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Human exposure to endocrine disrupting chemicals as a prenatal risk factor for cryptorchidism

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This review describes the most recent data on the effects of endocrine disrupting compounds on reproductive tract development, as well as controversies in the field. One of the most frequent conditions affected by endocrine disrupting compounds is cryptorchidism. Recent reports regarding the cause of this disorder continue to increase our understanding of this common and important problem. Endocrine disruptors are defined as exogenous substances with the ability to disrupt normal endocrine homeostasis and reproduction, and they include xenoestrogens, synthetic and natural hormones, phyto- and mycoestrogens, and other substances affecting endocrine signaling. Human exposure to endocrine disrupting chemicals is widespread. Epidemiological studies suggest associations between prenatal exposure to endocrine disrupting chemicals and numerous malformations of androgen dependent tissues. Animal models and epidemiological evidence link exposure to androgen disrupting chemicals with cryptorchidism, reduced sperm cell counts, increasing infertility, and testicular and prostate cancers. Since male sexual differentiation is androgen dependent, it is highly susceptible to endocrine disruptors. Whether the level of exposure contributes to the increasing prevalence of cryptorchidism is an ongoing debate. Further, there appears to be increased sensitivity to these agents during critical developmental periods when male differentiation is at its peak. Differences in the interpretation of the available studies underlie the disparate conclusions of scientific and regulatory body panels on the potential toxicological effects of endocrine disrupting chemicals at the current levels of human exposure. This review will highlight the evidence for endocrine disrupting chemicals that act through interference with the androgen receptor and lead to cryptorchidism.

Keywords: cryptorchidism; endocrine disruptors

Cryptorchidism, defined as the absence of at least one testis in the scrotum, is a frequent condition in the pediatric population. The prevalence of cryptorchidism at birth is 2.5%-9% (1). It affects 1%-1.9% of three-month-old boys and 0.8%-1.5% of 18-month-old boys (2), and may involve the use of considerable medical and economic resources.

Risk factors for cryptorchidism include genetic predisposition, preterm birth, low birth weight and prenatal exposure to endocrine disrupting chemicals (EDCs) or tobacco in either the mother or the father (3, 4). Mutations in the gene for insulin-like factor 3 (*INSL3*) and its receptors have been recognized as the causes of cryptorchidism in some cases, but some chromosomal alterations, above all the Klinefelter syndrome, are also frequently involved.

The role of *INSL3* in testicular descent is mainly related to its effects on gubernaculum differentiation during the transabdominal phase. The transabdominal stage occurs between the 10th and 23rd week of gestation in human fetuses and the inguinoscrotal phase starts at around 26 gestational weeks and ends between 28 weeks of gestation and birth. That is the reason why cryptorchidism is more frequent in

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preterm births. The inguinoscrotal phase is androgen dependent, and exposure to endocrine disrupting substances may affect normal androgen production and consequently interrupt normal descent of testes.

Familial cases of cryptorchidism have been described, and a family history of cryptorchidism is a risk factor for undescended testes (5); initial studies suggested that 6.2% of the brothers and 1.5%-4.0% of the fathers of patients with cryptorchidism had undescended testes.

Environmental factors acting as endocrine disruptors of testicular descent have been suggested to contribute to cryptorchidism and its increased incidence in recent years. Endocrine disruptors are defined as exogenous substances with an ability to disrupt normal endocrine homeostasis and reproduction, and they include xenoestrogens (industrial chemicals), synthetic and natural hormones, phyto- and mycoestrogens, and other substances affecting endocrine signaling (6). There are several ways how endocrine disrupting chemicals can alter endocrine functions:

1. by acting as either agonists or antagonists for the receptors for estrogens and androgens;
2. by altering the synthesis, transport and/or catabolism of endogenous hormones; and
3. by modifying the levels of expression and/or functioning of hormone receptors.

Endocrine disrupting chemicals are present in the air (7), water, soil, as well as in food products (soybeans, legumes) and plants (phytoestrogens in fruits, vegetables and grasses). Some derive from household products, while others are agricultural or industrial chemicals. Exposure can occur directly at the workplace or *via* consumer products such as food items, plastic and paints or indirectly *via* air, water and soil. The toxicity of such chemicals for different species of living organisms is determined by their individual chemical properties, duration and frequency of exposure, and their pharmacokinetics (absorption, distribution, transformation and elimination). The adverse effect of exposure at the developmental stage is irreversible, whereas most post-developmental effects are reversible (8, 9).

The Centers for Disease Control and Prevention (CDC) have classified the hormone-modulating effects of EDCs as estrogenic (approximately 48%), anti-androgenic (19%), anti-estrogenic (15%), androgenic (4%), those with effect on thyroid hormone status (42%) and others (10).

Germ, Sertoli and Leydig cells are all highly sensitive to the toxic effects of the variety of xenobiotics. Attenuation of fetal Leydig cell steroidogenesis is associated with development of congenital abnormalities such as cryptorchidism and hypospadias as a result of incomplete masculinization. Phthalates are one of the proven EDCs. They are widely used as plasticizers (to soften plastics), as well as solvents in inks, and are present, among other places, in food packaging and certain cosmetics (11). The exact biochemical or molecular mechanisms underlying the effects of diethylhexyl phthalate (DEHP) on the testis remain unclear. The mechanisms that have been proposed include alterations in testicular levels of zinc and zinc dependent enzymatic activities; elevated oxidative stress in the testis; modulation of estrogenic activity *via* interactions with estrogen receptors; and changes in the pathways involving peroxisome proliferator-activated receptors (PPARs) or other cellular molecular event pathways. Furthermore, in male rats, inhibition of steroidogenesis in fetal Leydig cells by phthalates gives rise to numerous malformations of androgen dependent tissues, including reduction in the anogenital distance, hypospadia, epididymal agenesis and testicular atrophy (12). These abnormalities are suggestive of suboptimal virilization of the Wolffian duct and urogenital sinus. Finally, recent investigations have revealed that treatment with phthalates attenuates the transcription of several key genes whose protein products are involved both in cholesterol transport and the biosynthesis of testosterone (13, 14).

Studies published during the last few decades have indicated that the birth prevalence of cryptorchidism may have increased in some regions (15, 16). The short time interval in which this high prevalence occurred indicates that environmental factors may contribute greatly to this effect (17). Several organochlorine pesticides can cause adverse effects in the male reproductive system in animals (18, 19). In animal studies, estrogen exposure during pregnancy resulted in the development of cryptorchidism and hypospadias in male offspring (20, 21).

An increased incidence of cryptorchidism in male panthers has been attributed to EDCs in the environment, such as 1.1-dichloro-2.2-bis(4-chlorophenyl)ethane (p,p'-DDE) (22). Dose dependent in utero exposure of male rats and rabbits to dichlorodiphenyldichloroethylene (DDT) resulted in reduced anogenital distance, hypospadias, cryptorchidism and epididymal agenesis (23-25).

Increased rates of orchidopexy in the areas with extensive pesticide use in agriculture have been reported (26). In their study, *Hosie et al*. demonstrated higher pesticide levels in fat tissue samples from boys operated on for cryptorchidism than in children operated on for other reasons (27).

Damgaard et al. showed in their study that simultaneous exposure to more than one chemical at low concentrations represented a risk factor for congenital cryptorchidism. In this study, the levels of persistent organochlorine pesticides in breast milk were compared with the birth prevalence of cryptorchidism. Breast milk was chosen as a surrogate bio-

marker of previous maternal exposure to persistent pesticides because these compounds accumulate in lipid tissue and thereby in breast milk (28). Concentrations of compounds in breast milk are a suitable proxy for fetal exposure during pregnancy. Primiparae, slim women, and smokers tend to have higher pesticide levels (29). *Hosie et al*. compared the levels of pesticides (DDT and metabolites, toxaphene, HCH, HCB, PCA, PeCB, and several chlorinated cyclodienes such as heptachlor) in fat tissue biopsies from 18 cryptorchid boys and 30 controls. Pesticide concentrations were higher in cryptorchid cases than in controls, but reaching significance for only a few (HCB and heptachloroepoxide).

There are numerous studies reporting associations between cryptorchidism and parental pesticide exposure, but most of these were registy-based and retrospective.

Distinction between maternal and paternal exposure is made only in some studies; *Pierik et al*. found that cryptorchidism was significantly associated with paternal but not maternal pesticide exposure (16). *Weidner et al*. (30) describe a significantly increased risk of cryptorchidism in sons of female gardeners. This study included 6 177 males born live in Denmark between 1983 and 1992 who were discharged from the hospital with the diagnosis of cryptorchidism and 1 345 males born with hypospadias. These results were coherent with earlier studies reporting an increased frequency of orchidopexy in the areas with extensive use of pesticides in Spain (26) and an increased occurrence of cryptorchidism in boys born on Norwegian farms where pesticides had been used (31). Unlike these studies that made no discrimination between paternal and maternal exposure, the study performed in Denmark showed no effect of paternal work in gardening on cryptorchidism. The inclusion of paternal exposure serves as a control because factors related to the lifestyle of agricultural families would lead to an apparent effect of both maternal and paternal exposure, while an effect seen only or predominantly in relation to maternal exposure provides a higher degree of evidence of a true effect (30).

Exposure to pesticides can occur *via* numerous exposure pathways, including household use of pesticide products, dietary exposure to pesticide residues and occupational exposure. Biological monitoring studies indicate that pesticide exposure is widespread in pregnant women in New York City, Salinas Valley in California, the Netherlands, and Norway (32-36). Pesticides have also been detected in amniotic fluid, umbilical cord blood, meconium, and infant urine, indicating the exposure of the fetus to pesticides (37, 38). In one of the most recent studies conducted in France, bisphenol A measured in cord blood correlated negatively with *INSL3* but not with testosterone (39). The differences in dimethyl (DM) metabolites in pregnant women across the world may be due to differences in pesticide use among different countries and differences in diet among populations. Up to 15% of tested food has been reported to have pesticide residues above maximum residue levels. The exact percent depends on the country where studies have been conducted (14% in the Netherlands and up to 6.1% in US) (36). These comparisons have limited value because of the differences in maximum residue levels between Europe and United States and differences in analytical methods between countries. Consumption of more fresh fruit and vegetables with pesticide residues is correlated to higher DM metabolites found in this population. As this habit is usually connected with Mediterranean population, it is expected to find higher total DM metabolite concentrations in this population compared with other populations of pregnant women. Unlike DM metabolites, which are higher in women taking more fresh fruit and vegetables, diethyl (DE) metabolites are likely to be higher in the samples of women using more household pesticides. The primary OP pesticides registered for use in residential setting usually metabolize to DE metabolites. DE metabolites are less stable and more difficult to detect (35). The finding that women with higher education levels have higher DM exposure levels (35) may be due to significant differences in eating habits between lower and higher socioeconomic groups, but it may also be in relation with the place of residence and household used pesticides. Up to 10% of certain OP insecticides may be stored in adipose tissue and gradually relesaed over time into the bloodstream and undergoing metabolism and excretion (40). A study in sons of Danish pregnant women working in greenhouses showed adverse effects of maternal occupational pesticide exposure on reproductive development, despite current greenhouse safeguards and special measures to protect pregnant women (41). Another study conducted more recently showed that increasing concentrations of organotin compounds, found in diet rich in fish products, had positive association with cryptorchidism in Denmark, unlike the opposite result in Finland (42).

Data on the possible mixture effects of the specific organochlorine pesticides *in vitro* are limited. A combination of 10 compounds including endosulfan, dieldrin, methoxyclor, and some DDT metabolites demonstrated a cumulative effect (43, 44).

Prenatal exposure to persistent organochlorine pesticides may adversely affect testicular descent in boys. Exposure to endocrine distuptors during fetal, neonatal life or prepubertal life can influence pubertal timing and reproduction (45).

As the exact etiology of cryptorchidism is not known, influencing the risk factors may be the way to decrease the incidence of undescended testes.

The research in the field of endocrine disruptors as the risk factors for cryptorchidism is very important. It should be followed by providing wide information to the public. Prolonged exposure of the developing male, during both fetal and postnatal life, to endocrine disruptors could reduce Sertoli cell number and sperm output in adult life (46). It has been shown that there is a reduction in the number, as well as delayed maturation of the germ cells in gonads of patients with cryptorchidism born in Vojvodina compared to patients from either Switzerland or USA (47). Vojvodina is mainly an agricultural region, and the use of pesticides is common and also not adequately governed by the regulations. The ecological approach used did not demonstrate a cause-effect relationship between environmental pesticide contamination and the decrease in the number of germ cells in cryptorchid patients from Vojvodina. Nor did it identify the route of exposure in pregnant women, which might have been occupational, environmental (e.g., drinking water) or dietary. To clarify these questions, it would have been necessary to obtain accurate information on the actual exposure of mothers during the vulnerable period in the months prior to conception and during early gestation.

Changes in testicular histology of cryptorchid patients inspired us to design a prospective study that should tell us whether the exposure to pesticides in Vojvodina is equal to the studies in other areas, as well as give us an opportunity to compare the extent of exposure between pregnant women who gave birth to healthy boys and those who gave birth to boys with undescended testis. Future studies in the field of endocrine disruptors, which are globally ubiquitous, could help design appropriate risk assessment as a tool offering an opportunity to systematically assess the potential risk posed by EDCs (48).

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SAŽETAK

Izloženost endokrinim disruptorima kao prenatalni čimbenik rizika za kriptorhizam

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Ovaj pregledni članak donosi najnovije podatke o učincima endokrinih disruptora na razvoj reprodukcijskog sustava, kao i o proturječjima u ovom području. Kriptorhizam je jedno od najčešćih stanja na koja utječu endokrini disruptori. Novija izvješća o uzroku ovoga poremećaja sve više doprinose razumijevanju ovoga čestog i važnog problema. Endokrini disruptori definiraju se kao egzogene tvari sposobne prekinuti normalnu endokrinu homeostazu i reprodukciju, a obuhvaćaju ksenoestrogene, sintetske i prirodne hormone, fito- i mikoestrogene te druge tvari koje utječu na endokrine signale. Ljudi su uvelike izloženi takvim kemikalijama. Epidemiološke studije ukazuju na udruženost prenatalne izloženosti endokrinim disruptorima i brojnih malformacija tkiva ovisnih o androgenima. Životinjski modeli i epidemiološki dokazi povezuju izloženost androgenim disruptorima s kriptorhizmom, smanjenim brojem spermija, povećanjem neplodnosti te s rakom testisa i prostate. Muška seksualna diferencijacija ovisna je o androgenima, a time i veoma osjetljiva na endokrine disruptore. I dalje traju rasprave o tome doprinosi li razina izloženosti rastućoj učestalosti kriptorhizma. Nadalje, izgleda da je osjetljivost na ova sredstva povećana tijekom kritičnih razvojnih razdoblja obilježenih vršnom diferencijacijom kod muškog spola. Razlike u tumačenju dostupnih studija obilježavaju neujednačene zaključke znanstvenih i regulatornih panela o potencijalnim toksikološkim učincima endokrinih disruptora uz današnju razinu izloženosti ljudi. Ovaj pregledni rad pokazuje dokaze za endokrine disruptore koji djeluju kroz interferenciju s androgenim receptorima i dovode do kriptorhizma.

Ključne riječi: kriptorhizam; endokrini disruptori