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Endocrine disrupting chemicals and higher risk of hypospadias

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ABSTRACT

Hypospadias is the second most common congenital anomaly after undescended testis worldwide. The prevalence of hypospadias in Europe stand at approximately 18.6 per 10,000 births and the number of registered cases between 2001 and 2010 in 23 EUROCAT registries is stable. Endocrine disrupting chemicals and potential EDCs can be found in various materials such as pesticides, metals, additives or contaminants in food and personal care products. Majority of studies indicate EDCs as a potential risk factor of hypospadias. According to some researches, pregnant women should avoid cosmetics with EDCs and exposure to other products containing them. However, because of incoherent experts' opinion further valuable studies are needed to confirm this thesis.

***Keywords*:** endocrine disruptors, hypospadias, maternal exposure, pesticides, occupational environment

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1. BACKGROUND

Hypospadias is defined as a congenital condition characterized by abnormal localization of urethral orifice which can impair male urinary and sexual functions [1,2]. Anatomic classification of this malformation takes into account many features e.g.: the level and site of urethral meatus, the prepuce, the glans, the width of urethral plate and penile rotation. Hypospadias is one of the most common congenital malformation in males. In Europe, the prevalence estimates in range from 5.10 to 36.83 per 10,000 births (average 18,6 per 10,000 births) and trends in particular countries are different [2]. In comparison Elliott et al. assessed the prevalence of hypospadias in USA at 42 per 10,000 live births, but they didn't observed increasing trend [3]. Prevalence of hypospadias varies depending on regional and ethnical parentage [4]. The exact cause of hypospadias is unknown. Scientists suggest that genes play role in hypospadias etiology. Also, environmental factors could be involved in the pathogenesis of this malformation what may be explained by increasing incidence of hypospadias in highly developed countries [5]. In recent years, scientists also reported the role of endocrine-disrupting chemicals in hypospadias development. The purpose of this study is to analyse available data for study on influence of Endocrine Disrupting Chemicals and elevated risk of hypospadias.

1. 1. Information sources

The databases PubMed and Google Scholar were used to collect data for the subject.

2. THE BEGINNING OF INTEREST IN EDCS

The concept of hormonally active chemicals was described already in 1930s in animal experiment. The number of environmental chemicals including bisphenol A demonstrated estrogenic properties. In 1950 Burlington et al. observed feminisation of cockerels exposed to DDT. Additionally, epidemiological study from 1971 indicated that the use of diethylstilbestrol (DES) during pregnancy may increase the risk of reproductive and immunologic abnormalities [6]. Wingspread Conference organized by professor Theo Colborn took place in USA in 1991. The group of multidisciplinary experts discussed the effects of human exposure to hormone disrupting chemicals. They draw attention to the problem of growing number of abnormalities such as: demasculinization, congenital deformations and thyroid dysfunction among wildlife populations. Therefore, they hypothesized that some substances which have been released into the environment may potentially disrupt the endocrine system of animals and humans [7] .The impact of exposure to endocrine disrupting chemicals during pregnancy and occurrence of hypospadias still remains controversial. The World Health Organization defines EDC as ‘’an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.”

Another definition was introduced by the U.S. Environmental Protection Agency (EPA) and described EDC as “an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process” [8].

Experimental studies about association between exposure on EDCs and influence on human health are incoherent. Some of them suggest that EDCs may increase the risk of: endometriosis, hormone related cancers (e.g. breast or testicular cancers), metabolic disorders, abnormal growth patterns and they may affect the neural and immune function. In 1979 Henderson et al. suggested that elevated level of estrogen at the time of testicular differentiation play a crucial role in testicular cancer [9]. The role of endocrine-disrupting chemicals in hypospadias development associated with disturbances of testosterone production were also proposed [10].

3. HOW THE EDCS AFFECT ENDOCRINE SYSTEM?

Many substances are included in EDCs and the list of them is still growing. It consists of susbtances like synthetic chemicals and their byproducts [8]. They are used as fungicides (vinclozolin), as plastics (for example bisphenol A (BPA), as plasticizers like phthalates, as pesticides including methoxychlor, chlorpyrifos or dichlorodiphenyltrichloroethane (DDT), as lubricants like polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs) or dioxins, and pharmaceutical agents like popular due to problems with reproduction - diethylstilbestrol (DES) [8]. Endocrine disrupting chemicals and potential EDCs are mostly man-made, present in various materials i.a. personal care products (parabens) [11].

Not only substances of artificial origin are included in EDCs, but also those of natural origin belong to this group. They could be found in food, e.g. phytoestrogens, including genistein and coumestrol [8]. WHO in the publication "Possible developmental early effects of endocrine disrupters on child health" divided EDCs into two gropus: sex hormones disrupters and thyroid hormone disrupters [12].

The first group includes: diethylstilbestrol, phthalate esters, flame retardants (polybrominated diphenyl ethers), phytoestrogens, dioxins, polychlorinated biphenyls, tributyltin, phtytoestrogens (genistein, daidzein), alkyl phenol ethoxylates, chlorinated pesticides (DDE), polychlorinated biphenyls, dicarboximide fungicides, herbicides, lead, cadmium and manganese [12]. The second group includes: PCBs, dioxins, flame retardants including tetrabromobisphenol A (TBBPA), polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs), pesticides (dichlorodiphenyltrichloroethane (DDT) (and the metabolite DDE), hexachlorobenzene (HCB), and nonylphenol), perfluorinated chemicals (PFC), phthalates, bisphenol A and ultraviolet filters [12]. Many chemicals known as EDCs are no longer approved or they are limited in their use. Notwithstanding, it is known that some of them are persistent in the environment [13]. Probably other environmental pollutants are involved. Therefore, it should be remembered that the effects of different EDCs classes can be additive and even synergistic [8].

Table 1. below shows examples of the most common EDCs, which are present in environment and which we are exposed to every day [14].

The different mechanisms of action of these substances have been suspected. However, the scientific findings suggest their involvement in nuclear receptors, nonnuclear steroid hormone receptors, nonsteroid receptors and orphan receptors, enzymatic pathways and other numerous mechanisms [8]. EDCs could disrupt hormone action by a direct influence on hormone receptor or on proteins controlling hormone: production, secretion, delivery and

metabolism [10]. EDCs may interact with hormone receptors as agonists or antagonists. Examples of agonistic EDCs are synthetic estrogens diethylstilbestrol (DES) and ethinylesradiol. Well-known inhibitors of receptors are herbicides, linuron and vinclozolin. What is more, endocrine disruptors have indirect influence on endocrine system by inhibiting enzyme-catalyzed reactions exerting antiestrogenic or androgenic properties. Influence on the hormone receptor concentration and transport of hormones are other possible ways to disrupt endocrine system. [15]. In 1993 Sharpe and Skakkebeak proposed hypothesis that lower level of gonadotrophins may be caused by exposure to EDCs because of increased negative feedback on the fetal pituitary and that can lead to abnormal development of the male fetal gonad [16] .

Table 1. Examples of Endocrine Disrupting Chemicals

Endocrine disrupting chemicals	Common occurrence	Target hormone
Industrial chemicals		
Bisphenol A	Plastic, thermal merchandise receipts, food cans, dental filings, medical equipment	Thyroid, cortisol
PCBs, Dioxins, PCP, PCDFs	Flame retardants	Estrogens
Phthalates		
BBP, DEHP, D-n-BP, DEP	Plastic, vinyl flooring, synthetic leather and toys	Estrogens
Alkylophenols		
p-Nonylphenol	Plastic	Estrogens
Organochlorine Pesticides		
DDT, DDE, Chlordane, Dieldrin, Heptachlor, Lindane, Endosulfan, Oxychlordane etc.	Insectides	Estrogens androgens
Haevy metals		
Cadminum, mercury, lead	Batteries, paints	Adrenaline, estrogens

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4. OVERVIEW OF RECENT STUDIES

In the last years scientists' interest in the EDCs as a potential cause of congenital malformation has grown. Occupations which are at risk of EDCs exposure include hairdressers, cleaners, laboratory technicians and agricultural workers. Table 2. shows findings of reviewed studies. Morales-Suárez-Varela et al. analysed association between occurrence of male genital malformations (included hypospadias) and parental occupational exposure to EDCs. The study included 45,341 boys born in 1997-2009. Danish scientists found some evidence, that potential maternal exposure to pesticides, phthalate esters, alkyl phenols, bis-phenols and other EDCs could increase the risk of hypospadias. They did not find any evidence of paternal exposure to EDCs related with male genital malformations [17]. Exposure to hexachlorobenzen (HCB) and possible exposure to p,p'-DDE in utero is a risk factor of hypospadias by affecting the androgen signalling according to scientists from Sweden who analysed serum samples from pregnant women [18]. Shekhar Yadav et al. examined the level of pesticides in serum from cases in which it was increased and the results indicate that some organochlorine pesticides (OCPs) may be associated with elevated risk of hypospadias [19].

In another study, Fernandez et al. measured the levels of 16 pesticides and estimated the total effective xenoestrogen burden (TEXB) in placenta tissue and their results also support hypothesis that the environment at work may play a role in hypospadias development. The study included fifty boys -among whom hypospadias was diagnosed in twenty-one cases and were limited to a small number of cases [20]. On the other hand, other scientist searched for relationship between hypospadias and proximity to agricultural pesticide applications and they did not find evidence supporting this thesis [21]. The Dutch scientists draw attention to paternal smoking, which may play a role in increased risk of hypospadias [22].

Winston et al. have looked at potential exposure to pesticides via drinking water and found only a weak relation between maternal consumption of atrazine and hypospadias. However, this study has also many limitations and does not confirm association between hypospadias and atrazine exposure in 100% [23]. French scientist observed increasing trend of hypospadias prevalence among boys born from 1980 to 1989 and only little evidence of such a trend among boys born between 1992 and 1996. In the 1992-96 period hypospadias occurred most commonly in the group exposed probable to phthalates, namely hairdressers . However, there was only little evidence for this relation.

Because of many limitations, authors advice to interpret results carefully [24]. Also, authors of larger case-control study found 2 to 3-fold higher risk of hypospadias in a group of children whose mothers were exposed to hair spray and phthalates in the workplace during pregnancy [25]. Diametrically opposed results were presented by other cohort study conducted among Danish population, in which more than 500 000 male infants were examined. According to the authors, exposure to EDCs by mothers hairdressers did not increase a risk of male malformations including hypospadias [26].

Table 2. Basic characteristics and main findings of the studies included in the review

Study	Country	Study groups	Methodology	Findings
M. Vrijheid et al.	England (2003)	35 962 – all congenital anomaly cases 3471 hypospadias cases All cases were notified by occupational codes	Analysis data (1980-1996) from the National Congenital Anomaly System	Little evidence for relation between risk of hypospadias and maternal occupation
F.H. Pierik et al.	Netherlands (2004)	56 hyospadias cases sourced from 8,698 male births 313 controls	Analysis of collected interviews with both parents: information of pregnancy aspects and personal characteristic, lifestyle, occupation, dietary	Smoking cigarettes by father was associated with hypospadias. There is no connection between maternal occupational, dietary and lifestyle aspects. Suboptimal maternal health and lower education, Turkish origin of parents increased the risk of hypospadias.

K.J. Meyer et al.	USA (2006)	354 cases of hypospadias born between 1998 and 2002 727 controls	Analysis data about parents and child : birth characteristic, maternal and paternal data i.e. physical condition, education, smoking, race, age. They were classified by potential exposure to EDCs	Except for diclofop-methyl, no evidence that exposure to pesticides increase risk of hypospadias was found
M.F. Fernandez et al.	Spain (2007)	702 mother –child cohort 21 cases of hypospadias 114 controls	Comparison of control data and hypospadias group. Questionnaire for parents: characteristics, pregnancy, and birth data were analysed. TEXB and levels of 16 organochlorine pesticides in placenta tissue were measured.	Increases risk of male urogenital malformations related to the combined effect on enviromental estrogens in placenta.
G. Ormond et al.	England (2009)	471 hypospadias cases 490 controls Born 1 January 1997 -30 September 1998	Telephone interviews of mother, occupational exposure, folate supplementation and vegetarianism	Occupational exposures to phtalathes and hair spray may increase a risk of hypospadias. Folate supplementation in early pregnancy may be protective

M.M. Morales-Suarez-Varela et al.	Denmark (2011)	45, 341 patients were performed 262 hypospadias cases delivered during 1997-2009	Telephone interviews about work during pregnancy, parent's job. They were classified as possibly or probably exposed to EDCs	There is some but limited evidence that occupational exposure to possible endocrine chemicals during pregnancy elevate the risk of hypospadias
C. Shekharyadav et al.	India (2011)	80 hypospadias cases 120 controls	Organochlorine pesticides levels in blood were measured CYP1A1. GSTM1, GSTT1 genes was evaluated by RFLP and multiplex PCR method.	Significant high levels of β-hexachlorexane (HCH), γ-HCH and *p,p'*-DDE in the cases. *GSTM1* and *GSTT1* genotypes were more common in cases compared to control
A. Rignell-Hydbom et al.	Sweden (2012)	237 cases of hypospadias born during 1986-2002 For each case a control boy was randomly selected	PCB-153, *p,p'*-DDE and HCB were measured in serum samples and used as biomarkers for Persistent Organochlorine Pollutans exposure	Fetal exposure to HCB and p,p'-DDE may be risk factor for hypospadias.
K.T. Jørgensen et al.	Denmark (2013)	Children born in Demark from 1980 to 2007	Analysis of the data i.e. : childbirths, hospital contacts, employment status of mothers during pregnancy	There is no connection between exposure to a EDCs by hairdressers and hypospadias

J. J. Winston et al.	USA (2016)	343 hypospadias cases 1,422 male controls	Atrazine concentrations in public water were measured. Maternal questionnaire data were used.	Weak association between atrazine exposure and hypospadias.

5. CONCLUSION

Recently, the EDCs are the object of scientists' interest who linked many disorders with EDCs exposure, especially maternal exposure during pregnancy. It is commonly known that morbidity of cancers, congenital malformations, metabolism and autoimmunological disorders have grown. The development in all areas of industry could reflect influence of environmental factors on human health. Do these factors play a role in hypospadias development? Most of reviewed studies indicate potential effect of EDCs exposure to hypospadias occurrence. Therefore, individuals exposed to EDC employed in such professions as agriculture, laboratories and hairdresser should be educated about potential effects. However, many of them had limitations such as: to small cases group or inability to measure EDCs concentrations in samples. We need further more precise studies to confirm this thesis in 100 %. Not only clinical studies could help to answer this question, but also long-term epidemiological observations are needed.

References

[1] E. Haraux , K. Braun , P. Buisson ,E. Stephan-Blanchard et al., Maternal Exposure to Domestic Hair Cosmetics and Occupational Endocrine Disruptors Is Associated with a Higher Risk of Hypospadias in the Offspring. *Int J Environ Res Public Health* 14 (1) (2016) 27.

[2] J.E. Bergman, M. Loane, M. Vrijheid et al., Epidemiology of hypospadias in Europe: a registry-based study. *World J Urol* 33 (2015) 2159–2167.

[3] S. Elliott, M.S. Halpern, J. Paik, Y. Maldonado, L.D. Shortliffe, Epidemiologic trends in penile anomalies and hypospadias in the state of California, 1985-2006. *Journal of pediatric urology* 7 (3) (2011) 294-298

[4] A. Springer, S. Bauman, Worldwide prevalence of hypospadias, *Journal of Pediatric Urology* 12(3) (2016) 152.e1-152.e7.

[5] L. Fredell, I. Kockum, E. Hansson, Heredity of hypospadias and the significance of low birth weight. *J Urol.* 167 (3) (2002) 1423-7.

[6] G.M. Solomon, T. Schettler, Environment and health: 6. Endocrine disruption and potential human health implications. *CMAJ* 163 (11) (2000) 1471–147.

[7] H. Langauer-Lewowicka, K. Pawlas, Endocrine disrupting chemicals – probability of adverse environmental effect. *Environmental Medicine* 18(1) (2015) 7-11.

[8] E. Diamanti-Kandarakis, J.P. Bourguignon, C.L. Giudice, R. Hauser, G.S. Prins et al., Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocr Rev.* 30(4) (2009) 293–342.

[9] J.P. Bonde, E.M. Flachs, S. Rimborg et al. The epidemiologic evidence linking prenatal and postnatal exposure to endocrine disrupting chemicals with male reproductive disorders: a systematic review and meta-analysis. *Hum Reprod Update*. 23 (1) (2017) 104–125.

[10] Å. Bergman, J. J. Heindel, S. Jobling, K. A. Kidd, R. T. Zoeller. State of the science of endocrine disrupting chemicals. WHO Publication (2012).

[11] C. Monneret, What is an endocrine disruptor? *Comptes Rendus Biologies* 340 (9) (2017) 403-405.

[12] J. Toppari, A. Adamsson, M. Boas, A. Juul, K. M. Main et al. Possible developmental early effects of endocrine disrupters on child health. WHO Publication 2012

[13] C.L. Acerini, I. A. Hughes, Endocrine disrupting chemicals: a new and emerging public health problem? *Arch Dis Child.* 91(8) (2006) 633–641.

[14] O.O Olujimi, O.S Fatoki, J.P. Odendaal, J.O. Okonkwo, Review: Endocrine disrupting chemicals (phenol and phthalates) in the South African environment: a need for more monitoring. *Water SA* 36 (5) (2010) 671-682.

[15] J. Lintelmann, A. Katayama, N. Kurihara et al., Endocrine disruptors in the environment (IUPAC Technical Report). *Pure Appl. Chem.* 75 (5) (2003) 631–681 .

[16] R.M. Sharpe, N.E. Skakkebaek, Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 341 (1993) 1392–1395.

[17] M.M. Morales-Suarez-Varela, G.V. Toft , M.S. Jensen et al., Parental occupational exposure to endocrine disrupting chemicals and male genital malformations: a study in the Danish National Birth Cohort study, *Environ Health* 10 (1) (2011) 3.

[18] A. Rignell-Hydbom, C.H. Lindh, J. Dillner et al., A Nested Case-Control Study of Intrauterine Exposure to Persistent Organochlorine Pollutants and the Risk of Hypospadias. *PLOS ONE* 7 (9) (2012) e44767.

[19] C. Shekharyadav, M. Bajpai ,V. Kumar et al., Hypospadias and variants in genes related to sex hormone biosynthesis and metabolism. *Hum Exp Toxicol* 30 (2011) 1464–1474.

[20] M.F. Fernandez, B Olmos, A. Granada et al., Human exposure to endocrine-disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias: a nested case-control study. *Environ Health Perspect* 115 (1) (2007) 8-14.

[21] K.J. Meyer, J. S. Reif, D.N.R. Veeramachaneni et al., Agricultural Pesticide Use and Hypospadias in Eastern Arkansas. *Environ Health Perspect.* 114 (10) (2006) 1589–1595.

[22] F.H. Pierik , A. Burdorf , J.A. Deddens , R.E. Juttmann , R.F. Weber, Maternal and paternal risk factors for cryptorchidism and hypospadias: a case-control study in newborn boys. *Environ Health Perspect* 112 (2004) 1570–1576.

[23] J. J. Winston, M. Emch, R. E. Meyer et al., Hypospadias and maternal exposure to atrazine via drinking water in the National Birth Defects Prevention study. *Environ Health* 15 (2016) 76.

[24] M. Vrijheid, B. Armstrong, H. Dolk, M. van Tongeren, B. Botting, Risk of hypospadias in relation to maternal occupational exposure to potential endocrine disrupting chemicals. *Occup Environ Med* 60 (2003) 543–550.

[25] G. Ormond, M. J. Nieuwenhuijsen, P. Nelson, M. B. Toledano, N. Iszatt et al., Endocrine Disruptors in the Workplace, Hair Spray, Folate Supplementation, and Risk of Hypospadias: Case–Control Study. *Environmental Health Perspective* 117 (2) (2009) 303-310.

[26] K.T. Jørgensen, M.S. Jensen, G.V. Toft, A.D. Larsen, J.P. Bonde, K.S. Hougaard, Risk of cryptorchidism and hypospadias among boys of maternal hairdressers – a Danish population-based cohort study. *Scand J Work Environ Health* 39 (3) (2013) 302-309.