There are many ways in which it can influence estrogens:

– by induction of hepatic metabolism of hormones,

– by inhibition of aromatase (CYP 19) in granulose cells,

– by increasing catechol-estrogen formation [39].

The effects of estrogens are diminished in women who smoke. This manifests through earlier menopause and reduction of positive response in the case of the lipid profile. There are higher levels of LDL cholesterol and lower HDL cholesterol in smokers taking HRT comparing to non-smokers taking HRT at the same age. The influence smoking on estrogen metabolism may lead to higher carcinogenicity this hormone. While in non-smoking women, the main method of metabolism E_2 is 2-hydroxyestradiol, in women who smoke under treatment with oral estradiol, significantly more 4-hydroxyestradiol is produced than 2-hydroxyestradiol. 4-hydroxy CEs is considered to be more carcinogenic in animal models and has a higher concentration ratio in some human tumors [40].

Conclusions

The authors concluded that estrogens have both positive and negative effects, which mostly depend on: the duration of therapy, the drug dose, the patient's physical condition, her weight (BMI), age, smoking, coexisting diseases and possession of specific genetic polymorphisms. The use of hormone replacement therapy and hormonal contraception coincides with both doctors and patients increasingly becoming aware of possible risks. However, due to the frequency of use of these therapies, it is important to continue the improvement of knowledge on the effects of estrogen on the human body.

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