ESTROGENS AND MALE REPRODUCTIVE HEALTH

Krassimira Atanassova[1], Nina Atanassova[2]

[1] Medical University – Sofia,
[2] Institute of Experimental Morphology and Anthropology with Museum, Bulgarian Academy of Sciences, Sofia

Summary

Endocrine disruptors (ED) are widely spread in industry, thus humans are largely exposed to their influence. ED are chemical substances which act as agonists or antagonists of steroid receptors. Changing the hormonal balance they affect the development and functions of target tissues, being a potential risk factor for several diseases and neoplastical transformation in reproductive organs.

ED are classified into three main classes – industrial ED (pesticides like DDT, polychlorinated biphenyls, alkylphenolic compounds, phthalate esters, etc.), synthetic (diethylstilboestrol, zeranole, ethinylestardiol, drugs for oral contraception), and phytoestrogens (produced in over 300 plants and fungi).

There are various routes via which humans are exposed to ED from the environment – drinking water, food chain, treatment with hormonal drugs.

Clinical aspects of estrogens for male reproductive health are illustrated both in cases of excess or lack of estrogens. A lot of cases of reproductive abnormalities have been detected in sons, whose mothers have been treated with estrogens during pregnancy (cryptochidism, hypospadias, testicular carcinoma, low sperm counts). Estrogen action involves direct (on target cells via receptors) and indirect mechanism via suppression of gonadotrophin and androgen production. Lack of estrogen action is demonstrated in cases with mutation of a gene for estrogen receptors-α where total sterility or infertility have been detected due to loss of motility of spermatozoa. In conclusion, estrogens are of significant importance for male reproductive health, having also a role in cardiovascular diseases, lipid metabolism, in bone growth and remodeling, as well as in cancerogenesis of reproductive organs. Future investigations, involving animal experimental models and clinical studies are needed to understand relationship between ED and reproductive disorders. Identification of biomarkers for inappropriate action of ED is of great importance for prediction and prevention of reproductive diseases as well as to estimate the risk of ED for reproductive health and fertility in the human male.

Keywords: oestrogens, endocrine disruptors, male reproductive health

Introduction

The classical view that the oestradiol is a female hormone, whereas the testosterone is a male one acquires wider consideration in the context of recent understanding on the role of estrogens in the male. However, data from the literature clearly indicates that precise balance between estrogens and androgens in both sexes is of fundamental importance for a variety of diseases of cardiovascular system, osteoporosis, and carcinoma of reproductive organs.

During last decade there is a growing interest on endocrine disruptors (ED) that emerged from concerns that human exposure during perinatal life adversely affects reproductive health. The original "oestrogen hypothesis", published by Sharpe and Skakkebaek [1] postulated that the apparent increase in human male reproductive developmental disorders (testis cancer, cryptorchidism, hypospadias, low sperm counts) might have occurred because of increased human oestrogen exposure during foetal/neonatal life. Ten years later Sharpe [2] reported secular increasing trend in the listed disorders considered to represent a syndrome of disorders (testicular dysgenesis syndrome, TDS) with a common origin in foetal life [3].

Endocrine disruptors are widely spread in industry, thus humans are largely exposed to their influence. Synthetic endocrine agents are used in clinics for a hormonal treatment. Endocrine disruptors are chemical substances which act as agonists or antagonist of steroid receptors. Changing the balance between estrogen and androgen action they affects the development and functions of target tissues. Moreover, they are potential risk factor for various diseases and neoplastical transformation in reproductive organs [4].

The review considers the following questions:

- Types of ED and routs of their exposure.
- Clinical importance of oestrogen for male reproductive health.

Types of ED and routs of their exposure

Endocrine disruptors can be classified into three main classes – industrial, synthetic and phytoestrogens.

Industrial ED are widely used man-made chemicals which has weak estrogenic effect. They include chlorinated chemicals, alkylphenolic compounds, phthalate esters, etc.

Chlorinated chemicals comprise organochlorine pesticides like DDT and polychlorinated biphenyls (PCB). As several of the organochlorine pesticides, or their metabolites, tend to accumulate in body fat, and human exposure may be substantial in some cases, chemicals of this type have to be given serious consideration in the context of human cancer induction [5]. DDT was prohibited a long time ago, but its accumulation in the environment as well as the long life of its molecule, its lipophilic nature and its transplacental route makes it a risk factor for reproductive health. Particular concern is also the mobilization of DDT stored in fat by breastfeeding mothers and its transfer via milk to their babies [6].

PCB are used in electric industry as dielectric fluids in transformers and capacitors, in hydraulic fluids, in adhesives and waxes. Human exposure to PCBs has been reasonably substantial in the recent past. The complexity of PCB structure and the resultant differences in oestrogenicity/anti–oestrogenicity make it extremely difficult to predict what, if any, biological effects might be caused [7].

Other chlorinated chemicals which are recognized as being extremely toxic are the dioxins. These are not made intentionally but are by–products of the manufacture of organochlorine compounds and their incineration, including by the petrol engine. Being anti-oestrogenic and/or anti-androgenic, dioxins have been shown to exert a range of effects on both the development and function of reproductive system [8].

Alkylphenolic compounds are used in household detergents, in shampoos, cosmetics, in plastic to prevent discoloration by sun light and it is possible to be released from the plastic. Other uses of alkylphenols are as petrol additives, as spermicides in condoms, in sprays for delivering pesticides. Some 60% of alkylphenols find their way into the aquatic environment, where they are recognized as being harmful to life, though probably more because of their detergent properties rather than because of their oestrogenicity. Low concentration of alkylphenols has been detected in drinking water and it is probably unlikely that any significant effect on man would occur. Our levels of exposure via other routs are unknown, but it is likely to be more substantial than our exposure via tapwater [9].

Two of the many phthalate esters are butyl benzyl phthalate (BBP) and di-n-butyl phthalate (DBP). Phthalate esters are plasticizers and as they are not integral part of the plasticware they can leach out overtime. They are found in printing inks, perfumes, etc. They are literally everywhere and ingestion by humans is both unavoidable and substantial. They exert estrogenic and anti-androgenic effects [10]. Recent data from experimental models demonstrated pronounced anti-androgenic in-utero effect of DBP on male offspring causing TDS [11].

Bisphenol-A is weakly oestrogenic in vitro and in vivo in a number of test systems. It is an ingredient of certain types of plastic (polycarbonates) and is also used in false teeth and teeth sealants, in acrylic resins, in photocopying, certain fungicides and in lacquer coat lining of tinned food cans [12]. Recently, bisphenol-A became widely notorious in the USA due to the fact that it leaks out in baby bottles although some data showed that infant dietary exposure is below tolerable daily intake in EU and US Environmental Protection Agency [13, 14].

Synthetic ED includes synthetic steroid (ethyniloestradiol, EE) and non-steroid estrogens such as diethylstilboestrol (DES), zeranole, drugs for oral contraception. Human exposure to synthetic oestrogens can be divided into two categories – exposures from intentional ingestion (oral contraception, hormone-replacement therapy) and unintentional absorption from foodstuffs, drinking water or cosmetic products. Principal potential routes of such exposure are: ingestion of growth-promoting oestrogens in meat/poultry; ingestion of oestrogens in cow's milk and milk-derived products; ingestion of "recycled" oesreogens in drinking water; absorption via the skin of oestrogens present in cosmetics/shampoos [4]. Synthetic hormones have strong estrogenic effect. DES was used in the past for treatment of pregnant women and it was banned as a lot of data demonstrated serious reproductive abnormalities in sons, born by estrogen–treated mothers [2]. DES had been used also as a growth stimulator in stock-breeding, but after 1981 it was prohibited in Western Europe. However, it is widely used in USA as well as zeranole as growth promoters. Concerning EE, it is used for water processing; thus, it is extremely accessible for humans. It was established that river pollution in UK with EE has caused a sex reversal in fish. [15].

Over 300 plants and fungi naturally produce compounds which have estrogenic activity. The richest dietary source of phytoestrogens for humans is soya and soya-derived products, although legumes, whole grains and flax-derived products are also potentially important, especially in vegetarians. The oestrogenic potency of these natural compounds is illustrated by the numerous instances in which ingestion severely disrupts normal reproduction in animals such as sheep ("clover disease"), pigs ("mouldy corn syndrome"), captive cheetahs and quail [16], effects which

can sometimes be irreversible. In the last two or three decades, the feeding of soy formula milk to infants as a substitute for breastfeeding milk has increased progressively in many Western countries. This has been presumed safe in view of the evidence for health-beneficial effects of soy in Asian diets. Studies by Setchell et al [17] has shown that infants fed on a 100% soy milk have blood levels of isoflavonoid phytoestrogens nearly 1000-fold higher than those in Asian infants breastfed by a mother who is consuming a soy-rich diet. The effects of such high exposure to phytoestrogens during infancy are essentially unknown and that is possible reason for concern. Data from experimental models on rat demonstrate transient inhibitory effect on spermatogenesis in puberty [18]. Cases could be made for this having both beneficial effects, in terms of future cancer risk (prostate, breast) or detrimental effect in terms of reproductive health.

Clinical importance of ED

Endocrine disruptors (ED) are widely spread in industry, thus humans are largely exposed to their influence. ED act as agonists or antagonists of steroid receptors, interfering with both estrogen receptors (α and β) and/or blocking androgen receptor. As a result hormonal balance is impaired that affect the development and functions of target tissues. Hence, ED are potential risk factors for several diseases and neoplastical transformation in reproductive organs [4].

Reproductive disorders of newborn (cryptorchidism, hypospadias) and young adult males (low sperm counts, testicular caner) are common and/or increasing in incidence. Each of these abnormalities is a risk factor for another one and they comprise a testicular dysgenesis syndrome (TDS). Cryptorchidism is an established risk factor for hypospadias as well as for testicular cancer and poor sperm quality/subfertility in adulthood [19]. Pre-malignant cells, from which testis cancer arises, carcinoma – in-situ (CIS) cells have their origin in foetal life and risk factors are subnormal androgen exposure and/or increased estrogen exposure.

TDS occurring in humans or which is induced in animal models by foetal exposure to certain phthalates is associated with impair hormone production by the foetal testis. The hormone dependence of masculinization renders this process susceptible to disruption by factor like ED interfering with hormone production or action and metabolism. This susceptibility is illustrated by high prevalence of congenital masculinization disorders and abnormalities in young adult men, mentioned above [20]. Therefore, environmental ED are potential risk for TDS as pathways via which this potentially occur are established. Being estrogenic and/or anti-androgenic, the mechanism of action of ED involve: suppression of gonadotrophin secretion via enhanced negative feedback by estrogens, suppression of testosterone production and action (expression of androgen receptors); suppression of insulin like factor 3 by foetal testis (responsible for testicular descent).

Altered puberty timing is also of concern for the development of reproductive tract cancers later in life. For example an early age of menarche is a risk factor for breast cancer, a low age at male puberty is associated with an increase risk for testicular cancer. Girls and possibly boys who exhibit premature puberty are at a high risk for developing features of metabolic syndrome, including obesity, type 2 diabetes, and cardiovascular disease later in adulthood. Therefore, altered puberty timing is considered as adverse effect in reproductive toxicity risk assessment for ED chemicals at individual and population level [21].

Clinical aspects of estrogens for male reproductive health are illustrated both in cases of excess or lack of estrogens. Excess of estrogen action is demonstrated by reproductive abnormalities detected in sons, whose mothers have been treated with estrogens during pregnancy (cryptorchidism, hypospadias, testicular carcinoma) [2].

As a consequence of estrogen application, the balance between androgens and estrogens is destroyed and determines disorders, mentioned above, including cancers of male reproductive organs, e.g. testicular and prostate cancer. Mechanism of estrogen action involves direct (on target cells via estrogen receptors) and indirect mechanism via suppression of gonadotrophin and androgen production and action [22]. In cases of enhanced local estrogen production due to a mutation of gene for a deactivating enzyme, similar abnormalities occur: hyperplasia/hypertrophy of Leydig cells, disturbance of seminiferous epithelial tissue and a decreased motility of epididymal spermatozoa [23].

Lack of estrogen action is demonstrated in cases involving mutation of a gene for estrogens receptors-α where total sterility or infertility have been detected due to loss of motility of spermatozoa. In the first case the plasma levels of oestrogens are higher, whereas in the second one - are considerably lower. These men have problems involving bones (osteopenia, osteoporosis, lack or detention of closing the epiphyses), insulin resistance and disturbance in lipid metabolism. In patient with estrogen deficiency, therapy with oestradiol, but not testosterone causes closing of the epiphyses and increase of bone density [24].

Clinical importance for androgen/estrogen balance is supported by the data that in USA black men demonstrate a lower risk to develop testicular carcinoma that white men [25]. The possible reason is the higher level of circulating androgens in pregnant black women than in pregnant white women. Different susceptibility between men and women to develop cardiovascular diseases is probably due to differences in estrogens levels and their ratio to androgen levels (opposite in both sexes) [26]. Another example is “clover disease” in sheep in which the ingestion of clover containing phytoestrogens resulted in the deaths, owing to hypertrophy of the bulbo-urethral glands, of castrated rams (with low circulating testosterone levels) but had little effect on intact rams (with high circulating testosterone levels) [16].

Conclusion

It is becoming increasingly clear that ED are of a significant importance for male reproductive health, having a role in cardiovascular diseases, lipid metabolism, bone growth and remodeling, etc. It is apparent that a surprising number of known hormonally active chemicals are present in our modern environment. It is also clear the some of these chemicals do cause variety of disorders. Faced with these facts it is reasonable to conclude that man is at risk of exposure to such chemicals. Therefore, future studies are needed to understand relationship among ED reproductive and metabolic disorders. It is important to find out what characteristics at birth can predict reproductive disfunction at puberty and adulthood. By research involving animal models and clinical studies, biomarkers for ED exposure and reproductive abnormalities will be identified. The proposed studies will facilitate prediction and prevention of reproductive disorders and provide new data to improve environmental risk assessment and risk management.

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